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Lithiation–Borylation Methodology: New Classes of Metal Carbenoid Precursors for the Iterative Homologation of Boronic Esters

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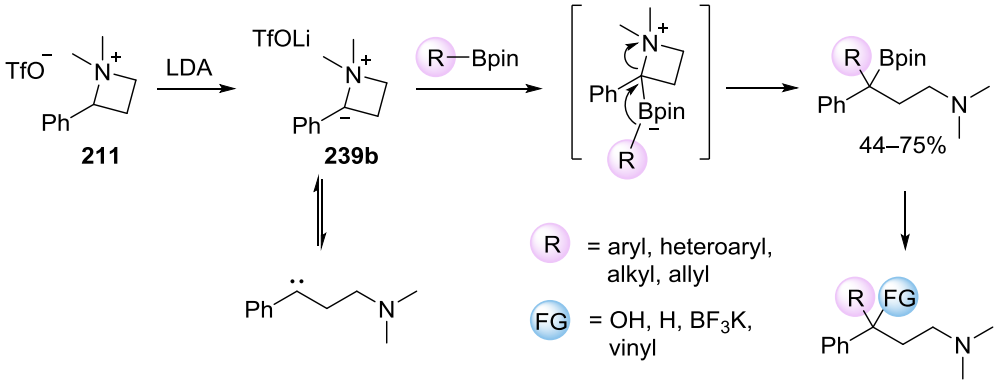
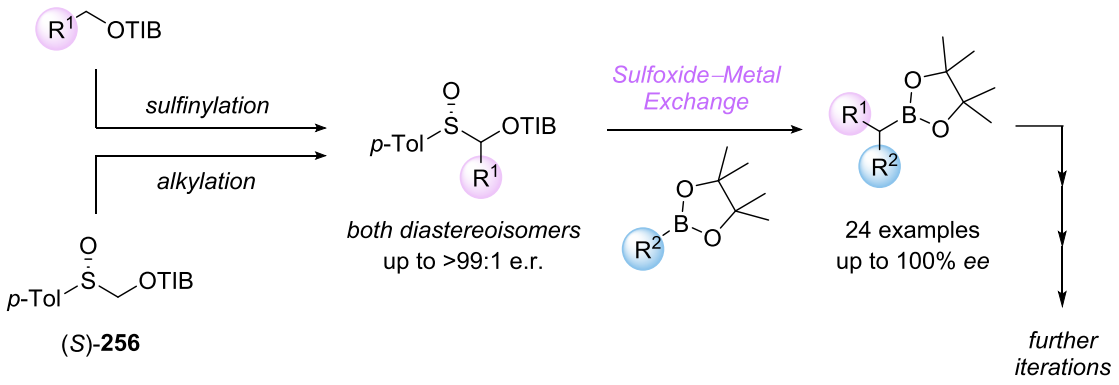
Abstract

The work described in this thesis details the development of new classes of metallated carbenoids to be used in the homologation of boronic esters. 2-Phenyl-azetidinium ylide **239b**, which could be generated *in situ* by deprotonation of 2-phenylazetidinium triflate **211**, reacted with boronic esters to give, after ring-opening 1,2-metallate rearrangement, γ-dimethylamino tertiary boronic esters (Scheme A). The process proved to be not stereospecific, owing to the configurational instability of the generated intermediated ylide, which presumably exists in equilibrium with the open chain carbene species. Further functional group transformations of the generated γ-dimethylamino tertiary boronic esters, including protodeboronation and Zweifel olefination, gave access to a range of substituted 3-aryl-1-aminopropanes, which represent a pivotal structural motif among biologically active compounds.



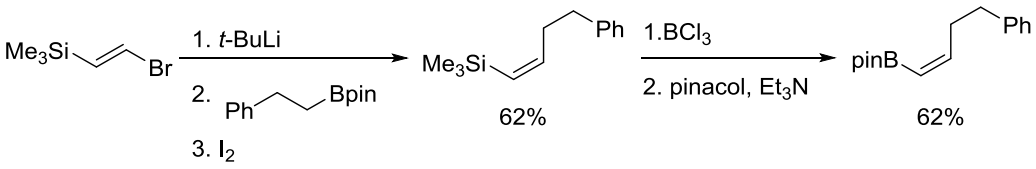
Scheme A. Synthesis of 3-aryl-1-aminopropane derivatives by lithiation–borylation–ring-opening of azetidinium ions.

The use of enantioenriched α-sulfinyl benzoates as precursors to lithium and magnesium carbenoids for the stereoselective reagent-controlled homologation of boronic esters has also been developed (Scheme B). α-Sulfinyl benzoates could be synthesised in very high enantiopurity from racemic lithiated benzoates by transmetalation to the corresponding magnesiated benzoates followed by electrophilic trapping with enantiomerically pure Andersen's sulfinate. Alternatively, the α-sulfinyl benzoates could be prepared by alkylation of methylene α-sulfinyl benzoate **256**. The carbenoid precursors were subsequently employed in the homologation of boronic esters, a process that proved to be efficient using either *t*-BuLi or *i*-PrMgCl·LiCl to trigger the sulfoxide–metal exchange, giving the homologated products in high yield and excellent stereofidelity. Three iterative homologations, without intervening chromatographic purification, could also be performed with similar levels of efficiency, showing the potential of this methodology for automation.



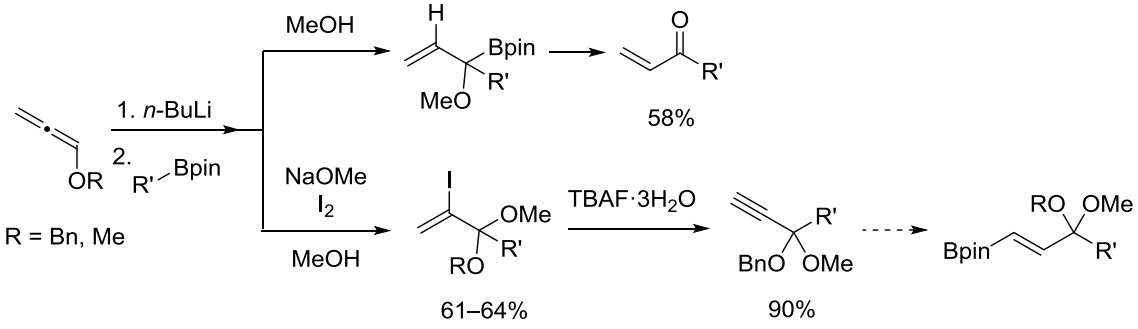
Scheme B. Stereoselective iterative homologations of boronic esters with α-sulfinyl benzoates.

The development of one-, two- and three-carbon building blocks for the homologation of boronic esters enabling the introduction of diverse functional groups has also been investigated. In particular, (2-bromovinyl)trimethylsilane allowed the two-carbon homologation of boronic esters under Zweifel olefination conditions, leading to the introduction of a C–C double bond (Scheme C). Subsequent borodesilylation returned the boronic ester group, essential for further iterative homologations to take place.



Scheme C. Zweifel olefination of boronic esters with (2-bromovinyl)trimethylsilane.

Finally, alkoxyallenes were successfully employed as three-carbon carbenoid precursors for the homologation of boronic esters, leading to the introduction of terminal and internal enones (Scheme D). This methodology will be further developed and applied to the total synthesis of 10-deoxymethinolide.



Scheme D. 3-Carbon homologation of boronic esters using lithiated alkoxyallenes.

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Firstly, I would like to thank Professor Varinder Aggarwal for giving me the opportunity of undertaking my PhD in his group. I am grateful for the guidance and support he has given me over the last four years and it has been a privilege to work in such a stimulating environment. I would also like to thank Dr. Eddie Myers and Dr. Adam Noble, the past and present research officers of the group, for additional help and support. Additionally, I would like to thank the EPSRC for fundings.

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I would also like to thank my Italian friends, who have always been present despite the distance: Alice, Valentina, Francesca, Giulia, Eleonora, Luisa, Chiara, Rocco, Andrea, Ivan and Michele, for your friendship in good and bad times throughout my PhD.

Finally, my warmest thank goes to my mum, dad and grandma for their unconditional love and support, which has contributed in a massive way to the person I am today.

Author's Declaration

I declare that the work in this dissertation was carried out in accordance with the requirement of the University's *Regulations and Code of Practice for Research Degree Programmes* and that it has not been submitted for any other academic award. Except where indicated by a specific reference in the text, the work is the candidate's own work. Work done in collaboration with, or with the assistance of, others, is indicated as such. Any views expressed in the dissertation are those of the author.

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Abbreviations

acac	acetylacetone
aq.	aqueous
Ar	aryl
Bn	benzyl
b.p.	boiling point
°C	Celsius degree
c-	cyclo-
cat.	catalyst
Cb	carbamate
CPME	cyclopentyl methyl ether
DCM	dichloromethane
DCME	dichloromethyl methy ether
DFT	density functional theory
DIAD	diisopropyl azodicarboxylate
DMF	dimethylformamide
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidone
DPEPhos	(oxydi-2,1-phenylene)bis(diphenylphosphine)
d.r.	diastereomeric ratio
E	electrophile
e.r.	enantiomeric ratio
ee	enantiomeric excess
equiv	equivalent
es	enantiospecificity
ESI	electronspray ionisation
Et	ethyl
g	gram
GC	gas chromatography
GCMS	gas chromatography-mass spectrometry
GP	general procedure
h	hour
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry

i-Pr	*iso*-propyl
IR	infrared
J	coupling constant
KHMDS	potassium bis(trimethylsilyl)amide
LDA	lithium diisoprpylamide
LG	leaving group
LiHMDS	lithium bis(trimethylsilyl)amide
lit.	literature
LiTMP	lithium tetramethylpiperidine
M	molar
m-	*meta*-
m-CPBA	*meta*-chloroperoxybenzoic acid
M.P.	melting point
Me	methyl
Mes	2,4,6-mesityl
mg	milligram
MHz	Megahertz
min	minute
mL	millilitre
mmol	millimole
mol	mole
MS	mass spectrometry
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
n-BuLi	*n*-butyllithium
n.d.	not determined
neop	neopentyl glycol
NMR	nuclear magnetic resonance
Nu	nucleophile
o-	*ortho*-
p-	*para*-
Ph	phenyl
pin	pinacol
PMDTA	*N*,*N*,*N*′,*N*″,*N*″-pentamethyldiethylenetriamine

PMB	*para*-methoxybenzyl
PMP	*para*-methoxyphenyl
ppm	parts per million
R_f	retention factor
rt	room temperature
s-BuLi	*sec*-butyllithium
TBAF	tetra-*n*-butylammonium fluoride
TBME	*tert*-butyl methyl ether
t-BuLi	*tert*-butyllithium
Tf	trifluoromethanesulfonyl
THF	tetrahydrofuran
TIB	2,4,6-triisopropyl benzoate
TLC	thin layer chromatography
TMEDA	*N*,*N*,*N'*,*N'*-tetramethylethylenediamine
t_R	retention time

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1. Introduction

Organoboron compounds have found widespread use in organic synthesis due to the possibility of transforming them into a variety of useful functionalities (see § 1.7). Since the seminal work of Herbert C. Brown on the hydroboration of alkenes,[1-3] an increasing number of protocols have been developed for converting organoboranes into different functional groups. The main drawback of using boranes, which contain a boron centre linked to three carbon substituents (Figure 1.1), is that they are normally air and moisture sensitive, and are therefore difficult to manipulate. In contrast, boronic esters, where the boron centre is connected to one carbon substituent and two oxygen substituents, are known to possess increased stability. This is due to the π-donation of electron density from the oxygen lone pairs into the empty p-orbital on boron, making the boron atom less electrophilic and therefore less prone to undergo decomposition.

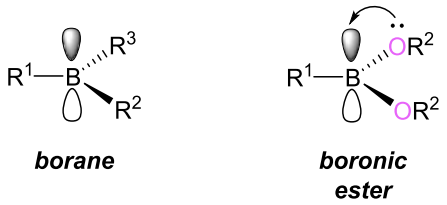


Figure 1.1. Comparison between boranes and boronic esters.

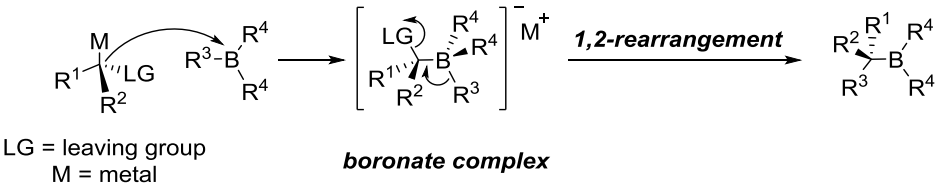
A variety of different methodologies have been developed to synthesise enantioenriched secondary and tertiary boronic esters, thus demonstrating the importance of these classes of compounds in modern organic synthesis.[4]

The following chapter will describe the methods available to homologate organoboron compounds through the generation of a new C–C bond. Alternative stereospecific transformations of the generated secondary and tertiary enantioenriched boronic esters will also be briefly discussed.

1.1. Homologation of Organoboron Compounds

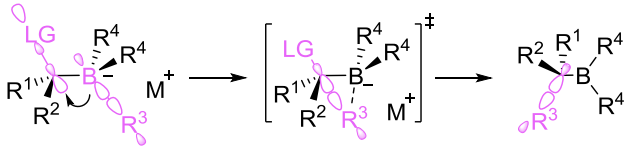
The homologation of organoboron compounds is a useful method to convert the carbon–boron bond into a variety of different bonds, usually with high levels of stereocontrol. These transformations normally take place through an initial nucleophilic attack to the empty p-orbital on the sp^2 hybridised boron atom, resulting in the formation of a boronate complex bearing a formal negative charge on the boron atom.[5] One of the substituents on the boron atom can then

undergo a 1,2-rearrangement to an adjacent electrophilic atom bearing a suitable leaving group to generate a new organoboron species (Scheme 1.1).[5]



Scheme 1.1. Boronate complex formation and 1,2-metallate rearrangement upon reaction of boron species and organometals.

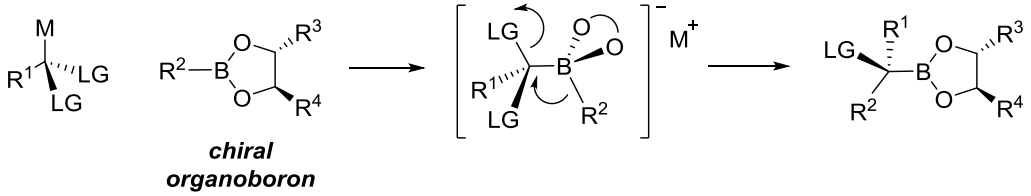
In order for this process to take place, a rotation about the C–B bond must occur to align the migrating group on boron antiperiplanar to the leaving group on the acceptor atom, allowing the σ orbital of the C–B bond of the migrating group to overlap with the σ* orbital of the C–leaving group bond. The migration proceeds through a concertated mechanism, thus explaining the inversion of configuration at the migrating terminus (Scheme 1.2).[6]



Scheme 1.2. Orbital overlap in 1,2-metallate rearrangement of boronate complexes.

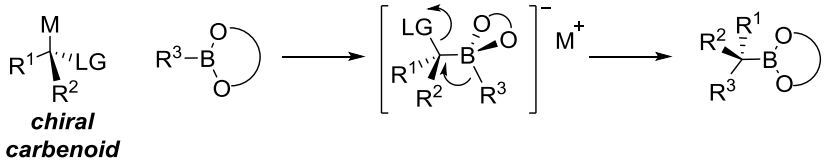
In particular, when a carbon nucleophile bearing a leaving group is employed in the sequence, a new C–C bond is formed. The species usually employed for this purpose are metal carbenoids, which, similarly to carbenes, possess the necessary nucleophilic component (carbon atom) as well as the required electrophilic part (leaving group).

High levels of stereoselectivity can be imparted to the process by either substrate control or reagent control.[7] In the first approach, pioneered by Matteson in 1980,[8] a prochiral carbenoid is reacted with a chiral organoboron to generate a new diastereomeric organoboron after 1,2-metallate rearrangement; the chiral auxiliary on the organoboron eventually controls all the subsequent transformations, thus ensuring high levels of diastereoselectivity (Scheme 1.3).



Scheme 1.3. Substrate-controlled approach to the homologation of boronic esters.

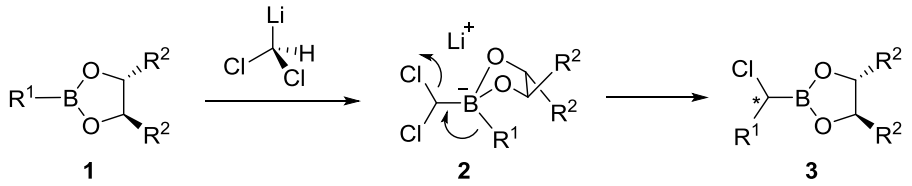
In a complementary reagent-controlled approach, a chiral carbenoid is reacted with an organoboron reagent to generate an initial boronate complex bearing an already stereodefined migratory terminus, eventually evolving to the homologated product; the enantioselectivity is in this case determined exclusively by the chirality of the carbenoid (Scheme 1.4).



Scheme 1.4. Reagent-controlled approach to the homologation of boronic esters.

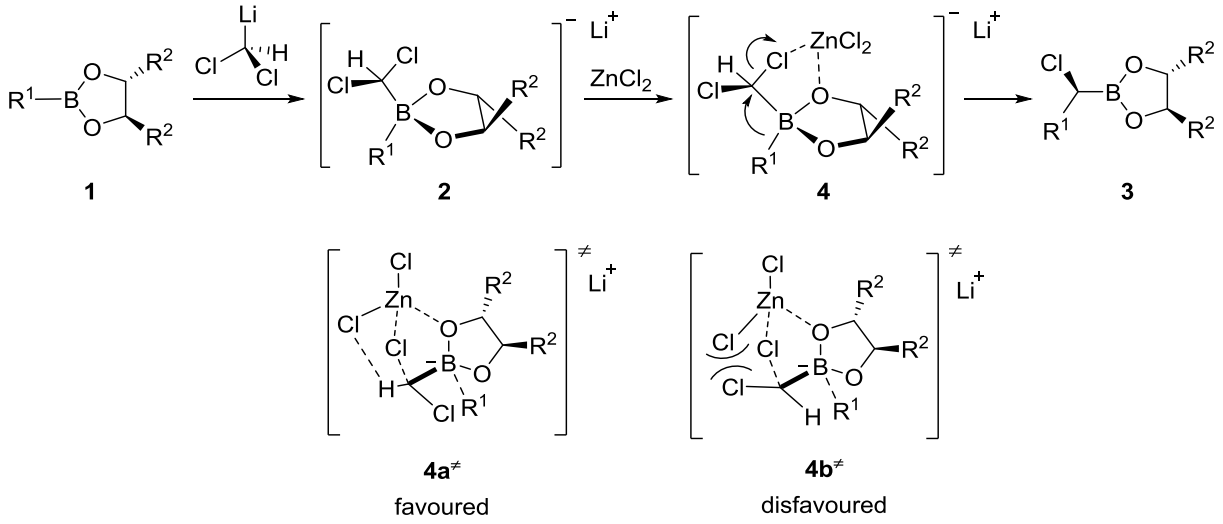
1.2. Matteson Homologation

Matteson and co-workers developed a method for the homologation of boronic esters possessing C_2-symmetrical chiral diols based on a key 1,2-metallate rearrangement of an intermediate boronate complex.[8-11] The general mechanism of the process is outlined in Scheme 1.5. (Dichloromethyl)lithium, generated *in situ* from dichloromethane and *n*-butyllithium at −100 °C, undergoes nucleophilic addition to an enantiopure boronic ester **1** to form boronate complex **2**. Upon warming the reaction to room temperature, the alkyl or aryl group (R) on boron migrates to the dihalomethyl carbon, with displacement of a chloride, to afford one-carbon homologated boronic ester **3**.



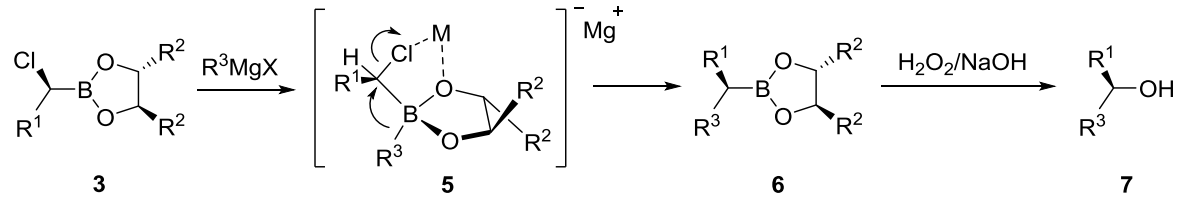
Scheme 1.5. General mechanism of the Matteson homologation.

High levels of stereoselection are observed during the 1,2-metallate rearrangement due to the presence of the chiral ligand on boron, and it was found that Lewis acidic $ZnCl_2$ was essential to ensure high diastereoselectivity.[12] Corey and co-workers proposed that the coordination of the metal cation to both the departing chloride and one of the oxygens of the boronic ester moiety leads to the stabilisation of only one of the four possible transition states (Scheme 1.6).[13] Using *ab initio* calculations, Midland and co-workers proposed a rational explanation for the observed stereoselectivity, showing that the lowest energy transition state (**4a**$^{\neq}$) is the one in which the metal is complexed to the less sterically hindered oxygen atom and with the nonparticipating chlorine atom placed *anti* to the metal.[14] From this favoured transition state, 1,2-metallate rearrangement affords exclusively boronic ester **3**.



Scheme 1.6. Possible transition state structures in the Matteson homologation.

The generated α-chloro boronic ester **3** can be further reacted with a Grignard reagent at low temperature to form a second boronate complex **5**; this undergoes a similar 1,2-metallate rearrangement to yield boronic ester **6**. Stereospecific oxidation using H_2O_2/NaOH finally affords enantiopure secondary alcohol **7** (Scheme 1.7).[10]



Scheme 1.7. Homologation and oxidation of α-halo boronic esters.

The potential of this homologation was demonstrated by Matteson and co-workers by its application to the stereoselective synthesis of various natural products, such as insect pheromones stegobinone **8**,[12, 15] japonilure **9**[16] and serricornin **10**[17] (Figure 1.2).

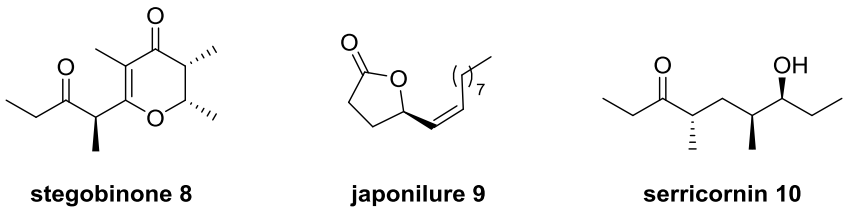
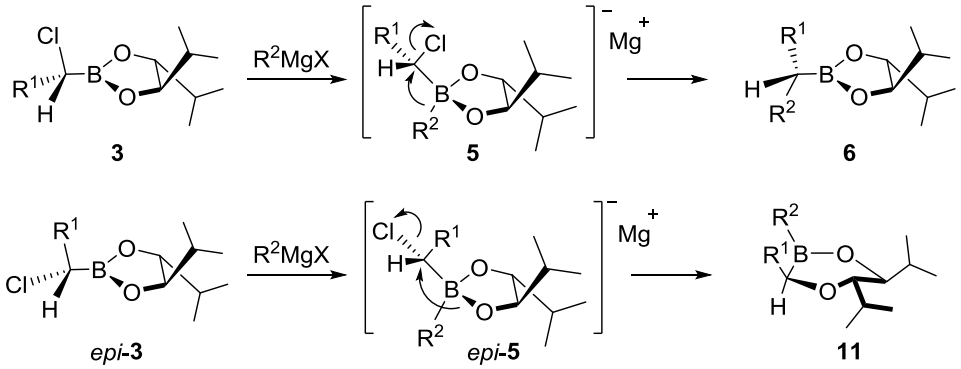


Figure 1.2. Examples of natural products synthesised through Matteson homologation.

Despite its power, the Matteson homologation still suffers from some disadvantages. In some cases, diastereomeric boronic esters show different behaviour when reacted with an organometallic reagent. For instance, when boronic ester **3** was reacted with a Grignard reagent, the expected homologated boronic ester was generated *via* intermediate boronate

complex **5** (Scheme 1.8). On the contrary, when diastereomeric boronic ester *epi*-**3** was reacted under the same reaction conditions only borinic ester **11** was isolated.[18] Boronate complex *epi*-**5** was presumably formed in the process, but in this case the less sterically hindered conformation is the one keeping R^1 *anti* to R^2, whilst one of the oxygen atoms of the boronic ester is placed *anti* to the chlorine leaving group. The species is therefore prone to undergo *O*-migration rather than *C*-migration to give the expanded ring **11**.



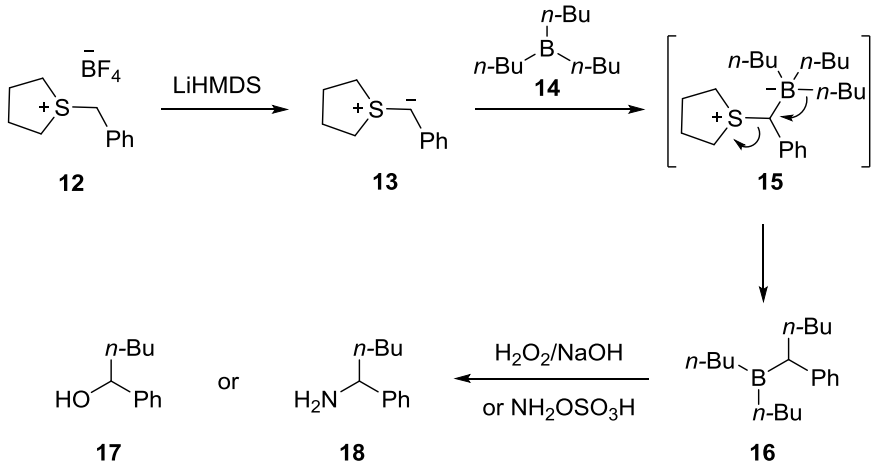
Scheme 1.8. Matteson homologation on diastereomeric boronic esters.

A second limitation of the methodology is that in some cases it is necessary to invert the stereochemistry of the diol in order to synthesise opposite stereoisomers. In practice, a three-step sequence must be performed, with the cleavage of the diol after the first homologation reaction to access the free boronic acid. This can be subsequently recondensed with the appropriate diol to generate the boronic ester of opposite stereochemistry, which can then be involved in the second homologation.

Finally, although Matteson homologations have been successfully applied to the synthesis of enantiomerically enriched secondary alcohols, much less success has been obtained in the synthesis of enantioenriched tertiary alcohols, as lower and less predictable levels of diastereoselectivity were observed.[19]

1.3. Homologation of Boranes by Chiral Sulfur Ylides

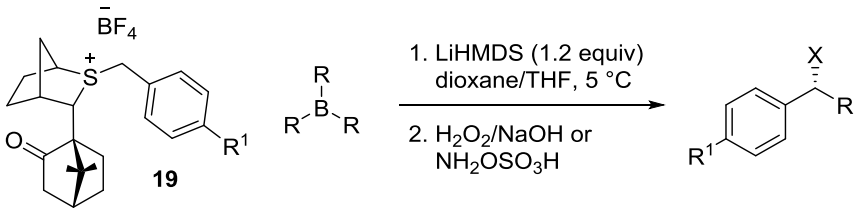
Aggarwal and co-workers showed the possibility of employing chiral sulfur ylides in the stereospecific reagent-controlled homologation of organoboranes.[20] Sulfur ylide **13** (Scheme 1.9), generated *in situ* by deprotonation of the corresponding sulfonium salt **12** with LiHMDS, undergoes nucleophilic addition to organoborane **14** to generate boronate complex **15**. After 1,2-metallate rearrangement, in which the sulfide acts as the leaving group, the homologated product **16** was isolated and subsequently converted into the corresponding alcohol **17** or amine **18**.



Scheme 1.9. Homologation of boranes using sulfonium salt **12**.

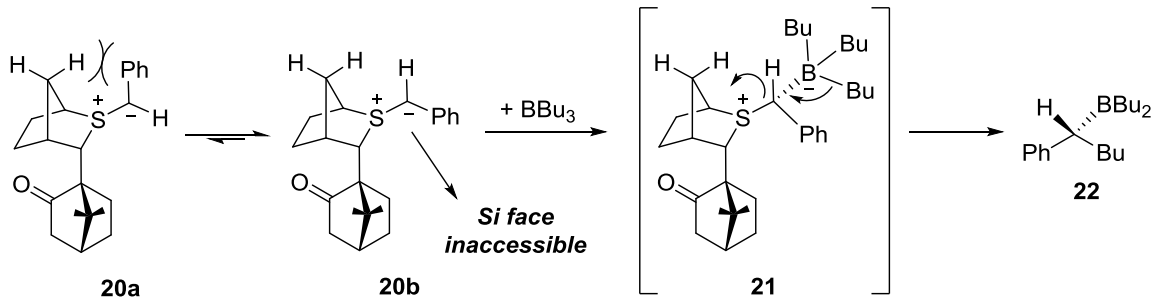
The process can be rendered asymmetric by using chiral sulfonium salt **19** in the sequence to give the corresponding alcohols and amines in good yield and excellent enantioselectivities (Table 1.1).[20]

Table 1.1. Homologation of boranes using chiral sulfonium salt **19**.



Entry	R	R^1	X	% Yield	% *ee*
1	*n*-Bu	H	OH	70	95
2	*n*-Bu	H	NH_2	72	97
3	Et	H	OH	73	96
4	Et	H	NH_2	68	97
5	Ph	Me	OH	87	95
6	Ph	Cl	NH_2	68	96

The high enantioselectivity observed is determined by the favoured sulfur ylide conformation **20b**, in which the α-aromatic substituent is oriented away from the adjacent bridging methylene hydrogens, thus making the *Si*-face less accessible; nucleophilic attack must then occur stereoselectivity upon the more available *Re*-face (Scheme 1.10).[21]



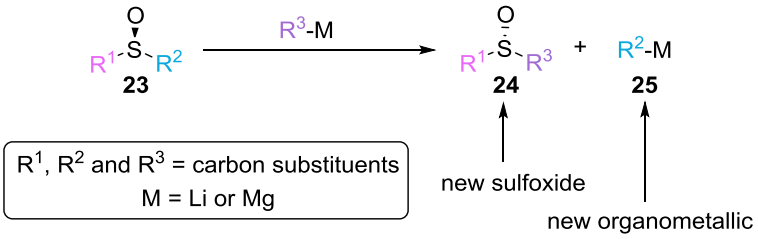
Scheme 1.10. Enantioselective control for the homologation of boranes with sulfonium salt **19**.

An important limitation of the methodology is that it only works efficiently with aryl substituted sulfur ylides, whilst low enantioselectivity was observed with non-stabilised alkyl- and silyl-substituted ylides.[22] Furthermore, only organoboranes can be employed in the process as sulfur ylides do not react with less electrophilic boronic esters due to the increasing barrier to migration of the corresponding "ate" complexes.[6, 21]

1.4. Homologation of Boronic Esters by Chiral Carbenoids Generated by Sulfoxide–Metal Exchange

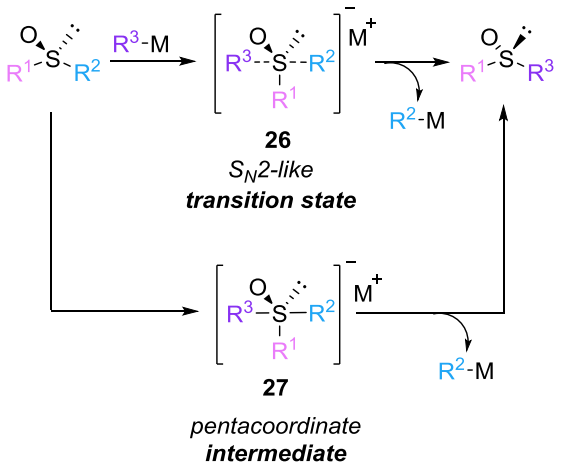
1.4.1. The Sulfoxide–Metal Exchange Reaction in the Synthesis of Chiral Metal Carbenoids

The sulfoxide–metal exchange reaction occurs when a sulfoxide **23** is reacted with an organometallic reagent, either an organolithium or organomagnesium, to generate a new sulfoxide **24**. In this process, the nucleophilic group on the organometallic reagent replaces one of the ligands on the sulfoxide; a new organometallic species **25** is also generated from the ligand which has departed from the original sulfoxide (Scheme 1.11).[23] The ligand displaced from the initial sulfoxide departs as an anion and is therefore the group with the lower pK_a.[24] The reaction has been shown to proceed with inversion of configuration at the sulfur centre.[25]



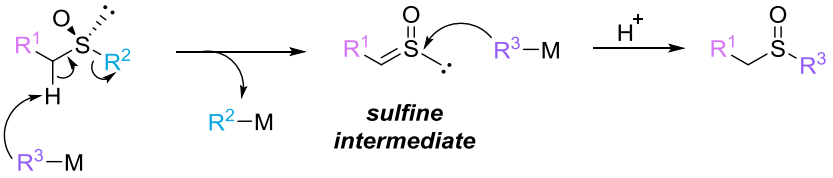
Scheme 1.11. Sulfoxide–metal exchange reaction.

The most plausible mechanism involves either a pentacoordinate S_N2-like transition state **26**, or a pentacoordinate intermediate **27** (Scheme 1.12). In the latter case it must be assumed that Berry pseudorotation does not occur to justify the observed transfer of chiral information.[24, 26]



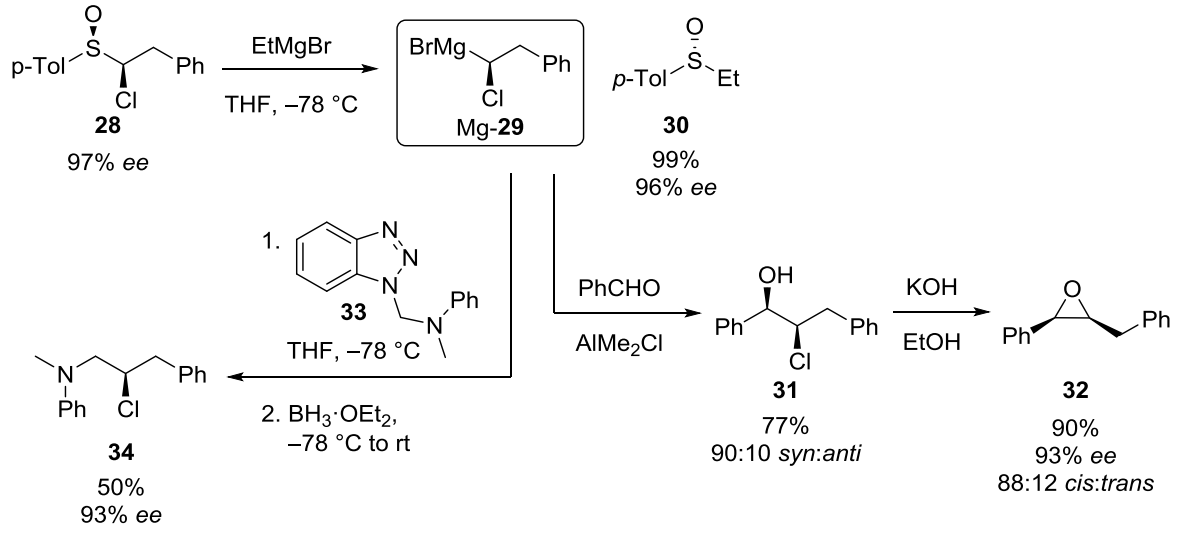
Scheme 1.12. Possible transition state/intermediate for the sulfoxide−metal exchange reaction.

An alternative pathway, which is known to operate in a few limited cases with loss of the chiral information,[26] involves the formation of an achiral sulfine intermediate (Scheme 1.13).



Scheme 1.13. Postulated sulfine intermediate pathway for the sulfoxide−metal exchange reaction.

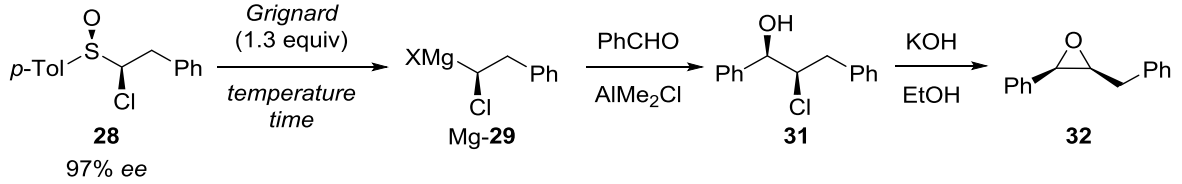
Hoffmann and co-workers have shown that α-chlorosulfoxides can be used as precursors to chiral carbenoids, which can be further reacted in stereoselective processes (Scheme 1.14).[27-28] Sulfoxide **28** was treated with EtMgBr in a sulfoxide−magnesium exchange reaction to generate Grignard reagent Mg-**29** together with the sulfoxide by-product **30**. The Grignard reagent Mg-**29** was subsequently trapped with benzaldehyde to afford chlorohydrin **31**, which was eventually converted into epoxide **32** in order to determine the *ee* (93%). This value gives an indication of the *ee* of the intermediate carbenoid, thus suggesting its configurational stability at low temperature. Similarly, the generated chiral carbenoid was trapped with α-aminomethylbenzotriazole **33** to give the corresponding product **34** in moderate yield and high *ee* (93%).[27]



Scheme 1.14. Synthesis of epoxide **32** and tertiary amine **34** using chiral carbenoid Mg-**29**.

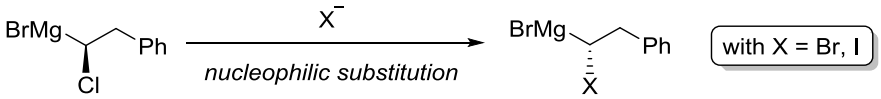
The authors further investigated the limits of the configurational stability of α-chloroalkyl Grignard reagent Mg-**29**, which was generated by treatment of sulfoxide **28** with various Grignard reagents; after trapping with benzaldehyde and subsequent ring-closure, epoxide **32** was isolated.[28] The results of the study are summarised in Table 1.2.

Table 1.2. Results for configurational stability of Mg-**24** using various Grignard reagents.



Entry	Grignard	Temperature (°C)	Time (min)	% Yield 32	% *ee* 32
1	EtMgBr	−50	15	70	64
2	EtMgCl	−50	15	69	89
3	*i*-Pr_2Mg	−50	15	83	92
4	EtMgBr	−40	15	58	17
5	*i*-Pr_2Mg	−50	60	56	93
6	*i*-Pr_2Mg	−20	15	48	91
7	*i*-Pr_2Mg + 1 equiv $MgBr_2$	−50	15	84	88
8	*i*-Pr_2Mg + 1 equiv MgI_2	−50	15	60	15

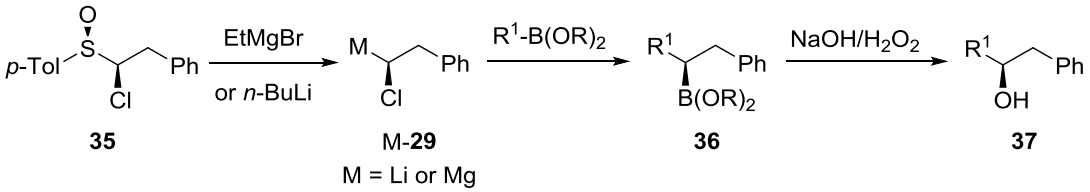
It was found that racemisation already occurred at −50 °C and that the extent of racemisation was highly dependent on the nature of the Grignard reagent employed; racemisation was higher with EtMgBr and minimal with *i*-Pr_2Mg (Table 1.2, entries 1 and 3, respectively). Racemisation with EtMgBr was found to be almost complete at −40 °C after only 15 minutes (Table 1.2, entry 4), while the carbenoid generated with *i*-Pr_2Mg proved to be configurationally stable at temperatures ranging up to −20 °C (Table 1.2, entry 6), upon which temperature decomposition occurred. However, the presence of salts, such as $MgBr_2$ and MgI_2, was found to be detrimental and led to rapid racemisation (Table 1.2, entries 7 and 8). The most likely mechanism for the observed racemisation is a nucleophilic substitution at the α-chloroalkyl Grignard reagent Mg-**29** by external halide ions present in the reaction mixture (Scheme 1.15).[28]



Scheme 1.15. Proposed mechanism for the racemisation of Mg-**29** *via* halide exchange .

1.4.2. Homologation of Boronic Esters by α-Chloroalkylmetal Chiral Carbenoids

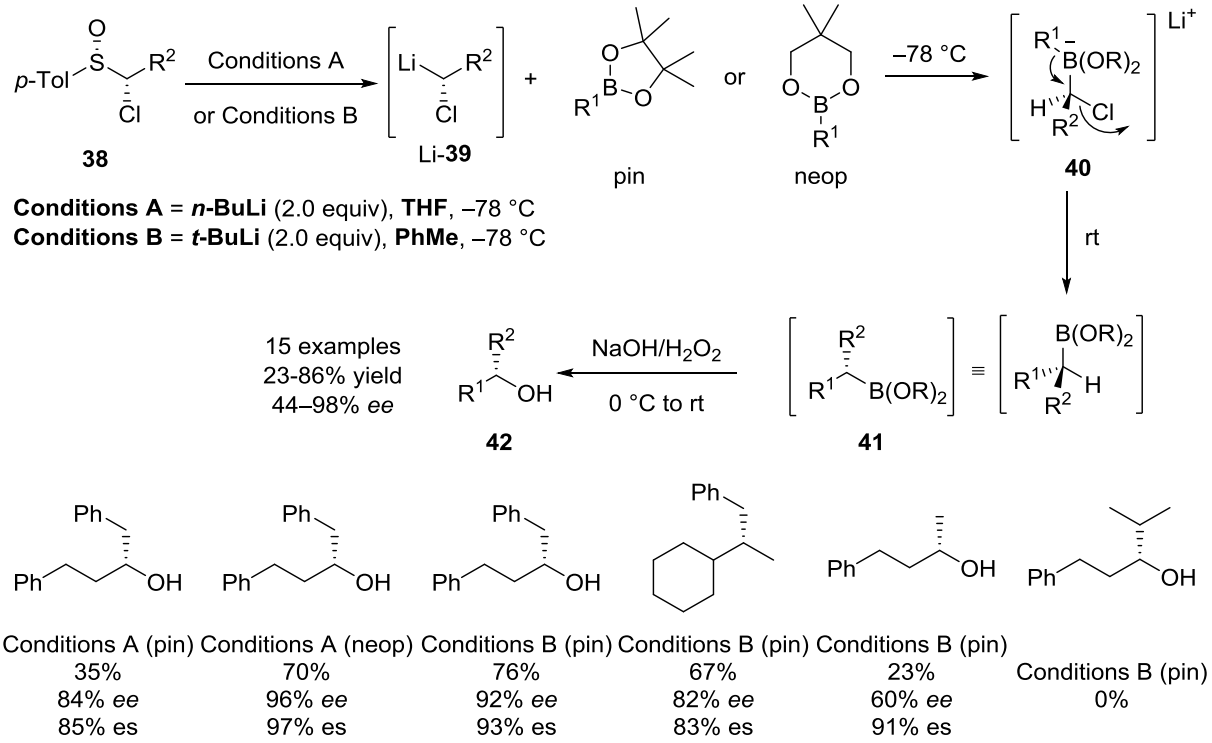
Blakemore and co-workers demonstrated that Hoffmann-type chiral magnesium carbenoids Mg-**29**, generated by sulfoxide−magnesium exchange, could be employed in the "Stereospecific Reagent-Controlled Homologation (StReCH)" of boronic esters to give, after *in situ* oxidation, secondary alcohols **37** (Scheme 1.16).[29-30] Despite the viability of the methodology, the homologated alcohols were isolated in moderate yield and with modest stereochemical fidelity. It was subsequently found that the corresponding lithium carbenoids Li-**29**, generated by sulfoxide−lithium exchange, were able to homologate different boronic esters to afford the products in better yield and higher stereospecificity.[29-30]



Scheme 1.16. Asymmetric homologation of boronic esters using α-halogen sulfoxides.

α-Chloroalkyllithium Li-**39** was generated by treatment of the corresponding α-chlorosulfoxide **38** using an organolithium, with the best results obtained using either *n*-BuLi in THF or *t*-BuLi in toluene (Scheme 1.17).[30] Due to the enhanced chemical and configurational lability of α-haloalkyllithiums compared to the corresponding α-haloalkylmagnesiums, *in situ* conditions (i.e. generation of the carbenoid in the presence of

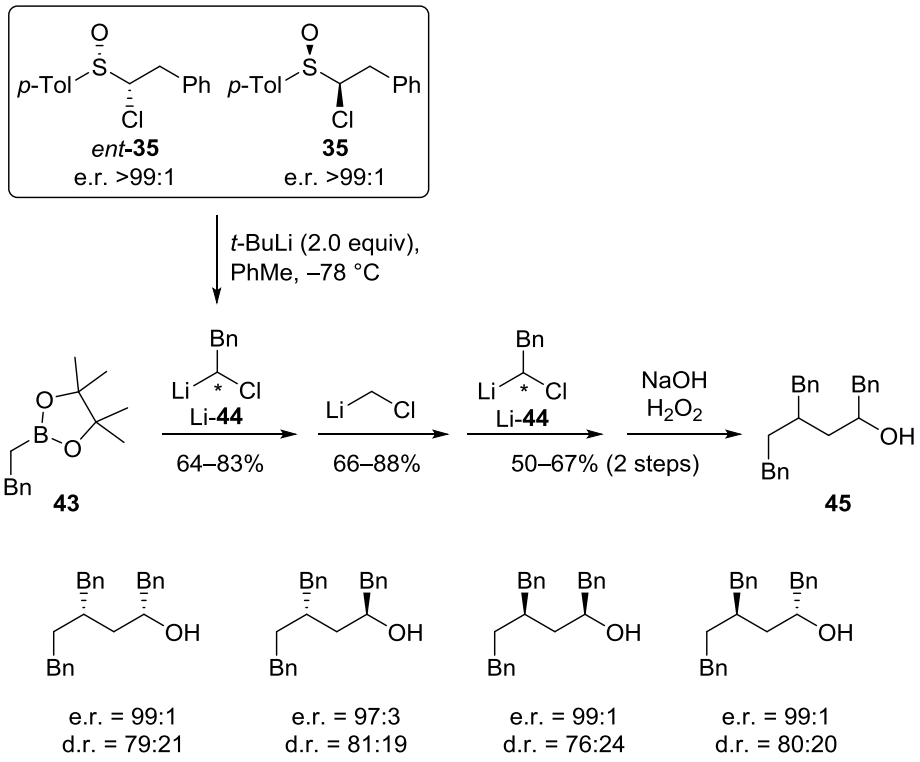
the boronic ester) must be adopted. Reaction of carbenoid Li-**39** with a pinacol or neopentylglycol boronic ester led to the formation of "ate" complex **40**, which, upon warming to a higher temperature, underwent 1,2-metallate rearrangement to give homologated boronic ester **41**. This could then be converted into the corresponding alcohol **42** by stereospecific oxidation with H_2O_2/NaOH. Moderate substrate scope was observed for the process in terms of boronic esters employed, while the scope of the chiral metal carbenoids was found to be limited to primary aliphatic sulfoxides, with secondary sulfoxides being unable to afford the homologated products.[30]



Scheme 1.17. Mechanism for the asymmetric homologation of boronic esters using chiral α-halogen lithium carbenoids and selected products of the reaction.

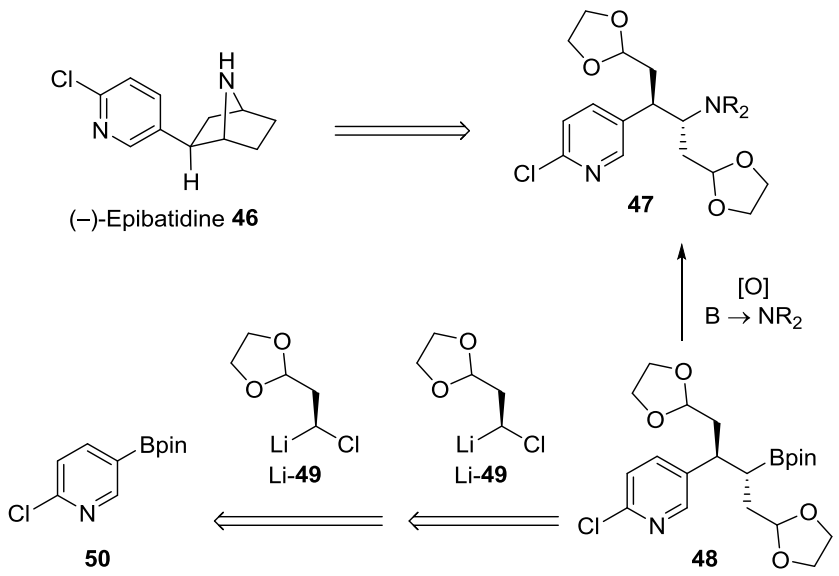
Blakemore and co-workers further extended this methodology to the iterative stereospecific homologation of boronic esters using enantioenriched metal carbenoids (Scheme 1.18).[30] Boronic ester **43** was reacted with α-chloroalkyl carbenoid Li-**44**, generated *via* sulfoxide−lithium exchange from the corresponding sulfoxide **35**, to give a one-carbon homologated boronic ester; this was subsequently reacted with chloromethyllithium (generated *in situ* by treatment of chloroiodomethane with *n*-BuLi) in a Matteson chain extension reaction. One final homologation of the resulting boronic ester with lithium carbenoid Li-**44**, followed by oxidation, afforded alcohol **45**. Judicious selection of the enantiomer of the sulfoxide employed in the first and last homologation cycles eventually allowed the synthesis of all four

stereoisomers of alcohol **45**. In all the cases the homologated alcohols were isolated in very high enantiopurity, although with only moderate diastereoselectivity.



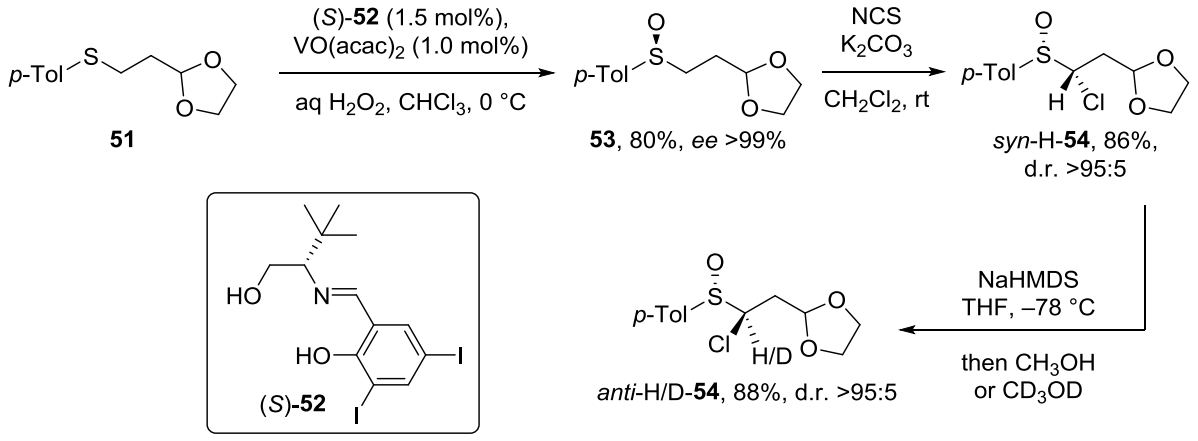
Scheme 1.18. Stereospecific iterative homologation of boronic ester **43** using lithium carbenoid Li-**44**.

Blakemore and co-workers also studied the possibility of applying their iterative stereospecific reagent-controlled homologation of boronic esters to the synthesis of (−)-Epibatidine **46**, an analgesic alkaloid that acts as an activator of nicotinic acetylcholine receptors (nAChRs).[31-33] The target was envisioned to come from acyclic precursor **48**, which could be synthesised through two consecutive StReCh iterations of boronic ester **50** with chiral lithium carbenoid Li-**49** of appropriate configuration, followed by a stereoretentive boronate amination reaction (Scheme 1.19).[34-35]



Scheme 1.19. Proposed retrosynthetic analysis of (−)-Epibatidine **46**.

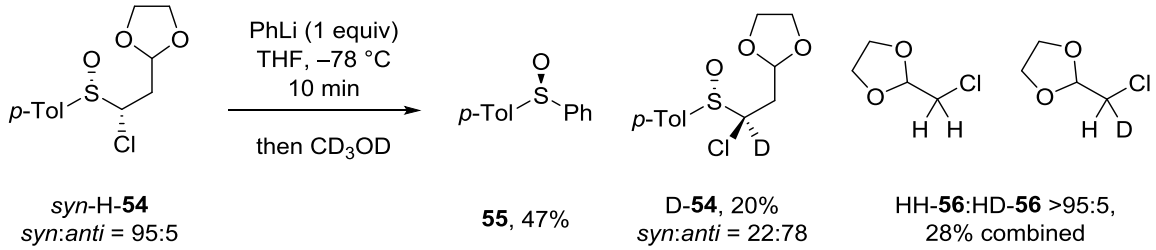
To address the synthesis of dioxolane-substituted chloroalkyllithium Li-**49** *via* sulfoxide−metal exchange, the appropriate α-chlorosulfoxide precursor **54** was prepared from the corresponding sulfide **51**[34] through a Jackson−Ellman−Bolm catalytic enantioselective sulfoxidation[36-38]. This afforded sulfoxide **53** in excellent enantioselectivity (Scheme 1.20). Subsequent Yamakawa chlorination[39] gave α-chlorosulfoxide *syn*-H-**54**, which was isolated in very high enantiopurity (>99% *ee*) after recrystallisation. *Anti*-H-**54** and *anti*-D-**54** were also prepared by epimerisation of *syn*-H-**54** followed by trapping with MeOH or CD_3OD.[34]



Scheme 1.20. Synthesis of α-chloro sulfoxides *anti*-H and *anti*-D-**54** through Jackson−Ellman−Bolm oxidation followed by Yamakawa chlorination.

α-Chlorosulfoxide *syn*-H-**54** was then treated with PhLi at −78 °C for 10 minutes, followed by quenching with CD_3OD. However, no expected deuterated α-chlorosulfoxide HD-**56** was detected (Scheme 1.21). What they observed instead was the formation of deuterated

α-chlorosulfoxides *syn* and *anti*-D-**54**, along with non-deuterated alkyl chloride HH-**56** and the expected by-product **55**.[34-35]



syn-H-**54**
syn:*anti* = 95:5

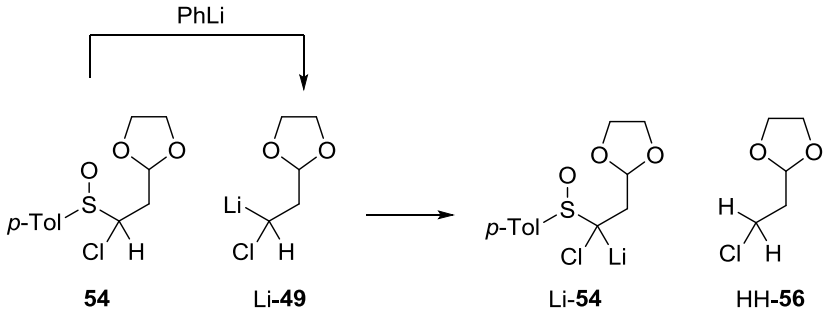
55, 47%

D-**54**, 20%
syn:*anti* = 22:78

HH-**56**:HD-**56** >95:5,
28% combined

Scheme 1.21. Sulfoxide–lithium exchange – deuteration studies on α-chlorosulfoxide *syn*-H-**54**.

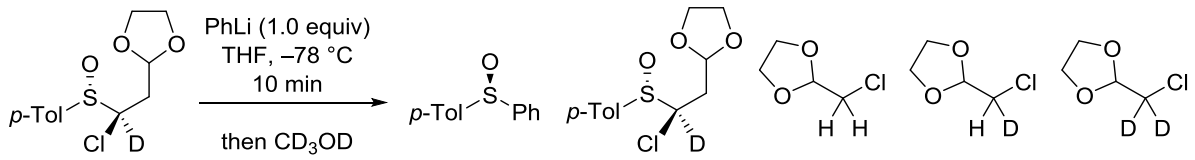
This result indicated that the putative lithium–sulfoxide exchange took place to generate lithium carbenoid Li-**49**, but this was immediately quenched by an internal proton source, presumably the acidic α-proton on the sulfoxide precursor *syn*-H-**54**. This led to the generation of the observed alkyl chloride HH-**56** together with α-lithiated sulfoxide Li-**54**, which was eventually deuterated upon quenching with CD_3OD to give D-**54** (Scheme 1.22).[34-35]



54 Li-**49** Li-**54** HH-**56**

Scheme 1.22. Proposed mechanism for the formation of D-**54** and HH-**56**.

The undesired deprotonation of α-chlorosulfoxide *syn*-H-**54** under reaction conditions was minimised by exploiting a primary kinetic isotope effect. Deuterated α-chlorosulfoxide *anti*-D-**54** was in fact revealed to be a superior carbenoid precursor than its nonlabeled analogue when involved in a sulfoxide–lithium exchange/deuteration sequence, due to the increased bond strength of the C–D bond over the C–H bond, although some deprotonation was still observed (Scheme 1.23).[34-35]



anti-D-**54**
syn:anti = 8:92

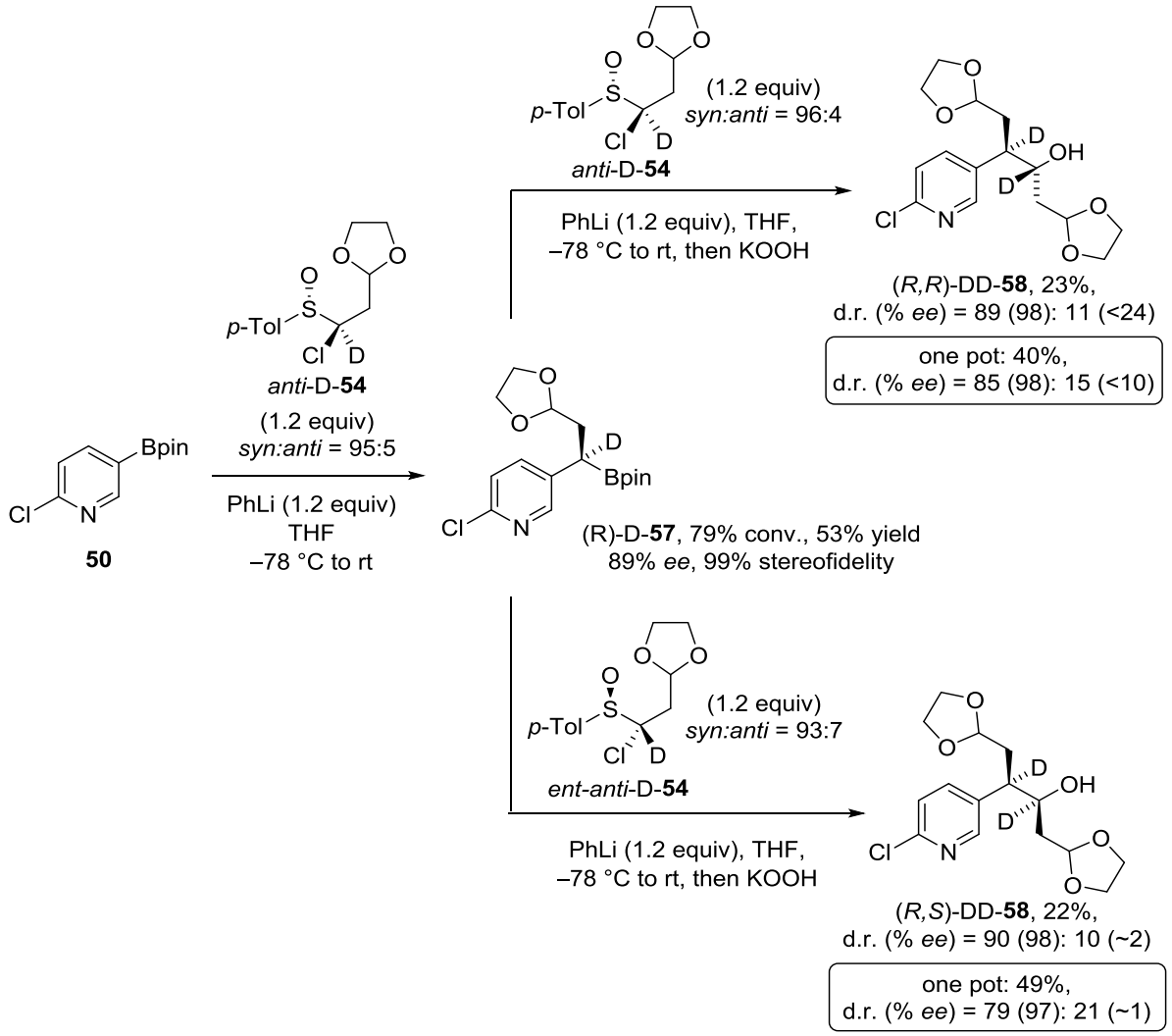
55, 63%

D-**54**, 16%
syn:anti = 27:73

HH-**56**:HD-**56**:DD-**56** = 14:59:27,
26% combined

Scheme 1.23. Sulfoxide–lithium exchange – deuteration studies on deuterated α-chloro sulfoxide *anti*-D-**54**.

Anti-D-**54** was then employed in the iterative homologation of boronic ester **50** (Scheme 1.24).[35] A first cycle of StReCh gave one-carbon homologated boronic ester (*R*)-D-**57** in moderate yield (53%), but perfect stereofidelity (99%). The subsequent StReCh of boronate (*R*)-D-**56** with either enantiomer of chlorosulfoxide *anti*-D-**54** finally gave, after oxidation, the two diastereoisomers of alcohol DD-**58**. In both cases, the diastereoselectivity of the process was found to be moderate (d.r. = 90:10), but the major diastereoisomer was isolated in high enantiopurity (98% *ee*). The sequence could also be performed in one-pot, avoiding the isolation and purification of intermediate boronic ester (*R*)-D-**57**.[35]



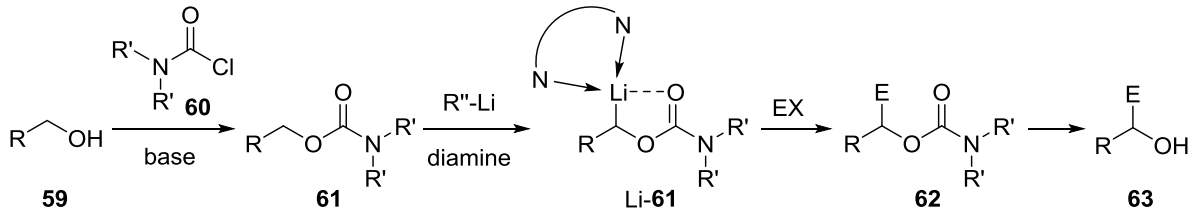
Scheme 1.24. One-pot, double StReCH cycle from boronic ester **50**.

1.5. Homologation of Boronic Esters by Lithiated Carbenoids

1.5.1. Hoppe Lithiated Carbamates

The first asymmetric deprotonation of primary *O*-alkyl carbamates **61** was reported by Hoppe and co-workers in 1990.[40] The required carbamate substrates, easily accessible by reacting the

corresponding alcohols **59** with carbamoyl chloride[41] under the addition of pyridine[42] or other bases[43-44], can be deprotonated using lithium bases, such as *n*- or *sec*-buthyllithium (*n*-BuLi, *s*-BuLi), in the presence of a stoichiometric amount of diamine. Trapping of the generated lithiated intermediate Li-**61** with an electrophile gives the corresponding substitued carbamates **62** in good yield (Scheme 1.25). The carbamate group can be eventually removed to give access to the corresponding secondary alcohols **63**.



Scheme 1.25. Deprotonation of Hoppe's carbamates and subsequent trapping with electrophiles.

In this process, the presence of the electron-withdrawing carbamate group is fundamental to enable the deprotonation step, as it allows the formation of a pre-lithiation complex by bringing the reactive groups into proximity (complex-induced proximity effect – CIPE).[45-46] Additionally, coordination of the carbonyl group to the lithium atom allows the stabilisation of the lithiated intermediate.

Hoppe and co-workers employed primarily three types of carbamate groups (Figure 1.3): diisopropyl carbamate (Cb), which can be removed only by reduction with $LiAlH_4$ or DIBAL-*H* in excess, and oxazolidine carbamates (Cby, Cbx), which can be more readily removed through an acid/base hydrolysis using a mixture of $MeSO_3H$ and MeOH followed by treatment with $Ba(OH)_2$.[47]

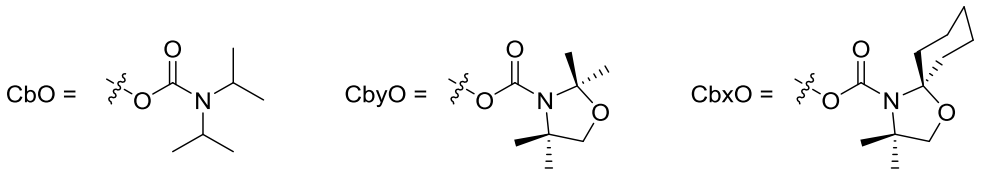
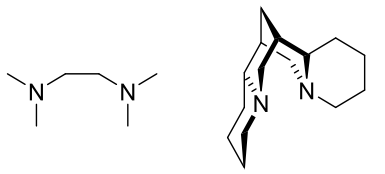


Figure 1.3. Carbamate groups employed by Hoppe and co-workers.

The presence of the diamine is essential in the process as it helps the stabilisation of the lithiated carbamate intermediate through the chelation of the nitrogen atoms with lithium. When *N*,*N*,*N'*,*N'*-tetramethylethylenediamine (TMEDA, **64**, Figure 1.4) is employed the racemic product is obtained. However, a stereoselective deprotonation can be performed using chiral diamine (−)-sparteine (**65**, Figure 1.4), a natural occurring alkaloid; in this case, the generated intermediate organolithium is configurationally stable at −78 °C and can be trapped by an

electrophile with retention of configuration to afford the corresponding products with very high levels of enantioselectivity.[40]

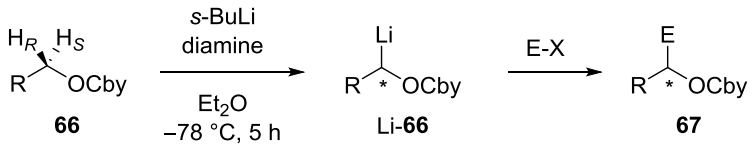


64, TMEDA **65**, (–)-sparteine

Figure 1.4. Diamines employed for the deprotonation of carbamates.

Deprotonation of primary alkyl carbamates **66** is normally conducted in Et_2O and is complete within 5 hours (Table 1.3). It has been shown that a range of different electrophiles can be used to trap the generated lithium carbenoid Li-**66** and the corresponding products **67** are isolated in good yield and, in the case of asymmetric deprotonation, high enantioselectivities.

Table 1.3. Examples of deprotonation of alkyl carbamates followed by trapping with electrophiles.

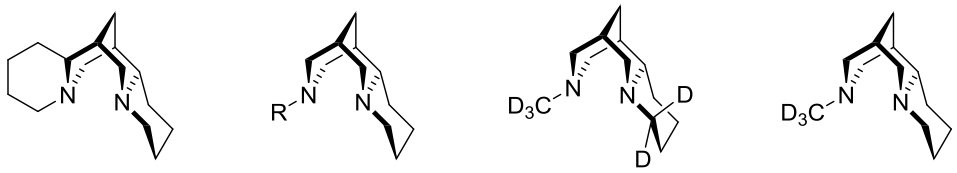


R	E–X	Diamine	% Yield	% *ee*
Me	Me_3SiCl	TMEDA	70	–
Me	CO_2	(−)-sparteine	75	>95
Me	Me_3SnCl	(−)-sparteine	73	>95
Hex	MeI	(−)-sparteine	81	96

Würthwein and Hoppe reported their study on the enantioselective deprotonation of *O*-alkyl carbamates in the presence of (−)-sparteine using quantum chemical DFT calculations. They outlined the preferred abstraction of the *pro-S* proton of the carbamate instead of the *pro-R* proton.[48] In the case of ethyl carbamate, calculations showed that the structure of the transition state in which the *pro-S* proton is involved in the hydrogen transfer is lower in energy than the three other possible transition states by 2.75 kcal/mol.[48] This data is in good agreement with the experimentally observed enantioselectivity of 99:1 in favour of the *pro-S* lithium compound after trapping with a suitable electrophile (a process that is known to occur with complete retention of configuration). At this stage of the reaction, considering the strong Li-methylene interaction, it is assumed that the lithiated carbamate is configurationally stable at −78 °C, so no equilibration due to epimerisation occurs. The reaction is therefore under kinetic control

and this explains why the lithium compound obtained is not the thermodynamically favoured product.[48]

Despite (−)-sparteine being commercially available, it has recently become very difficult to access. Its enantiomer, (+)-sparteine **68**, is also natural occurring and can be sourced commercially, although in the past it was difficult to access from natural sources. For this reason, O'Brien and co-workers have developed a series of (+)-sparteine surrogates (Figure 1.5) that can be readily prepared in three steps from (−)-cytisine, itself extracted from *Laburnum anagyoides* seeds.[49]



68, (+)-sparteine

69: R = Me
70: R = Et
71: R = *n*-Bu
72: R = CH_2*t*-Bu
73: R = *i*-Pr

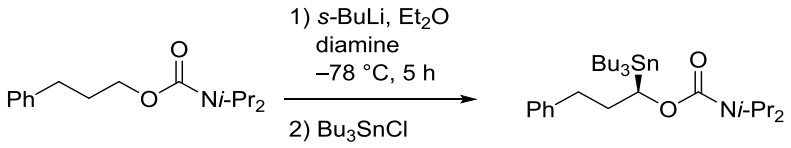
74

75

Figure 1.5. The (+)-sparteine surrogates.

N-Methyl diamine **69** and *N*-CD_3-substituted diamine **74** were in particular found to be the optimum (+)-sparteine surrogates, giving the highest yields and enantioselectivites (up to 95:5 e.r.) in the conversion of *O*-alkyl carbamate **76** into α-stannylated carbamate **77** (Table 1.4).

Table 1.4. Lithiation–trapping of *O*-alkyl carbamate **76** with different diamines.

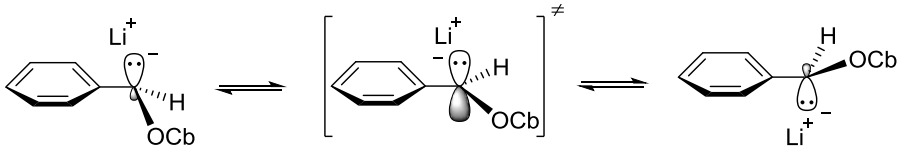


76

(*R*)-**77** (with diamines **68**–**75**)
(*S*)-**77** (with (–)-sparteine)

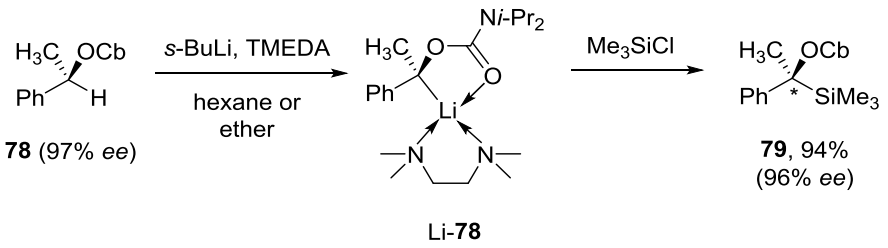
Diamine	% Yield	e.r. (*R*:*S*)
(−)-sparteine	73	1:99
69	84	95:5
74	82	96:4
75	68	96:4
70	64	95:5
71	72	91:9

Another important class of lithiated carbamates studied by Hoppe and co-workers are *O*-benzyl carbamates, first reported in 1990.[50] The main difference from the previously described *O*-alkyl carbamates is that the generated carbanion is now stabilised by the presence of the aromatic ring, thus increasing the tendency to form solvent-separated ion pairs. In the case of primary benzylic carbamates, this process facilitates the migration of the lithium cation from one face of the carbanion to the other, eventually causing racemisation (Scheme 1.26).



Scheme 1.26. Proposed mechanism for racemisation of benzylic lithiated derivatives.

The situation is different in the case of secondary benzyl carbamates as the presence of the alkyl group destabilises the generated carbanion, thus preventing the migration of the lithium cation from one enantiotopic face of the carbanion to the other. The result is that the intermediate is configurationally stable at −78 °C. Chiral secondary benzyl carbamates can therefore be used to produce new quaternary centres with high enantioselectivity, as shown in the example in Scheme 1.27.[51]



Scheme 1.27. Deprotonation of an enantiomerically enriched secondary carbamate.

Reaction of lithiated secondary benzyl carbamates with several different electrophiles proceeds with either complete retention or complete inversion of stereochemistry (Table 1.5).

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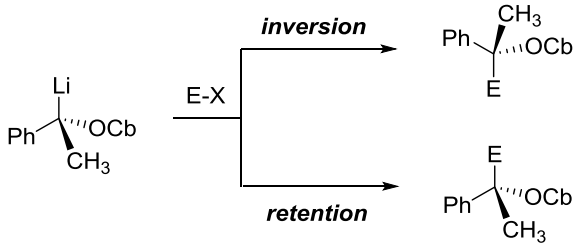
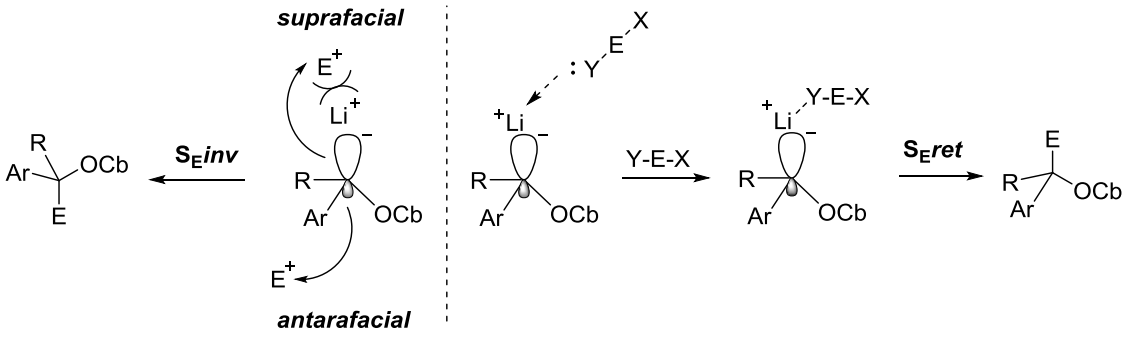
Table 1.5. Electrophiles reacting with lithiated carbamates with inversion or retention of configuration.



E–X	Course	% Yield	% *ee*
Me_3SiCl	inversion	94	96
Me_3SnCl	inversion	92	>95
MeOC(O)Cl	inversion	90	85
MeC(O)CN	inversion	43	92
MeOC(O)OMe	retention	85	94
HC(O)OMe	retention	60	>95
PhC(O)OMe	retention	95	>95

A possible explanation relies on the nature of the lithiated intermediate Li-**78**, in which the carbanion centre possesses more s character (between sp^2 and sp^3) than in non-benzylic carbamates due to the overlap of orbitals from the aryl ring. The carbon atom is thus flattened, but not completely planar, and this causes a build-up of electron density at the bottom face. The electrophile can approach the carbanion antarafacially, avoiding the steric hindrance by the complexed cation, or suprafacially, when a favourable interaction with the lithium cation can be established (Scheme 1.28). Electrophiles with an energetically low LUMO, but without any good complexing groups for the lithium cation (such as acid chlorides, cyanides or stannyl chlorides) would undergo an antarafacial attack. However, electrophiles with a higher energy LUMO and possessing an electron-donating group able to pre-complex lithium (such as esters, alcohols, alkyl halides or aliphatic aldehydes or ketones) would prefer a suprafacial approach.

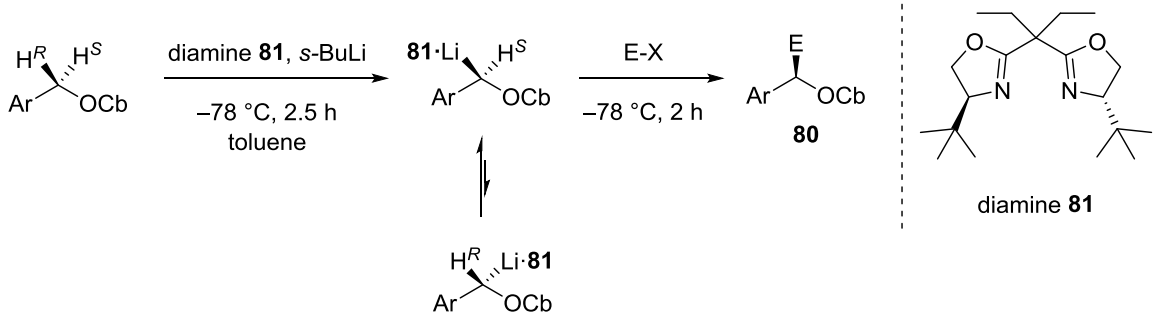


Scheme 1.28. Proposed mechanism for retention or inversion reactivity. Y = heteroatom with substituents.

As aforementioned, lithiated primary benzyl carbamates are instead configurationally labile and quickly racemise even at low temperatures, so that the chiral information of the enantioenriched carbenoid is significantly reduced or completely lost during the deprotonation process.

To overcome this problem, Hoppe and co-workers have developed a methodology to synthesise highly enantioenriched α-substituted benzyl alcohols **80** by generating epimeric complexes of lithiated secondary benzyl carbamates using chiral diamine ligands.[52] Optimal results were obtained using chiral bis(oxazoline) ligand **81** as the diamine (Table 1.6). *s*-BuLi was used to deprotonate the carbamate in the presence of the chiral ligand and the experiments showed that, contrary to what happens when (−)-sparteine is used, enantiotopic differentiation by the chiral bis(oxazoline) in the deprotonation step is poor and both the intermediate diastereoisomers are initially generated. With prolonged reaction times, the epimeric complex-ion pairs equilibrate to generate one diastereoisomer almost exclusively. This is because a dynamic thermodynamic resolution takes place after the deprotonation step, eventually allowing high enantioselectivity. The preferentially formed diastereoisomer can then be trapped with different electrophiles to yield highly enantioenriched substituted benzylic carbamates.[52]

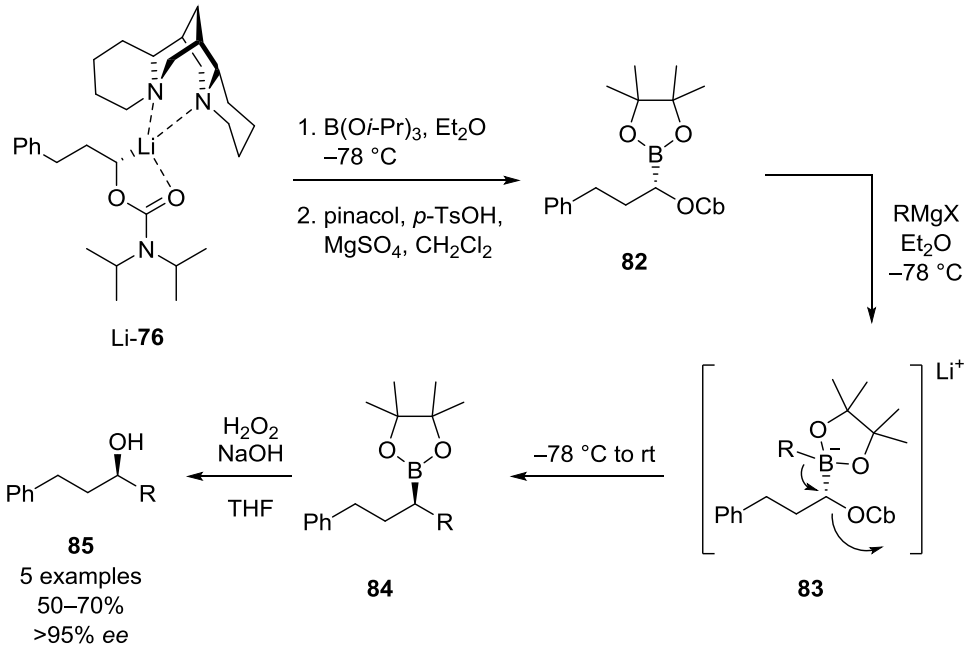
Table 1.6. Use of bis(oxazoline) ligand **81** for the lithiation of primary benzylic carbamates.



E–X	% Yield	% *ee*	Product configuration
Bu_3SnCl	88	98	*S*
Me_3SiCl	98	98	*S*
MeI	98	96	*S*
CO_2	99	95	*R*

1.5.2. Lithiation–Borylation with Primary Carbamates

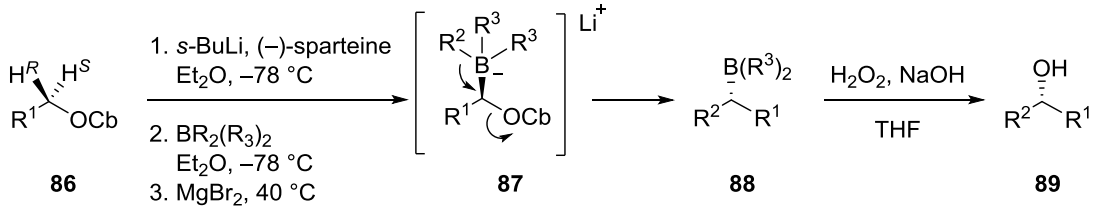
Hoppe and co-workers developed a new method for the synthesis of enantioenriched secondary alcohols employing alkyl carbamates.[53] They showed that chiral lithiated carbamate Li-**76** could undergo stereoretentive electrophilic trapping with B(O*i*-Pr)$_3$; subsequent *in situ* transesterification gave the corresponding α-carbamoyloxy-alkylboronate **82**. Treatment of **82** with a Grignard reagent at −78 °C afforded intermediate boronate complex **83**, which, upon warming to room temperature, underwent a stereospecific 1,2-metallate rearrangement, with the R' substituent migrating with inversion of configuration at the chiral centre. Stereoretentive *in situ* oxidation of the resulting secondary alkyl boronate **84** gave the corresponding secondary alcohol **85** in good yield and excellent enantioselectivity (Scheme 1.29).[53]



Scheme 1.29. 1,2-Metallate rearrangement from secondary boronic ester developed by Hoppe.

Aggarwal and co-workers developed this methodology further and found that Hoppe-type lithiated carbamates can be directly reacted with boranes or boronic esters to form "ate" complex intermediates **87**. After stereospecific 1,2-metallate rearrangement and *in situ* oxidation, secondary alcohols **89** were isolated in good yield and high enantioselectivity (Table 1.7).[54] As aforementioned, the carbamate group is essential to enable the deprotonation process; additionally, it acts as a leaving group, allowing the 1,2-metallate rearrangement.

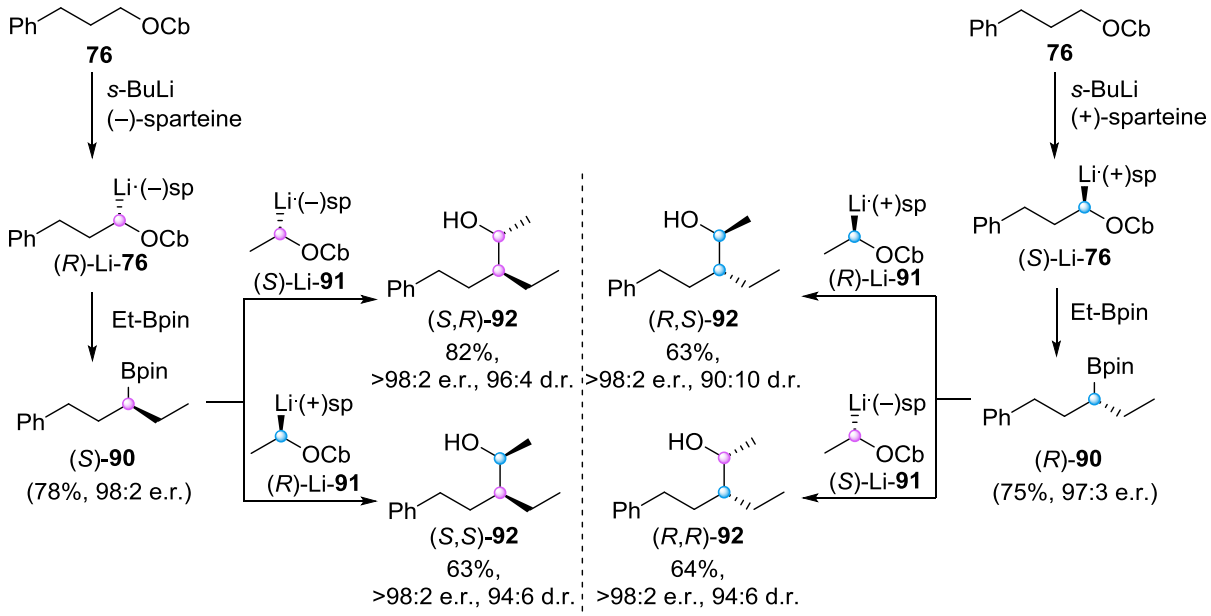
Table 1.7. Lithiation–borylation reaction with Hoppe-type carbamates.



R^1	R^2	$(R^3)_2$	% Yield	e.r.
$Ph(CH_2)_2$	Et	Et	91	98:2
$Ph(CH_2)_2$	*n*-Hex	9-BBN	90	98:2
$Ph(CH_2)_2$	Ph	9-BBN	94	97:3
$Me_2C{=}CH(CH_2)_2$	Ph	pinacol	73	98:2
$TBSO(CH_2)_2C(Me)_2CH_2$	Ph	pinacol	64	98:2
i-Pr	Ph	pinacol	70	98:2
Me	Ph	pinacol	70	97:3

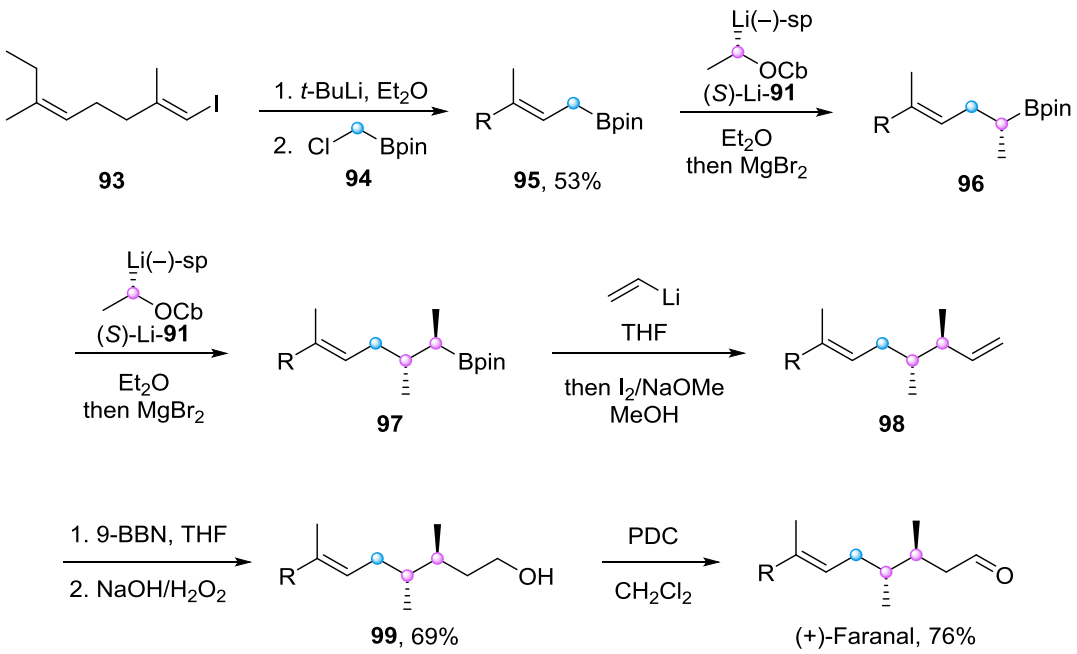
The scope of this methodology proved to be very broad and a wide variety of primary alkyl carbamates, as well as aryl and alkyl substituted boranes and boronic esters, could be employed in the process (Table 1.7). The main difference between these two boron species is that the 1,2-metallate rearrangement is much slower with boronic esters than with boranes, and sometimes it requires the use of Lewis acidic $MgBr_2$ in Et_2O at reflux; on the contrary, the rearrangement of the "ate" complexes derived from boranes begins at −40 °C without using any additive.

Aggarwal and co-workers showed that the lithiation−borylation methodology can also be performed in an iterative fashion by reacting the boronic ester obtained after the first homologation with a second lithiated carbamate (Scheme 1.30).[54] Carbamate **76** was therefore lithiated with *s*-BuLi in the presence of (−)-sparteine and the corresponding lithiated intermediate (*R*)-Li-**76** was trapped with ethyl pinacol boronic ester to afford the desired boronic ester intermediate (*S*)-**90**. The subsequent reaction of boronic ester (*S*)-**90** with lithiated carbamate (*S*)-Li-**91** gave, after *in situ* oxidation, alcohol (*S*,*R*)-**92** as a 96:4 mixture of diastereoisomers with >98:2 e.r. When O'Brien's sparteine surrogate (+)-**69** was used to generate lithiated carbenoid (*R*)-Li-**76**, epimeric alcohol (*S*,*S*)-**92** was obtained in equally high d.r. and e.r.[54] The process could also be repeated using lithiated carbamate (*S*)-Li-**76** to form intermediate boronic ester (*R*)-**90**; further homologation using both (*R*)-Li-**91** and (*S*)-Li-**91** gave the epimeric alcohols (*R*,*S*)-**92** and (*R*,*R*)-**92** in high d.r. and e.r. These high values of enantio- and diastereoselectivity clearly show that the stereochemical outcome of the second homologation reaction is not influenced by the stereochemistry of the boronic ester employed (i.e. good reagent control).



Scheme 1.30. Iterative homologation reaction of boronic esters (*S*)-**90** and (*R*)-**90**.

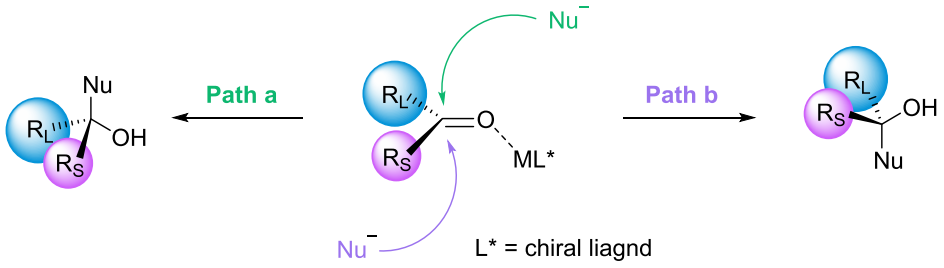
In 2009, Aggarwal and co-workers demonstrated the application of this iterative homologation methodology to the total synthesis of the insect pheromone (+)-Faranal (Scheme 1.31).[55] Vinyl iodide **93** was synthesised in four steps from propyne and subsequently subjected to a lithium−iodide exchange reaction triggered by *t*-BuLi. Trapping of the generated organolithium with chloromethyl boronate **94** gave allylic boronic ester **95** in 53% yield. Two iterative lithiation−borylation reactions using lithiated ethyl carbamate Li-(*S*)-**91** afforded boronic ester **97**, which was subsequently subjected, without isolation, to a sequence of Zweifel olefination, hydroboration and oxidation to give alcohol **99** in 69% yield and 96:4 d.r. The whole iterative sequence could also be performed without purification of any of the intermediates, with the final alcohol **99** being isolated in 40% yield and d.r. of 94:6. Final oxidation using PDC proceeded in 76% yield to afford (+)-Faranal.[55]



Scheme 1.31. Total Synthesis of (+)-Faranal.

1.5.3. Lithiation–Borylation with Secondary Carbamates

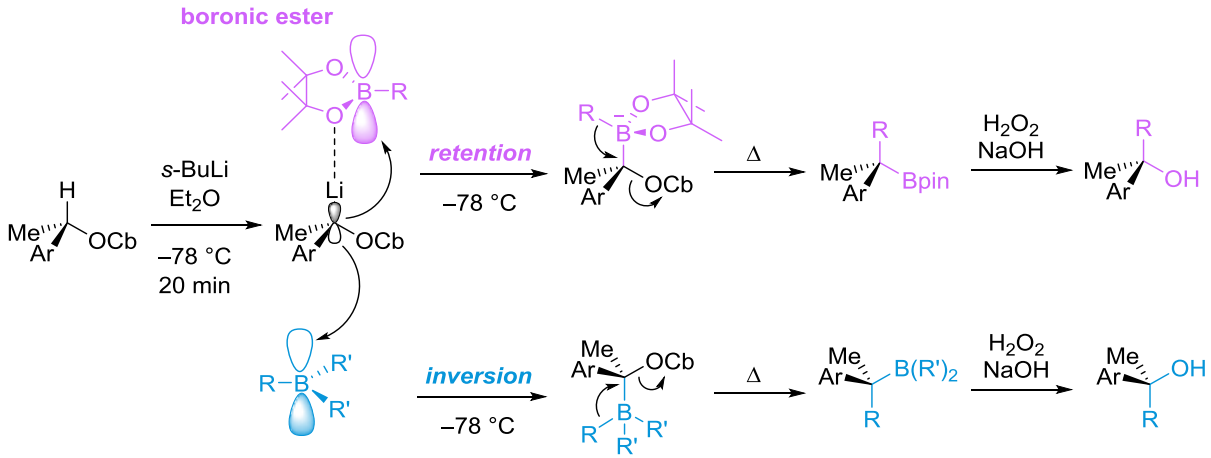
Aggarwal and co-workers further extended the lithiation–borylation methodology to the synthesis of enantiomerically enriched tertiary alcohols.[56] While the extensive work over the last half century has made the enantioselective synthesis of secondary alcohols relatively easy,[57-58] the asymmetric synthesis of compounds containing quaternary stereogenic centres, such as tertiary alcohols[59-61] is still challenging. Tertiary alcohols are generally synthesised by addition of an organometallic reagent to a ketone (Scheme 1.32). It is possible to make this process enantioselective by using chiral ligands.[62-64] However, the asymmetric induction is generally quite low as the process relies upon the steric difference between the substituents either side of the carbonyl group.



Scheme 1.32. Formation of tertiary alcohols *via* addition of organometallic reagents to ketones.

Work within the Aggarwal group has developed an innovative methodology for the synthesis of quaternary stereocentres by extending the use of the 1,2-metallate rearrangement of boronate complexes to secondary benzylic carbamates.[56] The stereospecific reaction of a chiral lithium

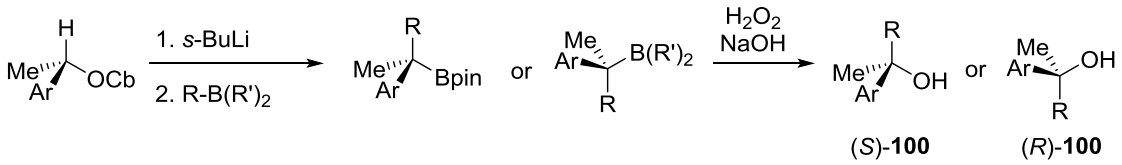
carbenoid, bearing both an aryl and an alkyl substituent, with a boron species gives a chiral "ate" complex. Subsequent stereospecific 1,2-metallate rearrangement, followed by oxidative work up, affords the desired tertiary alcohol. As chirality is transferred through the lithiation–borylation reaction, the final compound can be obtained with high levels of enantiospecificity. Both boranes and a broad range of boronic esters could be employed in this reaction. It is noteworthy that the process occurs with almost complete inversion of stereochemistry when boranes are employed, while complete retention of stereochemistry is observed in the case of boronic esters. This can be rationalised considering the complexation of the lithium atom to the metallated carbamate by the oxygen atom on the boronic ester, which causes the addition to take place on the same face as the metal. On the other hand, when a borane is employed, this kind of complexation cannot take place and the addition occurs on the face opposite to the metal, where the electron density is significantly higher, leading to inversion of configuration (Scheme 1.33).[50-51] The remarkable consequence is that it is possible to prepare both the enantiomers of a single tertiary alcohol starting from the same substrate simply using a different boron reagent. The enantiomerically enriched secondary alcohols necessary to synthesise the starting carbamates can be easily prepared by Noyori transfer hydrogenation[65] with e.r. values of up to 99:1.



Scheme 1.33. Lithiation–borylation of secondary benzylic carbamates leading to tertiary alcohols.

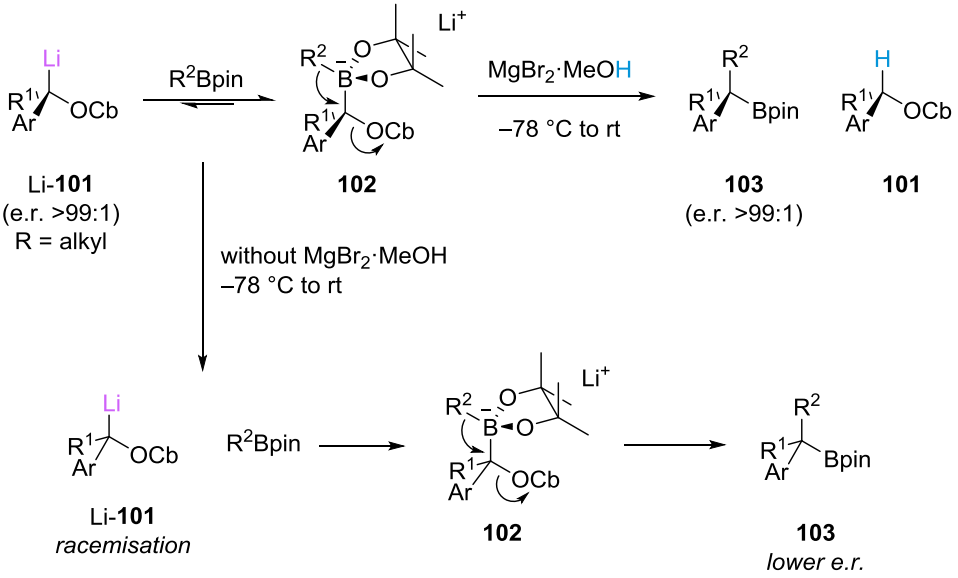
The substrate scope has been widely investigated using a broad range of alkyl, cyclopropyl, vinyl, allyl, aryl and heterocyclic boronic esters and different types of secondary alcohols bearing both electron-rich and electron-deficient aromatics, with excellent results in terms of enantiospecificity in all cases (Table 1.8).[56]

Table 1.8. Experimental data of lithiation–borylation of secondary benzylic carbamates.



Ar (e.r. carbamate)	R	$(R')_2$	% Yield 100	e.r. (*S*:*R*)
Ph (99:1)	Et	Et_2	91	99:1
Ph (99:1)	Et	pinacol	95	1:99
Ph (99:1)	vinyl	pinacol	75	2:98
Ph (99:1)	*p*-Cl-C_6H_4-	pinacol	92	99:1
p-MeO-C_6H_4- (98:2)	Et	pinacol	97	2:98
p-Cl-C_6H_4- (98:2)	Et	pinacol	92	4:96

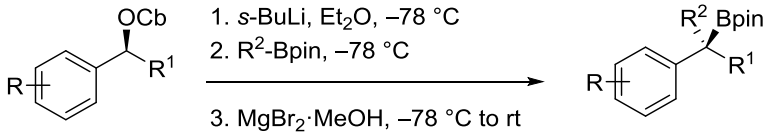
In some examples, with more sterically hindered carbamates bearing electron-withdrawing substituents on the aromatic ring, a small erosion of the enantiospecificity was observed. The postulated mechanism explaining this loss of stereochemical information is depicted in Scheme 1.34.[66] The formation of boron "ate" complex **102** is shown to be a reversible process at −78 °C, with its dissociation regenerating lithiated carbamate Li-**101** and the starting boronic ester. When the reaction mixture is warmed to higher temperatures, lithiated carbamate Li-**101** can racemise before recombination with the boronic ester, therefore resulting in the observed lowered enantiomeric excess of the homologated product.



Scheme 1.34. Postulated mechanism for the erosion of enantiospecificity in the homologation boronic esters by lithiated secondary benzylic carbamates.

A solution to this problem was found to be the addition of a more reactive electrophile after boronate complex formation. By doing this, any lithiated carbamate Li-**101** present in the reaction mixture can be quenched before recombination with the starting boronic ester, therefore preventing racemisation of tertiary boronic ester **103**. After careful screening of different electrophiles, MeOH was found to effectively fulfil the requirements and could be used in conjunction with $MgBr_2$ (usually added as a solution in MeOH) with the dual purpose of accelerating the rate of 1,2-metallate rearrangement and quenching the lithiated carbenoid Li-**101**. These conditions were applied to a broad range of benzylic secondary carbamates and varying sterically hindered pinacol boronic esters with the corresponding homologated tertiary boronic esters being isolated in high yield and excellent *ee* of 99% (Table 1.9).[66]

Table 1.9. Highly enantiospecific homologation of secondary carbamates with $MgBr_2$·MeOH.



101 **103**

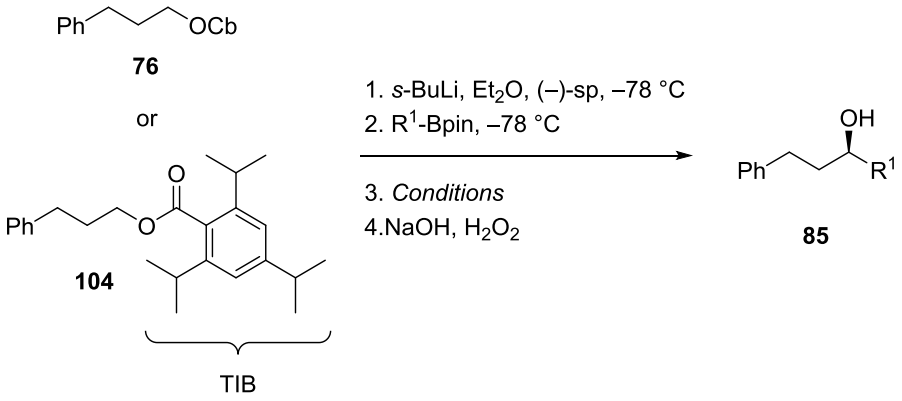
Entry	R	R^1	R^2	% Yield 103 (% *ee*)
1	H	Me	*c*-Hex	87 (99)
2	H	Et	*i*-Pr	74 (99)
3	4-Cl	Me	Et	91 (99)
4	4-F	Me	*i*-Pr	88 (99)
5	2-Me	Me	Ph	64 (99)
6	2-MeO	Me	*i*-Pr	79 (99)

1.5.4. Lithiation–Borylation with Benzoate Esters

One limitation of the lithiation–borylation of carbamates is that some boronic esters are very slow to undergo the 1,2-metallate rearrangement, requiring the addition of Lewis acidic additives to avoid the formation of the homologated products in low yield. In order to solve this problem, alternative leaving groups have been explored and it was found that the use of hindered alkyl 2,4,6-triisopropylbenzoates, instead of carbamates, allowed for a remarkably faster 1,2-metallate rearrangement.[67] Deprotonation of primary 2,4,6-triisopropylbenzoates with *s*-BuLi in the presence of TMEDA had initially been reported by Beak and co-workers.[68-70] More recently, Hammerschmidt and co-workers showed that the lithiated species generated

from the corresponding α-stannyl benzoates (by selective tin−lithium exchange) are configurationally stable at −78 °C.[71] In 2010, Aggarwal and co-workers reported the first enantioselective deprotonation of primary 2,4,6-triisopropylbenzoates, followed by trapping with boronic esters, to give, after 1,2-metallate rearrangement, the corresponding homologated products. The enhanced leaving group ability of the TIB group with respect to the carbamate group allowed for a remarkable improvement in the rate of the migration process and the products could be isolated in higher yields.[67] The enantioselectivity of this process was similar to when using the corresponding carbamates (Table 1.10).

Table 1.10. Comparison between TIB esters and carbamates in the homologation of boronic esters.

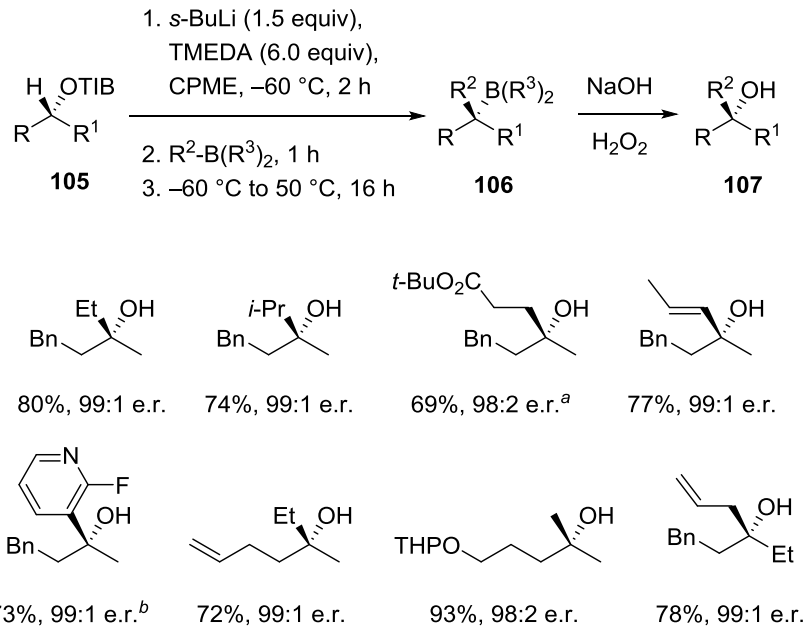


Entry	Carbenoid	R^1	Conditions[a]	% Yield	e.r.
1	Cb	Me	B	50	95:5
2	TIB	Me	C	76	96:4
3	Cb	*c*-Pr	A	71	98:2
4	TIB	*c*-Pr	C	86	96:4
5	Cb	$(CH_2)_2COO$*t*-Bu	B[b]	35	93:7
6	TIB	$(CH_2)_2COO$*t*-Bu	A	63	96:4
7	Cb	$(CH_2)_2CN$	B	0	n.d.
8	TIB	$(CH_2)_2CN$	A	46	97:3
9	Cb	Ph	B	88	99:1
10	TIB	Ph	C	79	96:4

[a] Conditions: A: 16 h, reflux; B: $MgBr_2 \cdot Et_2O$ (2.0 equiv), 16 h, reflux; C: 2 h, reflux. [b] 5 days, reflux.

Although this methodology could be applied to primary and secondary benzylic carbamates and benzoates, simple non-activated secondary dialkyl carbenoids still represent a challenge. The α-oxy proton is not sufficiently acidic to be removed by a strong base, as reported by both

Hoppe[40] and Beak.[70] Aggarwal and co-workers recently found conditions to perform the deprotonation of these challenging substrates to access, after borylation and 1,2-metallate rearrangement, enantioenriched tertiary alkylboronic esters.[72] This was achieved by performing the lithiation of unactivated chiral benzoates **105** with *s*-BuLi in the presence of a large excess of TMEDA (6.0 equiv) and using CPME as the solvent; the generated chiral lithium carbenoid was subsequently reacted with a range of different boronic species (Scheme 1.35). Neopentyl glycol boronic esters proved to be superior to the corresponding pinacol boronic esters and boranes, giving the corresponding homologated products in good yield and complete enantiospecificity. Remarkably, this protocol provides access to a broad range of enantiopure tertiary alcohols which would be otherwise difficult to synthesise using alternative methods.



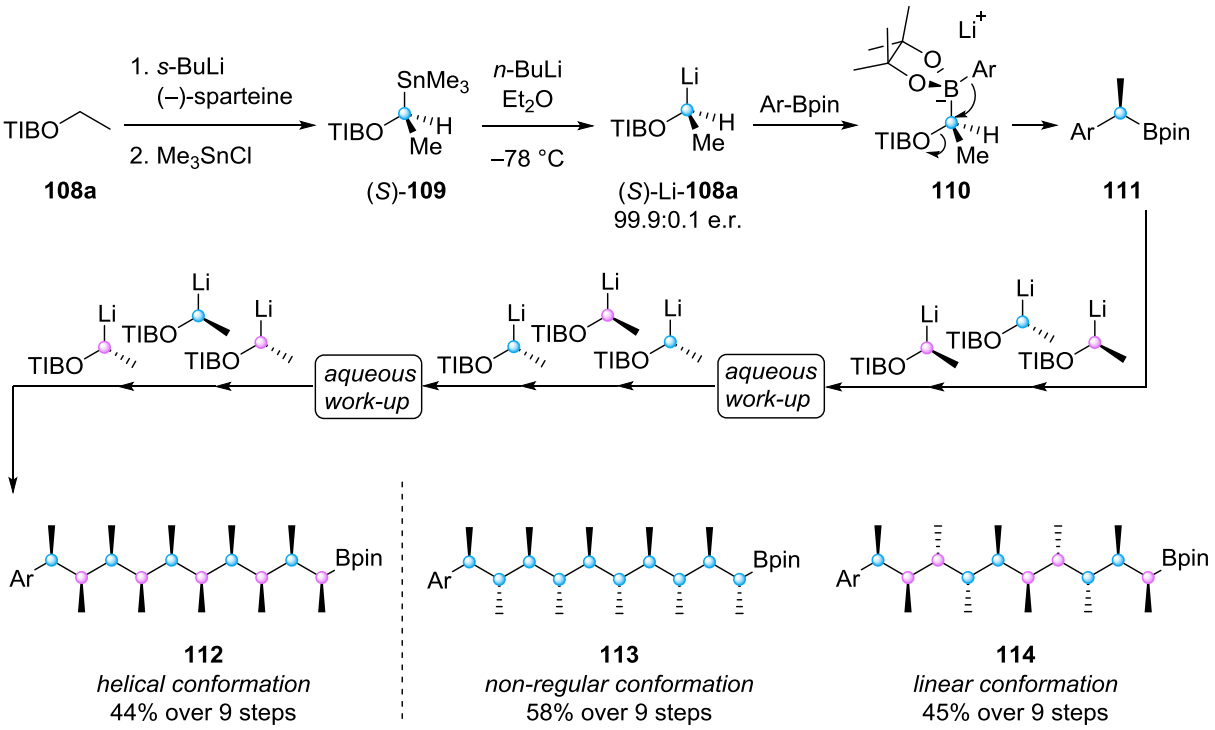
Scheme 1.35. Lithiation–borylation with dialkyl-substituted TIB esters. [a] MeOH (2.0 equiv) was added after "ate" complex formation; [b] TMSCl (6.0 equiv) was added after "ate" complex formation.

The analogous dialkyl tertiary carbamates could not be deprotonated under these conditions, thus demonstrating the superior ability of the benzoate group to promote lithiation.

1.5.5. Assembly-line Synthesis

Recent work within the Aggarwal group has further extended the lithiation–borylation methodology to allow for the one-pot iterative homologation of boronic esters. This can be compared to a molecular assembly line in which successive groups are added to a growing chain under reagent control of the relative and absolute stereochemistry (Scheme 1.36).[73] Enantioenriched stannanes (*R*)-**109** and (*S*)-**109** were synthesised by asymmetric deprotonation

of ethyl tri-isopropylbenzoate **108** with *s*-BuLi/(−)-sparteine or sBuLi/(+)-sparteine, followed by trapping with Me_3SnCl, and their e.r. could be increased to 99.9:0.1 by recrystallisation. Stannane (*S*)-**109** was readily converted into the required lithiated benzoate Li-**108a** by retentive tin−lithium exchange, using *n*-BuLi at −78 °C. The generated lithium carbenoid was then trapped with an aryl boronic ester to form the corresponding "ate" complex **110** which, upon warming to higher temperature, underwent stereospecific 1,2-metallate rearrangement. At this point, the reaction mixture was filtered to remove the insoluble lithium salt of 2,4,6-triisopropylbenzoate to give crude homologated boronic ester **111**, which was directly employed in a subsequent homologation. The process was repeated iteratively for a total of nine homologations, with an aqueous work-up being performed after every third homologation, to yield boronic ester **112** as a single diastereoisomer and a single enantiomer, demonstrating the high enantiospecificity of each homologation reaction.[73] By judicious selection of the enantiomers of stannane **109** employed in the sequence it was possible to prepare three different isomers of the final compound, the all-*syn* **112**, the all-*anti* **113** and the alternating *syn-anti* **114**, which were shown to adopt different conformations in solution.



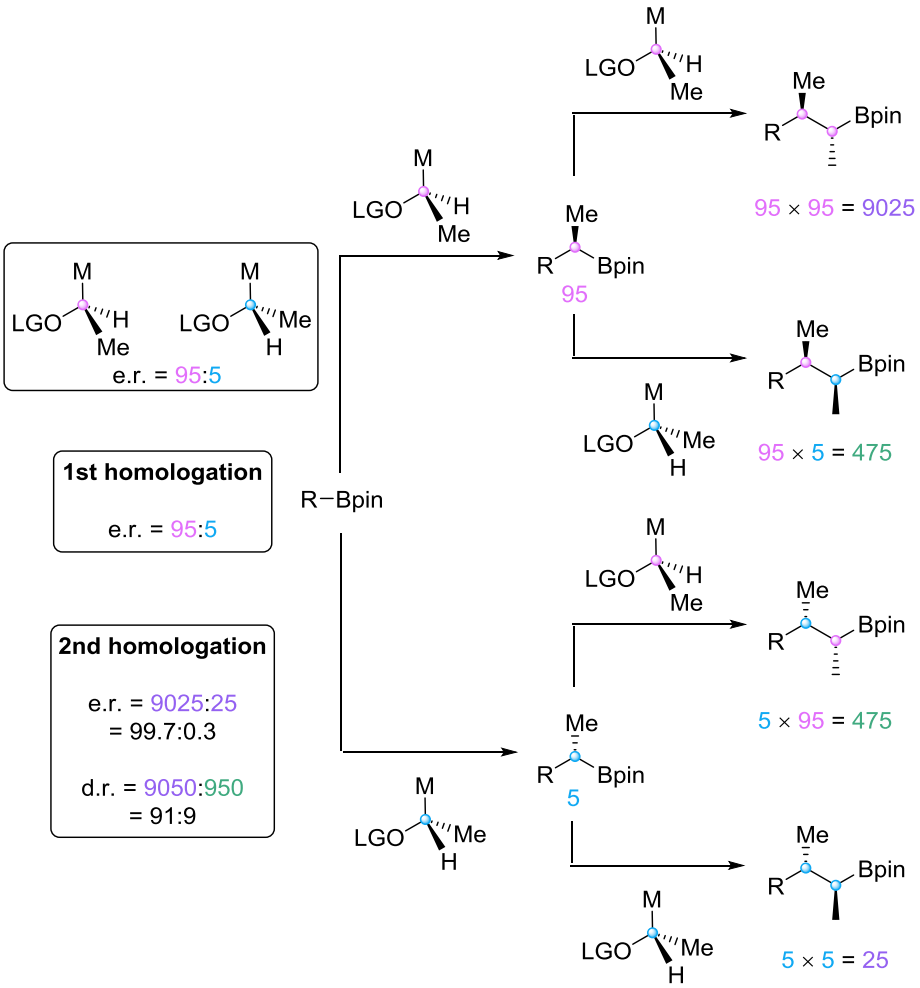
Scheme 1.36. Iterative assembly-line synthesis.

The described iterative homologation of boronic esters was applied to the synthesis of different natural products,[55, 74-77] demonstrating its high chemical and manpower efficiency.

For this iterative homologation of boronic esters to be possible three key criteria must be fulfilled:

- the generated metal carbenoid must possess a good leaving group, promoting a fast 1,2-metallate rearrangement and reducing reversibility that would eventually cause under-homologation.
- the generated metal carbenoid must be chemically and configurationally stable at low temperature and decompose at a lower temperature than the one required for 1,2-metallate rearrangement in order to avoid over-homologation.
- the metal carbenoid must be generated with very high e.r. (generally >99:1) to avoid the formation of diastereoisomers when iterative homologations are performed.

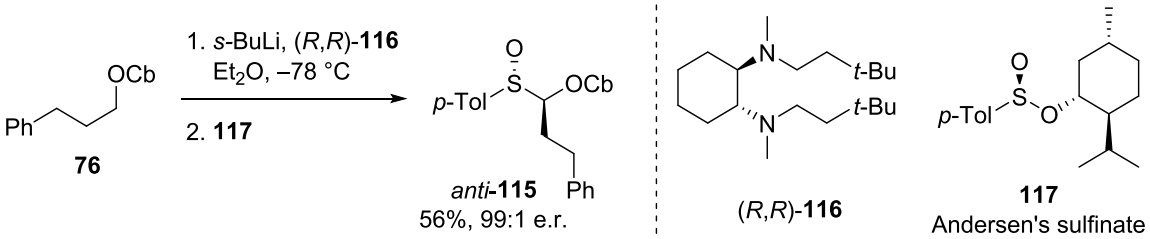
The importance of this last criteria is depicted in Scheme 1.37. If a metal carbenoid with an e.r. of 95:5 is used in the homologation of a boronic ester, assuming that the reaction occurs with full transfer of stereochemical information, the generated boronic ester will have an e.r. of 95:5. A second homologation with the same carbenoid (e.r. = 95:5) will give a major and a minor diastereoisomer (d.r. = 91:1) together with the corresponding enantiomers. In particular, the major diastereoisomer will show an increased e.r. of 99.7:0.3, as the majority of the undesired minor enantiomer of the starting boronic ester is converted to a different diastereoisomer. This amplification of enantioenrichement is better known as the Horeau principle.[78-79] It is clear that a highly enantioenriched carbenoid must be employed in an iterative process in order to avoid the formation of unwanted minor diastereoisomers, which would eventually lower the yield of the process and reduce the purity of the desired product.



Scheme 1.37. Demonstration of the Horeau principle and diastereoisomers formation in the iterative homologation of boronic esters.

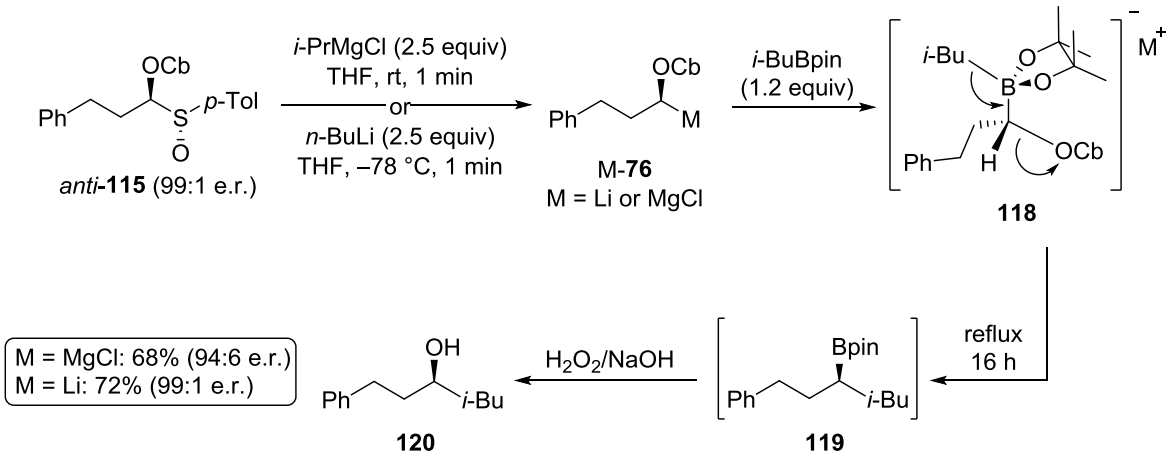
1.6. Homologation of Boronic Esters by α-Alkoxymetal Chiral Carbenoids

Peter O'Brien and co-workers showed that α-alkoxy sulfoxides can also be employed in the homologation of boronic esters.[80] In particular, α-sulfinyl carbamate *anti*-**115** was selected as suitable precursor for the necessary metal carbenoid, and it was efficiently synthesised from carbamate **76** by asymmetric deprotonation in the presence of chiral diamine (*R*,*R*)-**116**, followed by trapping with commercially available Andersen's sulfinate **117** (Scheme 1.38).



Scheme 1.38. Synthetic route to enantiomerically enriched α-sulfinyl carbamate *anti*-**115**.

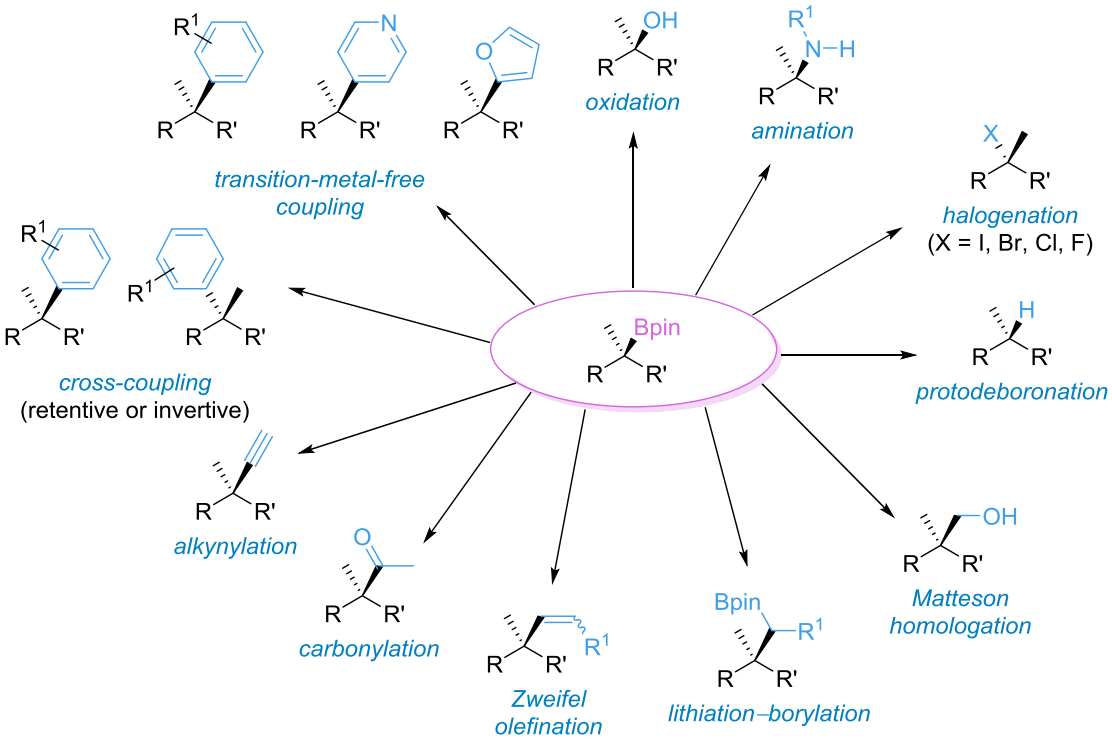
Anti-**115** was subsequently converted into the corresponding α-metallated carbenoid M-**76** through a selective sulfoxide–metal exchange employing either *i*-PrMgCl at room temperature or *n*-BuLi at −78 °C for only 1 minute. α-Metallated carbenoid M-**76** was then immediately trapped with *i*-BuBpin to generate "ate" complex **118**, which, after 1,2-metallate rearrangement and stereospecific oxidation, afforded one-carbon homologated alcohol **120** (Scheme 1.39). The product was isolated in both cases in good yield. However, while a complete transfer of stereochemical information was observed in the process initiated by *n*-BuLi, a small loss of enantiopurity was recorded when the Grignard reagent was employed.



Scheme 1.39. Homologation of boronic esters using metal carbamate M-**76** generated through sulfoxide–metal exchange.

1.7. Alternative Transformations of Boronic Esters

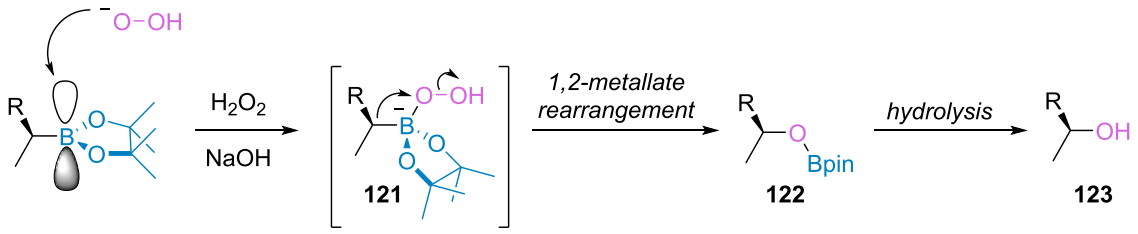
The boronic ester moiety can be converted into a variety of different functional groups (Scheme 1.40).[81-82] Most of these transformations proceed through the initial formation of a boronate complex, which undergoes a subsequent 1,2-metallate rearrangement, and are therefore stereospecific.



Scheme 1.40. Overview of the possible stereospecific transformations of enantioenriched tertiary boronic esters.

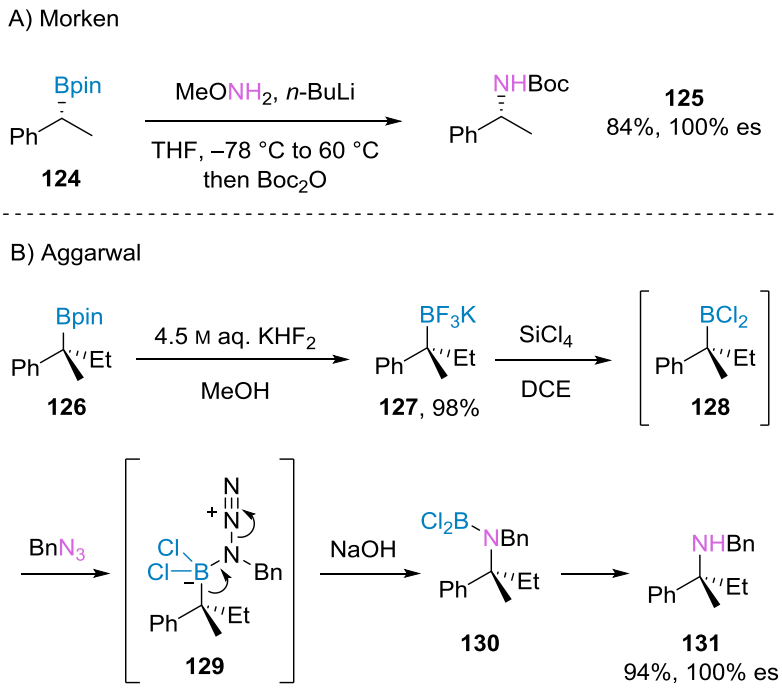
1.7.1. Carbon–heteroatom bond formation

The most common and versatile transformation of the C–B bond is its oxidation to give the corresponding alcohol in high yield and complete stereospecificity. This conversion is normally achieved using basic hydrogen peroxide,[56] as originally reported by Brown and co-workers for the oxidation of boranes.[83] The reaction proceeds through the initial attack of the peroxide anion to the empty p-orbital on boron to generate intermediate "ate" complex **121**. Subsequent 1,2-migration of the carbon substituent on boron onto the adjacent oxygen atom, with departure of the hydroxyl group, affords, after hydrolysis, alcohol **123** with complete retention of configuration (Scheme 1.41). Alternative oxidising agents that have been employed in the same transformation are sodium perborate,[84] oxone[85] and trimethylamine *N*-oxide.[86]



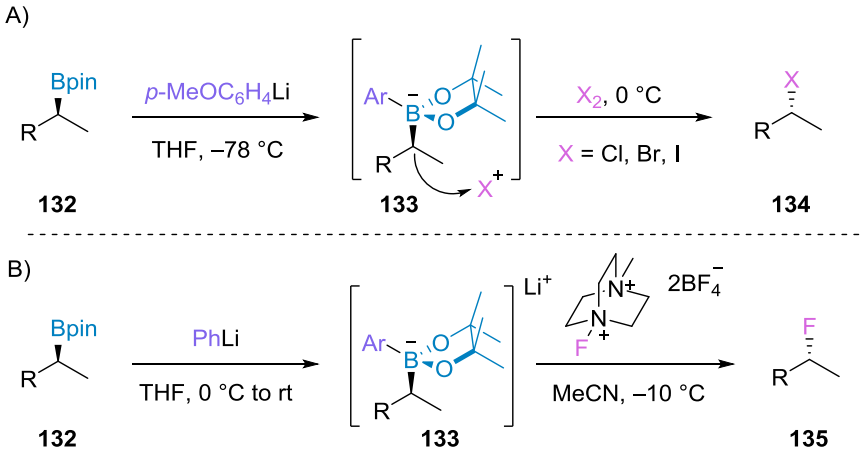
Scheme 1.41. Mechanism of the oxidation of boronic esters with basic hydrogen peroxide.

Morken and co-workers reported conditions to convert enantioenriched secondary boronic esters into the corresponding amines using methoxyamine and *n*-BuLi.[87] The generated *N*-Boc protected amines **125** were isolated in good yield and with very high levels of stereospecificity (Scheme 1.42A). Tertiary boronic esters were found to be unreactive under these conditions. Aggarwal and co-workers subsequently reported the stereospecific conversion of chiral tertiary boronic esters into amines in a two steps procedure *via* intermediate trifluoroborate salt **127**,[88] synthesised in quantitative yield by treatment with KHF_2 in MeOH.[89] Reaction with $SiCl_4$ generates dichloroborane **128**[90] that, upon treatment with an organic azide,[91] is converted into tertiary amine **131** with complete retention of stereochemistry (Scheme 1.42B).



Scheme 1.42. Conversion of secondary and tertiary boronic esters into amines.

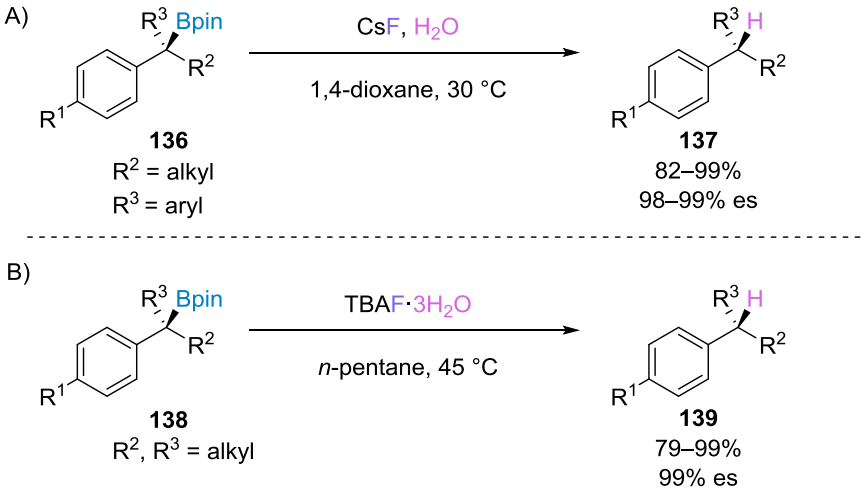
Aggarwal and co-workers also reported the stereospecific transformation of the C–B bond of tertiary boronic esters into a C–halogen bond (Scheme 1.43A).[92] This was achieved through the initial formation of nucleophilic boronate complex **133**, followed by reaction with halogens (I_2, Br_2, Cl_2) to form a new C–halogen bond in a stereospecific fashion. In this case, the products are obtained with inversion of configuration at the carbon centre. More recently, the range of halogens that can be introduced using this methodology was further expanded and the stereospecific fluorination of tertiary boronic esters was developed (Scheme 1.43B).[93] In this process, boronate complex **133** was reacted with Selectfluor II in acetonitrile to give alkylfluoride **135** in good yield. Importantly, the addition of styrene was found to be fundamental to ensure the complete enantiospecifity of the process.



Scheme 1.43. Stereospecific halogenation of tertiary boronic esters.

1.7.2. Carbon–hydrogen bond formation

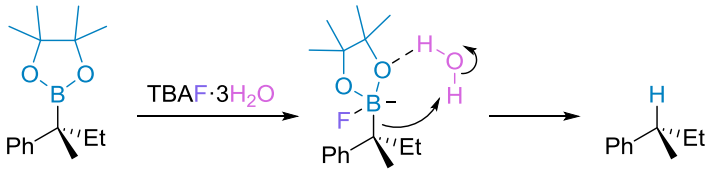
Protodeboronation of tertiary boronic esters could also be performed stereospecifically to generate useful tertiary alkyl stereocentres.[94] In particular, diarylalkyl boronic ester could be protodeboronated by reaction with CsF and H_2O in dioxane at 30 °C to afford compound **137** in excellent yield and es (Scheme 1.44A). Although aryl dialkyl boronic esters were found to be inert under these conditions, treatment with the more reactive TBAF·$3H_2O$ in *n*-pentane at 45 °C afforded protodeboronated products **139** in equally good yield and es (Scheme 1.44B). Both the described conditions delivered the corresponding products with complete retention of stereochemistry.



Scheme 1.44. Protodeboronation of tertiary boronic esters.

The proposed mechanism for the TBAF·$3H_2O$ mediated protodeboronation of tertiary boronic esters is shown in Scheme 1.45. Hydrogen bonding between the generated boronate complex

and a molecule of H_2O favours the delivery of the proton on the same side of the boron atom, therefore ensuring high levels of stereoretention.

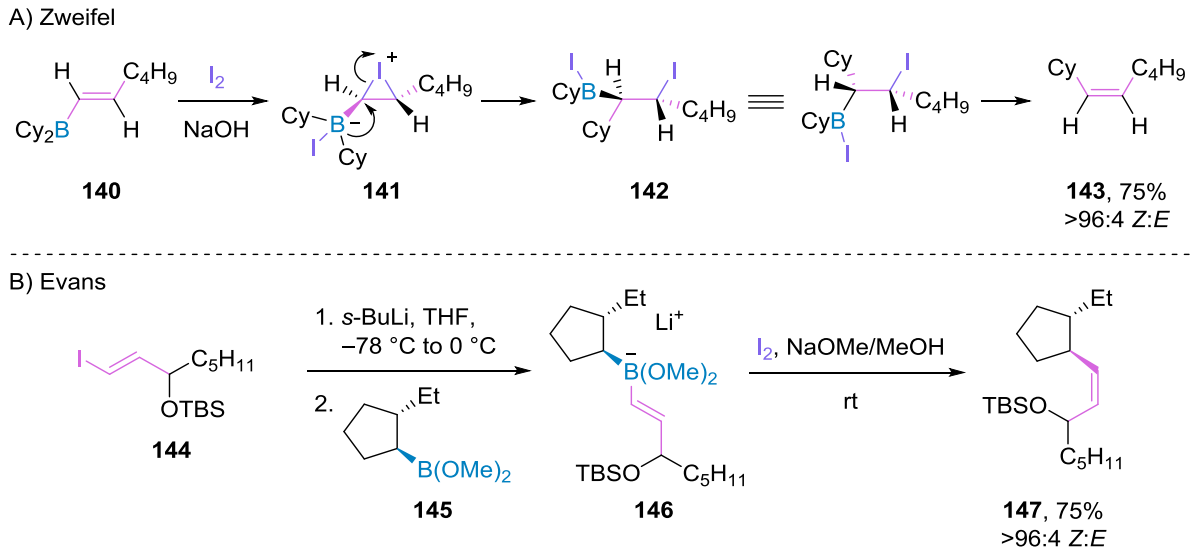


Scheme 1.45. Proposed mechanism for the TBAF mediated protodeboronation of tertiary boronic esters.

1.7.3. Carbon–carbon bond formation

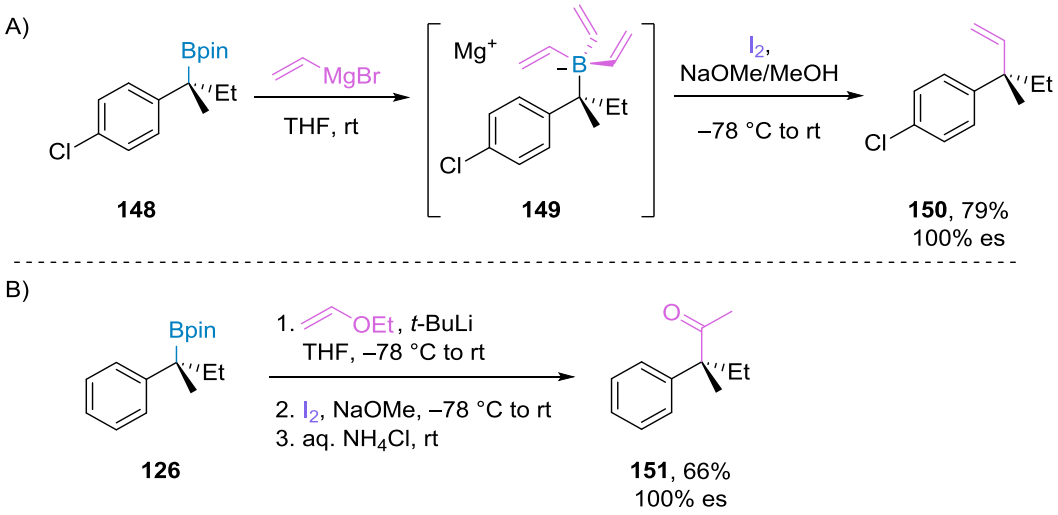
A growing area of interest concerns the possibility of further homologating boronic esters to generate a new C–C bond. The Matteson homologation, giving primary alcohols after *in situ* oxidation, and the lithiation–borylation of TIB esters or carbamates fall into this category and have already been discussed in § 1.2 and 1.5, respectively.

Chiral boronic esters can also be converted into the corresponding alkenes in a stereospecific fashion. This transformation was originally reported by Zweifel and co-workers in 1967.[95] They found that the addition of iodine to vinyl borane **140** in the presence of NaOH gave alkene **143** in 75% yield and as a single *Z* isomer. The mechanism of this transformation is depicted in Scheme 1.46A. After the initial formation of iodonium ion **141**, an alkyl group on boron undergoes stereospecific 1,2-migration to give iodo-borane **142**; a base-mediated deboronoiodination eventually affords *cis*-alkene **143**. Evans and co-workers subsequently showed that the process can also be performed employing a boronic ester and a vinyllithium to generate substituted alkenes as single isomers and with no loss of stereochemical information (Scheme 1.46B).[96]



Scheme 1.46. Examples of Zweifel olefination on boranes and boronic esters.

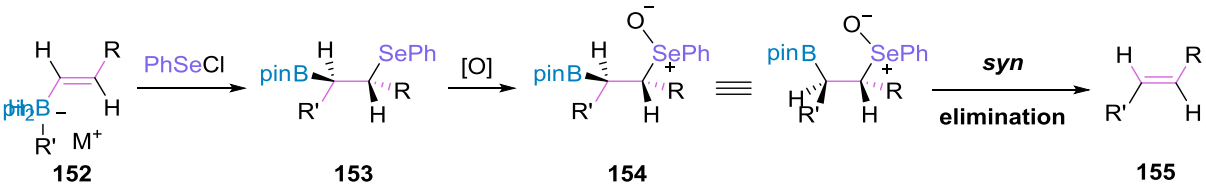
Aggarwal and co-workers further extended the scope of this methodology and reported the conversion of enantioenriched tertiary boronic esters into the corresponding terminal alkenes using 4 equivalents of vinylmagnesium bromide (Scheme 1.47A).[97] The reaction was found to proceed *via* intermediate boronate complex **149**, which, upon addition of iodine and NaOMe/MeOH, gave alkene **150** in 79% yield and 100% es. It was also discovered that the use of ethoxy vinyllithium in the same process allowed the isolation of the corresponding methyl ketone **151** (Scheme 1.47B).[72, 97]



Scheme 1.47. Functionalisation of tertiary boronic esters *via* Zweifel olefination.

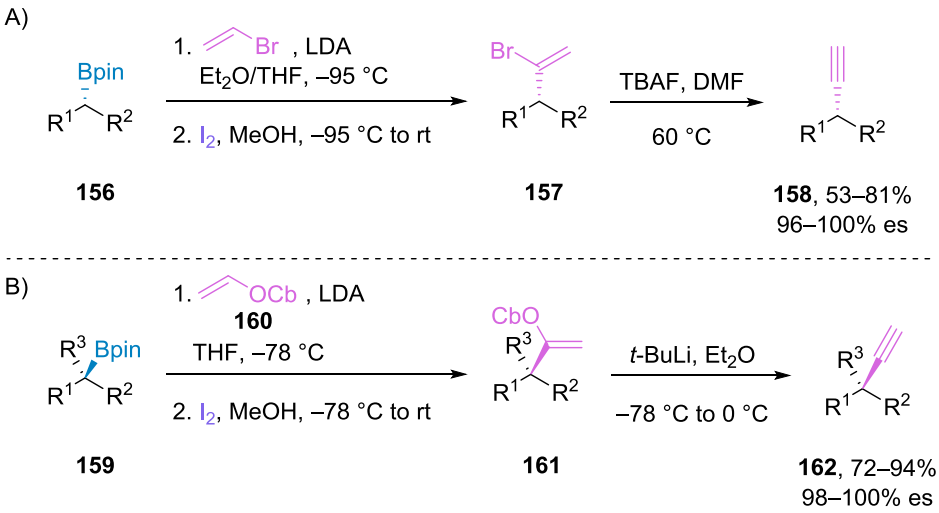
In the mechanism depicted in Scheme 1.46A, iodo-borane **142** undergoes *anti*-elimination to afford exclusively *cis*-alkene **143**. Aggarwal and co-workers recently found that when boronate complex **152** is treated with PhSeCl as the electrophile in the place of I_2, β-selenoboronate **153**

was formed. Chemoselective oxidation using *m*-CPBA gave selenoxide **154**, which allowed a *syn*-elimination to take place to afford *trans*-alkene **155** as a single isomer (Scheme 1.48).[98] These two protocols show the power of this methodology, offering stereodivergent access to both the alkene isomers.



Scheme 1.48. *E*-Selective Zweifel olefination using PhSeCl.

An extension of this methodology was subsequently developed in the Aggarwal group, providing access to terminal alkynes starting from enantioenriched boronic esters.[99] In the case of secondary boronic esters, this can be achieved by formation of a boronate complex using lithiated vinylbromide (generated *in situ* by treatment with LDA at −95 °C), followed by addition of I_2 in MeOH, to give bromo-alkene **157**; TBAF-mediated elimination gives the desired alkyne in good yield and complete enantiospecificity (Scheme 1.49A). Vinyl carbamate **160** was found to be a superior reagent for the alkynylation of enantioenriched tertiary boronic esters, with intermediate carbamate **161** undergoing smooth elimination by treatment with *t*-BuLi to afford alkyne **162** in excellent yield and es (Scheme 1.49B).

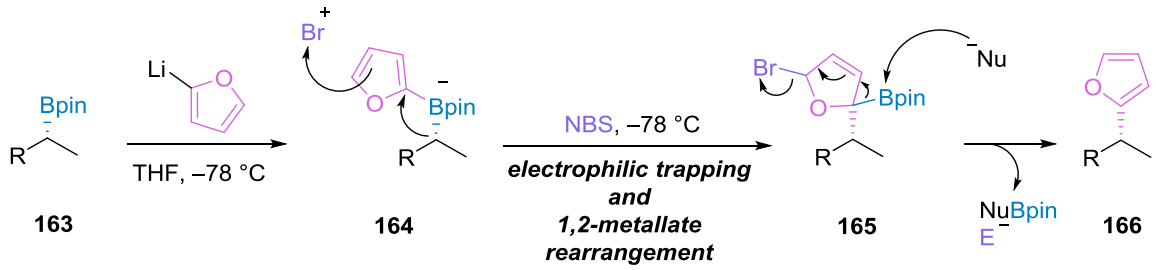


Scheme 1.49. Stereospecific alkynylation of secondary and tertiary boronic esters.

Enantioenriched secondary and tertiary boronic esters have also been employed in Suzuki–Miyaura reactions. In particular, Crudden and co-workers showed the first stereospecific Pd-catalysed cross-coupling reaction of secondary benzylic[100-101] and

dibenzylic[102] boronic esters with aryl iodides to give the corresponding coupled products in good yield and high levels of enantiospecificity. Both of these processes occur with retention of configuration, although Liao and co-workers subsequently showed that the corresponding trifluoroborate salts undergo this reaction with inversion of configuration.[103] In 2014, Biscoe and co-workers published the first example of enantiospecific Suzuki−Miyaura reaction of an unactivated dialkyl trifluoroborate salt with chlorobenzene, yielding the desired product in high es.[104]

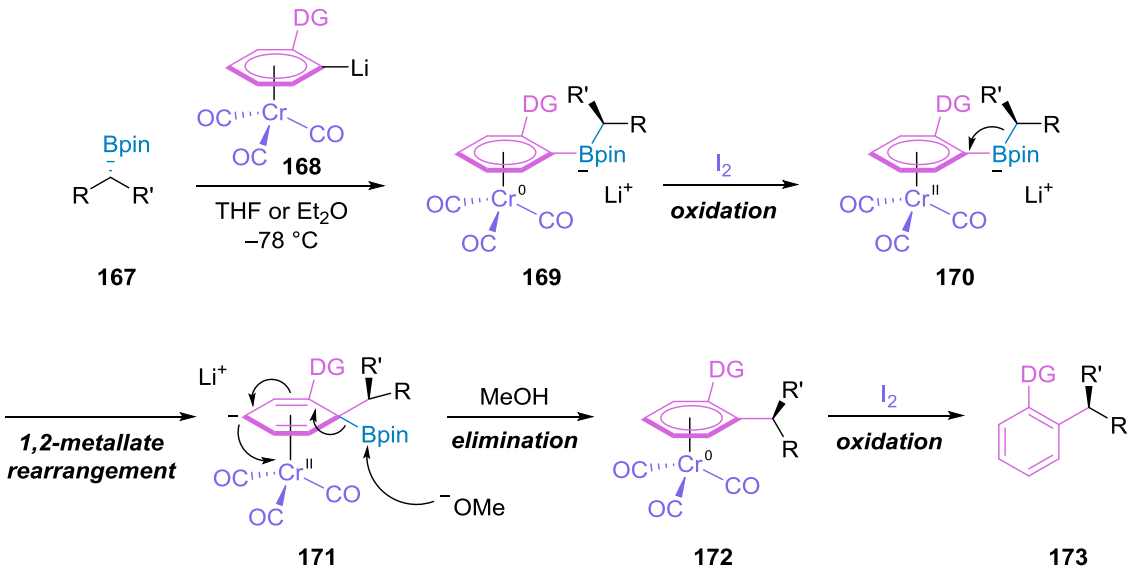
An important development was recently achieved by Aggarwal and co-workers in the transition-metal-free coupling reaction of enantioenriched boronic esters with aromatics (Scheme 1.50).[105-106] In this approach, boronate complex **164**, generated by addition of lithiated furan to boronic ester **163**, is activated by NBS; facile 1,2-metallate rearrangement can therefore occur to generate intermediate **165**, which, upon addition of a nucleophile, rearomatises to yield desired coupled product **166** in a completely enantiospecific fashion. Remarkably, the process can also be applied to enantioenriched tertiary boronic esters, which are normally very challenging substrates to couple with more traditional transition-metal mediated coupling reactions, while furan could be substituted by a range of different electron-rich aromatics. The scope of the aromatic partner was subsequently extended to include substituted *N*-heteroaromatics[107] and phenols.[108]



Scheme 1.50. Transition-metal-free coupling reaction of boronic esters with furan.

More recently, it was found that also aromatics lacking functional groups reactive towards an activator can be employed in similar cross-coupling reactions.[109] To this purpose, lithiated chromium arene **168** was reacted with boronic ester **167** to generate "ate" complex **169** (Scheme 1.51). Upon addition of iodine, oxidation occurred at the chromium centre, to give complex **170**; this made the aromatic ring sufficiently electron-withdrawing to undergo smooth 1,2-metallate rearrangement affording anion **171**. Subsequent methanol-mediated elimination of the boronic ester moiety gave chromium complex **172**, which could be easily converted into the desired coupled product by further oxidation. The process was found to applicable to a wide

range of different substituted arenes and secondary boronic esters, with the corresponding products isolated as single regioisomers in very good yield and complete enantiospecificity.



Scheme 1.51. Proposed mechanism for the enantiospecific coupling of boronic esters with chromium arene complexes.

1.8. Conclusions

Lithiation–borylation has been shown to be a valuable and powerful method to homologate chiral boronic esters. This methodology has been applied to the synthesis of complex molecules containing several contiguous tertiary and quaternary stereocentres as well as important natural and biologically active products. Many developments have been achieved in the past few years designed to improve the reaction and to extend the scope of the process.

The work described in this thesis aims at further improving the boundaries of this methodology, focusing in particular on three main projects: the use of azetidinium ions in lithiation–borylation reactions to synthesise 3-aryl-1aminopropane derivatives (see § 2); the use of α-sulfinyl benzoates as precursors to the necessary metallated carbenoids to be employed in stereospecific iterative homologation of boronic esters (see § 3); the possibility of introducing carbonyl, C–C double bonds and enone functionalities through a building-block based iterative assembly line synthesis approach (see § 4).

2. Synthesis of 3-Aryl-1-Aminopropane Derivatives by Lithiation–Borylation–Ring-Opening of Azetidinium Ions

Parts of the work described in this chapter have been adapted from the following communication article:

Casoni, G., Myers, E. L., Aggarwal, V. K., *Synthesis* **2016**, *48*, 3241–3253.

2.1. Introduction and Project Aims

The 3-aryl-1-aminopropane motif constitutes the basic core of a number of biologically active molecules and drug candidates (Figure 2.1);[110] bedaquiline, a potent antituberculosis marketed-drug, is probably the most noteworthy and structurally complex molecule belonging to this class of compounds.[111]

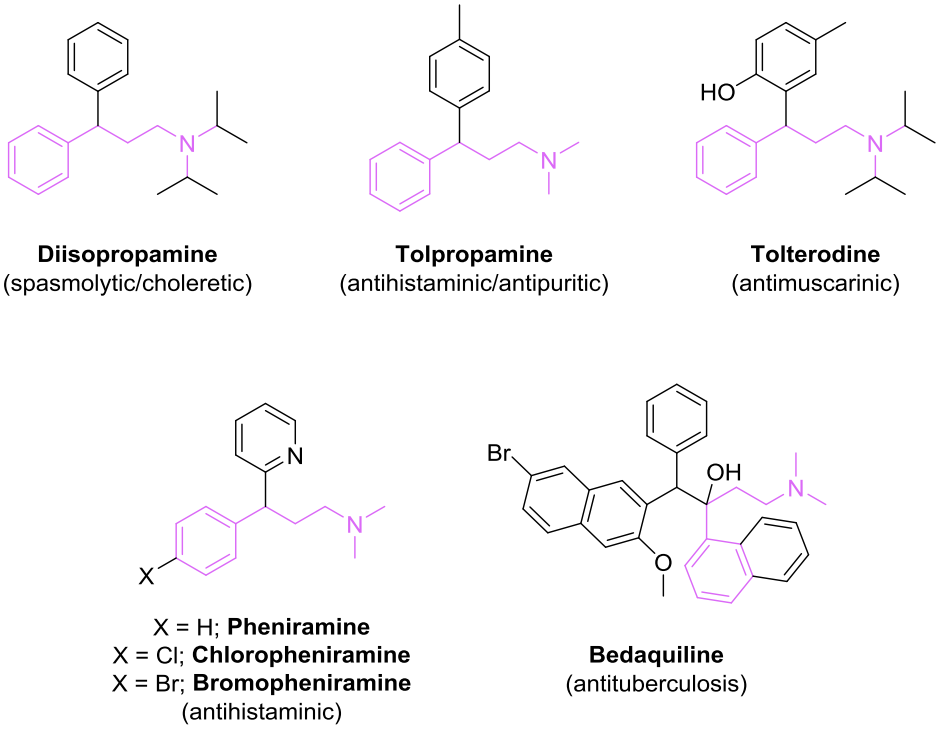
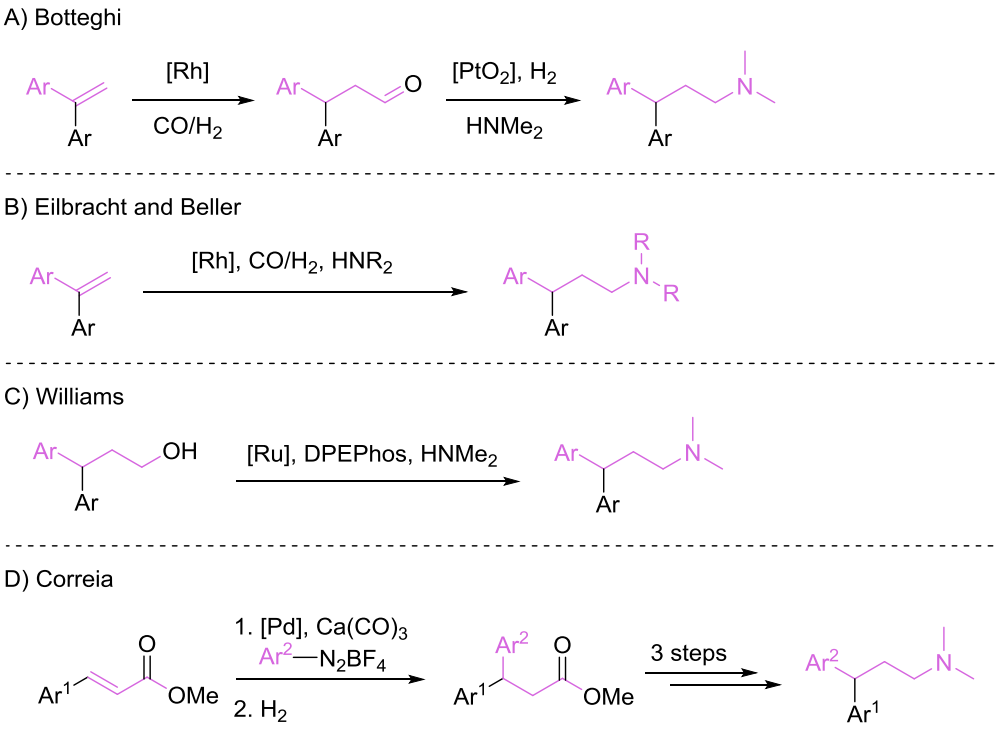


Figure 2.1. Marketed drugs containing the 3-aryl-1-aminopropane unit.

To date, there is a number of methods available to introduce the 3-aryl-1-aminopropane unit. Among these, the nucleophilic addition of aryl metal reagents to β-aminoketones giving the corresponding 3-arylaminoalcohols has been broadly applied to the synthesis of biologically active compounds.[112-113] 3,3-Diarylpropylamines are instead commonly accessed by nucleophilic substitution of the corresponding 3,3-diarylpropylhalides.[114-116] However, the high number of steps usually required to synthesise the necessary starting halides and the low

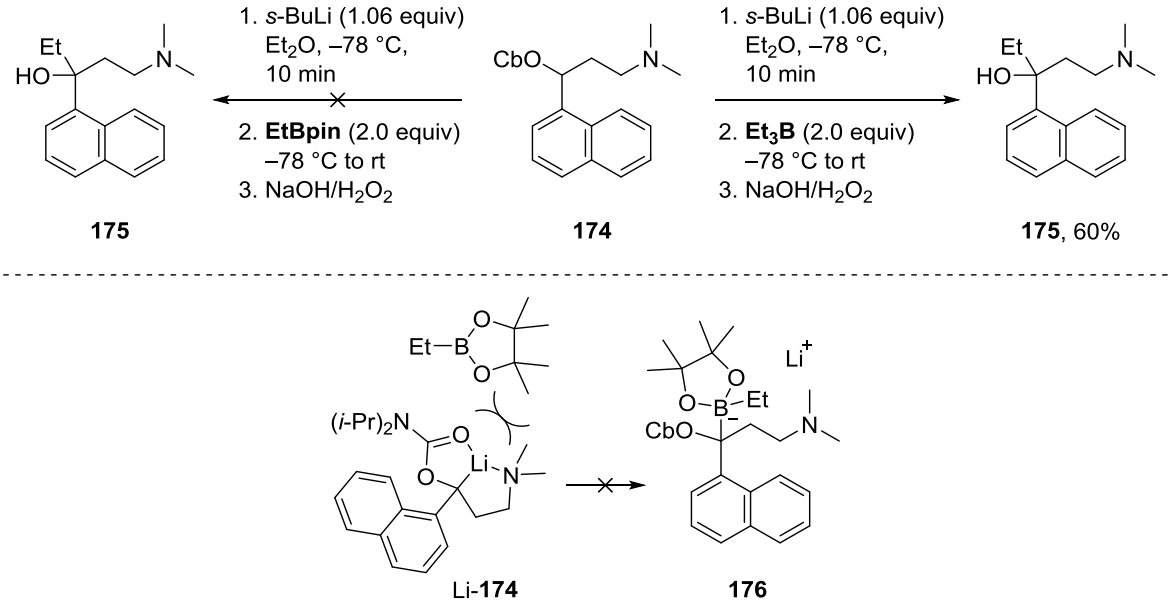
overall yields, together with the lack of atom economy and the toxic nature of many of the alkyl halides employed, has stimulated interest in discovering new methodologies for the synthesis of these useful motifs. Botteghi and co-workers showed that the 3,3-diarylpropylamine motif could be efficiently introduced through a rhodium-catalysed hydroformylation of readily accessible 1,1-diarylalkenes followed by reductive amination (Scheme 2.1A).[117] A few years later, a one-pot rhodium-catalysed hydroaminomethylation of 1,1-diarylalkenes to give the corresponding 3,3-diphenylpropylamines was successfully developed by Eilbracht[118] and Beller[119-120] (Scheme 2.1B). In 2009, Williams and co-workers published a novel route to 3-aryl-1-aminopropane derivatives based on a key ruthenium-catalysed *N*-alkylation of amines with alcohols (Scheme 2.1C) and this methodology was successfully applied to the synthesis of various pharmaceuticals.[121] More recently, a new synthetic methodology to access 3-arylpropylamines was developed by Correia and co-workers using a Heck-Matsuda arylation as the key step (Scheme 2.1D).[122]



Scheme 2.1. Comparison of literature known methods to introduce the 3-aryl-1-aminopropane motif.

Aiming to discover a new strategy to introduce this privileged motif, we sought to synthesise a range of different substituted 3-aryl-1-aminopropanes through C–B functionalisation of the corresponding γ-dimethylamino tertiary boronic esters, which we envisioned could be accessed through a lithiation–borylation reaction, as depicted in Scheme 2.2.

However, initial investigation revealed that benzylic amino carbamates are not suitable precursors for this type of transformation. In fact, when secondary amino carbamate **174** was subjected to a lithiation borylation reaction with ethyl pinacol boronic ester, followed by *in situ* oxidation, tertiary alcohol **175** could not be obtained (Scheme 2.2A). Interestingly, subjecting amino carbamate **174** to the same conditions, but using triethylborane, provided tertiary alcohol **175** in 60% yield. (Scheme 2.2B).[i] This can be rationalised considering the reduced electrophilicity of boronic esters compared to boranes: the lithiated carbamate, stabilised by intramolecular chelation, is presumably not reactive enough to attack the boronic ester. Another possible explanation is that the increased steric hindrance of the boronic ester compared to the corresponding borane prevents the formation of boronate complex **176**.

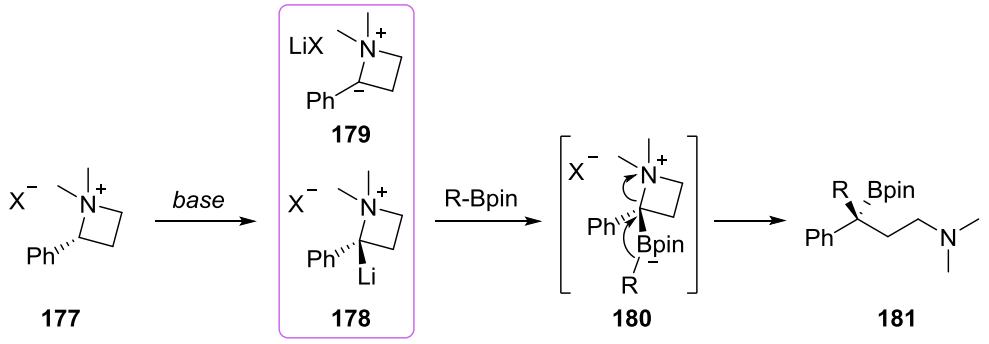


Scheme 2.2. Lithiation–borylation of carbamate **174** using EtBpin and Et_3B.

An alternative way to achieve the synthesis of substituted γ-dimethylamino tertiary boronic esters **181** through lithiation–borylation would be using azetidinium ions **177** as the starting materials (Scheme 2.3). Specifically, deprotonation of azetidinium ion **177** would generate the corresponding lithiated carbenoid **178**, which, upon reaction with a boronic ester, could lead to the formation of zwitterionic boronate complex **180**. Subsequent 1,2-metallate rearrangement, promoting the ring opening of the azetidinium, would finally afford γ-amino tertiary boronic ester **181**. Ideally, the process would be stereospecific. For this to be possible, lithiated carbenoid **178**, generated by deprotonation of enantiomerically enriched azetidinium ion **177**, must be configurationally stable at low temperature, meaning that it must stay in the

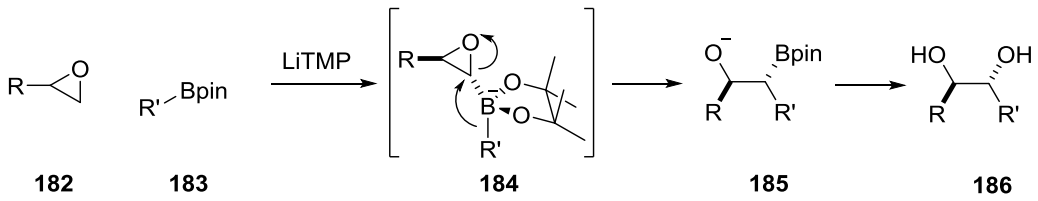
[i] Initial results on the lithiation–borylation of carbamate **174** were obtained by Dr. B. Partridge.

lithium-carbenoid stabilised form **178** rather than the ylidic form **179**. Trapping with boronic esters and subsequent 1,2-metallate rearrangement, processes that are usually stereospecific, would lead to the formation of enantioenriched γ-amino tertiary boronic ester **181**.



Scheme 2.3. Proposed lithiation–borylation of azetidinium ion **177** with boronic esters.

Previous work within the Aggarwal group showed that such ring-opening lithiation–borylation reactions can be successfully performed with terminal epoxides **182** (Scheme 2.4).[123] These compounds can in fact be deprotonated using LiTMP and the generated lithiated epoxide can be trapped *in situ* with a boronic ester **183** to give boronate complex **184**. Subsequent stereospecific 1,2-metallate rearrangement, followed by oxidation, affords *syn*-1,2-diols **186** as single diastereoisomers. The complete diastereoselectivity observed supports the proposed mechanism depicted in Scheme 2.4, where initial deprotonation occurs *trans* to the R substituent on the epoxide.

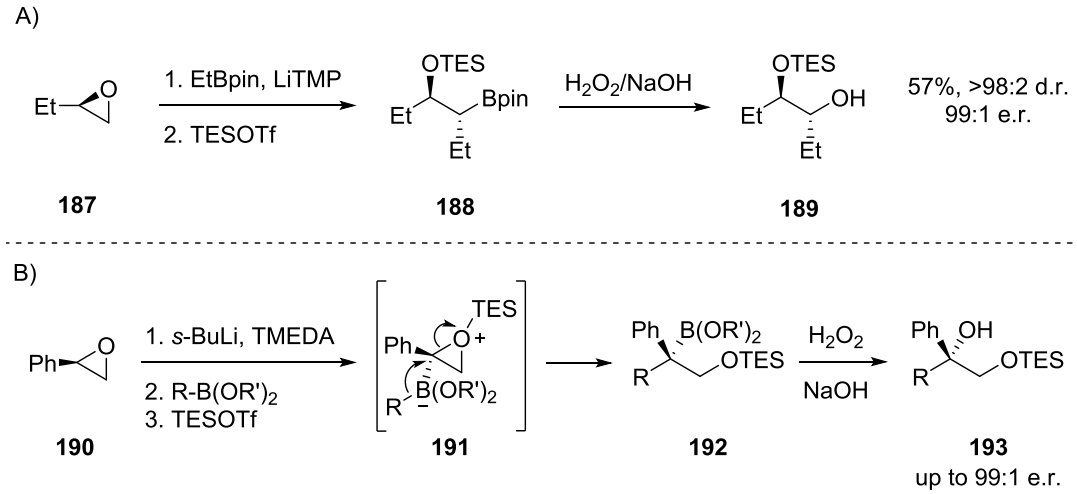


Scheme 2.4. Lithiation–borylation of terminal epoxides with boronic esters.

When enantioenriched (*R*)-butenoxide was reacted with ethyl pinacol boronic ester under these conditions, β-silyloxy boronic ester **188** was isolated, after *in situ* trapping with TESOTf, in good yield and excellent e.r. (Scheme 2.5A). This intermediate was subsequently further elaborated; in particular, a second homologation with lithiated epoxide Li-**187** gave access to substituted triols bearing four contiguous strereocentres with complete diastereocontrol.

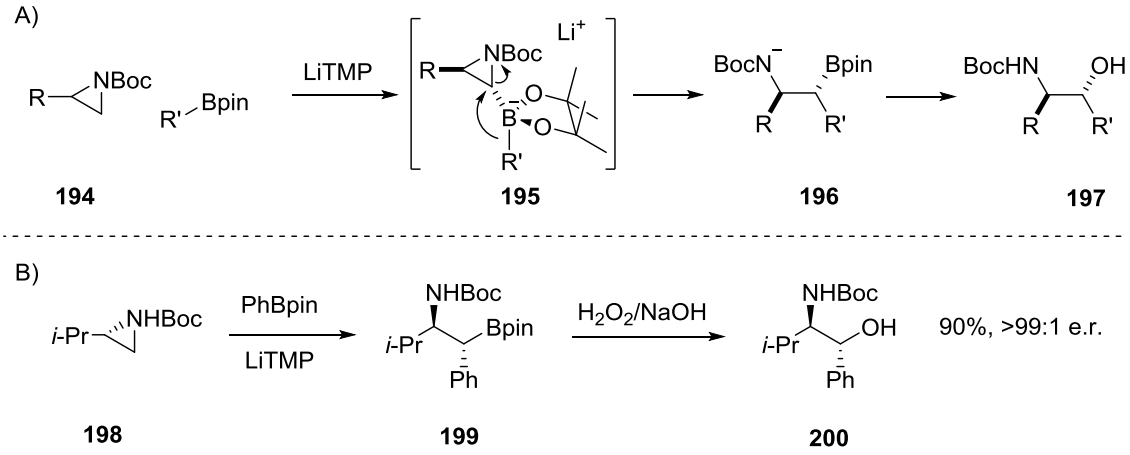
In the case of styrene oxide **190**, deprotonation was shown to occur in the position adjacent to the phenyl group. Trapping with different electrophiles at low temperature provided the corresponding styrene oxide derivatives with complete retention of stereochemistry.[124-125]

When this substrate was employed in the lithiation−borylation sequence, the *in situ* trapping of the generated β-alkoxy boronate intermediate with TESOTf was necessary to both prevent undesired boron-Wittig elimination and facilitate the 1,2-metallate rearrangement (Scheme 2.5B). The reaction proved to be stereospecific when performed at low temperatures (−98 °C) in Et_2O and using less sterically hindered neopentylglycol boronic esters.



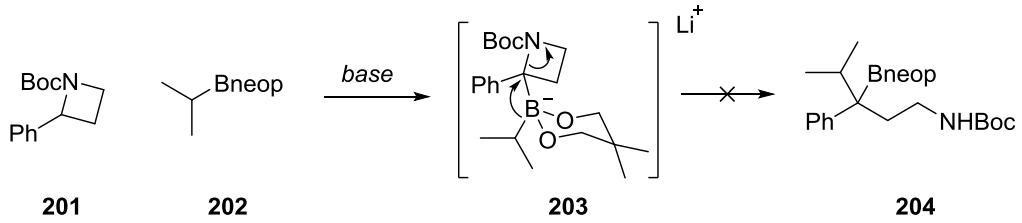
Scheme 2.5. Enantiospecific synthesis of 1,3-diols through lithiation−borylation of epoxides.

In a similar process, terminal *N*-Boc protected aziridines **194** were lithiated with LiTMP and *in situ* trapped with different boronic esters to give, after stereospecific 1,2-metallate rearrangement and oxidation, substituted *syn*-β-amino alcohols in a diastereospecific fashion (Scheme 2.6A).[126] When enantiopure aziridine **198** was employed in the sequence, the corresponding amino alcohol **200** was isolated in 90% yield and 99% *ee*, thus demonstrating the configurational stability of the generated lithium carbenoid (Scheme 2.6B).



Scheme 2.6. Lithiation−borylation of terminal *N*-Boc aziridines with boronic esters.

Unfortunately, the application of the lithiation−borylation sequence to the higher ring-size homologue *N*-Boc 2-phenylazetidine **201**, that is known to undergo regioselective lithiation at the α position when treated with a strong base,[127] met with failure (Scheme 2.7)[ii].

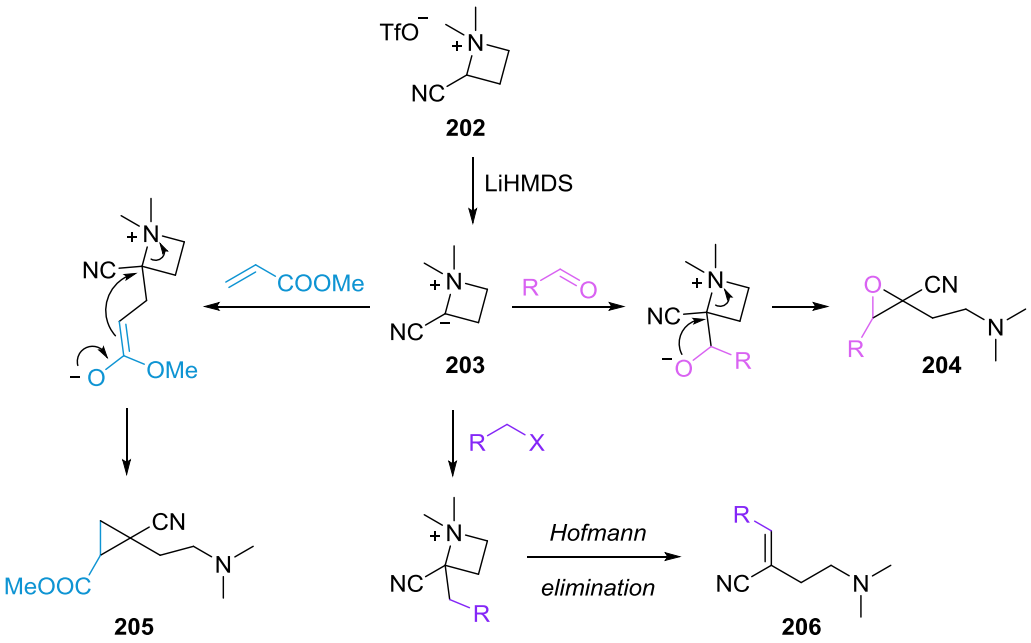


Scheme 2.7. Unsuccessful lithiation−borylation of *N*-Boc azetidine **201**.

Presumably, the 1,2-metallate rearrangement is too slow to allow the ring opening of the azetidine. In this sense, we reasoned that the corresponding azetidinium ions might be more reactive, since the presence of a positive charge on nitrogen would facilitate the ring-opening 1,2-metallate rearrangement step. Even if previous studies within our group revealed that ammonium ylides have rather poor leaving group characteristics,[128] azetidinium ylides represent a special class, since the driving force of the process would be the ring strain release.

Couty and David have recently showed that cyano-substituted azetidinium ion **202** can be deprotonated with LiHMDS to form ylide **203**; this intermediate could be subsequently trapped *in situ* with different electrophiles (Scheme 2.8). When ketones or aldehydes were employed, the generated intermediate alkoxide underwent intramolecular substitution to afford amino epoxides **204**.[129] Similarly, when acrylates were used as the electrophiles, the corresponding functionalised cyclopropanes **205** were accessed.[130] Finally, primary halides were also found to react with ylide **203**, to give, after Hofmann elimination, the corresponding substituted alkenes **206**.[131]

[ii] Initial results on the lithiation−borylation of *N*-Boc 2-phenylazetidine **201** were obtained by Dr. S. K. Roesner.



Scheme 2.8. Reactivity of azetidinium ylide **203** with different electrophiles.

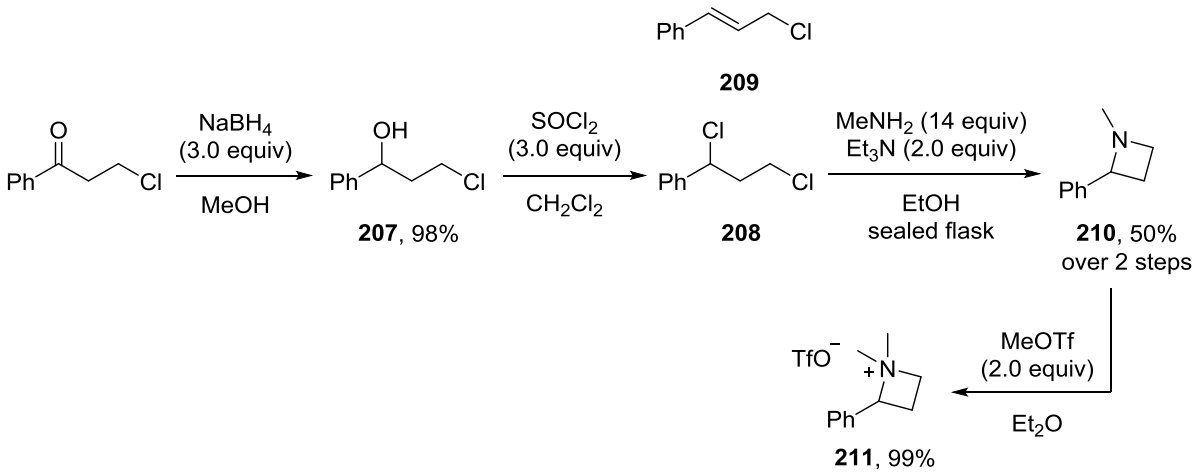
The work of Couty and David showed that stabilised cyano-substituted ylide **203** is configurationally unstable within seconds even at cryogenic temperature. However, no data was reported about the configurational stability of less stabilised ylides, such as phenyl-substituted ylide **178**.

With this background, we decided to investigate the synthesis of γ-amino tertiary boronic esters through the lithiation–borylation of phenyl-substituted azetidinium ion **177** and to test the viability of a stereospecific version of the process.

2.2. Results and Discussion

2.2.1. Synthesis of the Starting Material and Optimisation of the Lithiation–Borylation Reaction

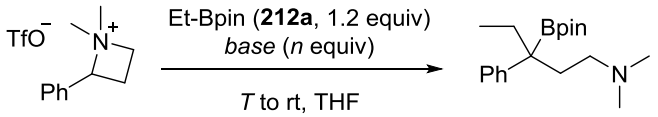
We first embarked on the synthesis of azetidinium triflate **211**, that was achieved in four steps starting from commercially available 3-chloro-1-propiophenone (Scheme 2.9). Reduction of the ketone gave 3-chloro-1-phenyl propanol **207**,[132] that was subsequently converted into the corresponding dichloride **208** by reaction with $SOCl_2$.[127] Crude **208** was then involved in a ring-closing double displacement reaction by treatment with methylamine to afford azetidine **210** in 50% yield over the two-steps.[127] The relatively low yield observed was due to a competing elimination process in the chlorination step, leading to the formation of chloro alkene **209** in considerable amounts (~20%). Final *N*-alkylation of azetidine **210** with methyl triflate gave desired triflate azetidinium salt **211** quantitatively.[130]



Scheme 2.9. Synthesis of phenyl-substituted azetidinium triflate **211**.

To probe the feasibility of the methodology, we attempted the generation of the corresponding azetidinium ylide from azetidinium triflate **211** by treatment with LiHMDS (1.7 equiv) in THF at −78 °C in the presence of ethyl pinacol boronic ester **212**, conditions analogous to those previously reported by Couty and David.[130] *In situ* trapping conditions were necessary to prevent decomposition of the generated ylide, which is known to be chemically unstable even at cryogenic temperatures. In fact, attempts to pre-form the ylide by treatment of azetidinium salt **211** with the base for only 10 minutes at −78 °C, followed by trapping with the boronic ester, only resulted in decomposition of the starting material. Upon warming the reaction mixture, generated under *in situ* conditions, to room temperature, 1,2-metallate rearrangement gave γ-dimethylamino tertiary boronic ester **213a**, which was isolated in 41% yield after chromatography on silica gel (Table 2.1, entry 1). Encouraged by this initial good result, we sought to optimise the process and find reaction conditions that gave improved yields. Attempts to perform the reaction at higher temperatures (−20 °C) resulted in only traces of the desired product (Table 2.1, entry 2). Warming the reaction mixture to reflux in order to favour the 1,2-metallate rearrangement or increasing the amount of base to 3.0 equivalents also led to disappointing results (Table 2.1, entry 3−4). Other non-nucleophilic bases were screened, among which KHMDS and LiTMP gave reduced yields (Table 2.1, entry 5−6); however, when LDA was used, desired tertiary boronic ester **213a** could be isolated in 57% yield (Table 2.1, entry 7). Further investigation showed that the addition of 2.0 equivalents of LDA gave the optimal result, with boronic ester **213a** being isolated in 69% yield after column chromatography (Table 2.1, entry 10).

Table 2.1. Optimisation of the lithiation−borylation reaction of azetidinium triflate **211**.



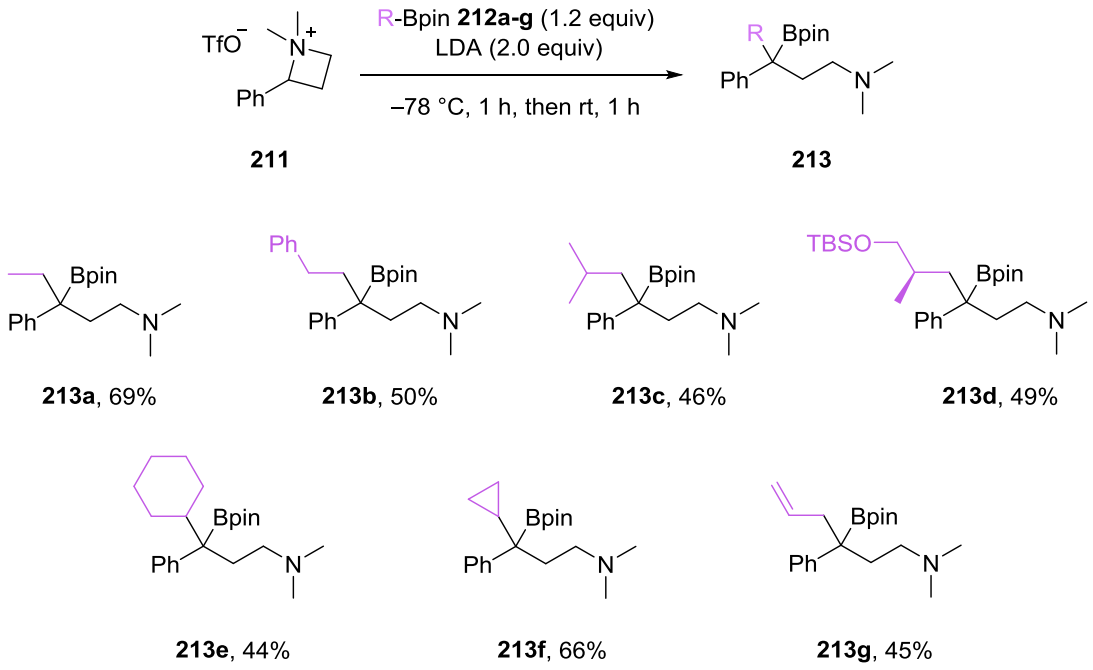
211 **213a**

Entry	Base	Equiv base	T (°C)	% Yield
1	LiHMDS	1.7	−78	41[b]
2	LiHMDS	1.7	−20	<5[b]
3[c]	LiHMDS	1.7	−78	23[d]
4	LiHMDS	3.0	−78	33[d]
5	KHMDS	1.7	−78	26[d]
6	LiTMP	1.7	−78	26[d]
7	LDA	1.7	−78	57[b]
8	LDA	1.2	−78	16[d]
9	LDA	1.5	−78	43[d]
10	LDA	2.0	−78	69[b]
11	LDA	3.0	−78	58[d]

[a] Reactions were performed using 0.2 mmol of **211**; [b] yield of isolated material; [c] after stirring the reaction mixture at −78 °C (1 h), the mixture was heated to reflux; [d] yield determined by ^{1}H NMR analysis of the crude mixture in the presence of 2,4-dimethoxybenzene as internal standard.

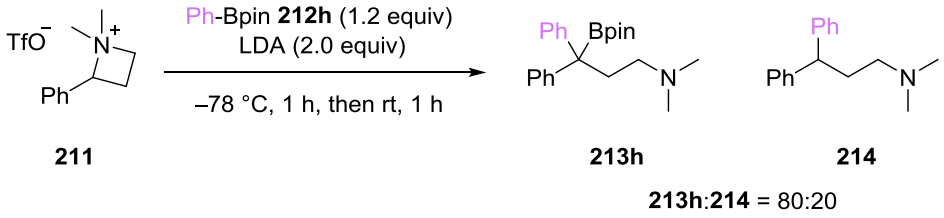
2.2.2. Substrate Scope

Having identified optimum conditions for the lithiation−borylation reaction we sought to explore the scope of the methodology, employing a range of different boronic esters (**212a-g**) (Scheme 2.10). Primary (**212a-d**) and secondary (**212e-f**) alkyl boronic esters were found to work well in the process, giving the corresponding γ-dimethylamino tertiary boronic esters **213a-f** in moderate to good yield. Allylic boronic ester **212g** was also tolerated in the process, giving the corresponding product in 45% yield.



Scheme 2.10. Scope of the alkyl boronic ester for the lithiation–borylation of **211**.

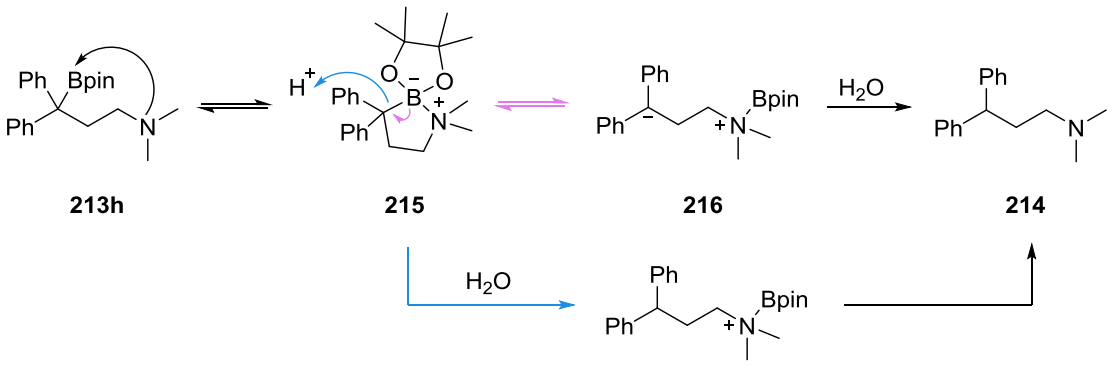
Aryl boronic esters were found to be more challenging substrates. When phenyl pinacol boronic ester **212h** was used under the optimised conditions, a mixture of the expected tertiary boronic ester **213h** and protodeboronated derivative **214** was isolated **213h**:**214** = 80:20), the two species being inseparable on silica gel (Scheme 2.11).



Scheme 2.11. Lithiation–borylation of **211** and boronic ester **212h** leading to a mixture of desired product **213h** and protodeboronated compound **214**.

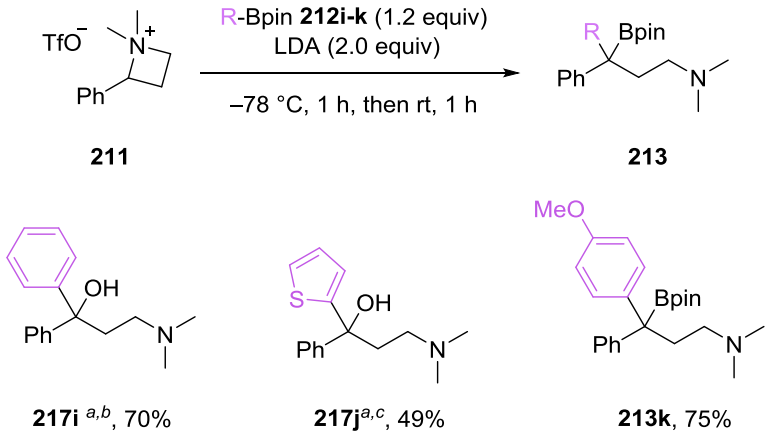
A plausible mechanism for the observed protodeboronation of **213h** is depicted in Scheme 2.12. Desired tertiary boronic ester **213h** is initially generated under the reaction conditions. Subsequent interaction between the dimethylamino group and the boron centre present on the molecule leads to the formation of a second boron "ate" complex **215**. Breaking of the C–B bond affords biaryl anion **216**, which is eventually converted into protodeboronated product **214**. The high stabilisation of dibenzylic anion **216** makes the process extremely facile when aromatic boronic esters are employed, while no protodeboronation was observed with alkyl boronic esters. The complexation of the boronic ester with the proximal dimethylamino group appears to play a key role in this process, since similar boronic esters missing this amino

functionality do not undergo protodeboronation so promptly.[56, 133] Alternatively, boronate complex **215** could be directly trapped by water to afford, after cleavage of the N–B bond, protodeboronated product **214**.



Scheme 2.12. Proposed mechanism for the protodeboronation of boronic ester **213h**.

Pleasingly, it was found that protodeboronation could be prevented by oxidising the unstable tertiary boronic esters **213i-j** *in situ*, prior to work-up, to afford the corresponding tertiary alcohols **217i-j** in good yields (Scheme 2.13). Electron-rich boronic ester **212k** was well tolerated in the process and gave the corresponding stable boronic ester **213k** in 75% yield with no protodeboronation observed, due to the presence of the electron-donor substituent making the intermediate dibenzylic anion less stable.

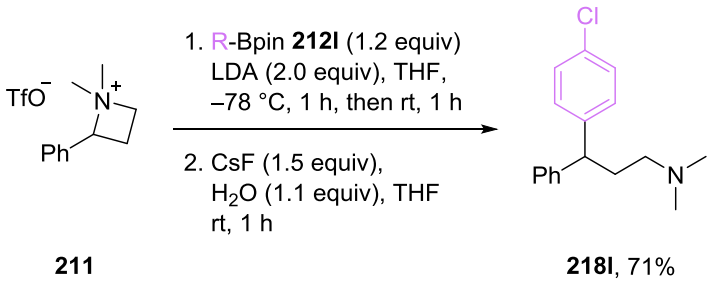


Scheme 2.13. Scope of the aryl boronic ester for the lithiation–borylation of **211**. [a] Isolation of the tertiary boronic ester was not possible due to protodeboronation; *in situ* oxidation using aqueous H_2O_2/NaOH allowed the isolation of the corresponding tertiary alcohol; [b] the *in situ* oxidation was performed at 0 °C; [c] the *in situ* oxidation was performed at −40 °C. [134]

In line with the mechanism proposed in Scheme 2.12, when *p*-chlorophenyl pinacol boronic ester **212l** was employed, the generated tertiary boronic ester was found to undergo extremely facile protodeboronation. Considering that γ-amino diarylmethines are found in many

biologically active molecules (Figure 2.1), we sought to find conditions to transform the tertiary boronic ester into the protodeboronated derivative directly.

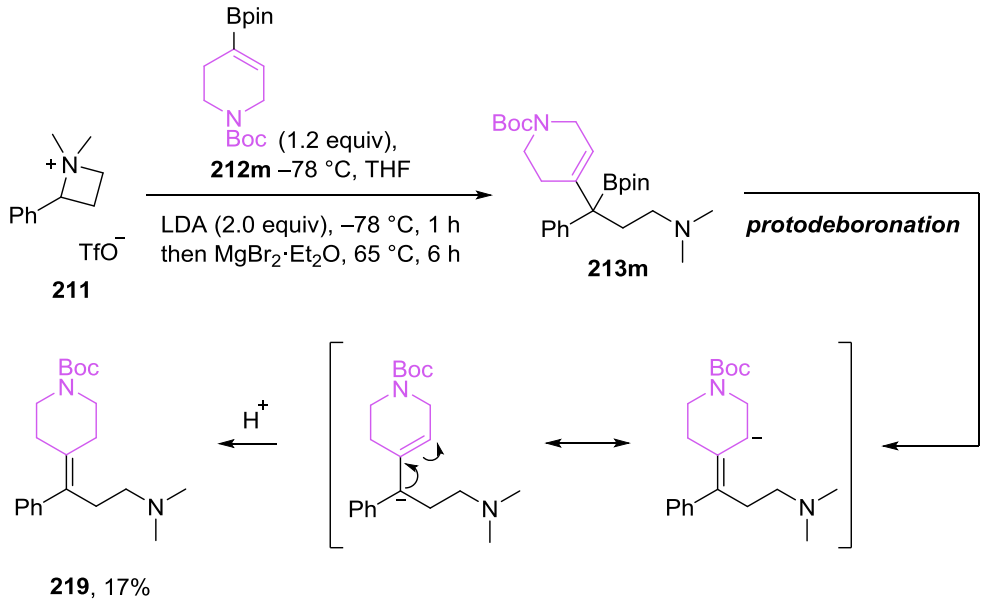
We therefore decided to apply our previously reported conditions for the protodeboronation of diarylalkyl boronic esters. Upon lithiation–borylation of **211** and **212l**, the reaction mixture was warmed to room temperature and CsF (1.5 equiv) was added, immediately followed by H_2O (1.1 equiv). Pleasingly, these conditions allowed the isolation of protodeboronated compound **218l** in 71% yield after chromatographic purification, with no trace of tertiary boronic ester left (Scheme 2.14).



211 **218l**, 71%

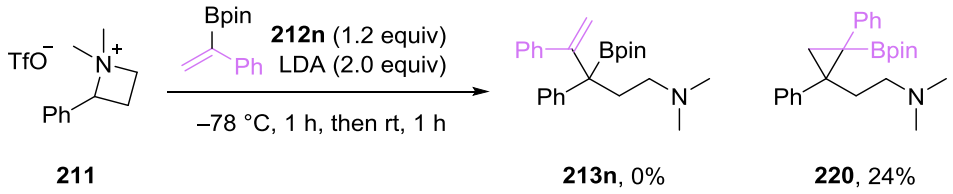
Scheme 2.14. Lithiation–borylation of azetidinium triflate **211** and boronic ester **212l** with *in situ* protodeboronation.

Vinyl boronic esters also proved to be challenging substrates for this transformation. When boronic ester **212m** was employed in the lithiation–borylation sequence, the expected product **213m** was not formed and unreacted starting material **212m** could be reisolated (Scheme 2.15). Since vinyl substituents are known to be poor migrating groups, $MgBr_2 \cdot Et_2O$ was added to the reaction mixture in order to increase the rate of 1,2-metallate rearrangement.[54] This led to full conversion of the boronate complex, but the only species that could be isolated after column chromatography was alkene **219**, although in low yield. This product could be accounted for by the generation of tertiary boronic ester **213m**, which underwent protodeboronation followed by isomerisation and protonation, to give compound **219**.



Scheme 2.15. Lithiation–borylation of azetidinium **211** and alkenyl boronic ester **212m**.

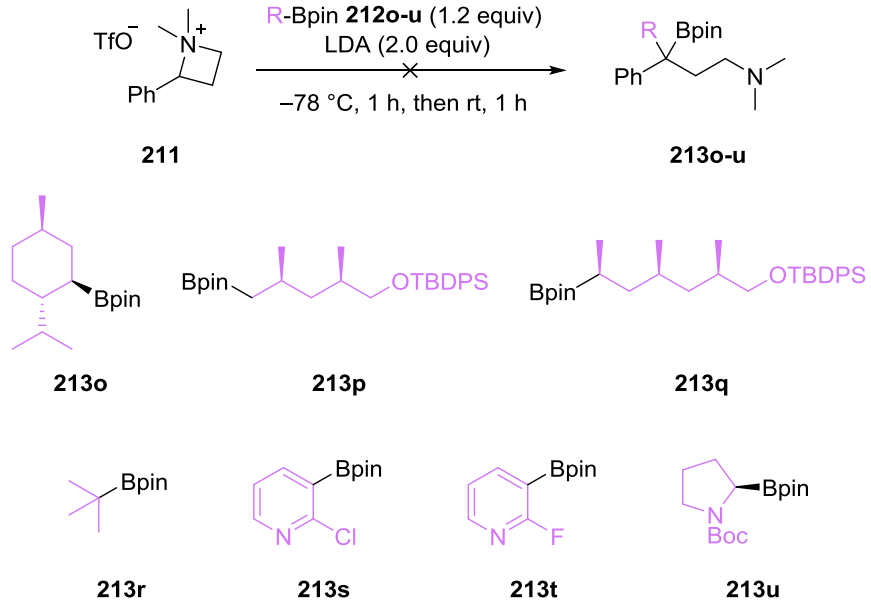
The low yield of isolated **219** might be explained considering the presence of acidic protons adjacent to the NBoc group on boronic ester **212m**, which might have also undergone deprotonation. Vinyl boronic ester **212n**, bearing no acidic protons, was therefore tested in the process; 1,2-metallate rearrangement was in this case performed at room temperature without any additive (Scheme 2.16). As before, expected tertiary boronic ester **213n** was not detected. However, cyclopropane **220** was isolated in 24% yield after column chromatography, therefore suggesting the formation of an intermediate carbene (for mechanistic discussion see § 2.2.4, Scheme 2.29).



Scheme 2.16. Lithiation–borylation of azetidinium **211** and alkenyl boronic ester **212n**.

Boronic esters **212o-u** were also tested in the lithiation–borylation sequence, but were found to be unreactive under these conditions (Scheme 2.17). In all the cases, the starting boronic esters **212o-u** were recovered and decomposition of azetidinium triflate **211** was observed, the high instability of the generated ylide therefore representing the limitation of this process. In particular, when more sterically hindered boronic esters, such as **212o-r**, were used, the formation of the boronate complex was probably more difficult, and the generated ylide decomposed before reacting. In the case of boronic esters bearing poor migrating groups, such

as **212s-u**, the boronate complex might have initially formed, but the difficult 1,2-metallate rearrangement might have made the process reversible, leading to the regeneration of the starting boronic esters together with decomposition of the ylide.

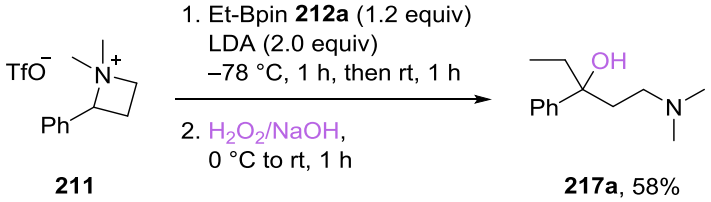


Scheme 2.17. Boronic esters that failed to undergo lithiation–borylation with azetidinium salt **211**.

2.2.3. Alternative Transformations of Tertiary Boronic Esters

To further demonstrate the synthetic utility of the generated tertiary boronic esters **213**, we sought to convert the C–B bond of **213a** into a variety of different functionalities.

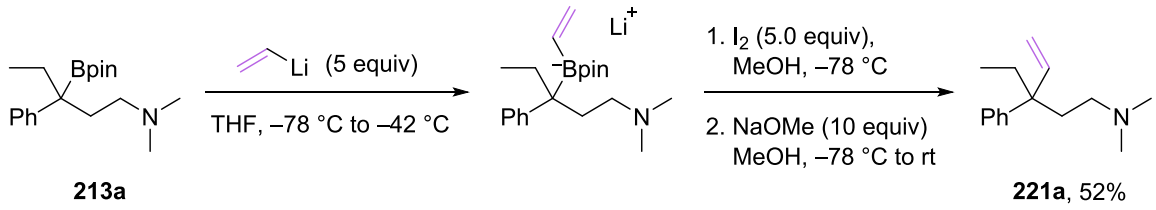
As already discussed for substrates **213j-k**, **213a** could be oxidised *in situ* using a mixture of H_2O_2/NaOH to afford tertiary alcohol **217a** in 58% yield (Scheme 2.18). Other oxidising conditions were also tested ($NaBO_3 \cdot 4H_2O$, $NaBO_3 \cdot 4H_2O$/CH_3COOH[135], oxone/acetone[136], $TMANO \cdot 2H_2O$[86]), but were found to be less effective and led to partial oxidation of the tertiary amine group.



Scheme 2.18. Lithiation-borylation of azetidinium **211** and boronic ester **212a** with *in situ* oxidation.

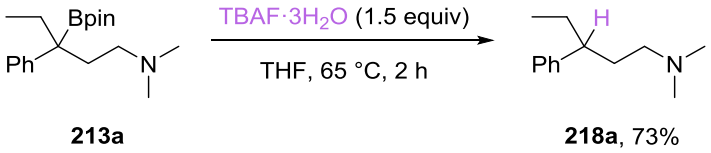
Zweifel olefination of tertiary boronic ester **213a** was also attempted to convert the C–B bond into a terminal alkene (see § 1.7.3). When **213a** was reacted under previously optimised Zweifel olefination conditions using 4.0 equivalents of vinylmagnesium bromide,[97] only traces

of desired alkene **221a** could be observed. However, the use of 5 equivalents of vinyllithium, freshly prepared by addition of *n*-BuLi to tetravinyl stannane, gave, after addition of iodine and NaOMe in MeOH, desired terminal alkene **221a**, which could be isolated in 52% yield after column chromatography (Scheme 2.19).



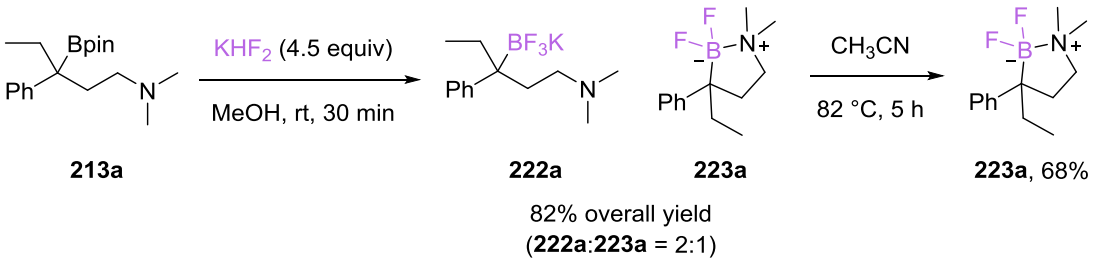
Scheme 2.19. Zweifel olefination of tertiary boronic ester **213a**.

As already mentioned, protodeboronation of dibenzylic tertiary boronic ester **213l** proved to be extremely facile and was achieved using CsF and H_2O.[94] Following the procedure previously reported by Aggarwal and co-workers, protodeboronation of aryl dialkyl boronic ester **213a** was instead carried out using TBAF·$3H_2O$ as a more reactive fluoride source (Scheme 2.20). Under these conditions, protodeboronated product **218a** was isolated in 73% yield after column chromatography.



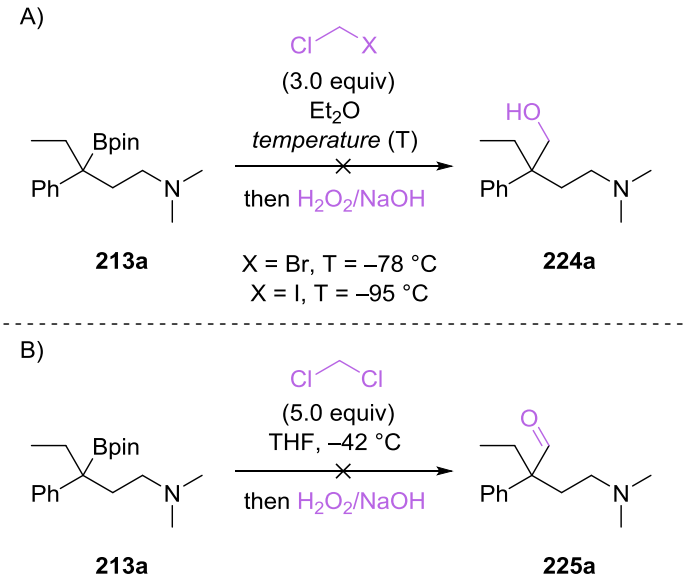
Scheme 2.20. Protodeboronation of tertiary boronic ester **213a**.

We were also interested in transforming tertiary boronic ester **213a** into the corresponding trifluoroborate salt **222a**. Interestingly, the reaction of **213a** with KHF_2 in MeOH under previously reported conditions,[89] gave a mixture of expected trifluoroborate salt **222a** and intramolecularly complexed difluoroborane **223a** in 2:1 ratio and 82% overall yield, as confirmed by both ^1H and ^{19}F NMR (Scheme 2.21). Difluoroborane **223a** must have been generated by spontaneous intramolecular ligand exchange with the proximal tertiary amine, similar to what had previously been observed by Luisi and Florio.[137] Pleasingly, heating the mixture at reflux in CH_3CN resulted in the complete conversion into difluoroborane **223a**, that was subsequently isolated in 67% yield after column chromatography.



Scheme 2.21. Attempted conversion of tertiary boronic ester **213a** into trifluoroborate salt **222a**.

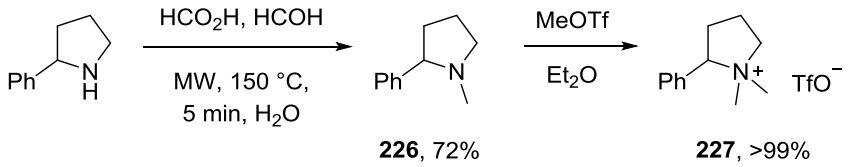
Matteson homologation of boronic ester **213a** was finally attempted (see § 1.2). The *in situ* generation of chloromethyllithium from chlorobromomethane and *n*-BuLi at −78 °C, followed by oxidation with H_2O_2/NaOH did not lead to the formation of desired alcohol **224a** and only starting boronic ester **213a** was reisolated (Scheme 2.22A). Using the more reactive chloroiodomethane as the carbenoid precursor at lower temperature (−95 °C) or adding $BF_3{\cdot}Et_2O$ as an activator did not give improved results and no expected product **224a** could be detected. A possible explanation is that the coordination of the pendant tertiary amine to boron deactivates the boronic ester, therefore inhibiting its reactivity with chloromethyllithium. Chloromethyllithium is known to be highly chemically unstable with respect to decomposition even at very low temperature,[138-139] and immediate trapping is necessary to prevent its decomposition. Attempts to use dichloromethyllithium, generated *in situ* by deprotonation of CH_2Cl_2 by LDA at −42 °C,[15] also met with failure and desired aldehyde **225a** was not detected (Scheme 2.22B).



Scheme 2.22. Attempted Matteson homologation of tertiary boronic ester **213a**.

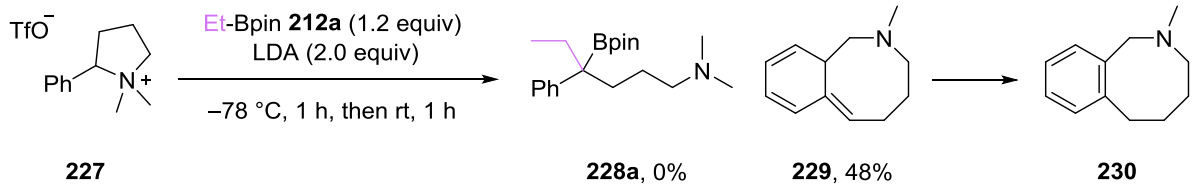
2.2.4. Mechanistic Studies

We then sought to study the mechanism of the transformation and in particular we were interested in investigating whether the release of ring-strain is key for the 1,2-metallate rearrangement to occur. Thus, we prepared the higher ring-size homologous pyrrolidinium triflate **227** and reacted it under previously optimised conditions for the lithiation−borylation−ring-opening of azetidinium salts. Triflate **227** was easily synthesised in three steps from commercially available 2-phenylpyrrolidine, that was subjected to reductive alkylation to give 1-methyl-2-phenylpyrrolidine **226** in 72% yield;[140] subsequent alkylation with MeOTf gave desired pyrrolidinium triflate **227** quantitatively (Scheme 2.23).



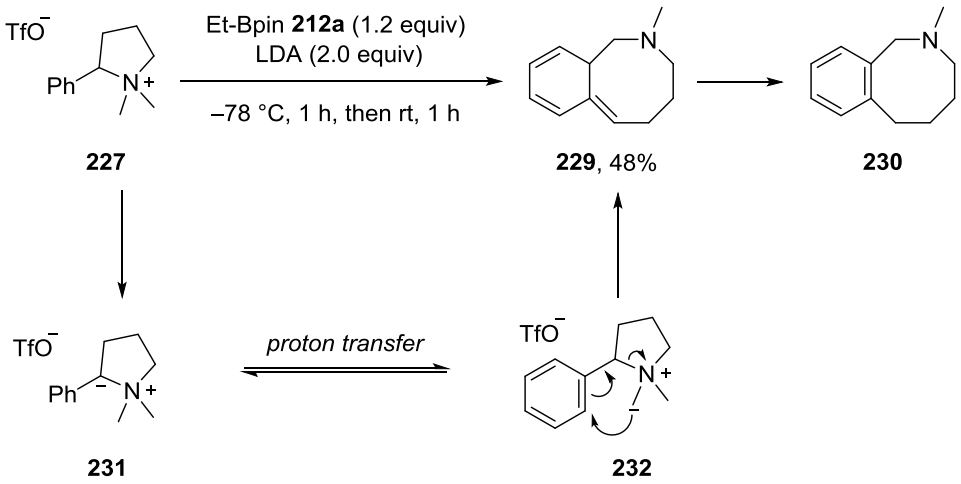
Scheme 2.23. Synthesis of pyrrolidinium triflate **227**.

A solution of pyrrolidinium salt **227** and ethyl pinacol boronic ester **212a** in THF was treated with LDA at −78 °C (Scheme 2.24). After warming the reaction mixture to room temperature, no expected tertiary boronic ester **228a** was observed; however, 1,2,3,4,7,8-hexahydroazocine **229** was initially isolated in 48% yield, but it was found to rapidly isomerise to give the corresponding benzo-fused 1,2,3,4,5,8-hexahydroazocine **230**.



Scheme 2.24. Lithiation−borylation of pyrrolidinium **227** and boronic ester **212a**.

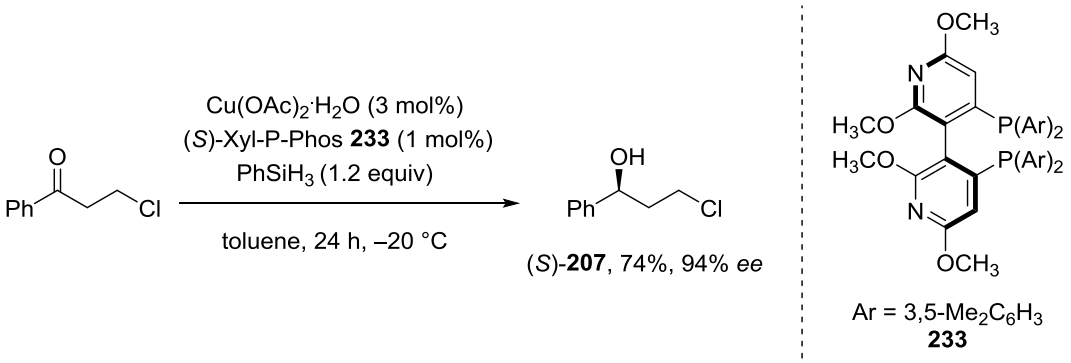
Azocine **229** is presumably formed through a Sommelet−Hauser rearrangement (Scheme 2.25). Benzylic ylide **231** is initially generated; subsequent proton transfer affords methylenic ylide **232** that quickly undergoes a 2,3-sigmatropic rearrangement to give azocine **229**.[141]



Scheme 2.25. Competing Sommelet–Hauser rearrangement of pyrrolidinium ylide **231**.

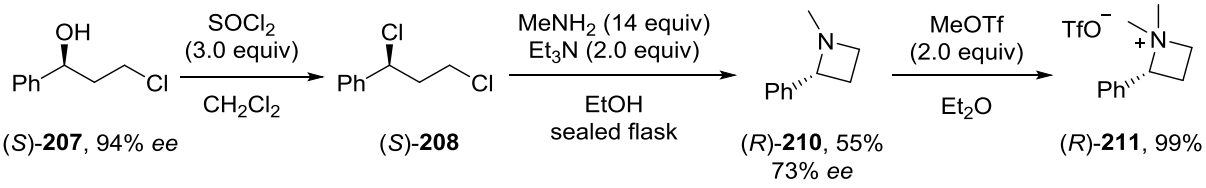
This result suggests that the trapping of the generated benzylic ylide **231** with the boronic ester might be slower than the Sommelet–Hauser rearrangement. Alternatively, benzylic ylide **231** is initially trapped by ethyl pinacol boronic ester, but the 1,2-metallate rearrangement is too slow and the boronate complex fragments to give back ylide **231** and the boronic ester. In this scenario, the release of ring-strain seems to be an essential factor for the success of the 1,2-metallate rearrangement of azetidinium triflate **211**.

We then turned our attention towards the configurational stability of the azetidinium ylide generated form enantioenriched azetidinium triflate (*R*)-**211**. (*S*)-3-Chloro-phenyl-1-propanol (*S*)-**207** was initially synthesised through the asymmetric reduction of commercially available 3-chloropropiophenone with $PhSiH_3$ in the presence of a copper salt ($CuOAc_2 \cdot 2H_2O$) and chiral ligand (*S*)-P-Phos **233** (Scheme 2.26).[142] Under these conditions, alcohol (*S*)-**207** was isolated in 74% yield and 94% *ee*.



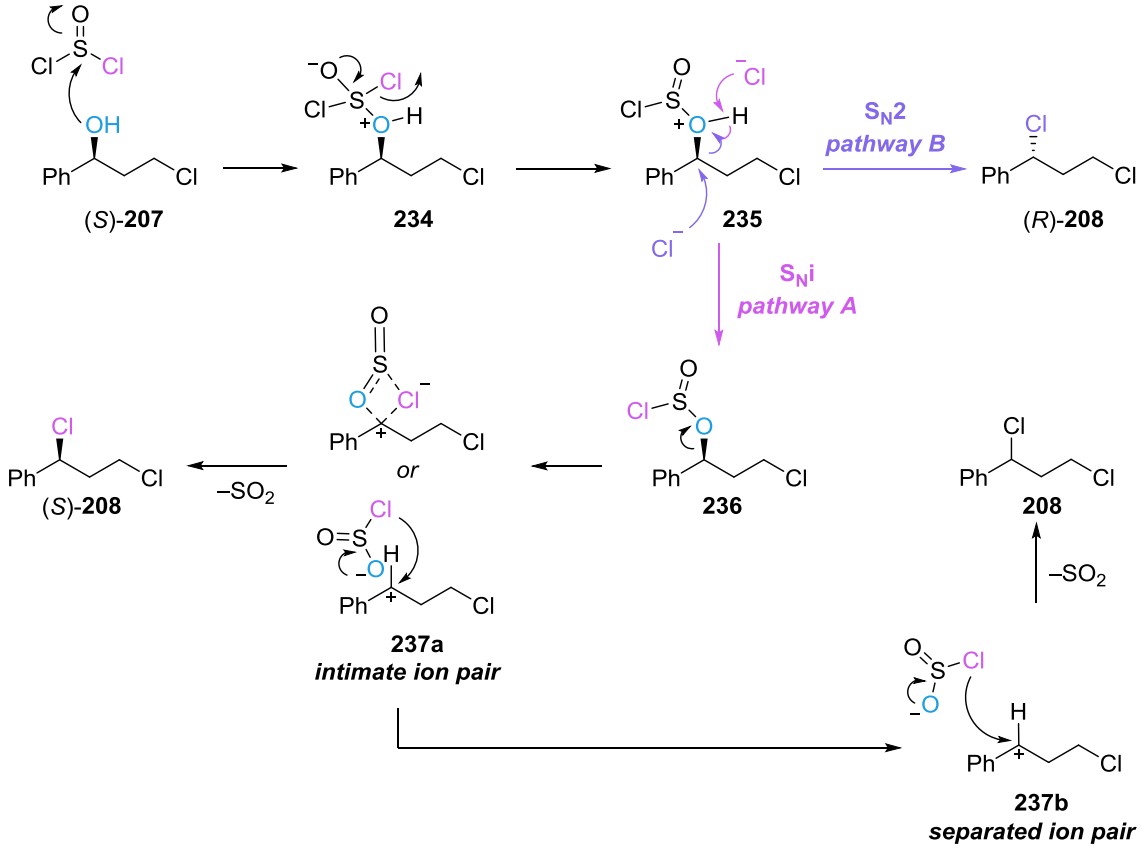
Scheme 2.26. Copper-catalysed asymmetric reduction of 2-chloropropiophenone.

Enantioenriched azetidinium ion (*R*)-**211** was then obtained from alcohol (*S*)-**207** through the usual ring-closing double displacement reaction of intermediate dichloride **208**[127] followed by *N*-alkylation (Scheme 2.27).



Scheme 2.27. Synthesis of enantioenriched azetidinium triflate (*R*)-**211**.

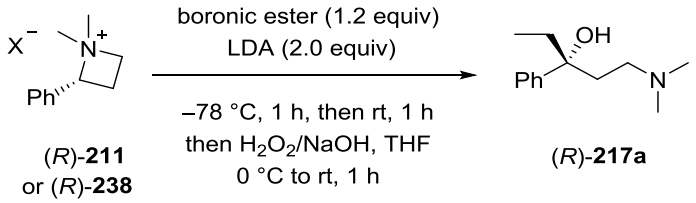
The absolute configuration of azetidine (*R*)-**211** was assigned assuming that the reaction with $SOCl_2$ occurred with retention of configuration,[143] while the subsequent cyclisation step occurred with inversion of configuration. The slight erosion in *ee* might derive from partial racemisation in the reaction with $SOCl_2$ owing to a possible S_N2 mechanism (Scheme 2.28, pathway B) competing with the predominant S_Ni mechanism (Scheme 2.28, pathway A). Additionally, partial conversion of intimate ion-pair **237a** to solvent-separated ion pair **237b** would generate a planar cationic intermediate, eventually leading to racemic dichloride **208**.



Scheme 2.28. Proposed mechanism of the chlorination of secondary alcohols with $SOCl_2$ through a S_Ni pathway (A) occurring with retention or through a S_N2 pathway (B) occurring with inversion.

A mixture of azetidinium salt (*R*)-**211** and ethyl pinacol boronic ester **212a** in THF was then subjected to lithiation–borylation conditions using LiHMDS as the base; unfortunately, tertiary alcohol (*R*)-**217a** isolated after *in situ* oxidation was found to be racemic, therefore revealing the configurational instability of the generated ylide (Table 2.2, entry 1).

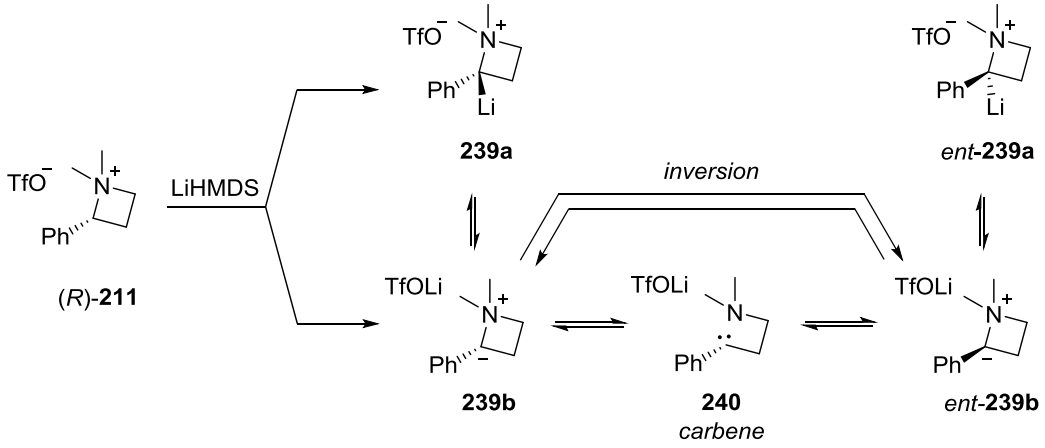
Table 2.2. Investigation of the enantiospecificity of the lithiation–borylation–oxidation reaction of (*R*)-**211**.[a]



Entry	Boronic ester	X	Base	Solvent	% Yield	% *ee*
1	Et-Bpin	$F_3CSO_3^-$	LiHMDS	THF	27	0
2	Et-Bpin	$F_9C_4SO_3^-$	LiHMDS	TBME	37	0
3	Et-Bneop	$F_9C_4SO_3^-$	LiHMDS	TBME	26	0
4	Et-Bpin	$F_9C_4SO_3^-$	LDA	TBME	n.d.	0

[a] Reactions were performed using 0.3 mmol of azetidinium salt; n.d. = not determined.

This lack of configurational stability exhibited by azetidinium ion (*R*)-**211** can be explained considering the presence of a positive charge on the adjacent nitrogen atom that increases the stability of the carbanionic centre. Lithium stabilised ylide **239a** would therefore dissociate to form solvent-separated ion pair **239b**, which, if pyramidilised, undergoes rapid inversion, with migration of the lithium cation from one enantiotopic face to the other, leading to the formation of enantiomeric ylide *ent*-**239** (Scheme 2.29). The process could also occur *via* ring-opened intermediate carbene **240**.



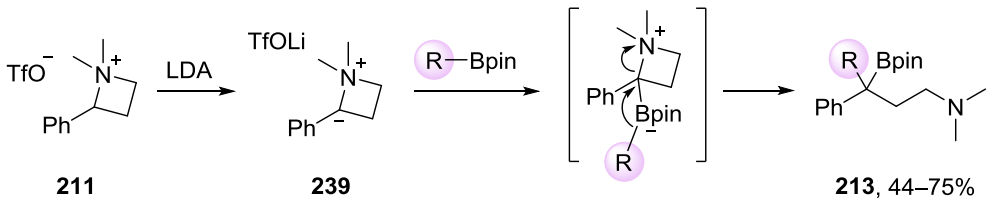
Scheme 2.29. Possible mechanism of racemisation of ylide **239**.

Solvent-mediated dissociation of lithium-stabilised anions is known to be favoured in coordinating solvents.[144] We therefore reasoned that the use of a less-coordinating solvent than THF would increase the configurational stability of ylide **239**. The lithiation−borylation−oxidation sequence was therefore performed in TBME. In this case, the corresponding nonaflate salt of (*R*)-**238**, simply accessed by counter-anion exchange using potassium nonaflate, was employed, since it was found to possess increased solubility in TBME than the corresponding triflate. Unfortunately, the process failed to give improved results and alcohol **217a** was isolated as the racemate (Table 2.2, entry 2). The very poor solubility of azetidinium salts (*R*)-**211** and (*R*)-**238** in most of the common organic solvents limited our choice and attempts of performing the reaction in even less-coordinating solvents, such as toluene or hexane, met with failure. The use of LDA in the place of LiHMDS as the base or the use of the less sterically hindered neopentylglycol boronic ester (EtBneop) also failed to induce enantioselection and only racemic alcohol **217a** was isolated (Table 2.2, entries 3−4).

Evidence for the configurational instability of lithium stabilised ylide **239** was thus revealed in both coordinating and less coordinating solvents, such as TBME. This suggests that racemisation occurs through the formation of a solvent-separated ion pair, that undergoes subsequent inversion through pyramidilisation or *via* formation of an intermediate carbene (Scheme 2.29); a cooperation of the two mechanisms is also not excluded. The process is therefore difficult to avoid, especially considering the poor solubility of azetidinium salts in less polar solvents. Moreover, the formation of intermediate carbene **240** was supported by the formation of cyclopropane **220** when the lithiation−borylation−oxidation sequence was performed using boronic ester **212n** (see § 2.2.2, Scheme 2.16). In this case, the rate of the 1,2-metallate rearrangement is too slow and the boronate complex dissociates to give a putative intermediate carbene, which can subsequently react with the alkene moiety on **212n**.

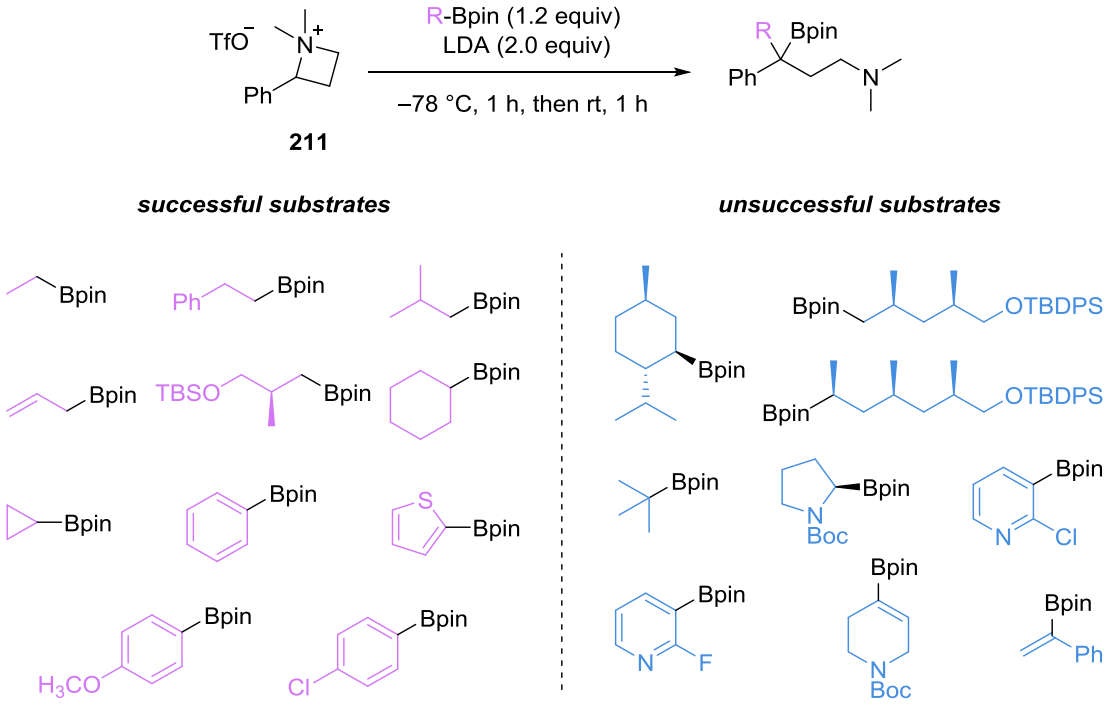
2.3. Conclusions

The lithiation−borylation−ring-opening of 2-phenyl azetidinium salt **211** has been efficiently developed. Ylide **239** was generated *in situ* by deprotonation of azetidinium salt **211** with LDA and immediately trapped with different pinacol boronic esters to give acyclic γ-dimethylamino tertiary boronic esters **213** in moderate to good yield (Scheme 2.30). This transformation is believed to occur through the initial formation of a zwitterionic boronate complex, which, upon warming to higher temperature, undergoes a ring-opening 1,2-metallate rearrangement. The relief of the ring strain proved to be key for the process to happen.



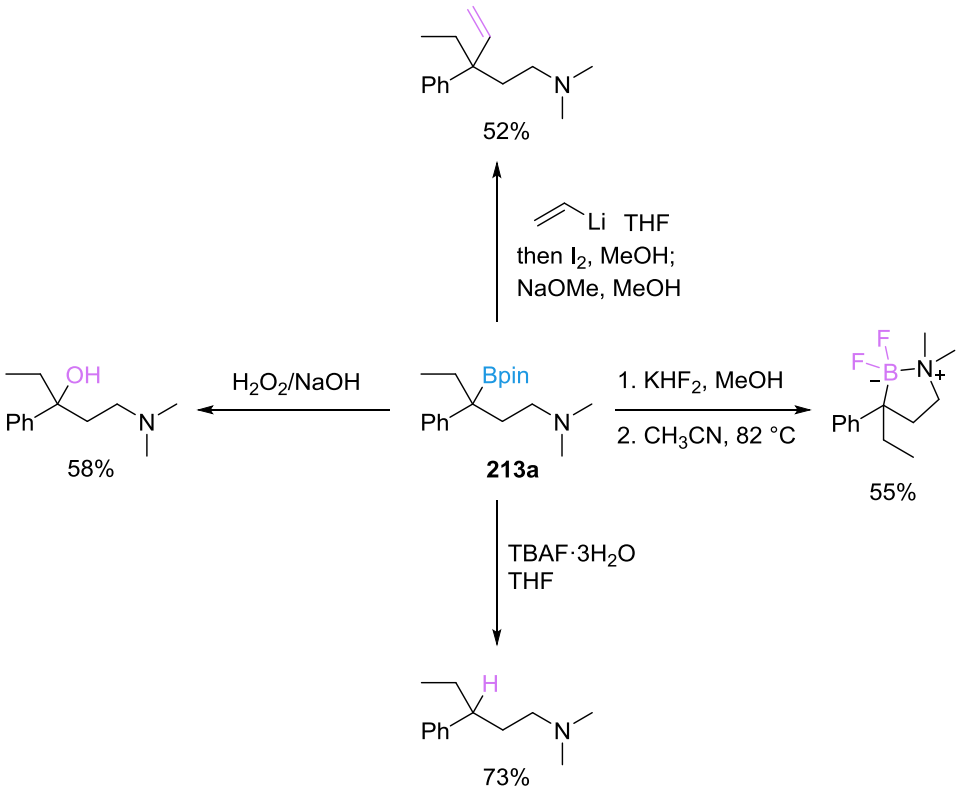
Scheme 2.30. Synthesis of 3-aryl-1-aminopropane derivatives through lithiation–borylation–ring-opening of azetidinium ions.

The reaction shows good scope (Scheme 2.31). Various primary and secondary alkyl boronic ester could be successfully employed, therefore providing access to different substituted 3-aryl-1-aminopropane derivatives, a structural motif that can be found in many important bioactive molecules. Aromatic boronic esters were also found to work well in the process, but the generated tertiary boronic esters were found to be unstable and underwent fast protodeboronation under reaction conditions. However, *in situ* oxidation with H_2O_2/NaOH allowed the isolation of the corresponding tertiary alcohols in good yield. Some limitations in the scope of this reaction have also been highlighted. In particular, the use of more sterically hindered boronic esters only resulted in the decomposition of the generated ylide, the boronate complex formation presumably being too slow. Similarly, slower migrating groups attached to boron led to a reversible boronate complex formation, eventually resulting in the decomposition of the ylide.



Scheme 2.31. Substrate scope of the boronic esters for the lithiation–borylation of azetidinium triflate **211**.

Several transformations of the resulting tertiary boronic esters have also been performed, including protodeboronation and Zweifel olefination (Scheme 2.32). Attempts to convert tertiary boronic ester **213a** into the corresponding trifluoroborate salt led instead to the isolation of intramolecularly complexed difluoroborane.



Scheme 2.32. Different transformations of tertiary boronic ester **213a**.

In situ formed azetidinium ylides proved to be configurationally unstable, presumably due to the formation of a solvent-separated ion pair, highly favourable in coordinating solvents. The ylide would therefore rapidly interconvert, through either pyramidilisation or *via* a ring-open carbene species. The intermediacy of a carbene was supported by the isolation of a cyclopropyl pinacol boronic ester when a sterically hindered vinyl boronic ester was employed in the reaction.

3. Stereoselective Iterative Homologations of Boronic Esters With α-Sulfinyl Benzoates

Parts of the work described in this chapter have been adapted from the following article:

Casoni, G., Kucukdisli, M., Fordham, J. M., Burns, M., Myers, E. L., Aggarwal, V. K., *J. Am. Chem. Soc.* **2017**, *139*, 11877−11886.

This project was conducted in collaboration with Dr. M. Kucukdisli and J. M. Fordham; their contributions to the project are highlighted within this chapter using footnotes and are included to provide a complete picture of the work.

3.1. Introduction and Project Aims

In nature, many enantioenriched substituted linear molecules, a small selection of which is depicted in Figure 3.1, possess an important biological profile and play a major role in improving and sustaining our standard of life. Despite their great potential, they still represent a tiny minority of the vast libraries of small molecules selected to be screened as potential drug candidates, with 2D heterocyclic small molecules still being the preferred choice. It is recognised that there is a great need to supplement these libraries by introducing more stereochemically rich 3D molecules.[145] The reason why these molecules are poorly represented is that they are difficult to synthesise in stereochemically pure form and in large quantities. To address this problem, we planned to develop an automated solution-phase method with inline purification that would potentially allow non-experts to prepare libraries of molecules bearing linear chains of carbon atoms where each atom can contain a substituent of any absolute and relative orientation. These carbon chains will be grown one carbon at a time by sequential addition of a readily available carbenoid precursor, which would be non-toxic and bench stable. Once generated *in situ*, the metallated carbenoid would be linked to the growing chain through a metalation−borylation reaction. The required carbenoid precursor must meet several criteria to make this automated process possible. First, it has to contain a group that can be rapidly and stereospecifically transformed into a reactive metal group; second, it has to contain a suitable leaving group; third, it must be synthesised in very high levels of enantiopurity to avoid the formation of undesired diastereoisomers (see § 1.5.5).

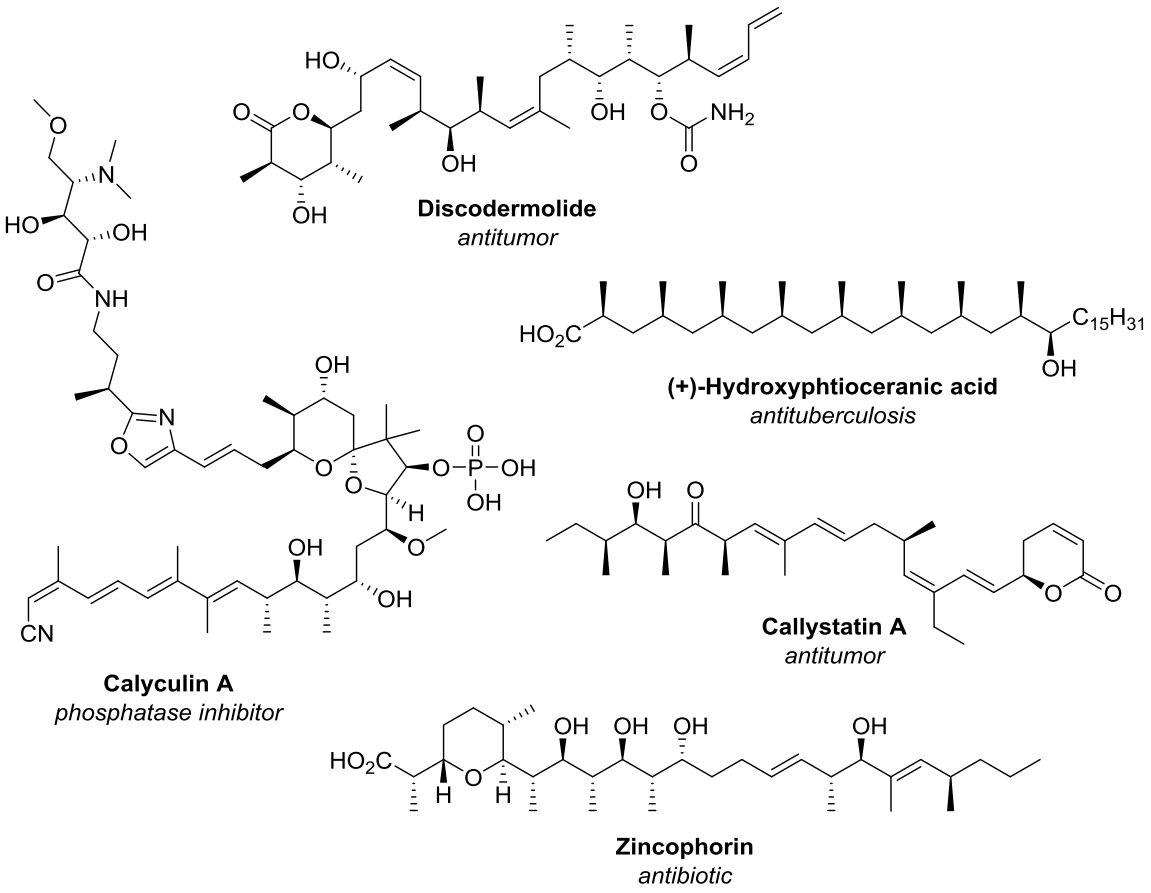


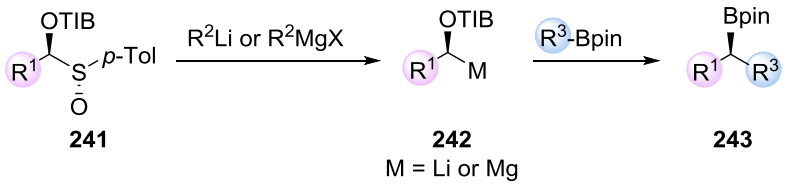
Figure 3.1. Enantioenriched substituted linear molecules possessing biological activity.

Aggarwal and co-workers have demonstrated that enantioenriched α-stannyl benzoates are excellent precursors to the α-lithiated benzoates necessary to perform iterative homologations of boronic esters, and substituted linear chains of carbon atoms could be accessed as single enantio- and diastereoisomers with very high levels of efficiency.[73] Unfortunately, α-stannyl benzoates possess a number of negative attributes that make their use undesirable. First, they are synthesised from highly toxic reagents, they are relatively toxic themselves and they give rise to toxic by-products when employed in lithiation−borylation reactions. Moreover, to be synthesised in very high levels of enantiopurity, they require the use of (+) and (−)-sparteine, the supply of which has decreased to the extent where they have become extremely expensive. Finally, only the methyl-substituted carbenoid precursors are crystalline, which means it is difficult to prepare other derivatives in highly enantiopure form. As an alternative, inspired by the α-chloro sulfoxides prepared by Blakemore and co-workers (see § 1.4.2),[29-30] we sought to employ substituted α-sulfinyl benzoates as precursors to α-metallated carbenoids, which were attractive owing to their relative non-toxicity when compared to the corresponding α-stannyl derivatives. Moreover, moving from the chloride to the triisopropyl benzoate leaving group

would avoid the side-reactions that were often observed in Blakemore's homologation protocol.

The first objective of this project is to prepare a range of different substituted α-sulfinyl benzoates. As aforementioned, the required carbenoid precursors must be generated in very high levels of enantiopurity and, ideally, without using any chiral diamine.

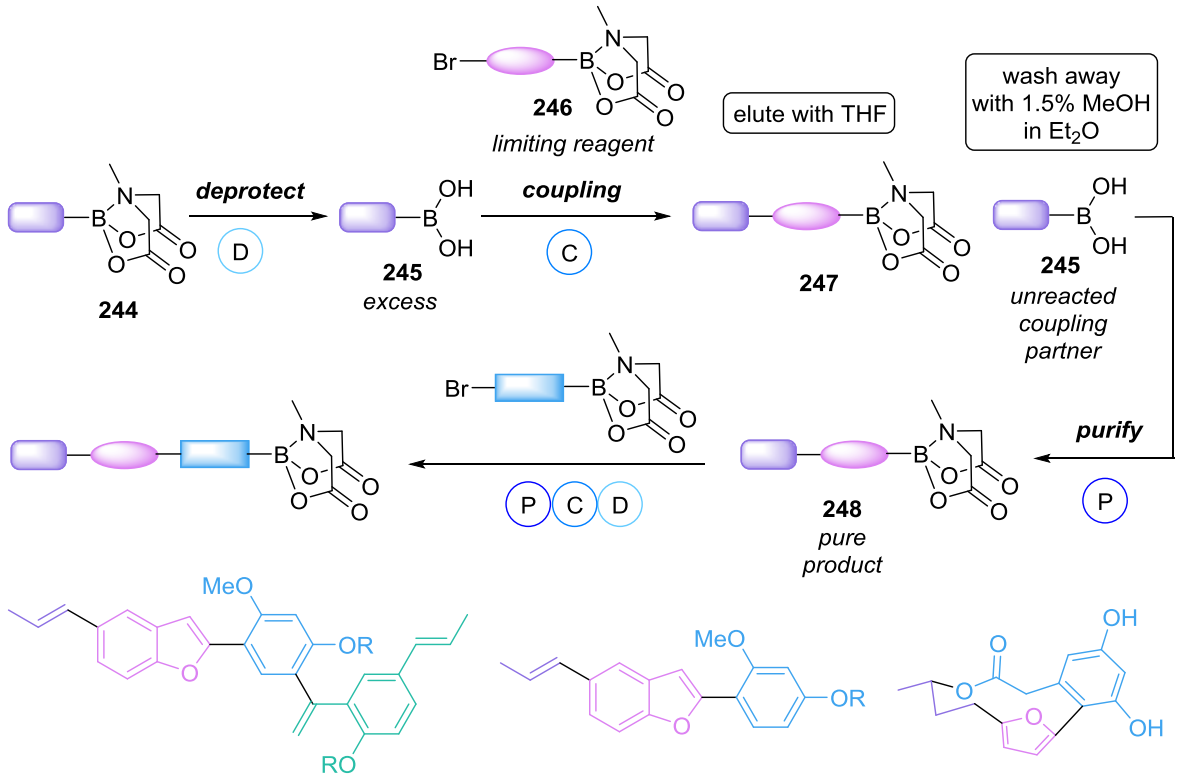
With the necessary α-sulfinyl benzoates **241** in hand, the efficiency with which they undergo sulfoxide–metal exchange will be investigated (Scheme 3.1). The α-metallated carbenoid **242** will be generated by treatment with different organolithium reagents (*n*-BuLi, *s*-BuLi, *t*-BuLi) and Grignard reagents (*i*-PrMgCl, *i*-PrMgCl·LiCl) under various conditions (solvent, concentration, temperature, stoichiometry). Trapping of the generated metallated benzoate **242** with different boronic esters will afford, after 1,2-metallate rearrangement, the homologated product **243**. In particular, high levels of conversion and stereospecificity are targeted.



Scheme 3.1. Proposed homologation of boronic esters using metal benzoates generated by sulfoxide–metal exchange.

Once the optimal conditions for effecting metalation–borylation reactions that give one-carbon homologated boronic esters in good yield and very high levels of enantioselectivity have been identified, the next objective will be to test the viability of an iterative process. This will be done by performing sequential homologations of boronic esters without intervening chromatographic purification, therefore demonstrating the possibility of rendering the protocol automatable. One of the most difficult parts of automating a synthetic process is the incorporation of a purification protocol that is sufficiently general that a wide range of products can be obtained in high purity. For example, the research group of Burke has recently developed a novel broadly applicable and fully automated method for clipping together *N*-methyliminodiacetic acid (MIDA) boronates through iterative cycles of deprotection, coupling and purification (Scheme 3.2).[146] MIDA boronate **244** was initially deprotected to yield free boronic acid **245** which was subsequently engaged in a coupling reaction with building block **246** to generate homologated MIDA boronate **247**. At this point, a general purification protocol was successfully implemented, exploiting the peculiar minimal mobility of MIDA boronates on silica gel chromatography when eluted with a mixture of MeOH/Et_2O,

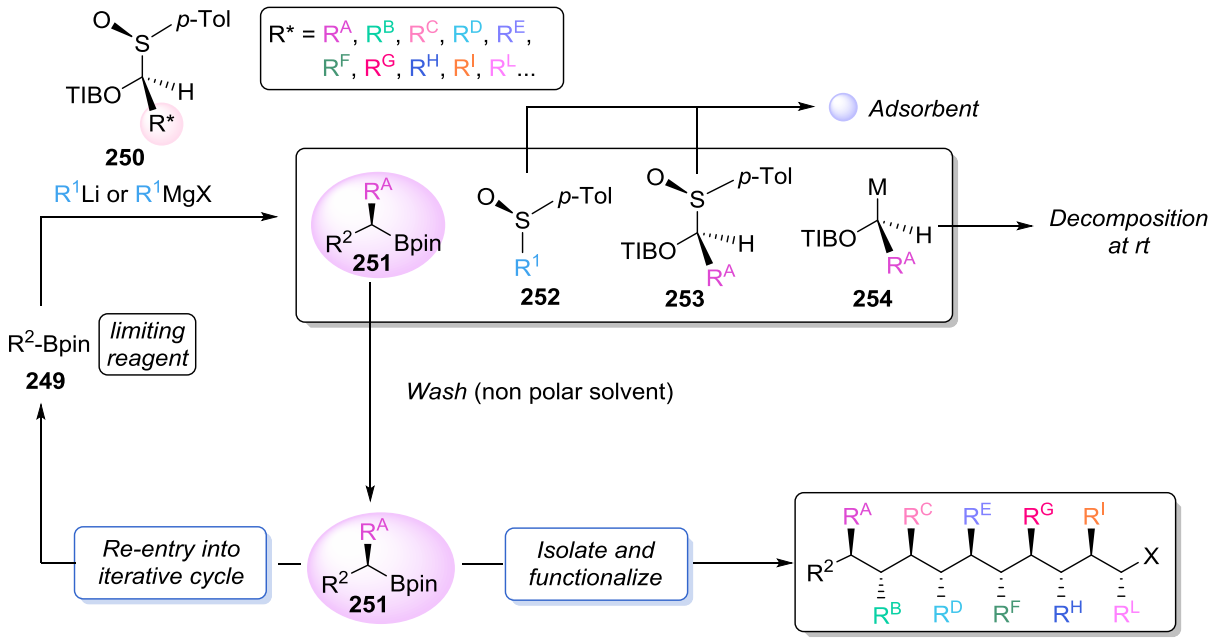
while they rapidly drop off when THF is added. A simple filtration of the crude reaction mixture over silica, washing with MeOH/Et_2O, allows the removal of the excess of reagents and by-products, while the desired MIDA boronate stays temporarily loaded; switching the eluent to THF releases the MIDA boronate, which is sufficiently pure to undergo a second cycle of deprotection, coupling and purification.



Scheme 3.2. Burke's molecule-making machine.

In the case of our proposed iterative homologation of boronic esters using α-sulfinyl benzoates, we suggest a novel automatable purification method relying on the difference in polarity between sulfoxides and boronic esters. The main steps in our envisaged automated metalation–borylation process would be as follows (Scheme 3.3). First, a solution of α-sulfinyl benzoate **250** would be cooled to a sub-zero temperature. Upon addition of an organometallic reagent (organolithium or Grignard reagent), α-metallo benzoate **254** would form within minutes, together with sulfoxide by-product **253**. After addition of boronic ester **249**, which would be the limiting reagent, an "ate" complex would be generated; then, upon warming to higher temperature, the boronate complex would undergo 1,2-metallate rearrangement to give homologated boronic ester **251**. By simply filtering the crude reaction mixture through a plug of silica gel and washing with a sufficiently non-polar eluent should allow desired boronic ester **251** to be eluted, while the excess of starting material **253** and by-product **252** would stay loaded on the silica gel. The excess of metallated benzoate **254** would instead decompose upon

warming to room temperature. Without any further manipulation or purification, boronic ester **251** could be introduced into a second cycle of metalation−borylation with another α-sulfinyl benzoate to elongate the chain by a further carbon atom, and this cycle will be repeated until the target molecule is eventually generated.



Scheme 3.3. Proposed automated iterative homologations of boronic esters with inline purification.

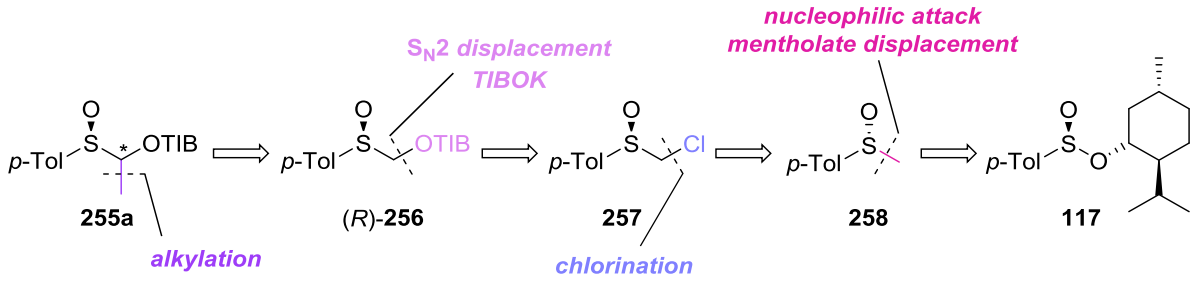
With the chemistry element of the plan complete, the long-term aim of this project is the design and realisation of an apparatus (glassware, syringe pumps, solvent pumps, cooling devices) able to perform iterative metalation−borylation reactions with inline purification and with the least amount of user manipulations, so that non-experts in application-based scientific fields will be able to grow complex linear molecules by themselves.

3.2. Results and Discussion

3.2.1. Synthesis of Enantioenriched α-Sulfinyl Benzoates

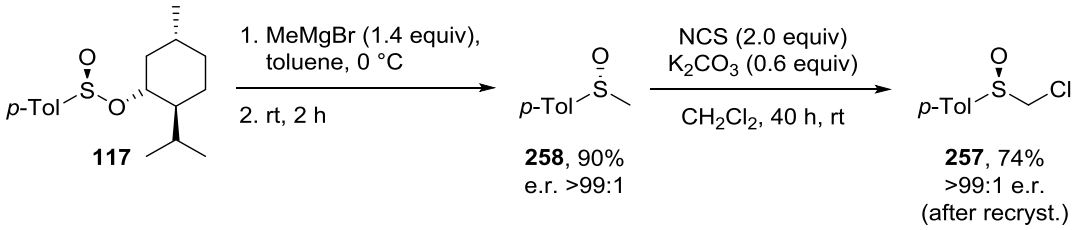
We first concentrated our efforts towards the synthesis of highly enantioenriched α-sulfinyl benzoates to be used as precursors for chiral metal carbenoids. We initially approached the synthesis of benzoate **255a** using the strategy shown in Scheme 3.4. Chiral sulfoxide **258** could be generated from commercially available Andersen's sulfinate **117** by displacement of mentholate with a nucleophilic methyl source. Subsequent chlorination of **258** would afford enantioenriched α-chlorosulfoxide **257**, which would then undergo an S_N2 reaction with triisopropyl benzoic acid to give intermediate sulfoxide **256**. Finally, an alkylation reaction in

the position alpha to the sulfinyl group would afford both diastereoisomers of chiral α-sulfinyl benzoate **255a**.



Scheme 3.4. Proposed retrosynthetic analysis of α-sulfinyl benzoate **255**.

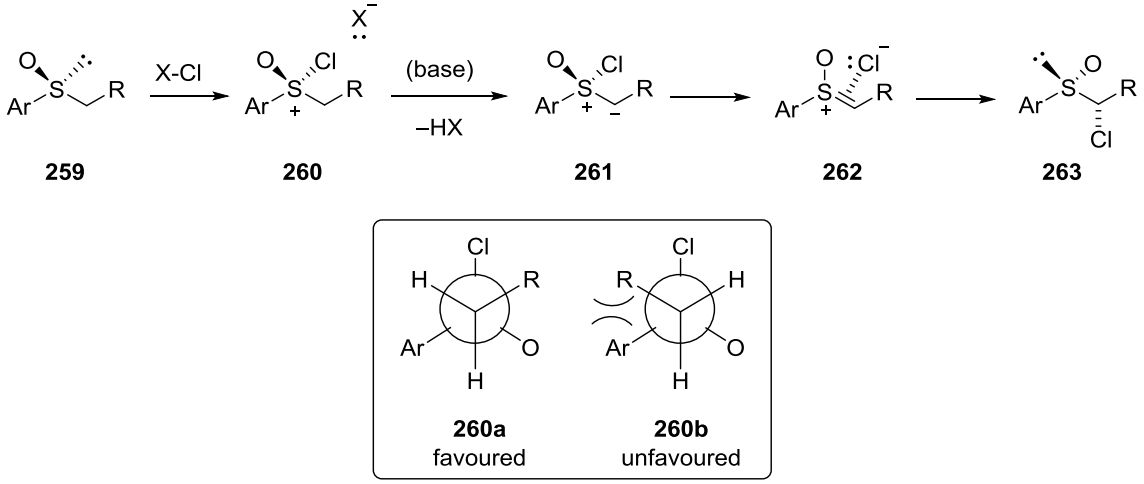
Andersen's sulfinate **117** was reacted with MeMgBr to give sulfoxide **258** in excellent yield and e.r. (Scheme 3.5). Following a procedure initially described by Yamakawa and co-workers, sulfoxide **258** was then chlorinated by treatment with NCS in the presence of K_2CO_3[147] to afford α-chlorosulfoxide **257** in 74% yield and 91:9 e.r. Subsequent recrystallisation gave access to enantiomerically pure α-chlorosulfoxide **257**.



Scheme 3.5. Synthesis of enantiomerically enriched α-chloro sulfoxide **257**.

The chlorination reaction was shown to occur with inversion of configuration at sulfur and, in the case of further substitution at the alpha position, it was shown to be partially diastereoselective, with preference for the formation of the *syn* diastereoisomer.[35] Furthermore, the presence of insoluble K_2CO_3 was found to be critical to suppress racemisation, although it dramatically slowed down the reaction rate (5 days for full conversion compared to 1−2 h in the absence of K_2CO_3). The proposed mechanism for the Yamakawa chlorination is depicted in Scheme 3.6.[35] Initial chlorination of sulfoxide **259** with NCS generates intermediate **260**, which is subsequently deprotonated by the base to give sulfur ylide **261**. Subsequent 1,2-electrophilic rearrangement affords α-chlorosulfoxide **263** *via* contact ion pair **262**. A rehybridisation process during the addition of chloride to thioxocarbenium ion **262** accounts for the inversion of configuration at sulfur. The *syn* diastereoselectivity is justified by the fact that intermediate **260** sits in the favoured conformation **260a** to minimise gauche interactions between the R and the aryl group; limited rotation about the alpha C−S bond in the ylide leads

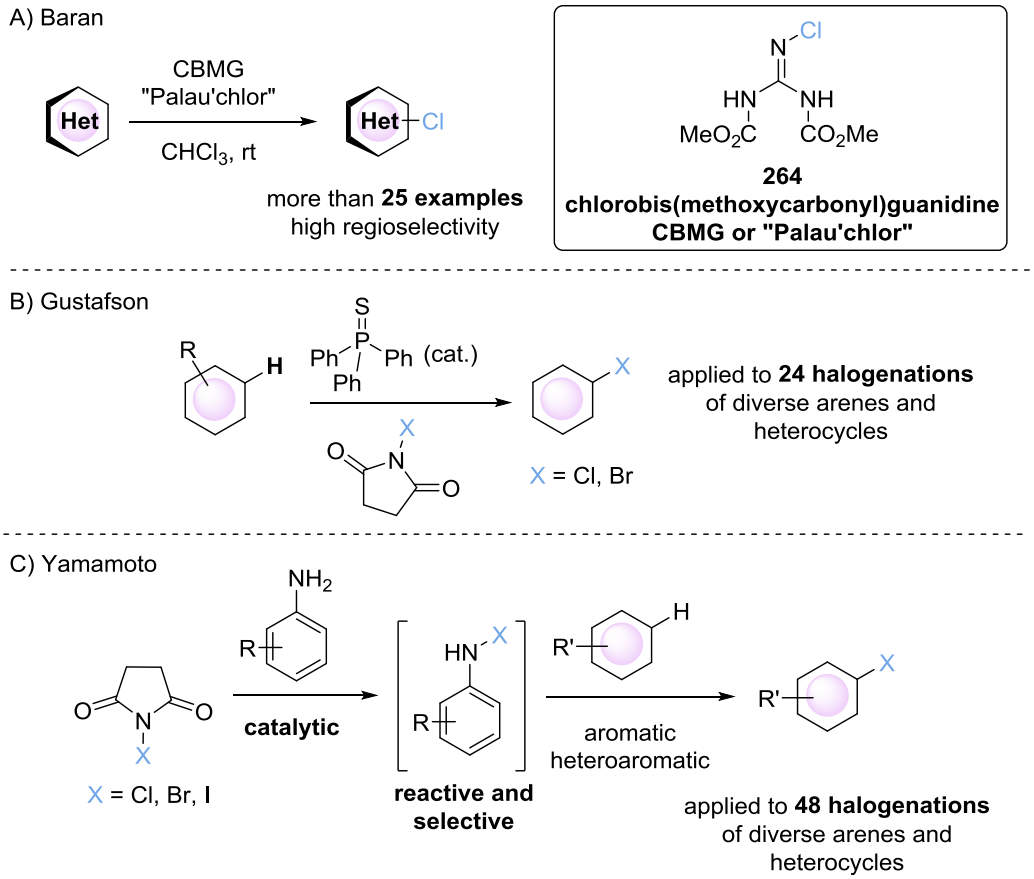
to the formation of the minor *anti* diastereoisomer. The partial racemisation observed under reaction conditions is presumably caused by either solvent separation of contact ion pair **262** or the intervention of a radical pathway for the 1,2-rearrangement.



Scheme 3.6. Mechanism of the Yamakawa chlorination proposed by Blakemore.

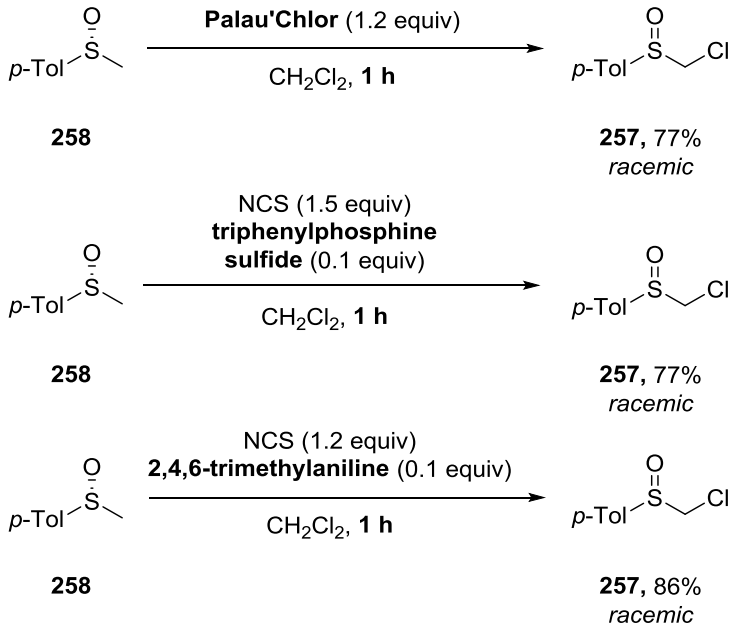
Despite the formation of the desired product in high enantiopurity, the Yamakawa chlorination still suffers from some drawbacks, such as the long reaction time and the need for recrystallisation to enhance the enantiopurity of **257**, eventually leading to a relatively low isolated yield. The viability of a different chlorination method was therefore tested.

In 2014, Baran and co-workers proposed a new method for the chlorination of arenes and heteroarenes based on the use of a novel guanidine-based chlorinating agent, CBMG or Palau'Chlor **264**.[148] The methodology was shown to be compatible with a variety of differently substituted arenes and heteroarenes, but also conjugated π-systems, sulphonamides and silyl enol ethers, using a mild, operationally simple and safe procedure (Scheme 3.7A). A new practical electrophilic halogenation of arenes and heteroarenes was also proposed by Gustafson and co-workers in 2015.[149] The methodology, which was found to efficiently halogenate a broad variety of aromatics under mild conditions, made use of *N*-halosuccinimides in the presence of phosphine sulfides as catalysts (Scheme 3.7B). In the same year, Yamamoto and co-workers proposed a similar methodology for the selective halogenation of different aromatics and heteroaromatics using *N*-halosuccinimides in the presence of an aniline catalyst, affording the corresponding halogenated products in excellent yield and regioselectivity (Scheme 3.7C).[150]



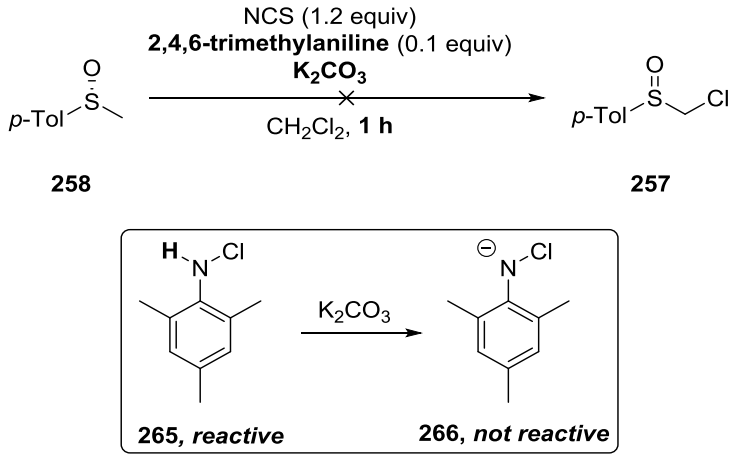
Scheme 3.7. Examples of electrophilic halogenation reactions of arenes and heteroarenes.

All of these three methodologies were tested for the α-chlorination of sulfoxide **258** and we were pleased to isolate desired α-chlorosulfoxide **257** in good yield in all the cases. Unfortunately, none of the methodologies were able to provide stereocontrol and sulfoxide **257** was always isolated as the racemate (Scheme 3.8).



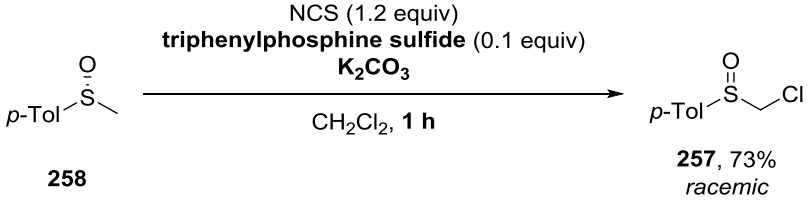
Scheme 3.8. Attempted enantiospecific chlorination of sulfoxide **258**.

Considering the crucial role played by K_2CO_3 in inducing enantioselectivity in the Yamakawa chlorination, we attempted to use it as an additive in the methodologies described above. Addition of K_2CO_3 to the aniline-catalysed chlorination reaction of sulfoxide **258** completely shut down any reactivity, and no desired product could be detected (Scheme 3.9). Presumably the base simply abstracted the acidic proton of aniline **265** generating anionic species **266** which is no longer catalytically active.



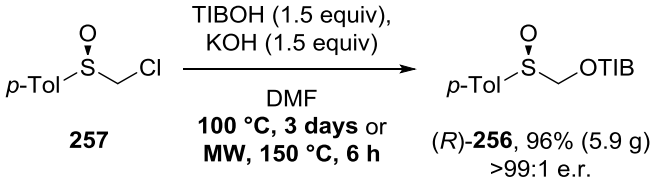
Scheme 3.9. Attempted enantiospecific chlorination of sulfoxide **258** with aniline catalyst **265** and K_2CO_3.

Performing the phosphine sulfide-catalysed chlorination of sulfoxide **258** in the presence of K_2CO_3 allowed the isolation of α-chlorosulfoxide **257** in 73% yield (Scheme 3.10). Unfortunately, no stereoinduction was observed and the product was found to be racemic.



Scheme 3.10. Attempted enantioselective chlorination of sulfoxide **258** with triphosphine sulfide catalyst and K_2CO_3.

Provided that the Yamakawa chlorination was the only successful method to access α-chlorosulfoxide **257** in high enantiopurity, we turned our attention towards the next step of the synthesis, which was the introduction of the benzoate group. To this aim, α-chlorosulfoxide **257** was coupled with the preformed potassium salt of 2,4,6-triisopropylbenzoic acid to afford, after heating the reaction mixture at 100 °C for 3 days, α-sulfinyl benzoate (*R*)-**256** in excellent yield and e.r. (Scheme 3.11). Pleasingly, it was found that α-sulfinyl benzoate (*R*)-**256** could be obtained in comparable yield and e.r. by heating the reaction mixture in the microwave for only 6 hours.

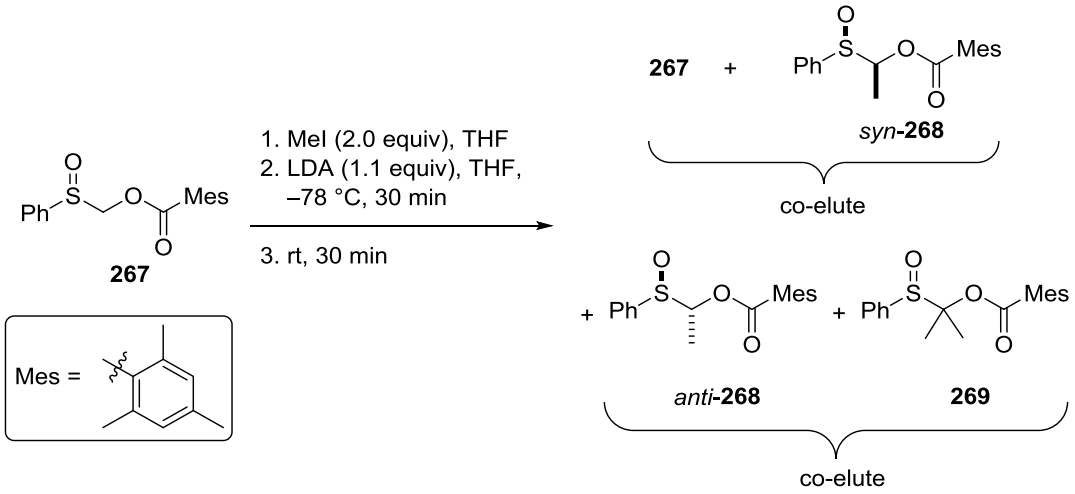


Scheme 3.11. Synthesis of enantiomerically enriched α-sulfinyl benzoate (*R*)-**256**.

With access to sulfoxide (*R*)-**256**, the next step was performing an alkylation reaction alpha to the sulfinyl group. Previous attempts to perform this alkylation on a similar substrate revealed that the deprotonation of α-sulfinyl benzoate **267** must be performed in the presence of the electrophile (i.e. *in situ* conditions) to avoid the decomposition of the generated metallated species.[iii] When the alkylation of sulfoxide **267** was attempted using MeI as the alkylating agent and LDA as the base, desired products *syn* and *anti*-**268** were obtained with a d.r. of 42:58, along with unreacted starting material **267** and double alkylated product **269** (Scheme 3.12). Although the two diastereoisomers *syn*-**268** and *anti*-**268** could be separated by

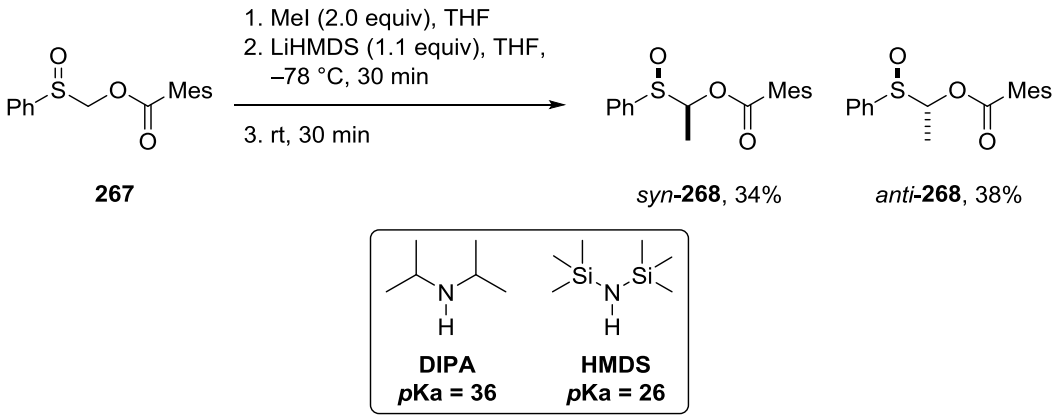
[iii] Initial results on the alkylation of α-sulfinyl benzoate **267** were obtained by Dr. M. Burns.

chromatography on silica gel, they co-eluted with starting benzoate **267** and double alkylated product **269**, respectively.



Scheme 3.12. Attempted alkylation of sulfoxide **267** using LDA.

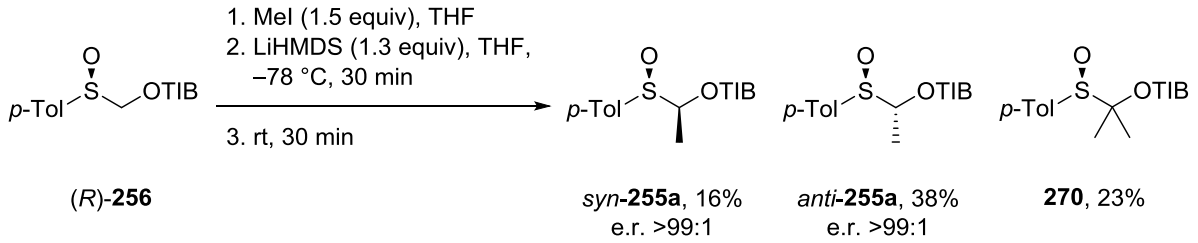
It was eventually found that the use of a weaker and more hindered base, such as LiHMDS, was beneficial in preventing double alkylation. Alkylation of sulfoxide **267** with MeI, under *in situ* conditions, using LiHMDS as the base, allowed the isolation of the desired products *syn* and *anti*-**268** in 79% overall yield with a d.r. of 48:52 (*syn*-**268**:*anti*-**268**, Scheme 3.13).[iv]



Scheme 3.13. Alkylation of sulfoxide **267** using LiHMDS.

Unfortunately, these conditions were found to be unsuitable for the TIB substrate (*R*)-**256**. When α-sulfinyl benzoate (*R*)-**256** was alkylated with MeI under *in situ* conditions, using LiHMDS as the base, desired diastereoisomers *syn*-**255a** and *anti*-**255a** were isolated in 16% and 33% yield respectively, along with a considerable amount of dialkylated product **270** (Scheme 3.14).

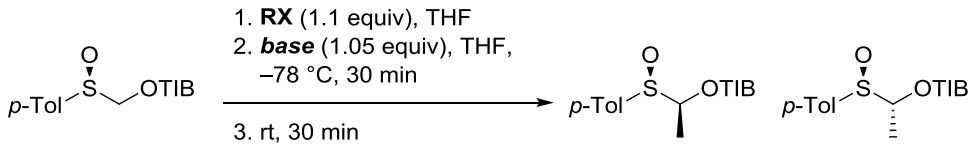
[iv] Initial results on the alkylation of α-sulfinyl benzoate **267** were obtained by Dr. M. Burns.



Scheme 3.14. Attempted alkylation of sulfoxide (*R*)-**256** using LHMDS.

Further optimisation revealed that the formation of the anion prior to the addition of MeI (i.e. *ex situ* conditions) was beneficial, leading to an increased yield (83% overall, determined by ^{1}H NMR, 25:75 *syn*:*anti*) and suppressed the undesired dialkylation process (Table 3.1, entry 1). Interestingly, the use of KHMDS and NaHMDS as the base with MeI as the alkylating agent, led to improved results compared to LiHMDS and the desired products *syn*-**255a** and *anti*-**255a** were obtained in good yield and d.r., the *syn* diastereoisomer *syn*-**255a** being the major species, with no trace of the double alkylated product **270** (Table 3.1, entries 2−3). However, when conditions reported in Table 3.1, entry 3 were used on a moderately large scale (7.7 mmol), desired sulfoxides *syn*-**255a** and *anti*-**255a** were formed in increased yield (98% overall), but decreased diastereoselectivity now in favour of the *anti* diastereoisomer *anti*-**255** (Table 3.1, entry 4). This difference in the observed d.r. can be rationalised by considering that the generated diastereomeric sulfoxides *syn* and *anti*-**255a** undergo epimerisation under the reaction conditions, the extent of the process being dependent on the scale, the base and the alkylating agent employed (see 3.2.3).

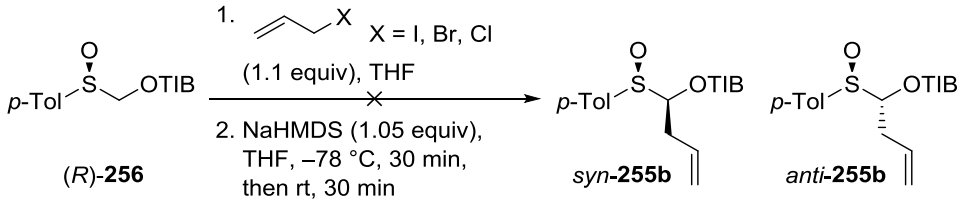
Table 3.1. Results for the alkylation of sulfoxide (*R*)-**256** using different bases.



Entry	Base	R−X	% Yield *syn*-255a[a]	% Yield *anti*-255a[a]	*syn*:*anti*[b]
1[c]	LiHMDS	MeI	20	63	12:88
2	KHMDS	MeI	48	19	83:17
3	NaHMDS	MeI	52	23	80:20
4[d]	NaHMDS	MeI	43[e]	56[e]	43:57

[a] Yield determined by ^{1}H NMR analysis of the crude reaction mixture using 1,4-dimethoxybenzene as the internal standard; [b] d.r. values determined by ^{1}H NMR analysis of the crude reaction mixture; [c] anion formed prior to the addition of the methylating agent; [d] reaction performed on a 7.7 mmol scale; [e] yield of isolated products.

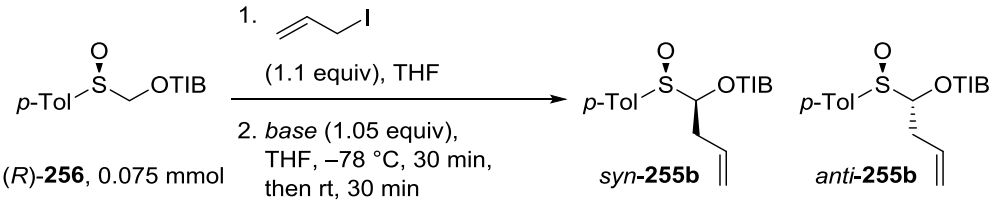
With conditions to achieve the methylation of sulfoxide (*R*)-**256**, we sought to test the generality of the methodology and use other alkylating agents to access different substituted α-sulfinyl benzoates. To this aim, we initially targeted allyl-substituted sulfoxide **255b**. Deprotonation of methylene sulfoxide (*R*)-**256** with NaHMDS and trapping of the generated anion with allyl iodide under *in situ* conditions resulted in a large amount of unreacted starting material and only traces of the desired diastereomeric products *syn*-**255b** and *anti*-**255b** were observed (Scheme 3.15). The use of different alkylating agents, such as allyl bromide or allyl chloride did not give a better result and no desired products could be isolated.



Scheme 3.15. Attempted synthesis of α-sulfinyl benzoates *syn* and *anti*-**255b** by alkylation.

It was eventually found that purification of allyl iodide prior to use by washing with aqueous $Na_2S_2O_3$ to remove any trace of I_2, was essential for the success of the reaction. Optimisation of the reaction conditions revealed that a careful choice of the base was important for the formation of sulfoxide **255b**, with LiHMDS giving the best result (Table 3.2, entry 3), while NaHMDS, KHMDS and LDA failed to provide any product (Table 3.2, entries 1−2 and 4). The conditions reported in entry 3 were found to be scalable (Table 3.2, entries 5−6) and when the process was performed on 3.8 mmol of starting benzoate (*R*)-**256**, desired sulfoxides *syn* and *anti*-**255b** were isolated in 86% overall yield with a d.r. of 86:14 in favour of the *anti* diastereoisomer.

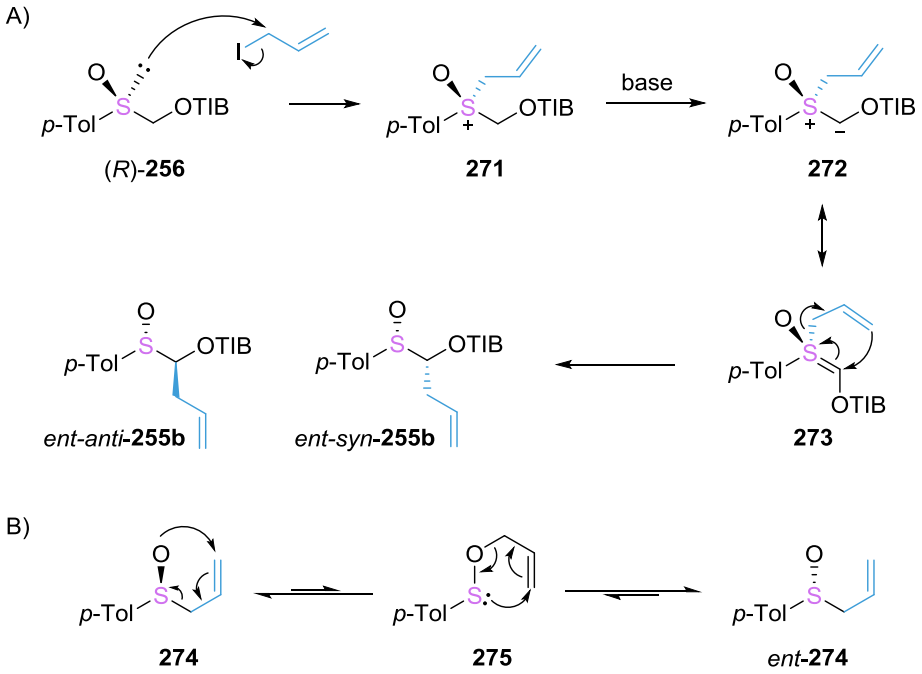
Table 3.2. Results for the alkylation of sulfoxide (*R*)-**256** using allyl iodide.



Entry	Base	% Yield *syn*-255b[a]	% Yield *anti*-255b[a]	*syn*:*anti*[b]
1	NaHMDS	0	0	n.d.
2	KHMDS	0	0	n.d.
3	LiHMDS	n.d.	46[c]	n.d.
4	LDA	0	0	n.d.
5[d]	LiHMDS	12	70	15:85
6[e]	LiHMDS	12	74	14:86

[a] Yields of isolated products; [b] d.r. values determined by ^{1}H NMR analysis of the crude reaction mixture; [c] yield determined by ^{1}H NMR analysis of the crude reaction mixture using 1,4-dimethoxybenzene as the internal standard; [d] reaction performed on a 0.75 mmol scale; [e] reaction performed on a 3.8 mmol scale; n.d. = not determined.

The e.r. of synthesised sulfoxides *syn*-**255b** and *anti*-**255b** was found to be 98:2, thus indicating a slight erosion in the enantiospecificity of the process, considering that starting sulfoxide (*R*)-**256** had an e.r. greater than 99:1. This partial lack of enantiospecificity can be rationalised considering the mechanism depicted in Scheme 3.16A. The sulfur lone pair on benzoate (*R*)-**256** initially reacts with allyl iodide to give intermediate **271**; this is subsequently deprotonated by the base to give ylide **272**, which is in resonance with sulfine **273**. At this point, a 2,3-sigmatropic rearrangement occurs to give sulfoxides *ent*-*syn*-**255b** and *ent*-*anti*-**255b**, bearing the opposite configuration at the sulfur centre than starting sulfoxide (*R*)-**256**. This pathway is mechanistically similar to the one operating in the case of optically active allylic sulfoxide **274**, where a concerted intramolecular α,γ-shift of the allyl group between the sulfoxide oxygen and the sulfur centre *via* optically inactive allyl sulfenate **275** leads to rapid racemisation (Scheme 3.16B).[151-152]



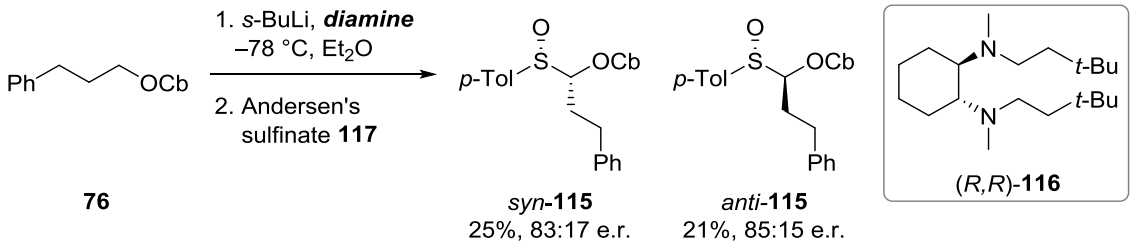
Scheme 3.16. Proposed mechanism accounting for the lack of enantiospecificity in the alkylation of sulfoxide (*R*)-**256** with allyl iodide.

The synthesis of enantioenriched sulfoxides *syn* and *anti*-**255b** highlighted the limitations of this methodology. The reaction conditions optimised for the alkylation of benzoate (*R*)-**256** with MeI proved not to be general, and further optimisation was necessary when allyl iodide was employed as the alkylating agent. Additionally, the e.r. of sulfoxides *syn* and *anti*-**255b** was found to be reduced due to a competing racemisation pathway. These drawbacks, together with the high number of steps and the long reaction times required to make benzoate (*R*)-**256**, prompted us to seek a shorter and more attractive method to access different substituted enantioenriched α-sulfinyl benzoates.

3.2.2. Synthesis of Enantioenriched α-Sulfinyl Benzoates by Sulfinylation

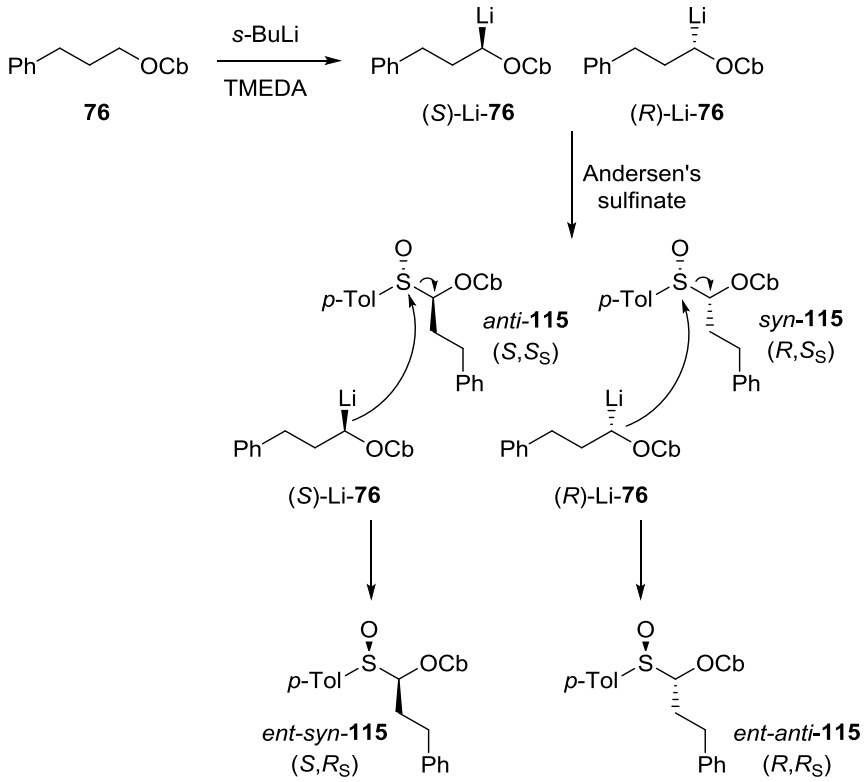
O'Brien and co-workers showed that enantiomerically enriched α-sulfinyl carbamates *syn*-**115** and *anti*-**115** could be synthesised from the corresponding carbamate **76**.[80] They found that treatment of racemic lithiated carbamate Li-**76** with commercially available and enantiopure Andersen's sulfinate **117**, gave desired carbamates *syn* and *anti*-**115** in good yield, but with only moderate levels of enantiospecificity (Table 3.3, entry 1).

Table 3.3. O'Brien's synthetic route to enantiomerically enriched α-sulfinyl carbamates *syn* and *anti*-**115**.



Entry	Diamine	% Yield *anti*-115 (e.r.)	% Yield *syn*-115 (e.r.)
1	TMEDA	23 (83:17)	32 (91:9)
2	(−)-sparteine	53 (99:1)	0.2 (n.d.)
3	(+)-sp surr	7 (87:13)	45 (99:1)
4	(*R*,*R*)-**116**	56 (99:1)	14 (93:7)
5	(S,*S*)-**116**	17 (95:5)	54 (99:1)

This erosion in the enantiospecificity was unexpected, since organometallic reagents are known to react with enantioenriched sulfinate esters with inversion of configuration at the sulfur centre.[153] The origin of this competing racemisation pathway was presumed to be a sulfinyl transfer reaction of lithiated carbamates (*R*)-Li-**76** and (*S*)-Li-**76** and the early generated sulfoxides *syn*-**115** and *anti*-**115**, eventually leading to the formation of products derived from a double-inversion pathway (Scheme 3.17).

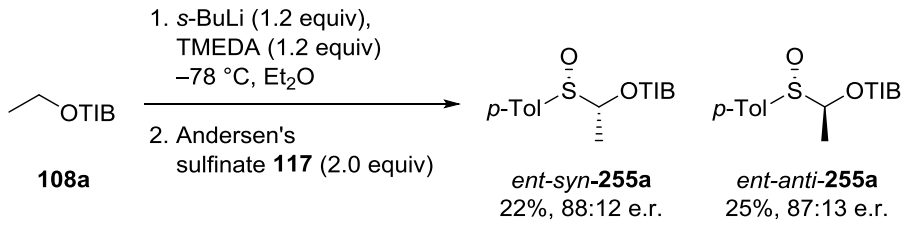


Scheme 3.17. Postulated mechanism for the observed racemisation of α-sulfinyl carbamates *syn* and *anti*-**115**.

O'Brien and co-workers overcame this problem by employing a chiral diamine, either sparteine or 1,2-diaminocyclohexane derivative **116**, in the deprotonation step; after trapping of the generated enantioenriched lithiated carbenoid with Andersen's sulfinate **117**, the major diastereoisomer of carbamate **115** was isolated with very high levels of enantiopurity (Table 3.3, entries 2−5).

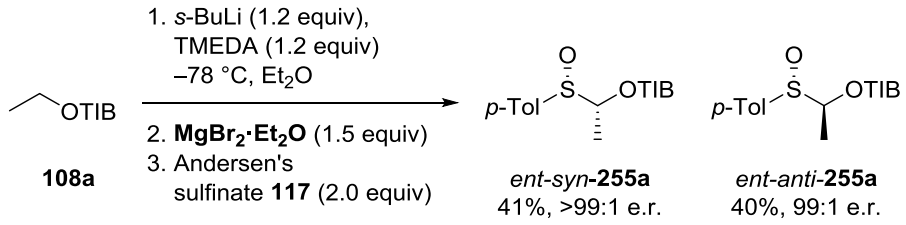
Preliminary studies showed that this racemisation pathway was also occurring in the sulfinylation of benzoate **108a** (Scheme 3.18).[v] Diastereomeric sulfoxides *ent-syn* and *ent-anti*-**255a**, which could be separated by chromatography on silica gel, were in fact isolated in 88:12 and 87:13 e.r., respectively. Increasing the number of equivalents of sulfinate **117** did not lead to improved e.r. values, which contradicted the competing sulfinylation pathway described above.

[v] Initial results on the sulfinylation of benzoate **108** were obtained by Dr. N. Ahmed.



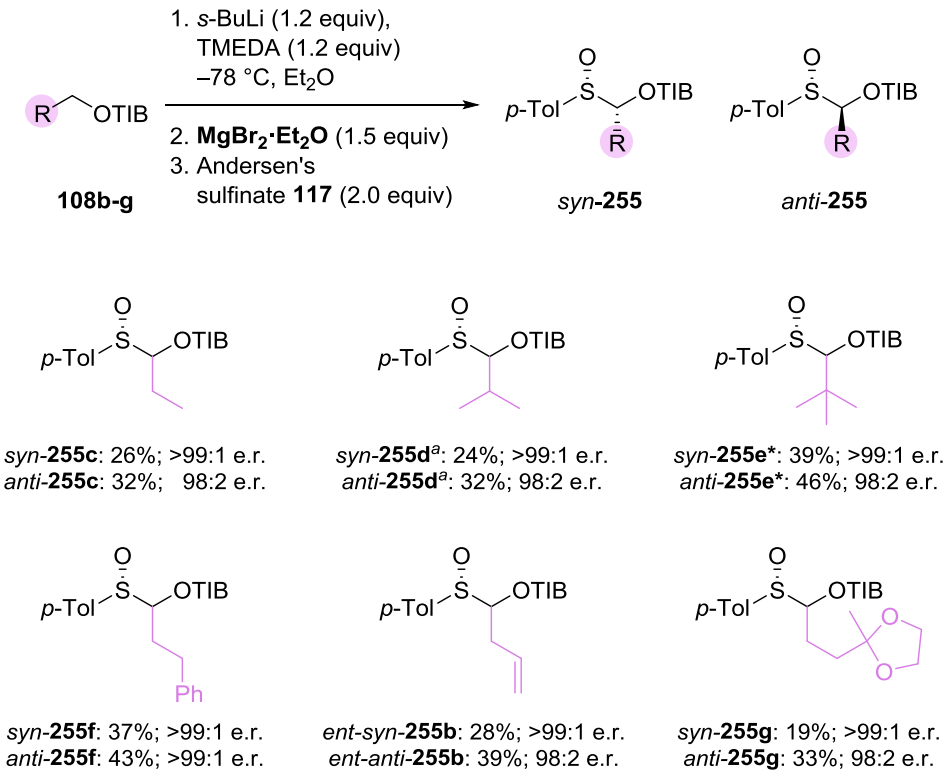
Scheme 3.18. Synthesis of α-sulfinyl benzoates *ent-syn* and *ent-anti*-**255a** though the sulfinylation of lithiated precursor Li-**108a** with Andersen's sulfinate **117**.

As mentioned previously, we sought to find a strategy to synthesise substituted α-sulfinyl benzoates that did not make us reliant on the use of chiral diamines. We therefore reasoned that employing a more tempered nucleophile than Li-**108a**, such as magnesiated carbenoid Mg-**108a**, would still allow the sulfinyl transfer reaction with Andersen's sulfinate **117**, but at the same time would prevent the proposed double inversion pathway. To test this, lithiated benzoate Li-**108a** was initially formed by treatment of benzoate **108a** with *s*-BuLi in the presence of TMEDA and subsequently transmetalated to the corresponding magnesiated carbenoid Mg-**108a** by addition of $MgBr_2 \cdot Et_2O$; trapping with Andersen's sulfinate **117** afforded sulfoxides *ent-syn* and *ent-anti*-**255a** in good yield (Scheme 3.19). Pleasingly, the process was shown to occur with very high levels of enantiospecificity and the diastereoisomers *ent-syn* and *ent-anti*-**255a** were isolated in near-perfect levels of enantiopurity.



Scheme 3.19. Synthesis of α-sulfinyl benzoates *ent-syn* and *ent-anti*-**255a** through the sulfinylation of magnesiated precursor Mg-**108a** with Andersen's sulfinate **117**.

These conditions were subsequently applied to the synthesis of a range of enantiopure α-sulfinyl benzoates (Scheme 3.20). Different substituents could be successfully introduced, including alkyl chains of varying steric hindrance (**255c-e**) and versatile functionalities, such as alkene *ent*-**255b** and ketal **255g**. Remarkably, both diastereoisomers could be obtained in good yield and with excellent levels of enantiopurity in all the cases, thus providing rapid access to both the *S*- and *R*-configured metal carbenoids through retentive sulfoxide−metal exchange.

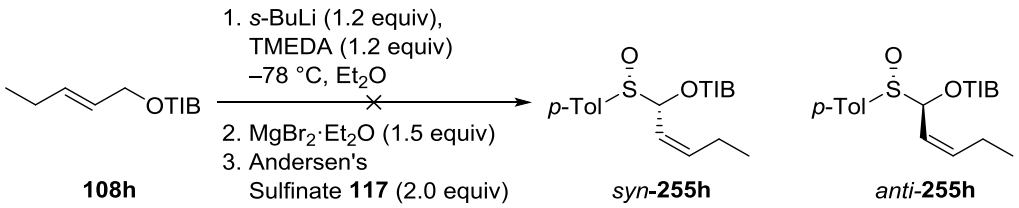


Scheme 3.20.[vi] Synthesis of α-sulfinyl benzoates **255b-g** through the sulfinylation of magnesiated precursors with Andersen's sulfinate **117**. [a] Diastereoisomers were not separable by column chromatography and yields were determined based on ^{1}H NMR analysis. A portion of the mixture was purified by reverse-phase HPLC to obtain analytically pure *syn* and *anti*-**255d**.

The relative and absolute configuration of the obtained α-sulfinyl benzoates was determined by comparing chiral HPLC traces of the products obtained from the sulfinylation reaction of (a) racemic magnesiated benzoate and racemic sulfinate reagent (mixture of all the four diastereoisomers), (b) racemic magnesiated benzoate and enantiopure Andersen's reagent (mixture of two diastereoisomers, epimeric at the carbon centre) and (c) enantioenriched magnesiated benzoate and racemic sulfinate reagent (mixture of two diastereoisomers, epimeric at the sulfur centre; see § 5.6.8).

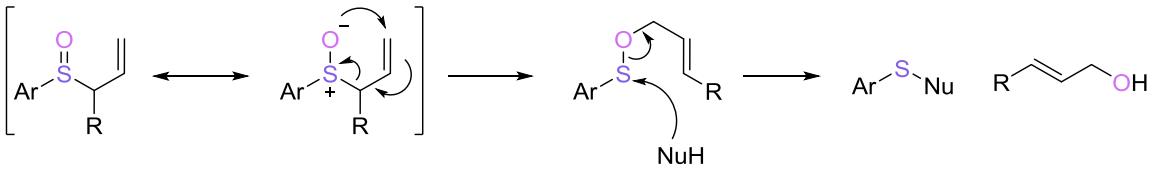
A few benzoates were found to be not compatible with these reaction conditions. For instance, vinyl substituted α-sulfinyl benzoates could not be accessed through this route. In fact, lithiation and transmetalation of TIB ester **108h**, followed by trapping with Andersen's sulfinate **117**, did not lead to the formation of diastereomeric sulfoxides *syn* and *anti*-**255h**, although ^{1}H NMR analysis of the crude reaction mixture showed complete consumption of starting material **108h** (Scheme 3.21).[vii]

[vi] Where indicated (*), the experimental work discussed in this chapter was conducted by Dr. M. Kucukdisli.
[vii] Lithiation/transmetalation/trapping of benzoate **108h** was conducted by Dr. M. Kucukdisli.



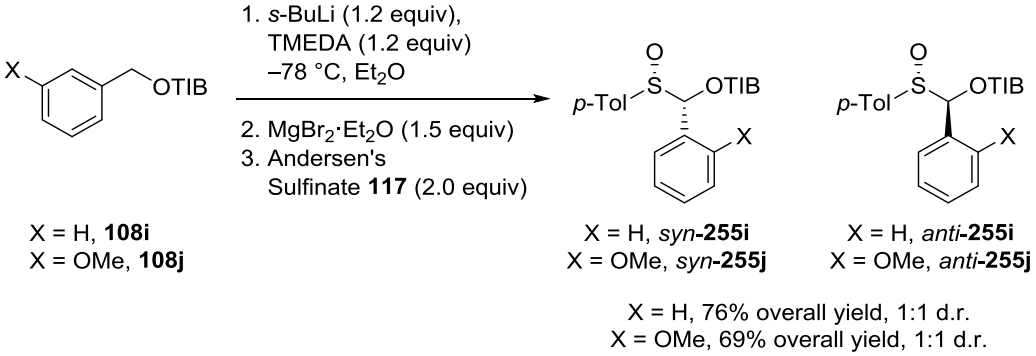
Scheme 3.21. Attempted lithiation/transmetalation/sulfinylation of benzoate **108h**.

In this case, the expected desired products *syn* and *anti*-**255h** were presumed to have formed under the reaction conditions; however, vinyl substituted sulfoxides are known to undergo rapid decomposition *via* a Mislow−Evans rearrangement (Scheme 3.22).[152]



Scheme 3.22. Mechanism of the Mislow-Evans rearrangement of allylic sulfoxides.

The synthesis of aryl substituted α-sulfinyl benzoates was also found to be problematic. In particular, lithiation/transmetalation followed by sulfinylation of benzylic TIB esters **108i-j** gave a diastereomeric mixture of desired benzylic sulfoxides *syn* and *anti*-**255i-j**. However, these were found to be inseparable by chromatography on silica gel (Scheme 3.23).[viii] The high instability of these compounds in acetonitrile made any attempt of purification by reverse-phase HPLC ineffective, with the consequence that enantio- and diastereopure aryl substituted α-sulfinyl benzoates could not be accessed using this protocol.



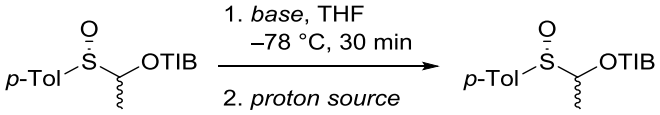
Scheme 3.23. Lithiation/transmetalation/sulfinylation of benzoates **255i-j**.

[viii] Lithiation/transmetalation/trapping of benzoates **108i-j** was conducted by Dr. M. Kucukdisli.

3.2.3. Base-Mediated Epimerisation of α-Sulfinyl Benzoates

In many cases, standard flash chromatography was sufficient to separate mixtures of *syn* and *anti* diastereomers. Diastereomeric pairs showed differences in retention factors (R_f values) of up to 0.2, the *anti* diastereoisomer always proving to be the more polar. However, in some cases, separation of the diastereoisomers was more challenging; for example, the isopropyl-substituted benzoates, *syn* and *anti*-**255d**, could only be separated using preparative HPLC. For this reason, we investigated the base-mediated epimerisation of a diastereomeric mixture of α-sulfinyl benzoates *ent-syn* and *ent-anti*-**255a**, under both kinetic and thermodynamic conditions; in this way, we were hoping to enrich the mixture heavily towards one diastereomer, thereby facilitating chromatographic separation. The Knochel−Hauser base, TMPMgCl·LiCl, was found to be the optimal reagent to affect the deprotonation, LiHMDS and NaHMDS being ineffective and LDA leading to complete decomposition. A 50:50 mixture of *ent-syn* and *ent-anti*-**255a** in THF was exposed to TMPMgCl·LiCl at −78 °C for 30 minutes followed by quenching with excess *i*-PrOH at the same temperature; the process resulted in a mixture more enriched in the *syn* diastereomer (*ent-syn*-**255a**: *ent-anti*-**255a** = 72:28; Table 3.4, entry 1).

Table 3.4. Optimisation of reaction conditions for the epimerisation of α-sulfinyl benzoate **255a**.

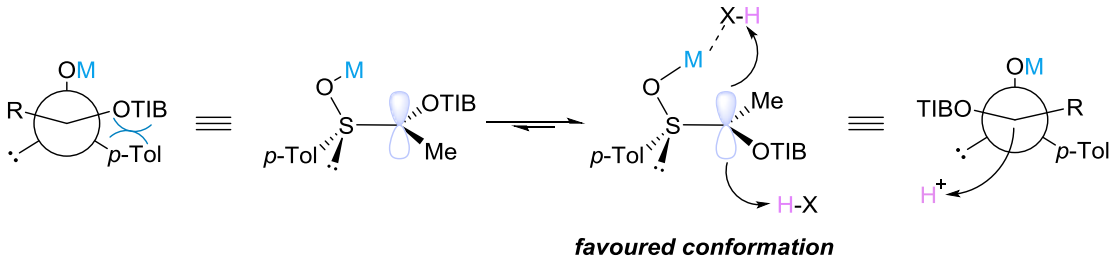


50:50 *ent-syn*-**255a**:*ent-anti*-**255a** → *ent-syn*-**255a**:*ent-anti*-**255a**

Entry	Base	Proton source	*syn*:*anti*[a]
1	TMPMgCl·LiCl	*i*-PrOH	72:28
2	TMPMgCl·LiCl	Meldrum's acid	80:20
3	TMPMgCl·LiCl	CH_3NO_2	78:22
4	TMPMgCl·LiCl	indene	86:14
5	*t*-BuOK	*t*-BuOH	53:47
6	dimsyl sodium	DMSO	55:45

Reactions were performed on 0.05 mmol scale; [a] d.r. values were measured by ^{1}H NMR analysis of the crude reaction mixture.

The origin of the selectivity for the *syn* diastereomer presumably arises from the favoured approach of the proton source from the less hindered *Re* face of the carbanion centre presented by the more thermodynamically stable conformer, that is, the one that places the large OTIB group gauche to the small substituent (the lone pair) of the vicinal sulfur centre (Scheme 3.24).



Scheme 3.24. Rationale for the observed preferential formation of the *syn* diastereoisomer *ent-syn*-**255a**.

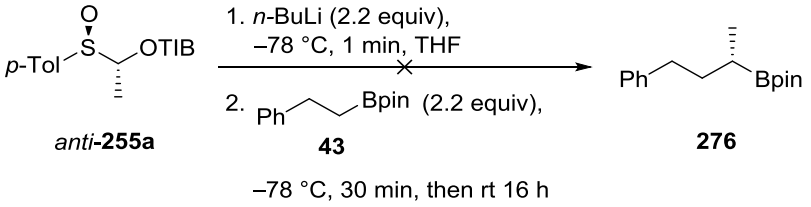
The minor *anti* isomer was presumably formed through the approach of the proton source from the *Si* face of this conformer, whose steric hindrance would be mitigated by a favourable interaction between the magnesium ion and the oxygen atom of the proton source. We therefore decided to explore other proton sources where such an interaction might be diminished or absent. Indeed, the use of less coordinating proton sources proved to be beneficial, with indene exhibiting the highest d.r. value (*ent-syn*-**255a**: *ent-anti*-**255a** = 86:14; Table 3.4, entry 4). We also tested epimerisation under conditions that would be expected to permit equilibration of the mixture, namely, KO*t*-Bu/*t*-BuOH and dimsyl sodium/DMSO; however, resulting mixtures were only very slightly enriched in favour of the *syn* diastereomer (Table 3.4, entries 5–6).

Unfortunately, when we subjected a mixture of the isopropyl-substituted benzoates, *syn* and *anti*-**255d**, to the optimised conditions (TMPMgCl·LiCl, THF, −78 °C; indene), the d.r. value did not change, suggesting that deprotonation did not occur, presumably owing to the increased steric hindrance.

3.2.4. Homologation of Boronic Esters with α-Sulfinyl Benzoates

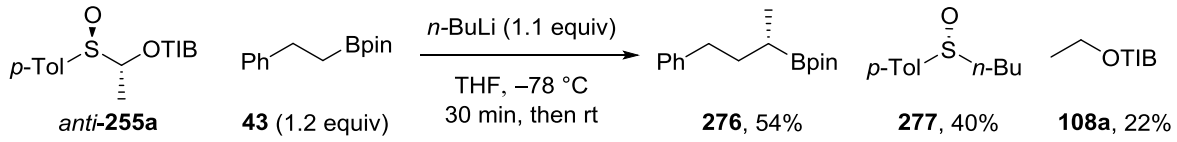
With a range of enantiopure α-sulfinyl benzoates in hand, we were prompt to test their efficiency as precursors to metal carbenoids, generated by sulfoxide–metal exchange, for the homologation of boronic esters. Optimisation of the sulfoxide–metal exchange/borylation sequence was carried out using enantioenriched α-sulfinyl benzoate *anti*-**255a** and boronic ester **43**. Since the work of Blakemore and co-workers showed that lithium carbenoids, generated from α-chloro sulfoxides, gave significantly improved results in the homologation of boronic esters compared to the corresponding magnesium carbenoids, we initially investigated the use of organolithium reagents to trigger the exchange. Conditions reported by O'Brien,[80] i.e. treatment of a solution of *anti*-**255a** in THF with *n*-BuLi at −78 °C for only one minute, followed by the addition of boronic ester **43** (*ex situ* conditions), were met with failure and no desired homologated boronic ester **276** could be detected (Scheme 3.25). This is presumably due to the chemical instability of the generated lithium carbenoid under reaction

conditions; the same lithium carbenoid generated by tin–lithium exchange from the corresponding α-stannyl benzoate is known to be stable for hours at cryogenic temperatures,[73] suggesting that the alkyl-aryl sulfoxide by-product generated by sulfoxide–lithium exchange was responsible for the observed instability.



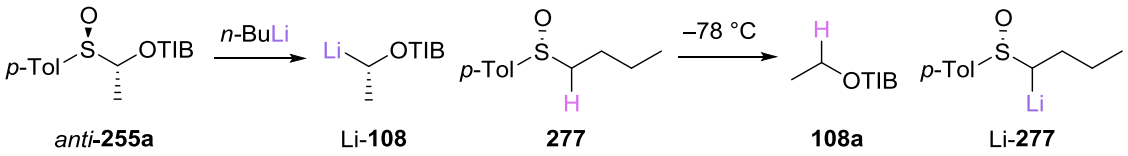
Scheme 3.25. Attempted homologation of boronic ester **43** with sulfoxide *anti*-**255a** under *ex situ* conditions.

However, adding *n*-BuLi to a mixture of *anti*-**255a** and boronic ester **43** in THF at −78 °C (*in situ* conditions) and stirring the reaction mixture at that temperature for 30 minutes before warming to room temperature, allowed the isolation of desired homologated product **276** in 54% yield (Scheme 3.26). Remarkably, the sulfoxide–lithium exchange was sufficiently rapid to prevent the reaction of *n*-BuLi with the boronic ester; additionally, trapping of the generated lithium carbenoid with the boronic ester proved to be faster than other undesired side-reactions. Aryl-alkyl sulfoxide by-product **277** was also isolated, although in moderate 40% yield. Unexpectedly, ethyl TIB **108a** was obtained in significant 22% yield.



Scheme 3.26. Homologation of boronic ester **43** with sulfoxide *anti*-**255a** under *in situ* conditions.

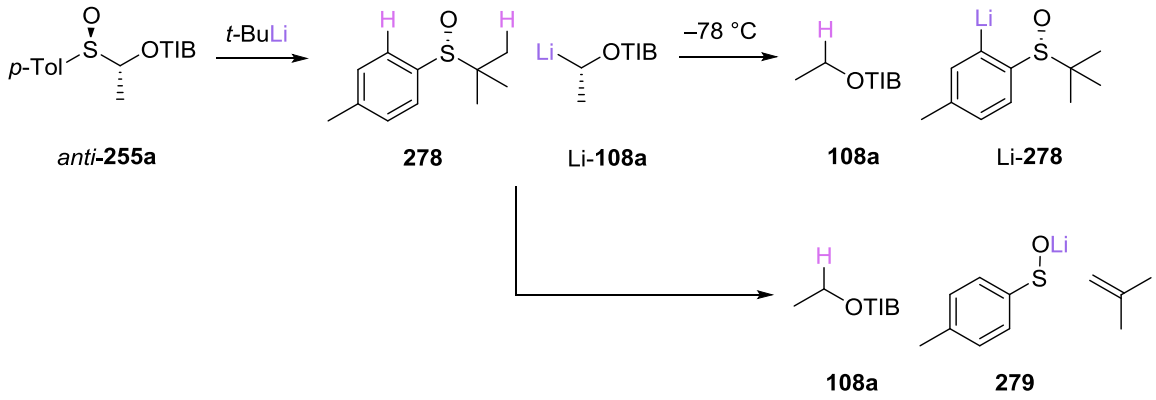
Ethyl TIB **108a** is presumably generated under reaction conditions due to the presence of the relatively acidic sulfoxide by-product **277**, which could act as an internal proton source and quench the generated lithium carbenoid Li-**108a** (Scheme 3.27).



Scheme 3.27. Plausible mechanism for the formation of ethyl TIB **108a** under reaction conditions when *n*-BuLi is employed.

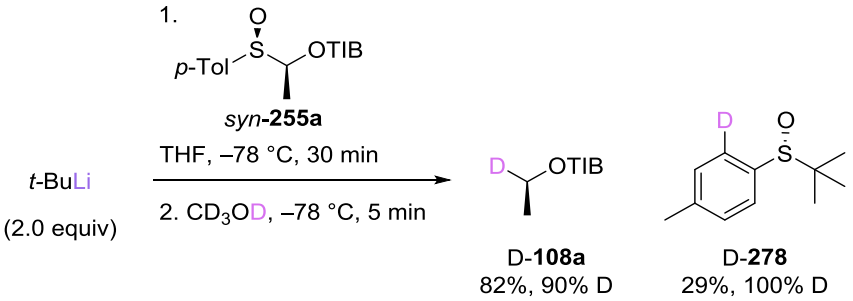
Not surprisingly, the use of *t*-BuLi under the same reaction conditions gave a slightly improved result, with boronic ester **276** being isolated in 59% yield. However, some ethyl benzoate **108a** was still formed, suggesting that ortho-protons on sulfoxide by-product **278** are still sufficiently

acidic to quench the generated lithium carbenoid (Scheme 3.28). Another possibility is that lithium carbenoid Li-**108a** promoted the elimination of isobutene from sulfoxide **278**, leading to the formation of ethyl TIB **108a** and sulfine **279**.[154]



Scheme 3.28. Plausible mechanism for the formation of ethyl TIB **108a** under reaction conditions when *t*-BuLi is employed.

This operating pathway was subsequently confirmed by the trapping experiment showed in Scheme 3.29.[ix] A solution of *t*-BuLi in THF was treated with a solution of sulfoxide *anti*-**255a** in THF at −78 °C for 30 minutes (reverse-addition protocol), followed by a quench with CD_3OD. Analysis of the ^1H NMR recorded on the crude reaction mixture using an internal standard revealed that sulfoxide by-product D-**278** was formed in 29% yield with full deuterium incorporation, therefore demonstrating its ability to act as an internal proton source quenching the generated lithium carbenoid.[155]



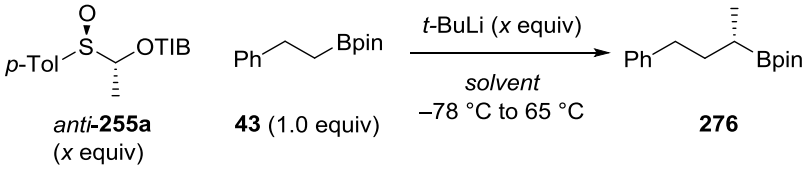
Scheme 3.29. CD_3OD-trapping experiment of lithiated benzoate Li-**108a**.

Further exploration of the reaction conditions revealed that the use of solvents other than THF, such as Et_2O, TBME, CPME or PhMe, resulted in a lower product to starting material ratio, as determined by GCMS analysis (Table 3.5, entries 2−5). Using *t*-BuLi (2.0 equiv) and *anti*-**255a** (1.05 equiv), with boronic ester **43** being the limiting reagent, proved to be the optimal

[ix] The CD_3OD-trapping experiment was conducted by Dr. M. Kucukdisli.

stoichiometry to affect the process; these conditions gave complete conversion of starting boronic ester **43** (**276**:**43** >99:1, as determined by GCMS analysis), with homologated product **276** isolated in 78% yield and excellent e.r. (99:1, 99% es, Table 3.5, entry 8).

Table 3.5. Optimisation of the reaction conditions for the homologation of boronic ester **43** using lithium carbenoids derived from α-sulfinyl benzoates.

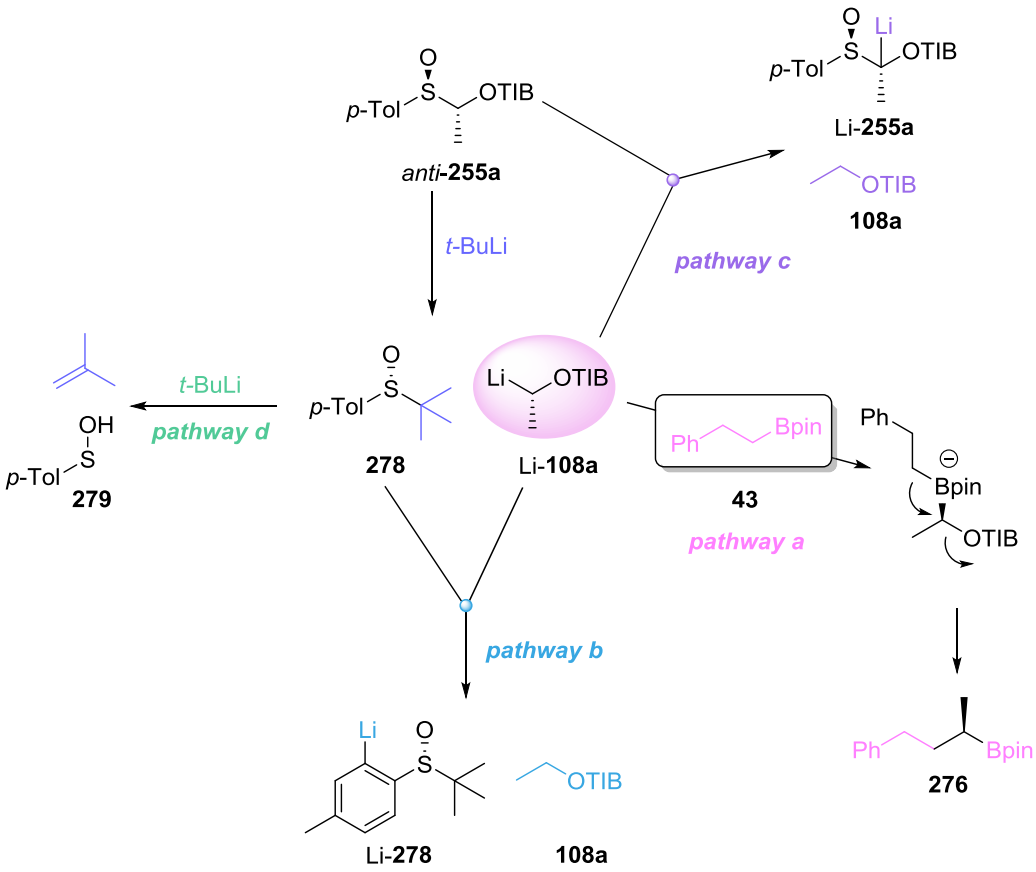


anti-**255a** (*x* equiv) | **43** (1.0 equiv) | **276**

Entry	Equiv *anti*-255a	Equiv *t*-BuLi	Solvent	276:43[a]
1	1.5	1.4	THF	92:8
2	1.5	1.4	Et_2O	20:80
3	1.5	1.4	TBME	58:42
4	1.5	1.4	CPME	28:72
5	1.5	1.4	PhMe	55:45
6	1.5	2.0	THF	96:4
7	1.2	2.0	THF	97:3
8	1.05	2.0	THF	>99:1

Reactions were performed on 0.1 mmol scale. TBME = *tert*-butyl methyl ether; CPME = cyclopentyl methyl ether.
[a] Determined by GCMS analysis of the crude reaction mixture.

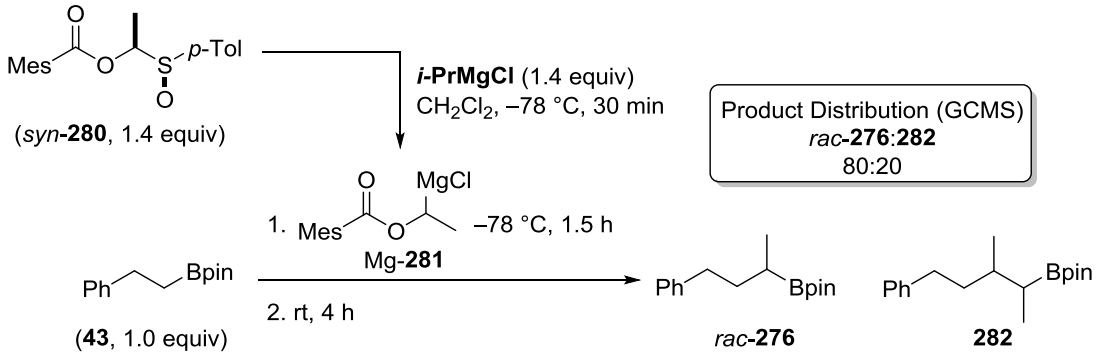
The extra equivalent of *t*-BuLi is presumably needed as a sacrificial base quenching deleterious internal proton sources, such as the already mentioned *ortho*-protons of aryl-alkyl sulfoxide by-product **278** (Scheme 3.30, pathway b), the α-proton of starting sulfoxide *anti*-**255a** (Scheme 3.30, pathway c) and adventitious moisture.[156] The low yield of isolated sulfoxide **278** might also suggest that base-mediated decomposition affording sulfenic acid **279** and isobutene might also be operating (Scheme 3.30, pathway d).



Scheme 3.30. Possible reaction pathways in the homologation of boronic ester **43** with lithium carbenoid Li-**108a**.

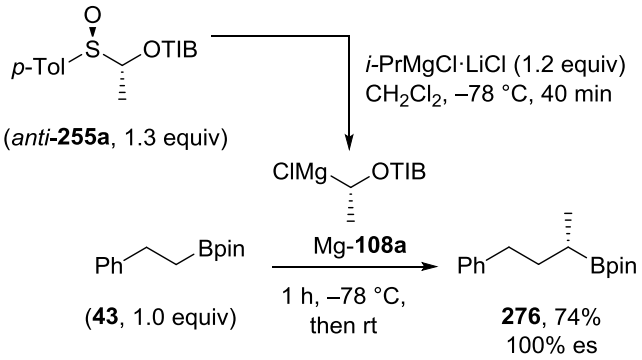
With the aim of identifying milder reaction conditions that would tolerate sensitive functional groups, we also investigated the possibility of homologating boronic ester **43** using *in situ* generated magnesium carbenoids, which are known to be more chemically and configurationally stable than the corresponding lithium carbenoids.[29, 80, 157] Preliminary studies indicated that the use of *i*-PrMgCl to trigger the putative sulfoxide−magnesium exchange of α-sulfinyl benzoate **280**, followed by trapping of the generated carbenoid with boronic ester **43**, resulted in an inseparable mixture of homologated boronic ester *rac*-**276** and over-homologated boronic ester **282** (Scheme 3.31).[x] *In situ* generated magnesium carbenoid Mg-**281** was presumably stable at the temperature where the 1,2-metallate rearrangement of the boronate complex occurs, with the consequence that desired boronic ester *rac*-**276** underwent further homologation with the metal carbenoid to form **282**. In contrast, lithium carbenoids are known to decompose at temperatures above −40 °C.[73]

[x] Initial results on the homologation of boronic ester **43** using α-sulfinyl benzoate **280** and *i*-PrMgCl were obtained by Dr. M. Burns.



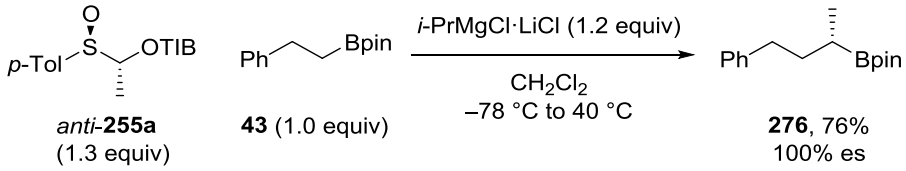
Scheme 3.31. Homologation of boronic ester **43** with magnesium carbenoid Mg-**281** generated with *i*-PrMgCl.

Knochel and co-workers showed that the presence of Lewis acidic lithium chloride in the reaction mixture is able to complex the generated magnesium carbenoid, reducing its stability and thus increasing its reactivity.[158-159] We therefore decided to test the use of turbo Grignard reagent *i*-PrMgCl·LiCl to trigger the sulfoxide−magnesium exchange. Pre-formation of magnesium carbenoid Mg-**108a** by treatment of sulfoxide *anti*-**255a** in CH_2Cl_2 at −78 °C, followed by trapping with boronic ester **43** (*ex situ* conditions), gave improved results, leading to complete conversion of starting boronic ester **43** to the desired one-carbon-homologated product **276**, with no trace of any higher homologous detected (Scheme 3.32).



Scheme 3.32. Homologation of boronic ester **43** with magnesium carbenoid Mg-**108a** generated with turbo Grignard reagent *i*-PrMgCl·LiCl under *ex situ* conditions.

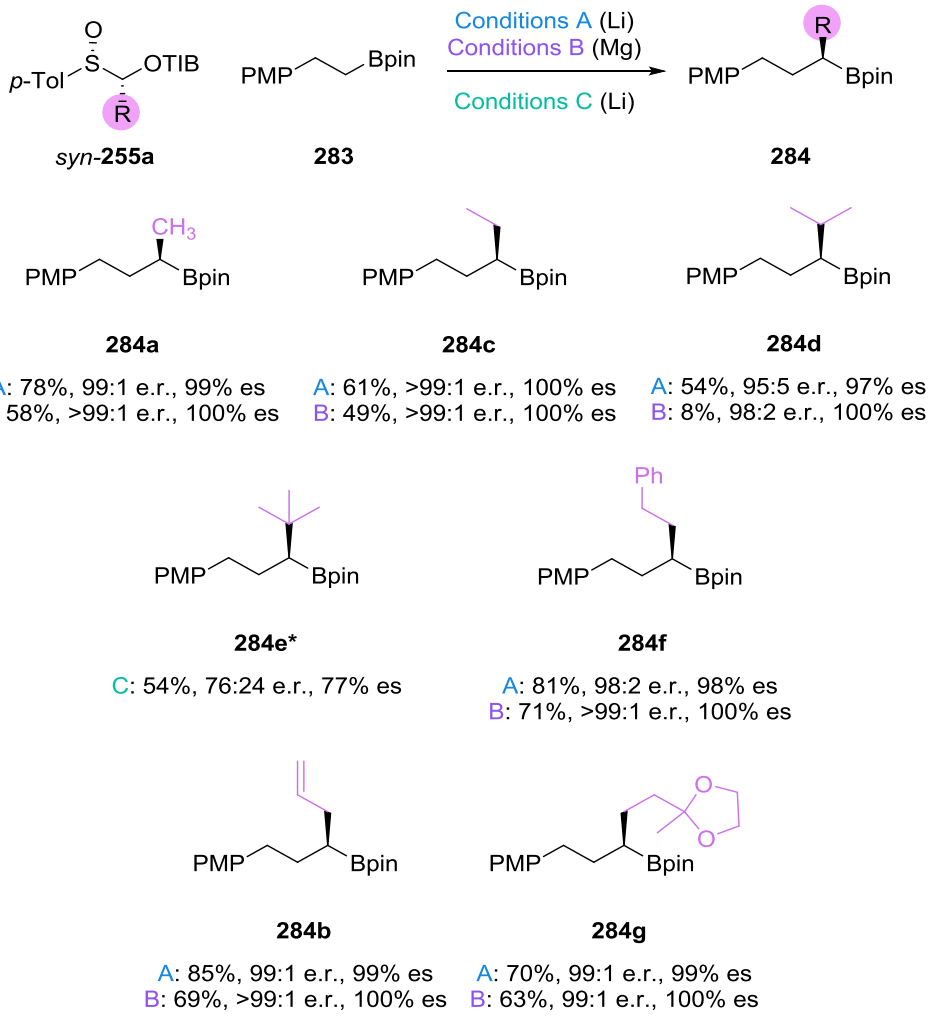
A similar result was obtained when the reaction was performed under *in situ* conditions, i.e. by addition of the turbo Grignard reagent to a mixture of sulfoxide *anti*-**255a** and boronic ester **43**. In this case, homologated boronic ester **276** was isolated in 76% yield and excellent enantiopurity (e.r. >99:1, 100% es, Scheme 3.33).



anti-**255a** (1.3 equiv) **43** (1.0 equiv) **276**, 76% 100% es

Scheme 3.33. Homologation of boronic ester **43** with magnesium carbenoid Mg-**108a** generated with turbo Grignard reagent *i*-PrMgCl·LiCl under *in situ* conditions.

With optimal conditions to homologate boronic esters using both lithium and magnesium carbenoids, we were prompt to screen the scope of this reaction. Boronic ester **283** was therefore homologated with a range of different substituted α-sulfinyl benzoates **255a-g** using both *t*-BuLi in THF (Conditions A) and *i*-PrMgCl·LiCl in CH_2Cl_2 (Conditions B, Scheme 3.34). Sulfoxides **255a-c,f**, bearing non-branched substituents, were found to perform well in the process, giving homologated products **284a-c,f** in good yields and excellent levels of enantiospecificity under both sets of reaction conditions, with the use of the lithium carbenoid giving slightly improved results. Not surprisingly, when α-sulfinyl benzoate **255d** bearing a more sterically hindered substituent was employed, appreciable amounts of homologated boronic ester **284d** could only be obtained through the generation of the more reactive lithium carbenoid, that gave homologated product **284d** in 54% yield and 95:5 e.r. (97% es). The insertion of magnesium carbenoids into C−B bonds of boronic esters is presumably much more sensitive to steric hindrance than the corresponding lithium carbenoids, with the consequence that branched-substituted magnesium carbenoids are not sufficiently reactive to homologate boronic esters.

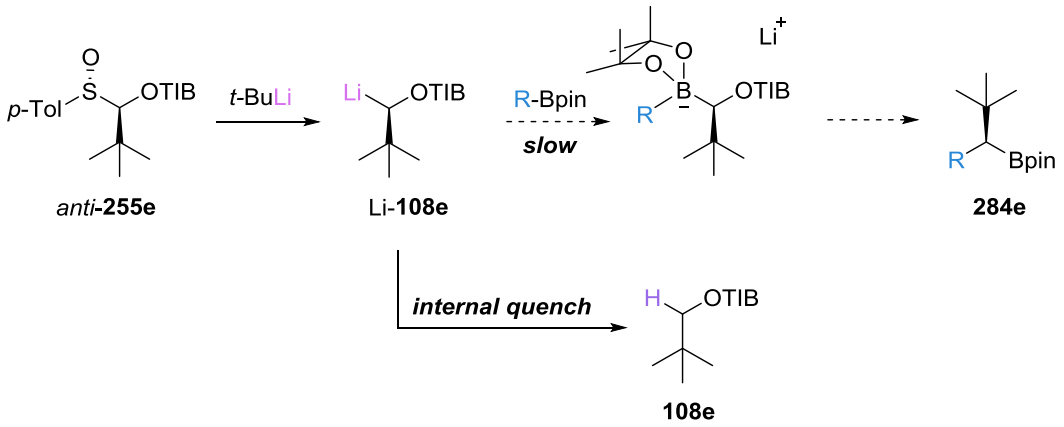


Scheme 3.34.[xi] Scope of α-sulfinyl benzoates for the homologation of boronic ester **283** using *t*-BuLi and *i*-PrMgCl·LiCl. Conditions A: **255** (1.05 equiv), **283** (1.0 equiv) and *t*-BuLi (2.0 equiv) in THF. Conditions B: **255** (1.3 equiv), **283** (1.0 equiv) and *i*-PrMgCl·LiCl (1.2 equiv) in CH_2Cl_2. Conditions C: addition of **255** (1.3 equiv) to *t*-BuLi (2.0 equiv) and PMDTA (*N*,*N*,*N*',*N*'',*N*''-pentamethyldiethylenetriamine, 2.0 equiv), then addition of **283** (1.0 equiv). Reaction performed on a 0.2 mmol scale. Yields are based on isolated products. The e.r. values were determined by chiral HPLC analysis of the corresponding alcohols.

When *tert*-butyl substituted sulfoxide **255e** was employed, no desired homologated boronic ester **284e** was observed under either set of reaction conditions. Detection of considerable quantities of neopentyl benzoate **108e** indicated that quenching of the generated carbenoid by an internal proton source was the predominant pathway (Scheme 3.35). A plausible explanation is that the boronate complex formation is in this case slower than normal owing to the increased steric hindrance. Pleasingly, desired homologated product could be isolated in good yield using a reverse-addition protocol, where α-sulfinyl benzoate **255e** was added to a solution of *t*-BuLi in Et_2O in the presence of *N*,*N*,*N*',*N*'',*N*''-pentamethyldiethylenetriamine (PMDTA), followed by the addition of the boronic ester (Scheme 3.34, Conditions C). The relatively low yield for

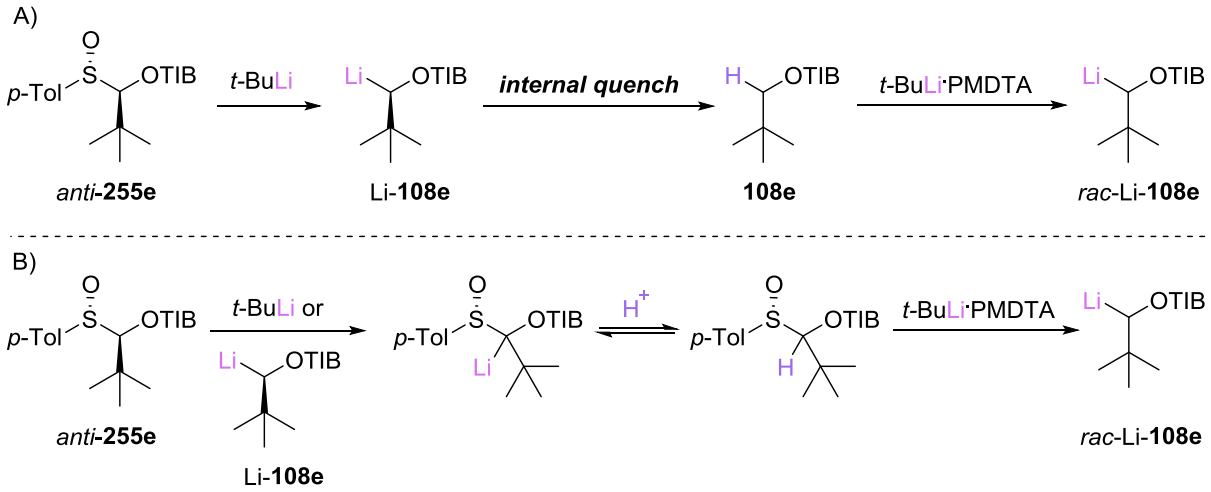
[xi] Where indicated (*), the experimental work discussed in this chapter was conducted by Dr. M. Kucukdisli.

isolated boronic ester **284e** suggests that in the case of sterically hindered benzoate **255e** either the sulfoxide−lithium exchange or the boronate complex formation (or both the processes) are slower than expected, so that quenching of the generated lithiated species Li-**108e** by the acidic α-proton on the carbenoid precursor **255e** is a competing pathway.



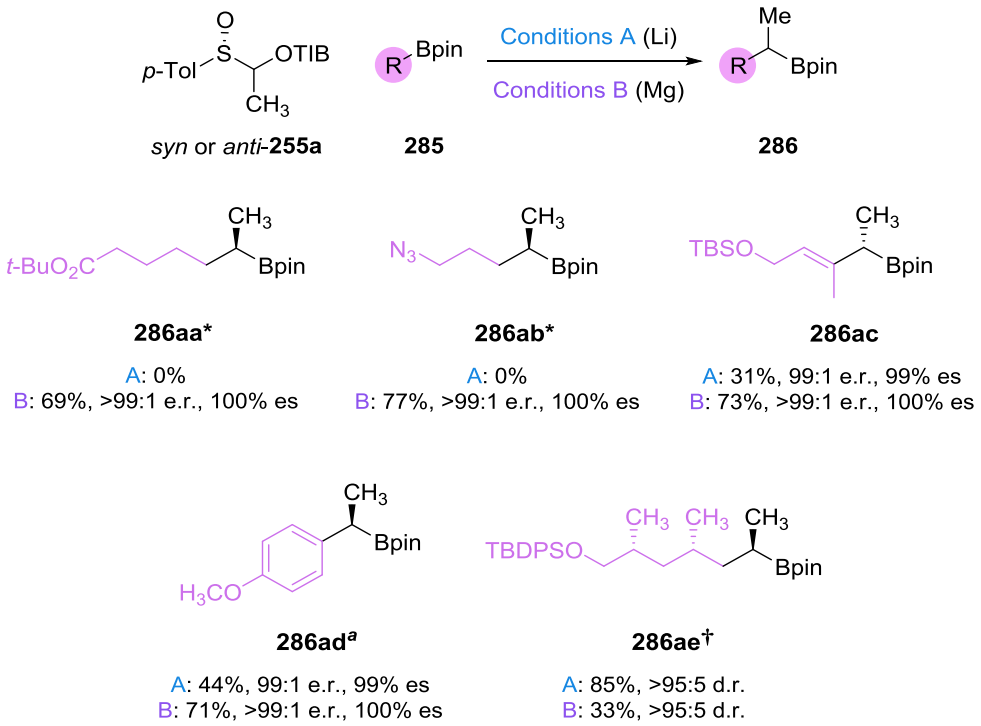
Scheme 3.35. Competing quenching of the *in situ* generated lithium carbenoid in the homologation of boronic ester **283** with sulfoxide *anti*-**255e**.

Unexpectedly, homologated product **284e** was isolated in moderate enantiospecificity (77% es). The two possible scenarios that account for this lack of enantiospecificity when sulfoxide **255e** was employed are shown in Scheme 3.36. One possibility is that neopentyl benzoate **108e**, generated by quenching of enantioenriched lithium carbenoid Li-**108e** by an internal proton source, undergoes deprotonation in the presence of a combination of *t*-BuLi and PMDTA to give racemic lithiated species *rac*-Li-**108e** (Scheme 3.36A). Alternatively, since the sulfoxide−lithium exchange is slower in this case, an α-deprotonation/reprotonation process could compete, eventually leading to a diastereomeric mixture of *syn* and *anti*-**255e** undergoing the homologation reaction (Scheme 3.36B).



Scheme 3.36. Possible mechanisms for the observed lack of enantiospecificity in the homologation of boronic ester **283** with sulfoxide *anti*-**255e**.

The scope of the boronic ester component was also briefly explored (Scheme 3.37). Boronic esters bearing sensitive functional groups, such as *tert*-butyl ester (**285a**) or azido (**285b**) groups, could only be successfully homologated with sulfoxide **255a** by reaction with the corresponding magnesium carbenoid, to give boronic esters **286aa** and **286ab**, respectively. This is not surprising, considering the high reactivity of organolithiums towards these functional groups, therefore preventing the formation of the desired boronate complex. Magnesium carbenoids were also found to be superior reagents for the homologation of vinyl and aryl boronic esters (**285c-d**), while when the lithium carbenoid was employed, although the expected products were isolated, the yields were significantly reduced. Finally, more sterically hindered boronic ester **285e** was also successfully homologated with sulfoxide **255a**. In this case, better results were obtained using the more reactive lithium carbenoid that allowed the isolation of homologated boronic ester **256ae** in 85% yield and as a single diastereoisomer.



Scheme 3.37.[xii] Homologation of boronic esters with α-sulfinyl benzoate **255a** using *t*-BuLi and *i*-PrMgCl·LiCl. Conditions A: **255a** (1.05 equiv), **285** (1.0 equiv) and *t*-BuLi (2.0 equiv) in THF. Conditions B: **255a** (1.3 equiv), **285** (1.0 equiv) and *i*-PrMgCl·LiCl (1.2 equiv) in CH_2Cl_2. Reaction performed on a 0.2 mmol scale. Yields are based on isolated products. The e.r. values were determined by chiral HPLC analysis of the corresponding alcohols. The d.r. values were determined by ^{13}C NMR analysis; [a] *ent-anti*-**255a** was used.

3.2.5. Synthesis of Enantioenriched α-Sulfinyl Benzoates by Alkylation

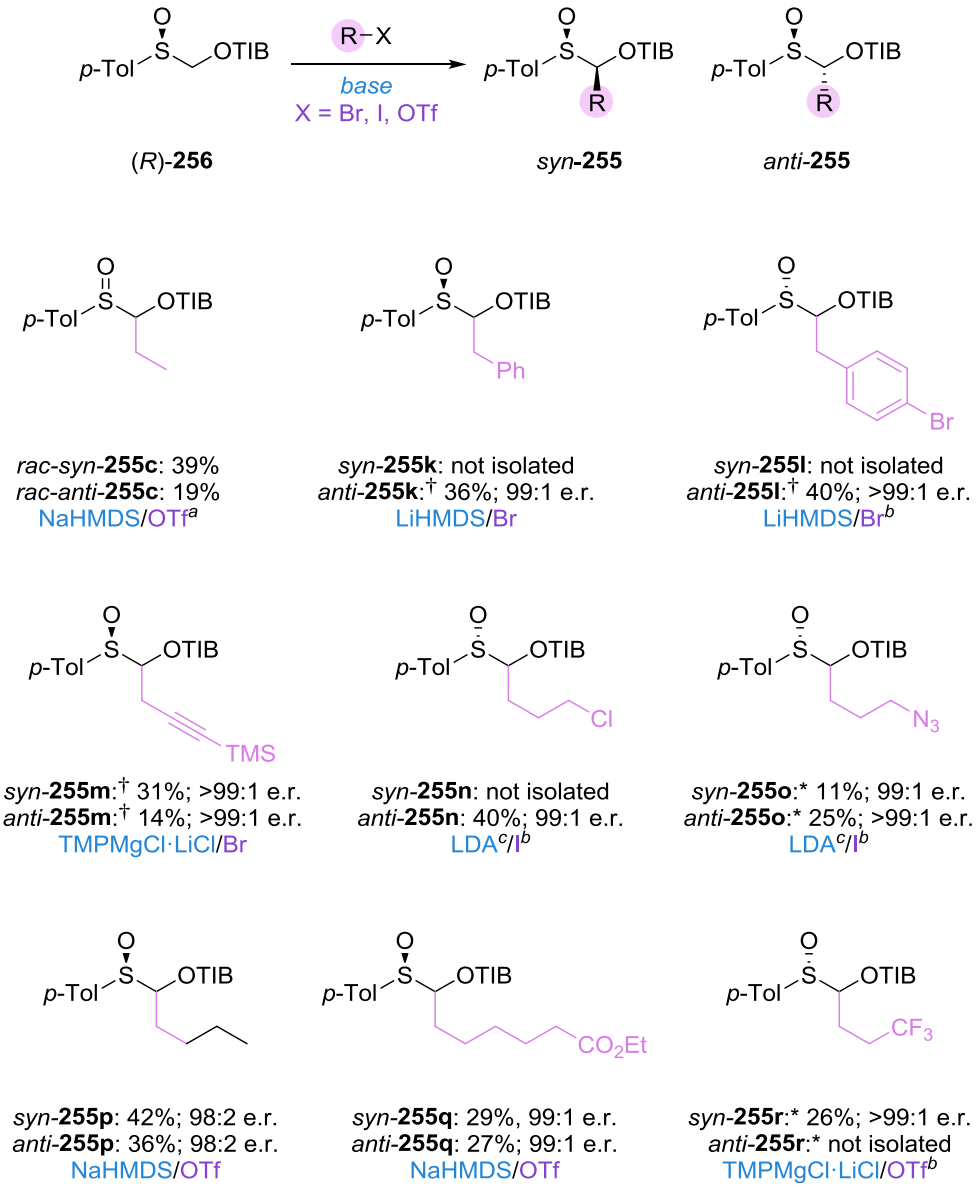
Compared to tin–lithium exchange, sulfoxide–metal exchange is extremely fast; this has been shown by the fact that the metal carbenoid could be generated under *in situ* conditions, indicating that the exchange occurs more rapidly than the reaction of the organolithium with the boronic ester. This means that sensitive functional groups, that would normally be reactive towards organometals, could potentially be tolerated in the process, thus marking a substantial advance in the lithiation–borylation methodology. However, the protocol described for the synthesis of enantioenriched α-sulfinyl benzoates nullifies this potential, since the strong base necessary for the initial deprotonation of benzoates is not compatible with the presence of sensitive functional groups. We therefore decided to explore a different strategy to access substituted α-sulfinyl benzoates.

We have already shown that methylene sulfoxide **256** can be deprotonated at the alpha position using relatively weak bases, such as LDA and LiHMDS, and subsequently trapped with methyl

[xii] Where indicated, the experimental work discussed in this chapter was conducted by Dr. M. Kucukdisli (*) and J. M. Fordham (†).

iodide or allyl iodide (see § 3.2.1). We wondered if general conditions to alkylate sulfoxide **256** could be developed in order to introduce a range of different functional groups. Unfortunately, the conditions to perform this alkylation reaction were found to be highly dependent on the electrophile employed and extensive optimisation was required to achieve the synthesis of a variety of substituted α-sulfinyl benzoates (Scheme 3.38). In particular, very reactive electrophiles were found to be fundamental to ensure the success of the process, with triflates generally performing better than the corresponding halides. With less reactive electrophiles, trapping of the *in situ* generated anion became in fact too slow and decomposition pathways became evident. For instance, ethyl substituted benzoate **255c** could only be accessed by treatment of a solution of sulfoxide *rac*-**256** and EtOTf (1.1 equiv) in THF with NaHMDS (1.05 equiv), while EtBr, EtI and EtOMs failed to provide the desired product. Under these conditions, a separable mixture of *syn* and *anti*-**255c** was isolated in 58% yield (*syn*-**255c**:*anti*-**255c** ca. 2:1). The same protocol was also found to be successful when butyl triflate was used as the alkylating agent to give α-sulfinyl benzoates *syn* and *anti*-**255p** in 56% overall yield (*syn*-**255p**:*anti*-**255p** ca. 1:1). Benzoate **255q**, bearing an ester-terminated pentyl substituent, was also obtained employing the corresponding triflate under the same reaction conditions. Alkylation of sulfoxide (*S*)-**256** using commercially available 1-chloro-3-iodo propane as the electrophile proved to be more challenging. LDA, LiTMP and NaHMDS failed to provide desired sulfoxides *syn* and *anti*-**255n** and only decomposition of the *in situ* generated anion was observed. Addition of AgOTf to favour the alkylation step by precipitating AgI did not give improved results. However, performing the alkylation reaction using LDA as the base in the presence of hexamethylphosphoramide (HMPA) as an activator resulted in the formation of desired sulfoxides *syn* and *anti*-**255n**, with *anti*-**255n** being the major product.

Further optimisation allowed the synthesis of α-sulfinyl benzoates **255k-m,o,r**. Remarkably, sensitive functional groups, such as azido (**255o**) and trifluoromethyl groups (**255r**) could be successfully installed together with other useful substituents (**255k-m**) which would have not been possible to introduce *via* sulfinylation of the corresponding benzoates.



Scheme 3.38.[xiii] Optimal reaction conditions for the alkylation of α-sulfinyl benzoate **256** with a range of electrophiles. [a] Prepared from *rac*-**256**; [b] prepared from (*S*)-**256**; [c] in the presence of HMPA.

As aforementioned, the diastereoselectivity of these alkylation reactions was highly variable and difficult to predict. In general, we noticed that the generation of lithium carbenoids resulted in preferential formation of the *anti* diastereoisomer, while the use of magnesium bases gave the *syn* diastereoisomer as the major product. In contrast, poor diastereocontrol was observed when sodium bases were employed. This seems to suggest that the coordination of the metal centre to the electrophile plays a key role in determining the diastereoselectivity of the process, as well as its influence on the aggregation state of the generated carbanion.[160]

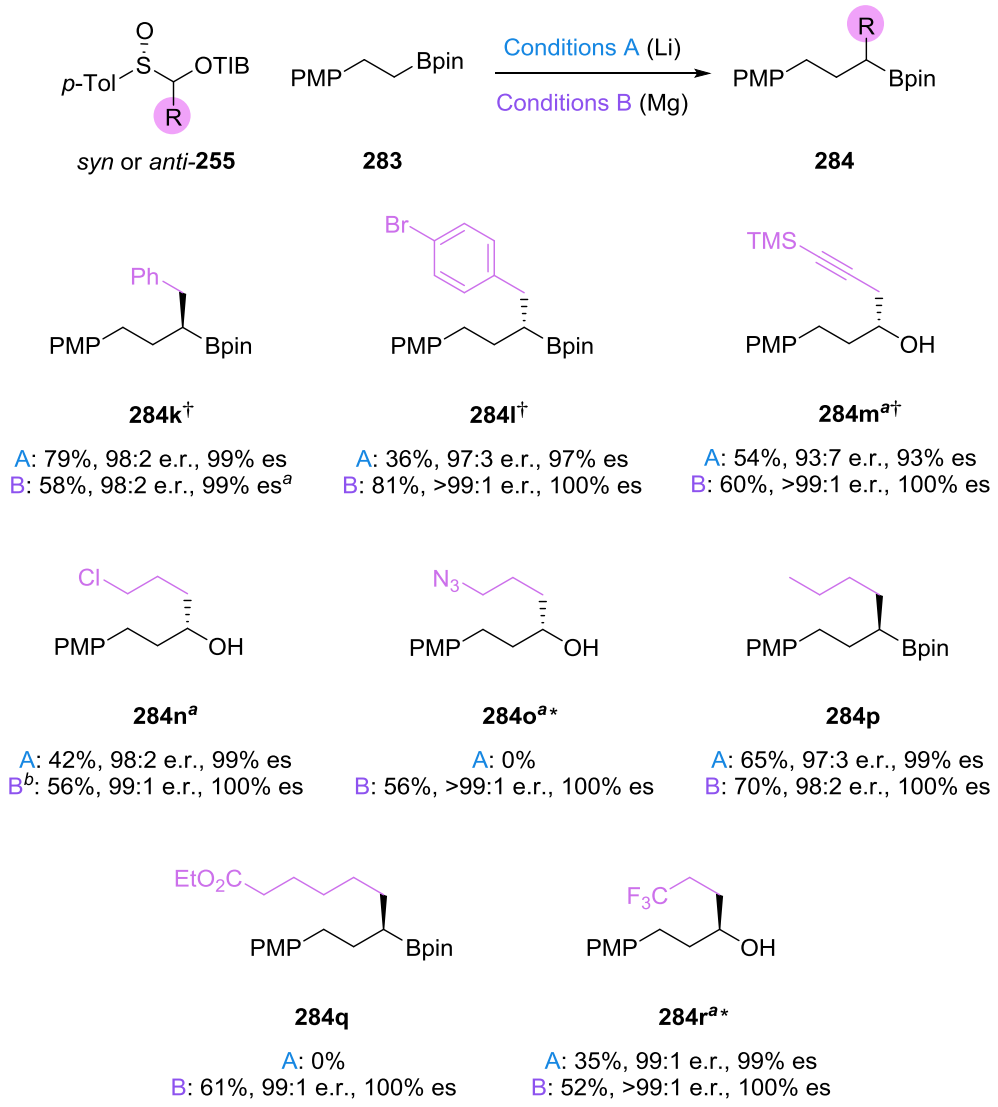
[xiii] Where indicated, the experimental work discussed in this chapter was conducted by Dr. M. Kucukdisli (*) and J. M. Fordham (†).

A variety of other electrophiles were also tested in the process, such as Togni reagents I and II, Umemoto reagent and the Eschenmoser's salt, but were found to be unable to afford the corresponding alkylated α-sulfinyl benzoates, with decomposition of the generated lithium carbenoid becoming apparent in most of the cases.[xiv]

3.2.6. Homologation of Boronic Esters with Functional Group-Rich α-Sulfinyl Benzoates

α-Sulfinyl benzoates **255k-r** were subsequently tested as precursors to lithium (*t*-BuLi) and magnesium (*i*-PrMgCl·LiCl) carbenoids in the homologation of boronic ester **283** (Scheme 3.39). Unsurprisingly, better results in terms of both yields and enantiospecificity were obtained through the generation of the less reactive magnesium carbenoids. In the case of azidopropyl and ester-terminated pentyl substituted sulfoxides **255o** and **255q**, no product could be isolated when *t*-BuLi was employed; however, the use of milder reaction conditions using *i*-PrMgCl·LiCl gave access to homologated products **284o-q** in good yield and excellent stereospecificity.

[xiv] Alkylation of methylene sulfoxide **256** using Togni reagents I and II, Umemoto reagent and Eschenmoser's salt as the electrophiles was performed by J. M. Fordham.



Scheme 3.39.[xv] Homologation of boronic esters with lithium or magnesium carbenoids derived from α-sulfinyl benzoates, as prepared through the alkylation of α-sulfinyl benzoate (*R*)-**256** or (*S*)-**256**. Conditions A: **255a** (1.05 equiv) and *t*-BuLi (2.0 equiv) in THF. Conditions B: **255a** (1.3 equiv) and *i*-PrMgCl·LiCl (1.2 equiv) in CH_2Cl_2. Reactions performed on a 0.2 mmol scale. Yields are based on isolated product. The e.r. values were determined through chiral HPLC analysis of the corresponding alcohols. [a] Boronic ester oxidised to the corresponding alcohol prior to isolation; [b] magnesium carbenoid formed prior to the addition of the boronic ester.

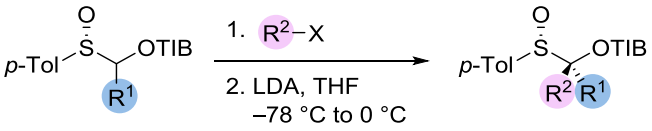
3.2.7. Synthesis of Fully Substituted α-Sulfinyl Benzoates

We next embarked on the synthesis of fully substituted α-sulfinyl benzoates, that, if used in the homologation of boronic esters, would afford useful enantioenriched tertiary boronic esters.[xvi] Alkylation of methyl-substituted sulfoxide **255a** with benzyl iodide using LDA as the base afforded fully substituted sulfoxide **287aa** in 77% yield (Table 3.6, entry 2). As previously

[xv] Where indicated, the experimental work discussed in this chapter was conducted by Dr. M. Kucukdisli (*) and J. M. Fordham (†).
[xvi] The synthesis of fully substituted α-sulfinyl benzoates was conducted by Dr. M. Kucukdisli.

observed, the use of a very reactive electrophile was found to be essential (Table 3.6, entries 1−2).

Table 3.6. Synthesis of disubstituted α-sulfinyl benzoates through alkylation of monosubstituted derivatives.



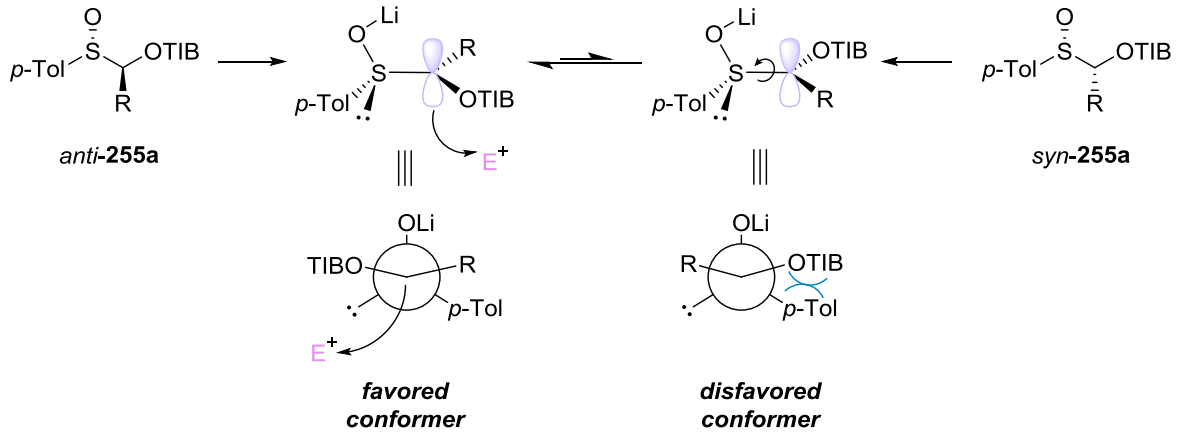
syn or *anti*-**255a** **287**

Entry	R^1	R^2	X	Product	d.r.[a]	% Yield
1	CH_3	$PhCH_2$	Br	**287aa**	>95:5	10
2	CH_3	$PhCH_2$	I	**287aa**	>95:5	77
3	CH_3	CH_2=$CHCH_2$	I	**287ab**	>95:5	76
4	CH_3	CH_3CH_2	OTf	**287ac**	60:40	38
5	CH_3	CH_3CH_2	I	–	–	–
6	CH_2=$CHCH_2$	CH_3	I	**287ab**	80:20	n.d.
7	$PhCH_2CH_2$	CH_3	I	**287ad**	92:8	59

Reaction conditions: benzoate **255a** (1.0 equiv), R^2-X (1.5 equiv), LDA (1.8 equiv) in THF, −78 °C. [a] Determined by ^{1}H NMR analysis.

Importantly, α-sulfinyl benzoate **287aa** was obtained in very high diastereoselectivity (>95:5), with the major diastereoisomer being the one placing the benzoate group opposite to the oxygen atom of the sulfinyl group. The use of either the *syn* or the *anti* diastereoisomer of the starting sulfoxide **255a** led to the formation of the same major product, therefore suggesting the intermediacy of a common carbanionic species.[161] A plausible mechanism accounting for the observed diastereoselectivity is shown in Scheme 3.40. The carbanion generated by deprotonation of sulfoxide **255a** exists as two different conformers; only the more thermodynamically stable, which is the one displaying the large benzoate substituent on the same side of the lone pair on the sulfur centre, is involved in the subsequent trapping step. The electrophile then approaches the carbanion from the *re* face, which is not hindered by the presence of the oxygen atom on the sulfinyl group.[162] Furthermore, the attack of the electrophile from the *re* face leads to an increase in the dihedral angle between the R substituent on the carbanionic carbon centre and the *p*-tolyl group on the vicinal sulfur centre, while the approach from the more hindered *si* face would reduce this angle, which would increase the strain. This model can also account for the low diastereoselectivity observed in the case of the alkylation of methylene sulfoxide **256**. In this case, the absence of a substituent on the

carbanionic centre brings no such strain when the electrophile approaches from the *si* face. Furthermore, a deprotonation/reprotonation process at the alpha position might also be operating under reaction conditions, which would also lead to poor diastereocontrol (see § 3.2.1 and 3.2.3).



Scheme 3.40. Proposed model rationalising the observed diastereoselectivity observed in the alkylation of α-sulfinyl benzoates.

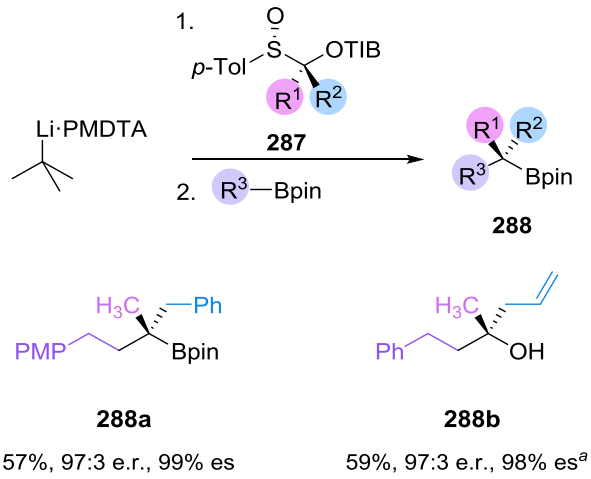
Sulfoxide **255a** was also alkylated using allyl iodide as the electrophile to access sulfoxide **287ab** in 76% yield and perfect diastereoselecivity (Table 3.6, entry 3). Unfortunately, alkylation of sulfoxide **255a** using smaller electrophiles, such as methyl iodide and ethyl triflate, gave inferior results, with the corresponding fully substituted α-sulfinyl benzoates being isolated as inseparable mixtures of diastereoisomers (Table 3.6, entries 5–7). It might be postulated that the smaller size of the incoming electrophile leads to a reduced facial selectivity, with the *si* face also becoming accessible. Additionally, in the case of ethyl triflate, coordination of the triflate group to the lithium counter anion might direct the attack of the electrophile from the more hindered face of the favoured conformer.[160]

3.2.8. Synthesis of Enantioenriched Tertiary Boronic Esters

Diastereo- and enantiopure fully substituted α-sulfinyl benzoates **287aa** and **287ab** were subsequently tested in the homologation of boronic esters to access α-tertiary boronic esters (Scheme 3.41).[xvii] Unsurprisingly, homologation of boronic ester **283** with sulfoxide **287aa** failed under both sets of the previously described conditions for the generation of the lithium and magnesium carbenoids. Similarly to the case of *tert*-butyl substituted sulfoxide **255e**, the sulfoxide–metal exchange for sulfoxide **287aa** is significantly slower owing to increased steric

[xvii] The homologation of boronic esters using fully substituted α-sulfinyl benzoates was conducted by Dr. M. Kucukdisli.

hindrance, with the consequence that the *t*-BuLi attacks the boronic ester to produce an ineffective boronate complex. When the reverse-addition protocol developed for the homologation of boronic esters using sulfoxide **255e** (addition of the sulfoxide to a solution of *t*-BuLi in Et_2O in the presence of PMDTA at −78 °C, followed by addition of the boronic ester, see § 3.2.4) was applied, we were pleased to isolate, after oxidation, desired homologated product **288a** in 57% yield and 99% es. The same conditions were subsequently applied to the homologation of boronic ester **43** with sulfoxide **287ab**, to give homologated alcohol **288b** in good yield and similar levels of enantiospecificity, in contrast with the result obtained with *tert*-butyl substituted sulfoxide **255e**, where the corresponding homologated product was isolated in lower e.r. (see § 3.2.4) This is consistent with the mechanism depicted in Scheme 3.40, suggesting that the observed lack of enantiospecificity is due to a base-mediated epimerisation at the alpha position of sulfoxide **255e** under reaction conditions.



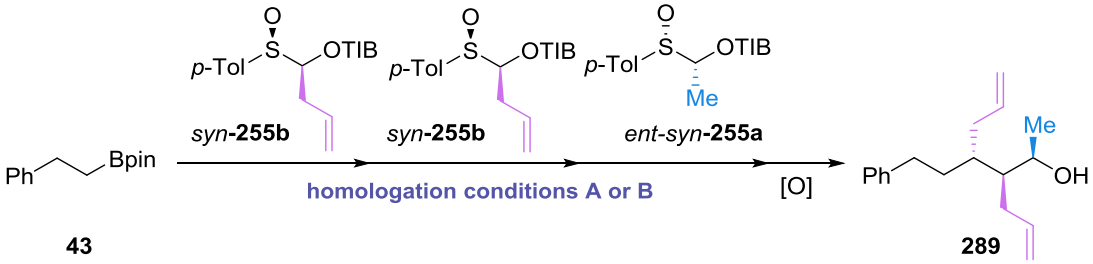
Scheme 3.41. Homologation of boronic esters with disubstituted α-sulfinyl benzoates. Conditions: addition of benzoate **287** (1.3 equiv) to a solution of *t*-BuLi (2.0−2.3 equiv) and PMDTA (2.0−2.3 equiv) in Et_2O, then boronic ester (1.0 equiv). [a] The boronic ester was oxidised to the corresponding alcohol prior to isolation.

3.2.9. Iterative Homologation of Boronic Esters Using α-Sulfinyl Benzoates

Having shown that substituted α-sulfinyl benzoates can be efficiently employed to homologate boronic esters, we sought to investigate the possibility of performing several iterative homologations. In particular, we wished to avoid chromatographic purification after each step, hoping that a simple filtration through a plug of silica gel would be sufficient to remove the highly polar side-products generated in each iteration. We initially planned to subject phenethyl pinacol boronic ester **43** to two consecutive homologations using allyl-substituted benzoate *syn*-**255b** followed by a third homologation with methyl-substituted benzoate *ent*-*syn*-**255a**; this three-pot process would eventually afford, after final oxidation, triple homologated

alcohol **289** (Table 3.7).[xviii] As expected, boronic ester **43** could be efficiently homologated using either lithium or magnesium carbenoids generated *in situ* from sulfoxide *syn*-**255b**. GCMS analysis of the crude reaction mixture showed very high ratios of desired product to starting material **43** in both cases (99:1 and 98:2 respectively, Table 3.7, entries 1−2). The second homologation process proved to be more challenging and low product to starting material ratio was observed by GCMS analysis (26:74, Table 3.7, entry 2) when the magnesium carbenoid was employed. The increased steric hindrance around the boron centre presumably decreased the rate for the formation of the intermediate boronate complex to an extent that internal quenching of the carbenoid became the privileged pathway. Pleasingly, the more reactive lithium carbenoid was found to give improved results, with high product to starting material ratios determined by GCMS analysis (96:4, Table 3.7, entry 1). The third iteration was conducted using the lithium carbenoid generated from methyl-substituted benzoate *ent-syn*-**255a**. However, low product to starting material ratio was observed by GCMS analysis when standard optimal conditions were applied (60:40, Table 3.7, entry 1), and alcohol **289** was isolated in only 29% yield over the four steps (65% yield per iteration, Table 3.7, entry 1). Further optimisation revealed that using an excess of both α-sulfinyl benzoate *ent-syn*-**255a** (1.5 equiv) and *t*-BuLi (3.0 equiv) gave an improved product to starting material ratio observed by GCMS analysis (85:15, Table 3.7, entry 3), with the targeted triple homologated alcohol **289** isolated in 41% yield and >95:5 d.r. (75% yield per iteration, Table 3.7, entry 3).

Table 3.7. Iterative homologation of boronic esters using α-sulfinyl benzoates.



43 289

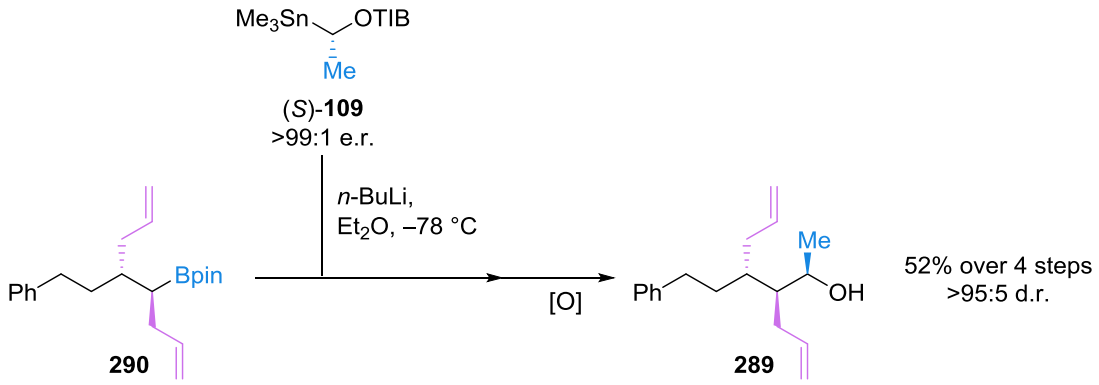
Entry	Conditions	1st P:SM	2nd P:SM	3rd P:SM	% Yield 289	d.r.
1	A	98:2	96:4	60:40	29	>95:5
2	B	99:1	26:74	–	–	–
3	A’	98:2	96:4	85:15	41	>95:5

Conditions A: boronic ester (1.0 equiv), sulfoxide (1.05 equiv) and *t*-BuLi (2.0 equiv) in THF (*in situ* conditions). Conditions B: boronic ester (1.0 equiv), sulfoxide (1.3 equiv) and *i*-PrMgCl·LiCl (1.2 equiv) in CH_2Cl_2 (*in situ* conditions). Conditions A’: boronic ester (1.0 equiv), sulfoxide (1.5 equiv) and *t*-BuLi (3.0 equiv) in THF (*in situ* conditions). The first two homologations were carried out on a 1.0 mmol scale and the third on a 0.33 mmol scale. The oxidation step was performed using $NaBO_3 \cdot 4H_2O$. Product to starting material ratios were determined

[xviii] The iterative homologations of boronic ester **43** using α-sulfinyl benzoates were conducted by J. M. Fordham.

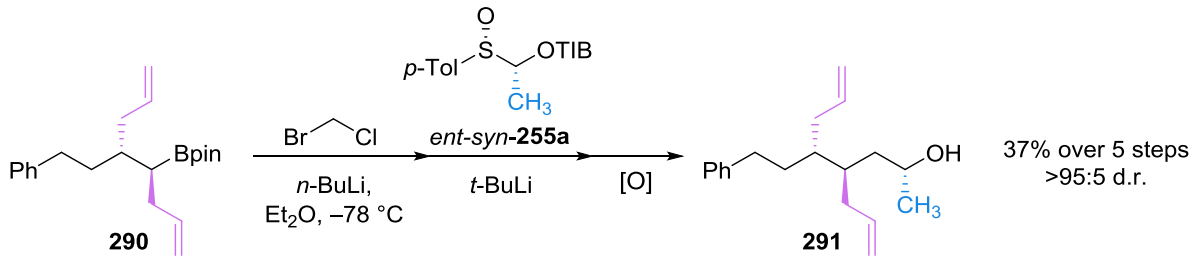
by GCMS analysis of the crude reaction mixtures. Yields reported are those of alcohol **289** isolated by column chromatography (over the four steps). Diastereomeric ratios were determined by ^{13}C NMR analysis.

The efficiency of the third homologation could be further improved using methyl substituted α-stannyl benzoate (*S*)-**109** as the carbenoid precursor. Treatment of a solution of benzoate (*S*)-**109** (1.35 equiv) with *n*-BuLi (1.3 equiv), followed by addition of double homologated boronic ester **290** allowed the isolation of alcohol **289** in 52% yield and as a single diastereoisomer (80% yield per iteration, Scheme 3.42). The high product to starting material ratio observed by GCMS analysis when the required lithium carbenoid was generated from α-stannyl benzoate is an indication of the impact of the acidity of monosubstituted α-sulfinyl benzoates in the homologation of sterically hindered boronic esters, where the internal quenching of the generated lithium carbenoid competes with the formation of the required boronate complex (see § 3.2.4).



Scheme 3.42. Homologation of boronic ester **290** using α-stannyl benzoate (*S*)-**109**. Reaction conditions: (*S*)-**109** (1.35 equiv) and *n*-BuLi (1.3 equiv) in Et_2O, then boronic ester **290** (1.0 equiv). The oxidation step was performed using $NaBO_3{\cdot}4H_2O$ (10 equiv) in THF/H_2O (3:2). Diastereomeric ratios were determined by ^{13}C NMR analysis.

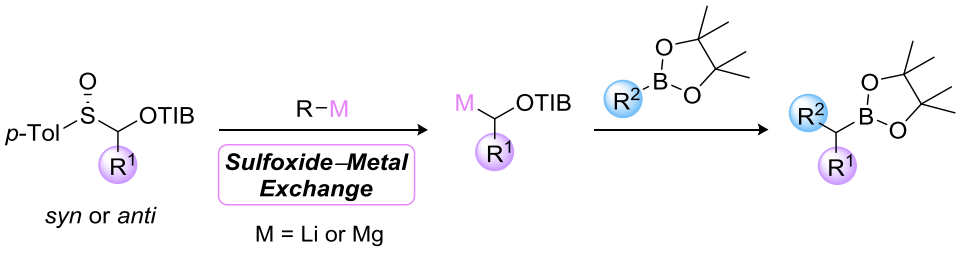
To further demonstrate the relevance of steric hindrance on these type of iterative homologation processes, we embarked in the synthesis of alcohol **291**, which required a similar protocol to the one applied to access alcohol **289**, but with the incorporation of a Matteson homologation between the second and the third iteration (Scheme 3.43). The alleviation of the steric encumbrance around the boron centre through the introduction of a methylene unit led to a higher product to starting material ratio observed by GCMS analysis and desired alcohol **291** was isolated in 37% yield over the five steps (82% yield per iteration), thus providing an efficient way to overcome the limitations of the methodology.



Scheme 3.43. Iterative homologation of boronic ester **290** using sulfinyl benzoate *ent-syn*-**255a** with an intervening Matteson homologation. Reaction conditions: boronic ester **290** (1.0 equiv), bromochloromethane (3.0 equiv) and *n*-BuLi (2.5 equiv) in Et_2O; *ent-syn*-**255a** (1.1 equiv) and *t*-BuLi (2.0 equiv) in THF (*in situ* conditions). The oxidation step was performed using $NaBO_3 \cdot 4H_2O$ (10 equiv) in THF/H_2O (3:2). Diastereomeric ratios were determined by ^{13}C NMR analysis.

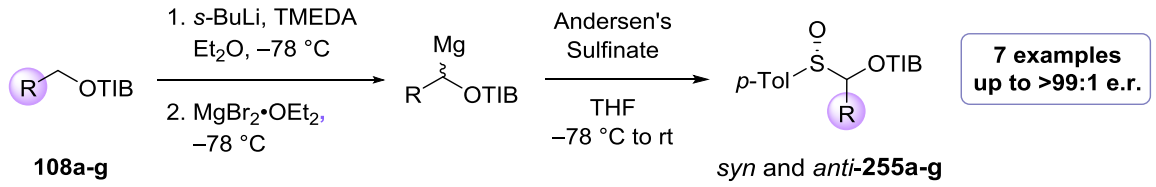
3.3. Conclusions

The results reported demonstrate that α-sulfinyl benzoates can be successfully employed in the homologation of boronic esters to introduce a variety of different functional groups (Scheme 3.44). The required metal carbenoid is generated through a selective sulfoxide–metal exchange using either organolithium or organomagnesium reagents.



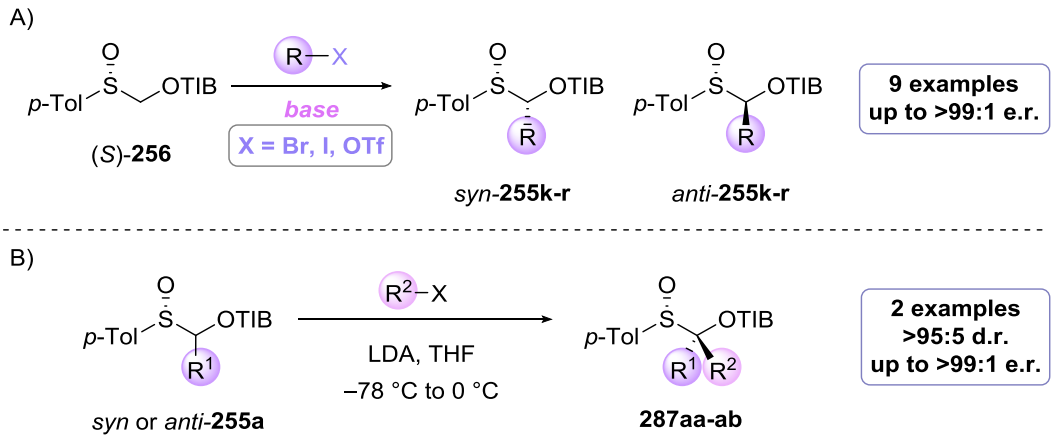
Scheme 3.44. Stereospecific homologation of boronic esters using α-sulfinyl benzoates as the carbenoid precursors.

α-Sulfinyl benzoates **255** were efficiently synthesised in good yields and very high levels of enantiopurity from the corresponding racemic lithiated benzoates. Importantly, these compounds were accessed without using sparteine, which is currently difficult to source commercially. Extensive optimisation of the reaction conditions revealed that transmetalation to the corresponding magnesiated benzoate was essential to prevent racemisation in the subsequent electrophilic trapping with enantiomerically pure Andersen's sulfinate, as previously observed by O'Brien and co-workers. High levels of enantiospecificity could be achieved for both the *syn* and *anti* diastereoisomers of a range of α-sulfinyl benzoates **255** bearing substituents of varying steric demand (Scheme 3.45).



Scheme 3.45. Synthesis of enantioenriched α-sulfinyl benzoates **255** *via* sulfinylation of benzoates **108**.

Alternatively, α-sulfinyl benzoates could be prepared by alkylation of methylene α-sulfinyl benzoate **256**, which could be deprotonated using relatively weak bases, such as LDA or LiHMDS (Scheme 3.46A). The advantage of this second approach is that sensitive functional groups, that would be reactive towards strong lithium bases, can be successfully introduced. Fully substituted α-sulfinyl benzoates **287aa-ab** were also synthesised through this alkylation protocol, providing the desired substrates with very high levels of and enantio- and diastereoselectivity (>95:5) (Scheme 3.46B).



Scheme 3.46. Synthesis of enantioenriched α-sulfinyl benzoates *via* alkylation.

Optimal reaction conditions have been developed to convert these building blocks into the corresponding lithium (*t*-BuLi in THF) and magnesium (*i*-PrMgCl·LiCl in CH_2Cl_2) carbenoids to allow the homologation of different pinacol boronic esters. *In situ* conditions (generation of the metal carbenoid in the presence of the boronic ester) were found to be essential for the generation of the lithium carbenoid owing to the instability of this species under reaction conditions. In particular, internal quenching of the generated carbenoid was found to compete with the formation of the desired boronate complex, thus inhibiting the conversion of the starting boronic ester into the desired homologated product. Magnesium carbenoids proved to be more stable and were allowed to be formed prior to the addition of the boronic ester, although generation under *in situ* conditions were ultimately found to give optimal results. Homologation of boronic esters proceeded smoothly to give the corresponding one-carbon

extended products in generally good yields and with excellent levels of enantiospecificity. Remarkably, the use of magnesium carbenoids allowed carbon chains to be grown with the incorporation of sensitive functional groups, such as alkyl/aryl halides, azides and esters; the use of lithium carbenoids, which are less sensitive to steric hindrance, allowed sterically encumbered carbon–carbon bonds to be forged. Fully substituted α-sulfinyl benzoates gave access to versatile enantioenriched tertiary boronic esters.

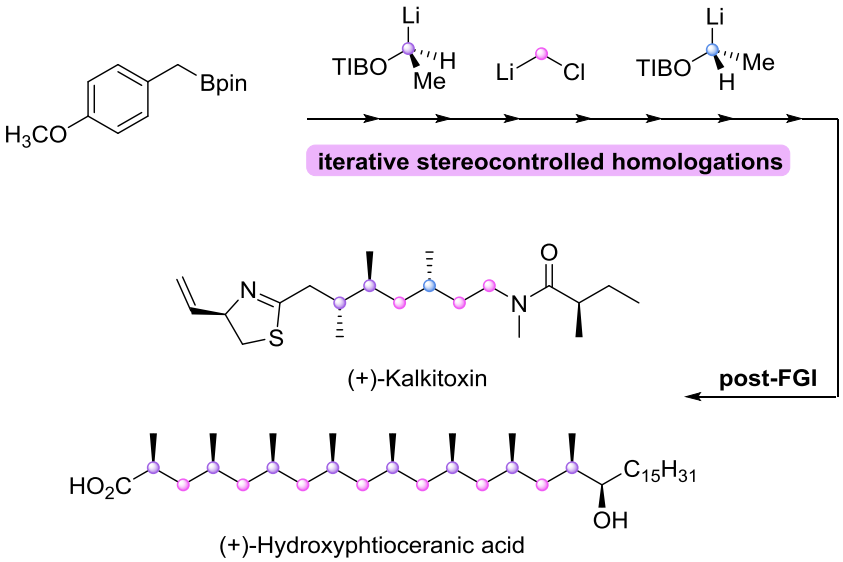
We have also shown that this class of carbenoid precursors can be used in three- and four-step iterative homologation processes, without intervening column chromatography, to give contiguously substituted carbon chains with very high levels of enantio- and diastereoselectivity, therefore showing the potential of this methodology to be automated.

4. Building Block-Based Approach for the Iterative Installation of Functional Groups Containing Double Bonds

4.1. Introduction and Project Aims

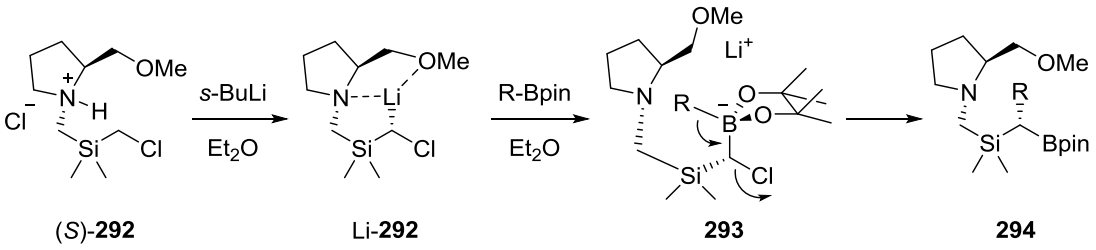
The development of synthetic methodologies allowing the stereoselective formation of new carbon−carbon bonds in an iterative fashion, under complete reagent control, represents an important progression that will herald a new era for automated synthesis.[146, 163] The iterative homologation of boronic esters through lithiation−borylation reactions, enabling the growth of chains of carbon atoms with complete control of stereochemistry at each carbon centre, independent of the presence of pre-existing stereocentres, is part of this group of reactions and is therefore particularly attractive. In this case, automation is made possible by the development of appropriate enantiomerically enriched chiral carbenoids to be used as building blocks in each iteration.

Aggarwal and co-workers have already described an efficient building-block based strategy to access linear molecules containing contiguous substituted stereocentres through the iterative homologation of boronic esters using enantioenriched α-stannyl benzoates as carbenoid precursors.[73] This methodology allowed the synthesis of linear molecules bearing 10 sequential methyl substituents with excellent levels of enantiospecificity; the relative stereochemistry could be modulated by changing the stereochemistry of the building-block employed in each step (see § 1.5.5). The power of this methodology relies on the fact that no additional manipulations, such as functional group interconversions or protections, need to be performed between each iteration. Alternation of this iterative synthetic strategy with the Matteson homologation, which is based on the use of chloromethyllithium as the carbenoid precursor (see § 1.2), allowed the efficient total synthesis of two important polydeoxypropionates, (+)-kalkitoxin and (+)-hydroxyphtioceranic acid (Scheme 4.1).[74]



Scheme 4.1. Iterative assembly line-synthesis for the total synthesis of polydeoxypropionate natural products, (+)-kalkitoxin and (+)-hydroxyphthioceranic acid.

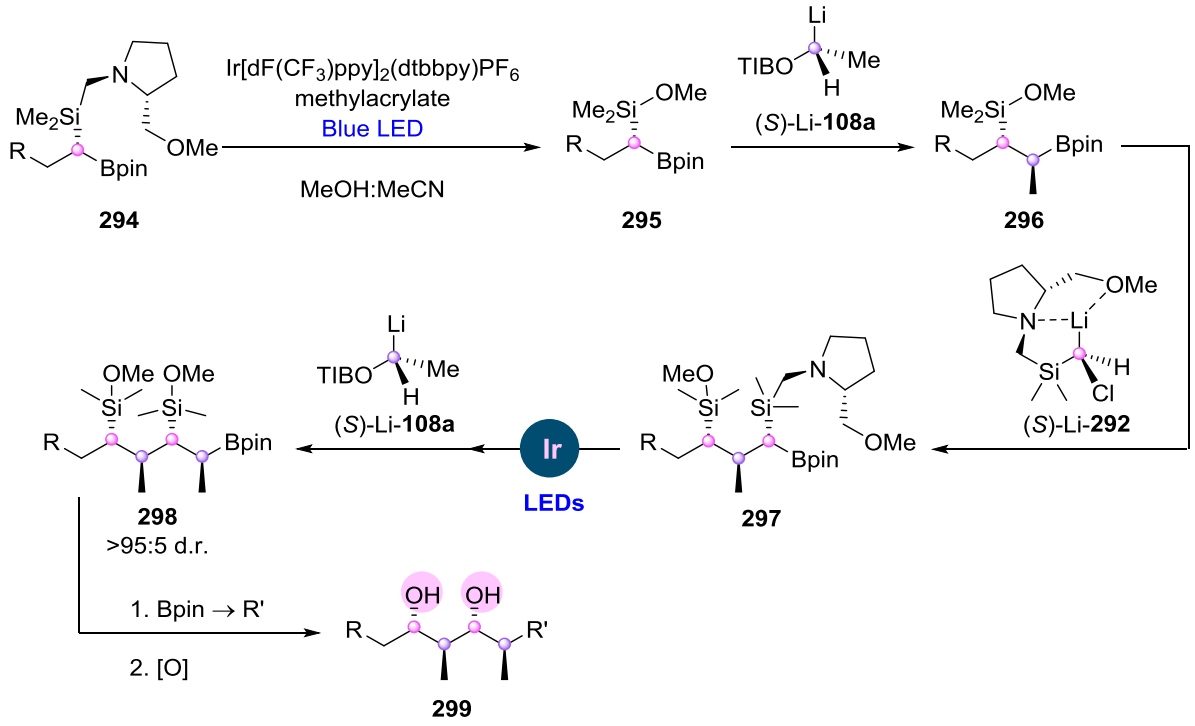
More recently, this methodology has been further expanded, and a new class of building blocks has been developed to allow the introduction of oxygen functionalities, therefore providing access to more complex structural motifs.[164] This was achieved through the use of enantioenriched α-chloromethyl silanes (*R*) and (*S*)-**292** as the carbenoid precursors; deprotonation with *s*-BuLi at −78 °C, followed by trapping with boronic esters, gave, after stereospecific 1,2-metallate rearrangement, the corresponding homologated α-silyl boronic esters **294** in high yield and excellent diastereoselectivity (Scheme 4.2). The silyl group acts a masked oxygen functionality, that can eventually be unmasked by oxidative cleavage of the silicon−carbon bond.



Scheme 4.2. Stereoselective homologation of boronic esters with α-lithiated chloromethyl silane **292**.

An iterative homologation protocol was also successfully developed by subjecting α-silyl boronic ester **294** to a further homologation with lithiated benzoate (*R*)-Li-**108a**, generated *in situ* from α-stannyl benzoate (*S*)-**109**. Beforehand, cleavage of the sterically encumbered pyrrolidine group using photoredox catalysis was performed to access the corresponding methoxysilane **295**; coordination of the nitrogen atom to the boron centre was in fact found to

reduce the reactivity of intermediate **294**, thus inhibiting boronate complex formation. Homologation of **295** with lithiated carbenoid (*S*)-Li-**108a** proceeded smoothly to give boronic ester **296**, which was subsequently further homologated with α-chloromethyl silane (*R*)-Li-**292** in excellent yield and d.r.; photoredox cleavage of the aminomethyl group, followed by another homologation with lithiated benzoate (*S*)-Li-**108a** afforded boronic ester **298** in 59% yield and >95:5 d.r. Modified Tamao oxidation of the silyloxy groups using urea-H_2O_2 complex finally gave access to diol **299** (Scheme 4.3). Importantly, each set of double homologation/photoredox cleavage was conducted with only one chromatographic purification.

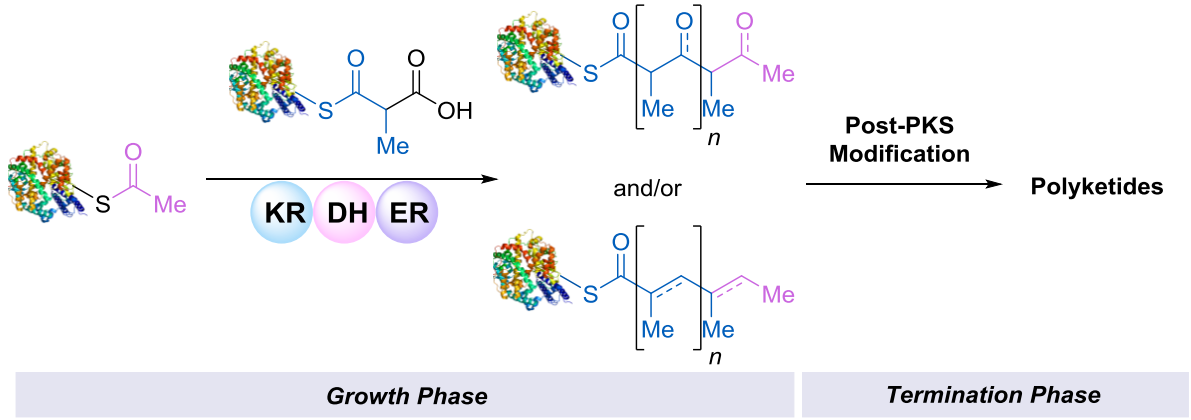


Scheme 4.3. Iterative assembly line synthesis for the construction of polypropionates.

Other diastereoisomers of diol **299** could also be accessed by careful selection of the chiral building blocks employed in each iteration; after final Tamao oxidation, all the targeted polyols were obtained in similarly good yield and >95:5 d.r., therefore demonstrating the absence of any matched/mismatched effects.[165]

One important outcome of this methodology is that it provides rapid access to polypropionates, carbon chains containing alternating methyl and hydroxy groups, which are common repeating motifs found in many polyketide structures. Polyketides are an important class of complex molecules displaying various biological activities, and they represent the basic chemical skeleton of many potent pharmaceutical agents, such as antibiotics, immunosuppressants,

antifungal and anticancer drugs.[166-168] In nature, the biosynthesis of polyketides involves a series of iterative reactions catalysed by different enzymes belonging to the family of polyketide synthases (PKSs). In particular, a simple thioester starting unit undergoes sequential chain extensions, reductions and dehydrations using appropriate 2-, 3- and 4-carbon building blocks (Scheme 4.4).[169]



Scheme 4.4. Nature's synthesis of polyketides; DH = dehydratase; ER = enoyl reductase; KS = ketosynthase; KR = ketoreductase.

Aggarwal's assembly-line synthesis aims to emulate this biosynthetic pathway performed by nature by constructing substituted chains of carbon atoms through a series of stereocontrolled iterative homologations of boronic esters using various building blocks. However, the current methodology only allows the introduction of methyl and hydroxyl substituents, while building blocks allowing the introduction of other functional groups have not been developed yet. This would be beneficial given the remarkable structural diversity of polyketides.

For example, carbonyls, C–C double bonds and enones can be identified as ubiquitous functional groups in many members of the polyketide family (Figure 4.1).

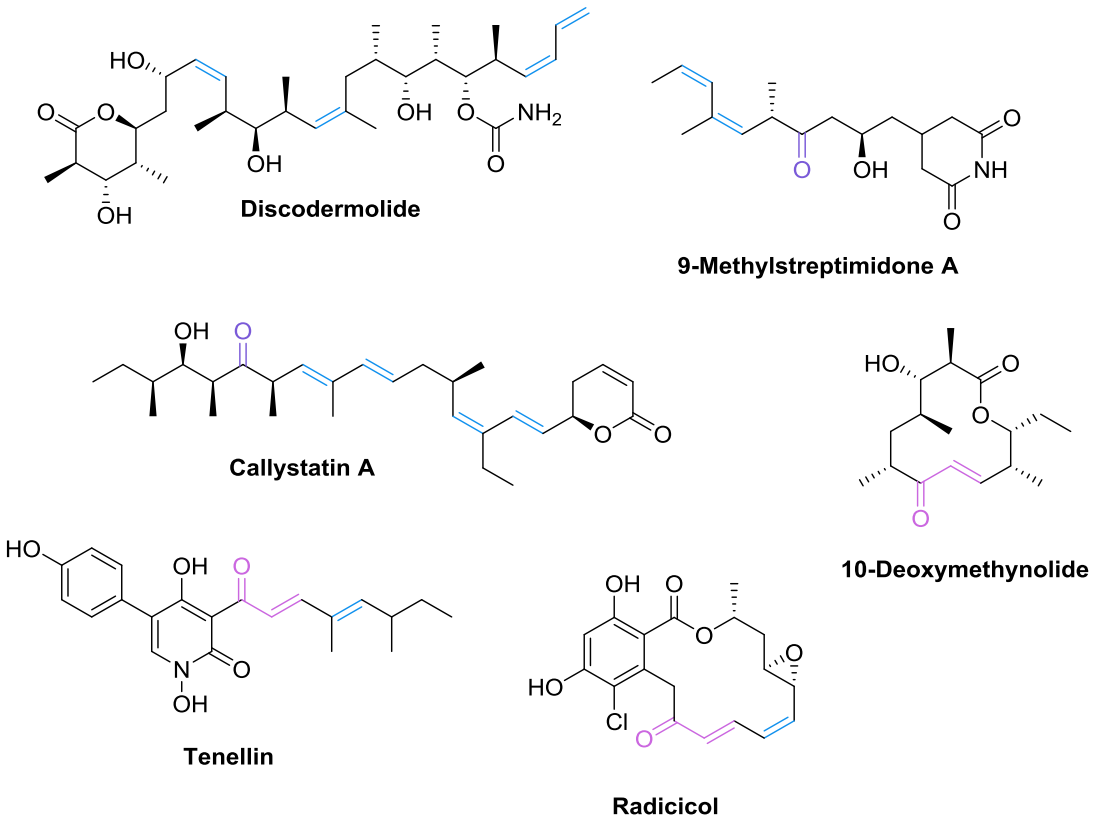
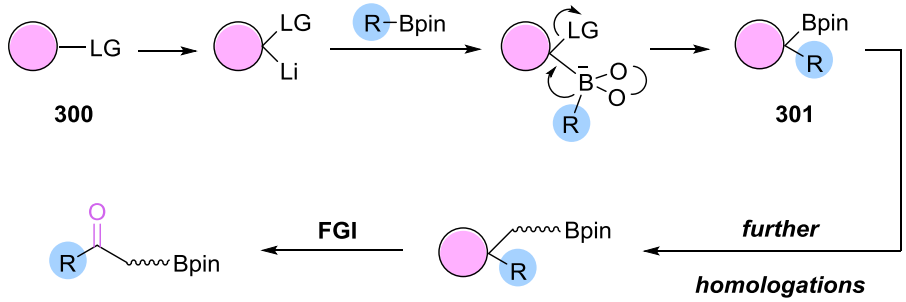


Figure 4.1. Examples of polyketide structures containing carbonyl, double bond and enone functionalities.

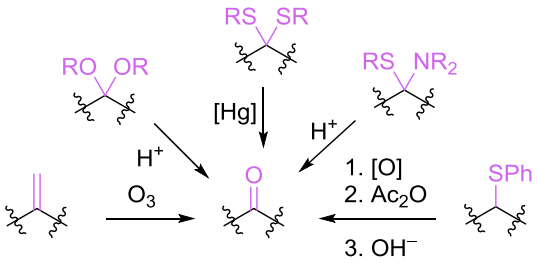
The aim of this project is the development of simple 1-, 2- and 3-carbon building blocks to be used in the homologation of boronic esters, allowing the introduction of these functionalities. The combination of these new building blocks with the ones previously developed will enable the transformation of simple boronic esters into linear chains of carbon atoms bearing a variety of different functional groups, therefore extending the boundaries of the assembly-line methodology with the possibility of creating even more diversity.

The introduction of a carbonyl group through the homologation of boronic esters requires the development of an appropriate 1-carbon building block. Specifically, carbonyl groups must be introduced as masked functionalities, since they are not compatible with the conditions required for lithiation–borylation reactions. Homologation of boronic esters with a suitable building block **300** would therefore generate intermediate boronic ester **301**, which could then undergo further homologations with different building blocks; a final functional group interconversion would eventually release the targeted carbonyl functionality (Scheme 4.5).



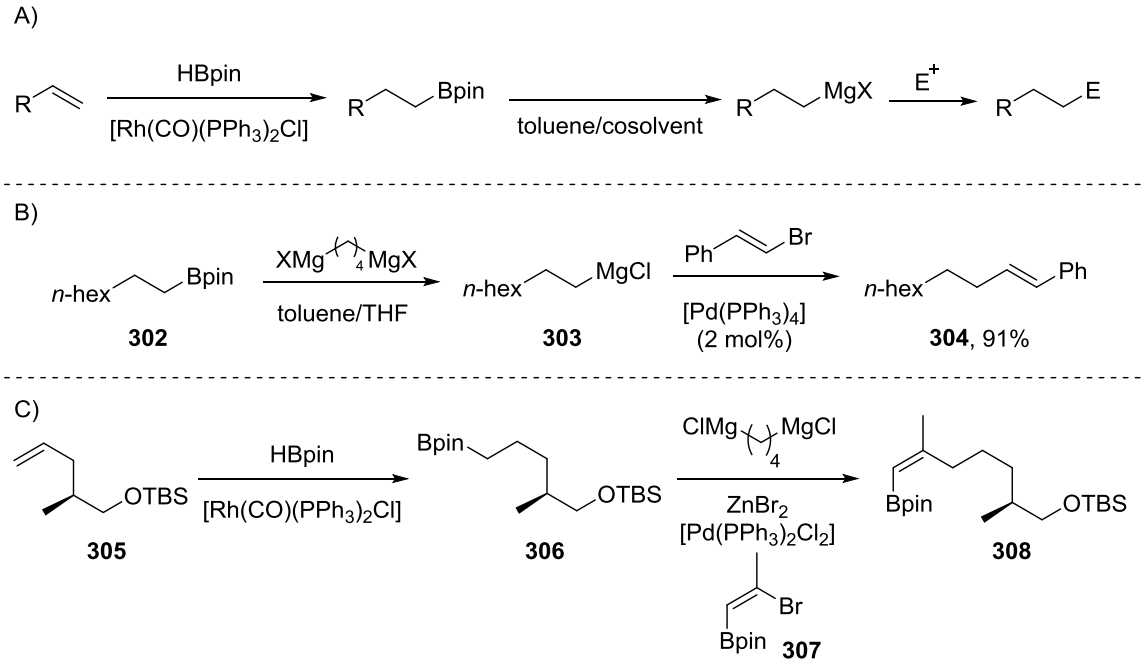
Scheme 4.5. Development of a 1-carbon building block allowing the homologation of boronic esters with the introduction of a masked carbonyl functionality.

The required building block should therefore fulfil the following criteria: first, it must be possible to rapidly convert it into a reactive lithium carbenoid, by either deprotonation or lithium/halogen exchange; second, the carbenoid carbon must be attached to both a suitable leaving group, to allow the 1,2-metallate rearrangement, and a functional group, stable under lithiation borylation reaction conditions, acting as a masked ketone (Scheme 4.6). The most common way of masking a carbonyl functionality is using the corresponding ketal, a functional group that is known to be stable under various reaction conditions and can be easily removed by treatment with acid. Thioketals can also be used as protected carbonyl groups, although they are more stable to hydrolysis under acidic conditions than the corresponding ketals, thus requiring harsher methods for their removal, such as the use of oxidising agents or mercury salts. However, the acidity of 1,3-dithianes makes this carbonyl masking group particularly attractive, since the corresponding readily accessible anion, if attached to a suitable leaving group, could be employed in lithiation−borylation reactions. Hemiaminal thioethers will also be considered as potential masking groups for the targeted carbonyl functionality. Alternatively, a C−C double bond could be introduced as a masking carbonyl group, that could be eventually converted into a ketone by simple ozonolysis followed by reductive work-up. Another possibility would be developing a building block that allows the insertion of a thioether functionality, that would release the required ketone in a three-step process, involving an initial oxidation to the corresponding sulfoxide, followed by Pummerer rearrangement and hydrolysis of the resulting α-acyloxy-thioether. All these potential strategies will be considered in the design of new building blocks, that will be subsequently tested in the homologation of boronic esters.



Scheme 4.6. Possible masking groups for carbonyl functionalities.

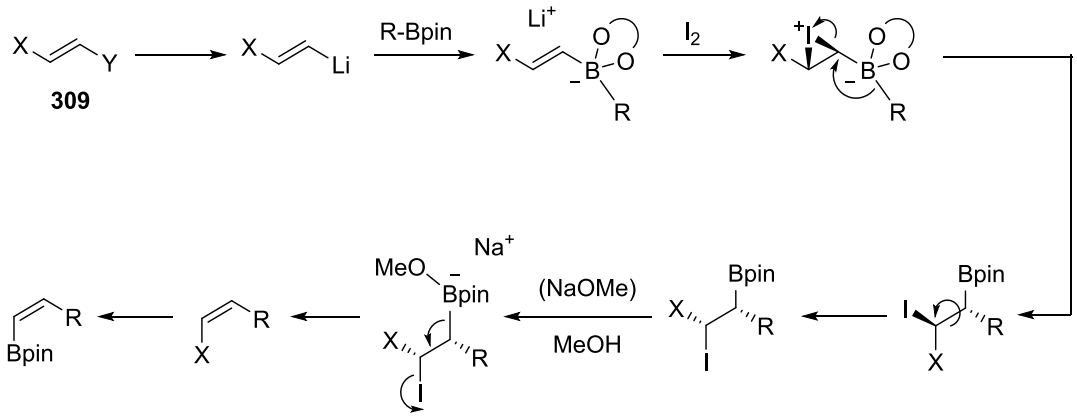
A 2-carbon building block is required for the introduction of double bonds through the homologation of boronic esters. In this case, there is no need to mask the targeted functionality, since it is known that alkenes are well tolerated in lithiation−borylation reactions. In 2012, Breit and co-workers reported a novel methodology to convert alkenes into primary and secondary alkylmagnesium reagents through sequential hydroboration and boron−magnesium exchange (Scheme 4.7A).[170] The generated alkylmagnesium species were successfully trapped with a variety of carbon electrophiles to generate new C−C bonds using a simple and efficient protocol. Interestingly, alkylmagnesium intermediate **303**, generated from the corresponding pinacol boronic ester **302**, could also be successfully employed in a palladium catalysed Kumada cross-coupling reaction with β-bromostyrene to give coupled product **304** in excellent 91% yield (Scheme 4.7B). This methodology was subsequently applied to the total synthesis of epothilone D, a polyketide studied as potential cancer drug.[171] In one of the key steps, alkylboronic ester **306**, obtained by catalytic hydroboration of alkene **305**, was subjected to boron−magnesium exchange, using 1,4-di(chloromagnesium)butane, to give the corresponding alkylmagnesium intermediate; this was subsequently used in a Negishi cross-coupling reaction with vinyl bromide **307** to afford vinyl boronic ester **308** (Scheme 4.7C). The process thus allowed a 2-carbon homologation of starting boronic ester **306** with the introduction of a C−C double bond; more importantly, the cross-coupling reaction enabled the reintroduction of the boronic ester group, therefore giving access to a substrate suitable for further homologations.



Scheme 4.7. Breit's synthesis of alkylmagnesium reagents through hydroboration and boron−magnesium exchange.

Although the process is reported to work with secondary boronic esters,[170] no example was reported that made use of enantioenriched substrates. In particular, we were concerned about the configurational stability of the generated alkylmagnesium species at the temperature required for the boron−magnesium exchange; this made us hesitant about adopting this methodology and prompted us to seek new protocols.

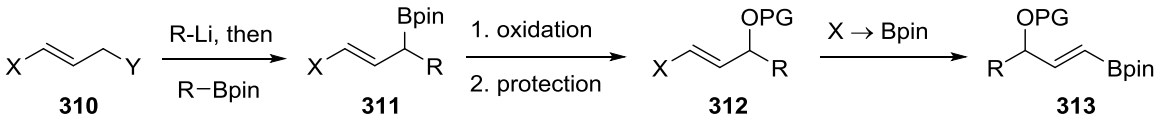
A powerful method to convert enantioenriched secondary and tertiary boronic esters into terminal and internal alkenes using vinyl metals is the Zweifel olefination, which is known to proceed with very high levels of stereoselectivity (see § 1.7.3). It was reasoned that the introduction, on the vinyl metal partner, of a suitable substituent that could be eventually converted into a boron group would effectively enable a 2-carbon homologation of boronic esters, maintaining the boronate group, with the introduction of a double bond (Scheme 4.8). One of the aims of this project is the design and synthesis of an appropriate 2-carbon alkenyl building block **309** bearing one substituent (Y), that can be rapidly converted into an organolithium; and a second one (X), that is stable under the homologation reaction conditions, but would allow the reintroduction of the boronic ester functionality. Once identified, the building block could be tested in the homologation of different boronic esters.



Scheme 4.8. Proposed homologation of boronic esters with introduction of C–C double bonds through Zweifel olefination.

Finally, a 3-carbon building block will also be developed to enable the introduction of enone functionalities. As mentioned before, the carbonyl group must be introduced in a masked form due to its instability under the typical homologation reaction conditions and released only at the end of the assembly-line synthesis process.

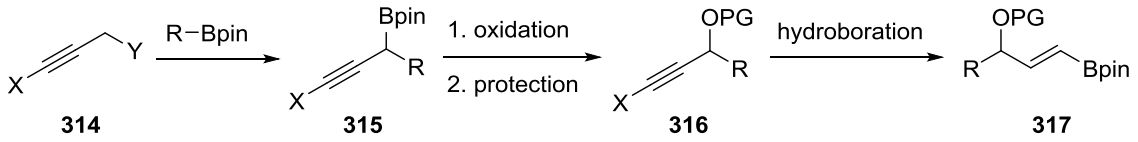
A building block that could be suitable for this protocol is alkene **310** (Scheme 4.9). An appropriate leaving group (Y) must be identified to allow the formation of a sufficiently stable lithium carbenoid that, upon reaction with a boronic ester, would undergo 1,2-metallate rearrangement to give homologated product **311**; subsequent oxidation and protection of the generated alcohol would finally give intermediate **312**. The vinyl substituent (X) must also be carefully chosen to make the reintroduction of the boronic ester group possible, so that further iterative homologations, using different building blocks, could elongate the carbon chain. Final deprotection and oxidation of the generated hydroxyl group will liberate the required enone functionality.



Scheme 4.9. Proposed homologation of boronic esters with introduction of enone functionalities using alkenyl building block **310**.

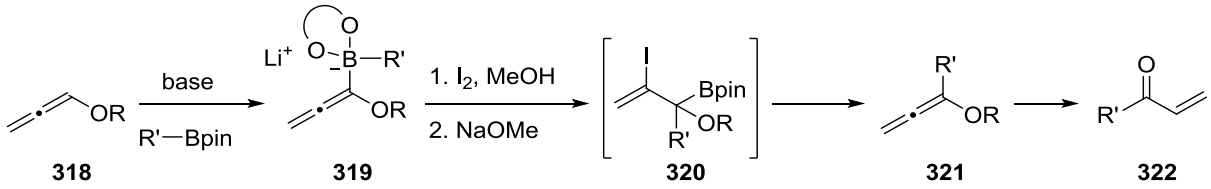
Propargylic substrate **314** could also be employed in a similar process (Scheme 4.10). In this case, the intermediate 3-carbon homologated vinyl boronic ester **317**, bearing a protected oxygen functionality, would be accessed through hydroboration of the terminal alkyne.[xix]

[xix] The use of propargylic 3-carbon building blocks in the homologation of boronic esters was studied by J. M. Fordham.



Scheme 4.10. Proposed homologation of boronic esters with introduction of enone functionalities using propargyl building block **314**.

A different approach would involve the use of alkoxyallenes as 3-carbon building blocks for the homologation of boronic esters. In this case, a modified Zweifel olefination protocol, using the lithiated alkoxyallene in the place of a vinyl metal, would allow the conversion of boronic esters into terminal enones (Scheme 4.11). This methodology will be investigated and, if successful, further extended to allow the use of this new type of building block in an iterative fashion through the reintroduction of the boronic ester functionality.

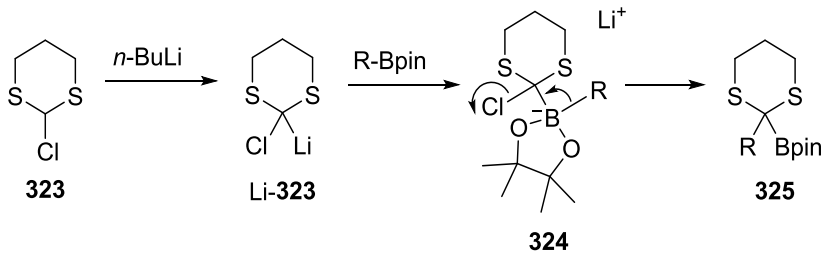


Scheme 4.11. Proposed homologation of boronic esters with introduction of enone functionalities using alkoxyallene **318**.

4.2. Results and Discussion

4.2.1. Development of a 1-C Building Block for the Introduction of Masked Carbonyl Functionalities through the Homologation of Boronic Esters

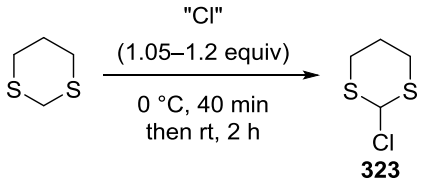
Initial investigations focused on the development of a building block to homologate boronic esters with the introduction of a thioketal group as a masked carbonyl functionality. 2-Chloro-1,3-dithiane **323** was at first selected as a suitable carbenoid precursor, since deprotonation would readily occur at the 2 position to generate lithium carbenoid Li-**323**; upon addition of a boronic ester, "ate" complex **324** would form and subsequently undergo 1,2-metallate rearrangement to give homologated product **325** (Scheme 4.12). Further iterative homologations would elongate the carbon chain until the targeted carbonyl functionality is released by hydrolysis of the dithiane group.



Scheme 4.12. Proposed homologation of boronic esters using 2-chloro-1,3-dithiane **323**.

Despite the number of protocols reported in the literature, the synthesis of 2-chloro-1,3-dithiane **323** proved to be challenging. Treatment of a solution of 1,3-dithiane in anhydrous CH_2Cl_2 with NCS at 0 °C for 40 min, followed by stirring the reaction mixture at room temperature for 2 h,[172] resulted in complete conversion of starting material, but no desired product was detected (Table 4.1, entry 1). Using different solvents, such as DCE or toluene, or recrystallising NCS prior to use did not give improved results and chlorinated product **323** could not be obtained (Table 4.1, entries 2–5). The use of sulfuryl chloride[173] or trichloroisocyanuric acid (TCCA) as the chlorinating agents also met with failure (Table 4.1, entries 6–7).

Table 4.1. Attempted synthesis of 3-chloro-1,2-dithiane **323**.

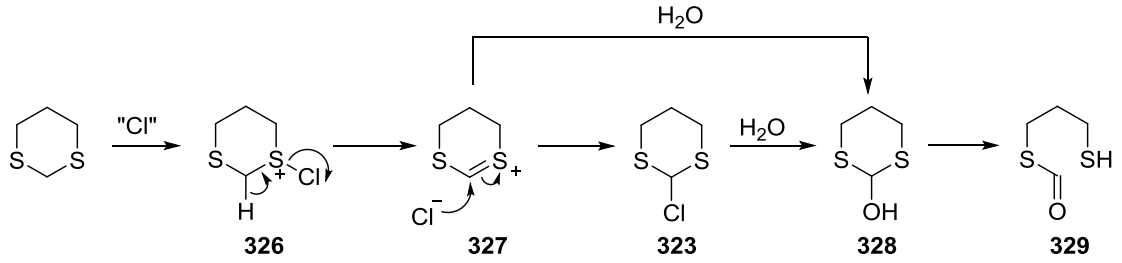


Entry	Chlorinating agent	Solvent	% Yield
1	NCS	CH_2Cl_2	0
2[a]	NCS	DCE	0
3[a]	NCS	PhMe	0
4[b]	NCS	CH_2Cl_2	0
5[b]	NCS	PhMe	0
6[c]	SO_2Cl_2	$CHCl_3$	0
7[b,c]	SO_2Cl_2	$CHCl_3$	0
8	TCCA	PhMe	0

[a] The reaction mixture was stirred at room temperature for only 20 min; [b] NCS was freshly recrystallised from H_2O before use; [c] SO_2Cl_2 was added at −30 °C.

In all the cases, a major species was detected by ^{1}H NMR, recorded on the crude reaction mixture, showing a diagnostic signal at 10.13 ppm, indicative of the presence of an aldehyde

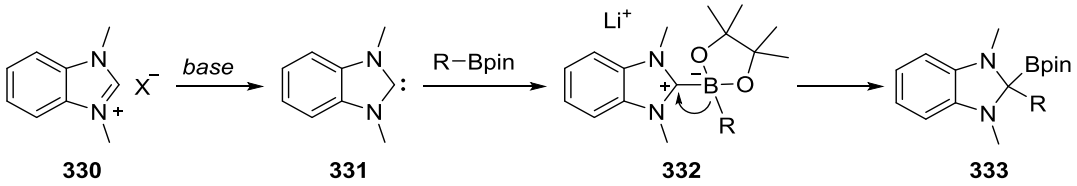
group. This suggested that desired product **323** was initially formed under reaction conditions, but it underwent rapid hydrolysis, presumably upon aqueous work-up, to give hydroxy dithiane **328**, which is rapidly converted into thioformate **329** (Scheme 4.13).



Scheme 4.13. Proposed mechanism for the decomposition of chlorothiane **323** to thioformate **329**.

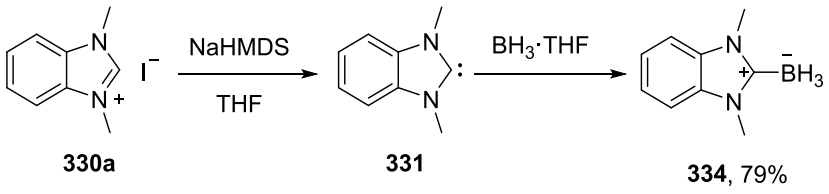
Although other strategies could have been attempted to achieve the synthesis of 2-chloro-1,3-dithiane **323**, the high instability observed made clear that it did not possess the required attributes for a readily available and bench-stable carbenoid precursor. Attention was therefore turned towards the development of a different building block.

Imidazolium salts were then considered as possible carbenoid precursors. It was reasoned that, upon deprotonation of *N*,*N*-dimethyl imidazolium salt **330**, *N*-heterocyclic carbene **331** would form; reaction with a boronic ester would generate ylidic boronate complex **332**, which, after 1,2-metallate rearrangement, would afford cyclic aminal **333**, bearing the targeted masked carbonyl functionality (Scheme 4.14).



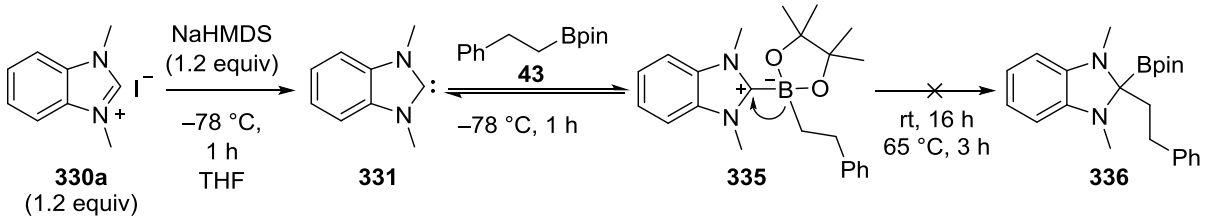
Scheme 4.14. Proposed homologation of boronic esters using imidazolium salts as carbenoid precursors.

Curran and co-workers have shown that *N*-heterocyclic carbene **331**, generated *in situ* from the corresponding imidaziolium iodide **330a**, could be trapped with borane tetrahydrofuran complex to give *N*-heterocyclic carbene borane **334** in good yield (Scheme 4.15).[174]



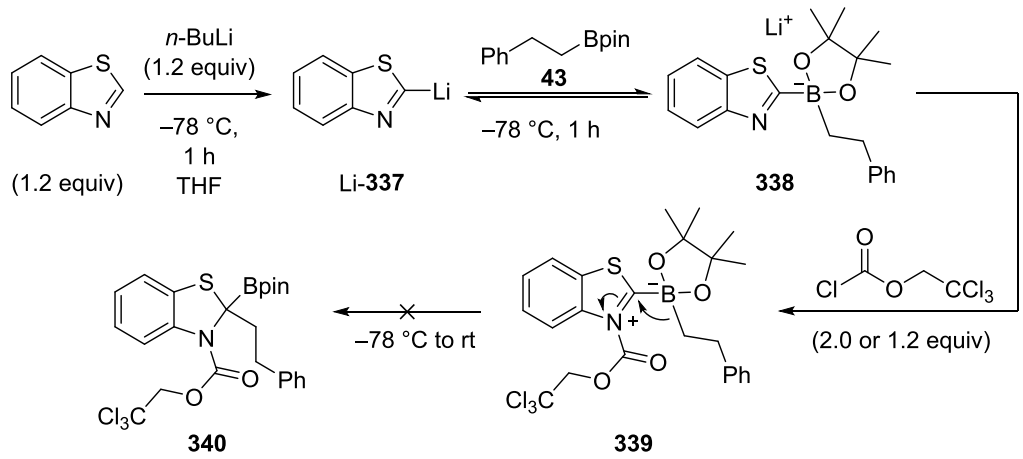
Scheme 4.15. Curran's synthesis of *N*-heterocyclic carbene borane **334**.

Conditions reported by Curran and co-workers were thus applied and *in situ* generated *N*-heterocyclic carbene **331** was trapped with phenethyl pinacol boronic ester **43**. Although analysis of the reaction mixture by ^{11}B NMR spectroscopy revealed full boronate complex formation (δ = 6.2 ppm), no desired aminal **336** was detected after warming the reaction mixture to higher temperatures, and only starting boronic ester **43** was recovered (Scheme 4.16). This suggested that the desired 1,2-metallate rearrangement was not occurring, and ylide **335** was instead reversing to regenerate starting material **43**.



Scheme 4.16. Attempted homologation of boronic ester **43** using imidazolium salt **330a**.

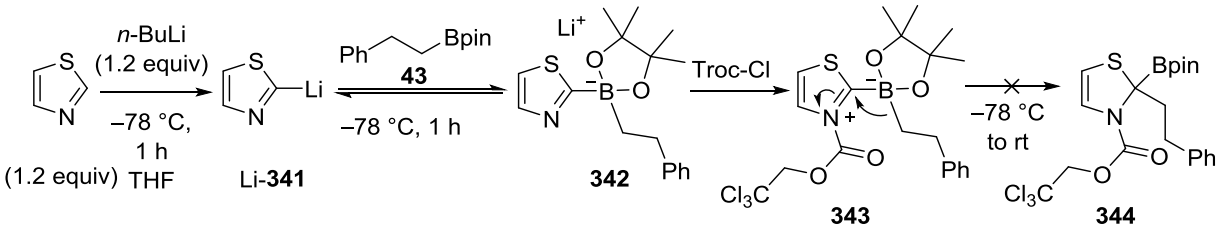
It was considered that *in situ* activation of the generated boronate complex, instead of preforming the *N*-heterocyclic carbene, could have been beneficial in promoting the desired 1,2-metallate rearrangement. To prove this, commercially available benzothiazole was deprotonated with *n*-BuLi to give lithiated intermediate Li-**337**, which, upon addition of phenethyl pinacol boronic ester **43**, was fully converted into boronate complex **338**, as confirmed by *in situ* ^{11}B NMR spectroscopy analysis (δ = 5.8 ppm, Scheme 4.17). It was thought that *N*-activation of boronate complex **338** using 2,2,2-trichloroethyl chloroformate (Troc-Cl),[107] would trigger the 1,2-migration, leading to dearomatised thioaminal **340**. However, similar to what was observed for ylide **335**, the desired 1,2-metallate rearrangement did not occur under these conditions, and only starting boronic ester **43** was reisolated, thus suggesting a reversible formation of boronate complex **338**.



Scheme 4.17. Attempted homologation of boronic ester **43** using benzothiazole.

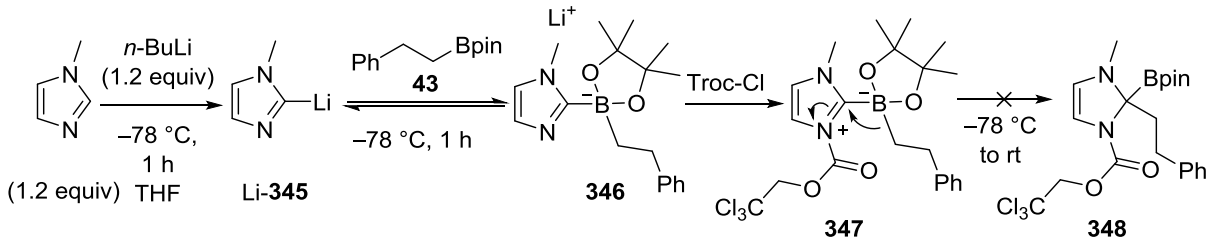
The use of $ClCO_2CMe_2CCl_3$ (Me_2Troc-Cl) as the *N*-activator, which proved to be superior to Troc-Cl in inducing the 1,2-metallate rearrangement of boronate complexes generated from *N*-benzyl amines,[175] also met with failure, and desired thioaminal **340** could not be formed.

With the aim of reducing the steric hindrance around the boron centre and making the 1,2-metallate rearrangement more favourable, thiazole was employed in place of benzothiazole in the same process (Scheme 4.18). As expected, ^{11}B NMR spectroscopy showed full boronate complex formation (δ = 5.9 ppm); however, upon addition of Troc-Cl, the desired 1,2-migration did not occur and only boronic ester **43** was recovered.



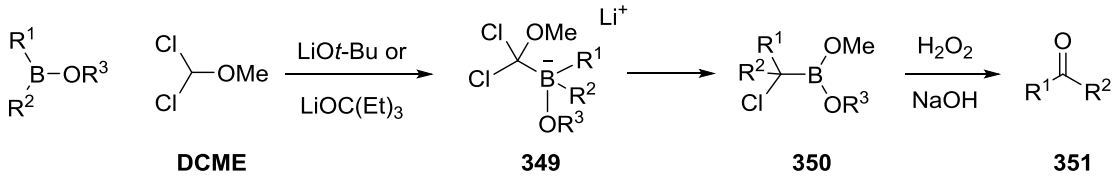
Scheme 4.18. Attempted homologation of boronic ester **43** using thiazole.

1-Methylimidazole was also tested as a potential carbenoid precursor for the homologation of boronic ester **43**, hoping that the increased electronegativity of nitrogen compared to sulfur would make the migrating terminus more electron deficient, thus promoting the desired 1,2-migration (Scheme 4.19). However, this was not the case and generation of boronate complex **346** was also found to be reversible under these conditions.



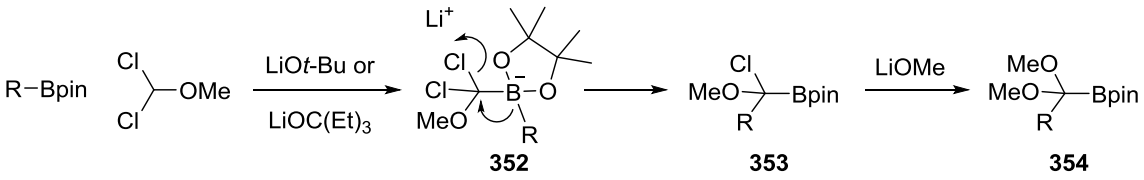
Scheme 4.19. Attempted homologation of boronic ester **43** using 1-methylimidazole.

An alternative approach to the homologation of boronic esters with the introduction of a masked carbonyl functionality is using the DCME reaction.[176-177] Brown and co-workers showed that α,α-dichloromethyl methyl ether (DCME) can be reversibly deprotonated with sterically hindered bases, such as lithium *tert*-butoxide or $LiOC(Et)_3$, to form a lithium carbenoid; addition to borinic esters leads to the formation of boronate complex **349**, that undergoes two subsequent 1,2-migrations to give intermediate α-chloroboronate **350**; oxidation with basic hydrogen peroxide gives access to ketone **351** (Scheme 4.20).



Scheme 4.20. Brown's conversion of borinic esters into ketones using α,α-dichloromethyl methyl ether.

It was postulated that employing a boronic ester in the place of borinic esters in a similar process would give access, after a single 1,2-metallate rearrangement, to homologated intermediate **353**; addition of a methoxide base would eventually form desired ketal **354** (Scheme 4.21).

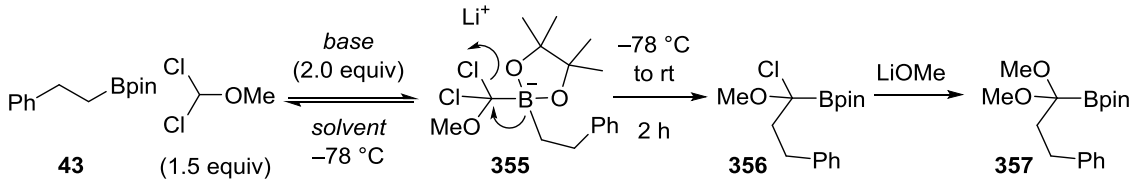


Scheme 4.21. Proposed homologation of boronic esters using DCME as the carbenoid precursor.

Generation of the lithium carbenoid by treatment of a solution of DCME in Et_2O with LiO*t*-Bu at −78 °C in the presence of phenethyl pinacol boronic ester **43** (*in situ* conditions), followed by warming the reaction mixture to room temperature, resulted in only unreacted starting boronic ester **43** (Table 4.2, entry 1). The presence of a permanent boronate complex in the ^{11}B NMR spectrum recorded on the reaction mixture (δ = 4.9 ppm) suggested that the formation

of the required boronate complex was slow, owing to the decreased electrophilicity and the increased steric hindrance of boronic esters if compared to the corresponding borinic esters; the base could therefore react with the boron centre, leading to an improductive boronate complex. However, attempts to pre-form the lithium carbenoid before adding the boronic ester (*ex situ* conditions) did not give improved results and only unreacted starting material **43** was reisolated, thus confirming the low rate of boronate complex formation (Table 4.2, entry 2). Using THF as the solvent or LDA as a non-nucleophilic base also met with failure (Table 4.2, entries 3–4).

Table 4.2. Attempted homologation of boronic ester **43** using DCME.

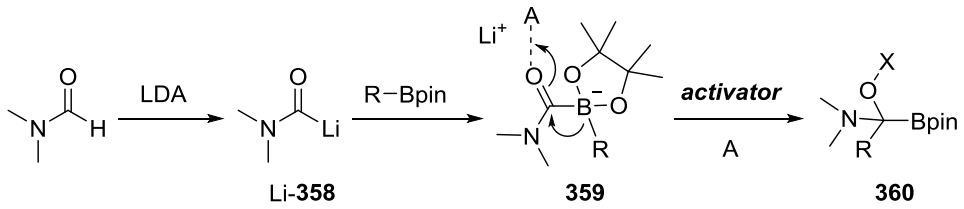


43 (1.5 equiv) **355** **356** **357**

Entry	Base	Solvent	Conditions	% Yield 357
1	LiO*t*-Bu	Et_2O	*in situ*	0
2	LiO*t*-Bu	Et_2O	*ex situ*	0
3	LiO*t*-Bu	THF	*in situ*	0
4	LDA	Et_2O	*in situ*	0

It was concluded that the lithium carbenoid generated *in situ* by deprotonation of DCME was not sufficiently reactive to attack the boron centre of boronic esters. A different class of building blocks to introduce masked carbonyl functionalities was therefore explored.

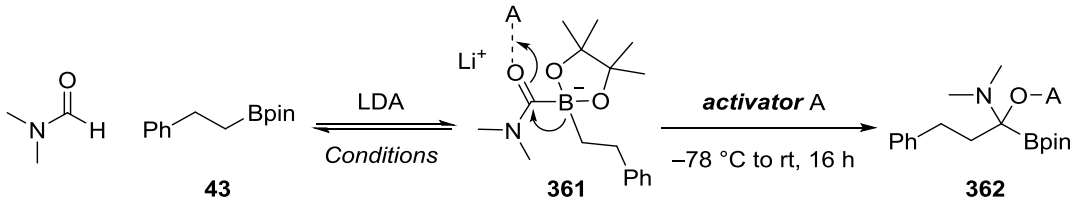
Efforts were then focused on the use of *N*,*N*-dimethylformamide (DMF) as the carbenoid precursor. It is in fact known that DMF can be deprotonated by LDA at low temperature to generate lithiated carbonyl intermediate Li-**358**.[178] It was argued that trapping of the generated lithiated species with a boronic ester would afford boronate complex **359**, that, upon addition of an activating agent, would undergo 1,2-metallate rearrangement to give desired hemiaminal ether **360** (Scheme 4.22).



Scheme 4.22. Proposed homologation of boronic esters using DMF as the carbenoid precursor.

To test this possibility, a solution of DMF (1.1 equiv) and phenethyl pinacol boronic ester in THF was treated with freshly prepared LDA at −78 °C (Table 4.3, entry 1).[179] However, after stirring the reaction mixture for 5 h at that temperature, *in situ* ^{11}B NMR spectroscopy revealed incomplete boronate complex formation; addition of TMSCl as the activating agent, followed by warming the reaction mixture to room temperature overnight, did not lead to the formation of desired product **362** and only unreacted boronic ester **43** was reisolated. Modified conditions reported by Senanayake and co-workers (use of excess of DMF −3.1 equiv− in toluene)[180] initially gave more promising results, with full boronate complex formation observed on the ^{11}B NMR spectrum recorded on the reaction mixture (δ = 8.6 ppm); however, despite testing various activating agents to promote the 1,2-metallate rearrangement, homologated product **362** was never observed, with boronic ester **43** being the main species observed by ^{1}H NMR analysis of the crude reaction mixture (Table 4.3, entries 2−5). This indicated that the 1,2-rearrangement was too slow and the boronate complex formation was reversible.

Table 4.3. Attempted homologation of boronic ester **43** using DMF.

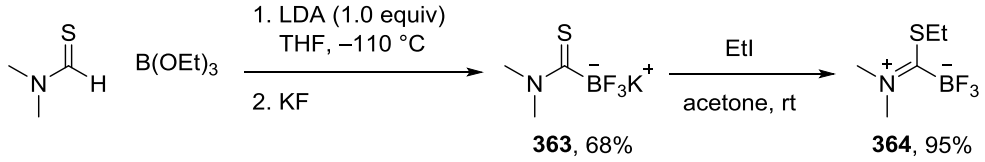


Entry	Conditions	Activator	% Yield 362
1	A	TMS-Cl	0
2	B	TMS-Cl	0
3	B	Troc-Cl	0
4	B	TES-OTf	0
5	B	Tf_2O	0

Reaction conditions: conditions A, **43** (1.0 equiv), DMF (1.1 equiv) and LDA (1.1 equiv) in THF at −78 °C for 5 h; conditions B, **43** (1.0 equiv), DMF (3.1 equiv) and LDA (3.1 equiv) in PhMe at −78 °C for 1 h.

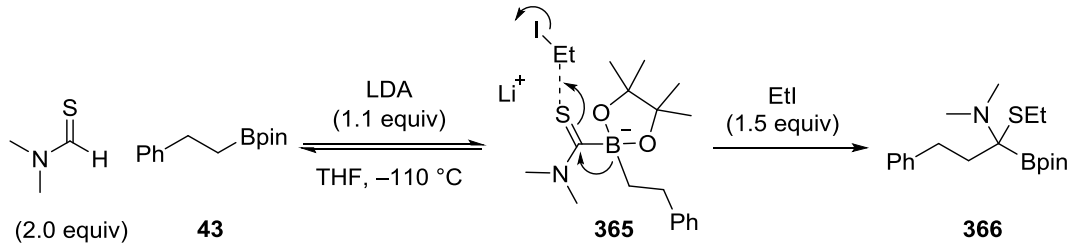
In 2014, Bode and co-workers reported the synthesis of thioamide derivative **363** by deprotonation of *N*,*N*-dimethyl thioformamide at −110 °C[181] in the presence of $B(OMe)_3$,

followed by treatment with aqueous KF.[182] Subsequent *S*-alkylation with ethyl iodide gave imidate **364** in good yield (Scheme 4.23).



Scheme 4.23. Bode's synthesis of imidate **364**.

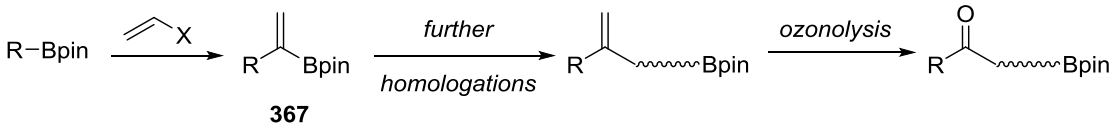
These conditions were tested for the homologation of boronic ester **43** (Scheme 4.24). Despite *in situ* ^{11}B NMR spectroscopy revealing full boronate complex formation (δ = 6.1 ppm), no desired thioaminal **366** could be detected after addition of ethyl iodide and only starting boronic ester **43** was recovered.



Scheme 4.24. Attempted homologation of boronic ester **43** using *N*,*N*-dimethyl thioformamide.

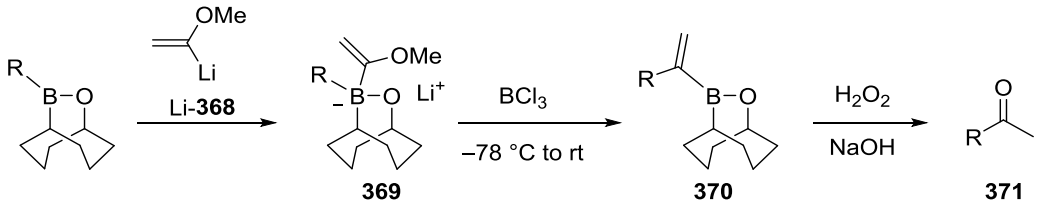
The use of less sterically hindered and more reactive activating agents than ethyl iodide, such as methyl iodide and methyl triflate, also met with failure and thioaminal **366** could not be accessed.

Due to the difficulties encountered in finding a suitable building block able to homologate boronic esters with the introduction of a ketal-type substituent as a masked carbonyl functionality, attention was turned towards a different masking group. In particular, terminal C−C double bonds can be easily converted into ketones by ozonolysis followed by reductive work-up. It was therefore reasoned that homologation of boronic esters using a building block allowing the introduction of α,α-disubstituted C−C double bonds would provide rapid access to vinyl boronic esters **367**; subsequent homologations using various building blocks would elongate the linear chain of substituted carbon atoms before final manipulations would release the targeted carbonyl functionality (Scheme 4.25).



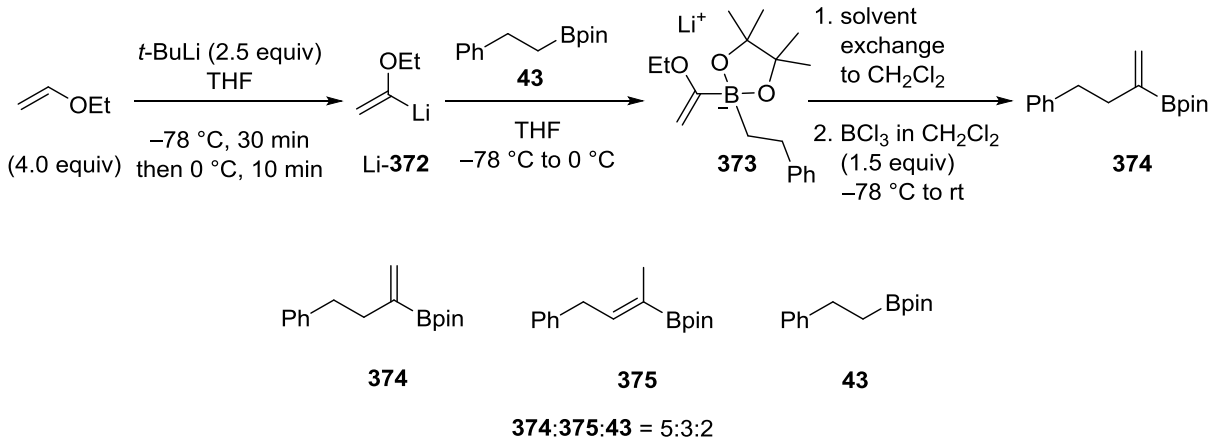
Scheme 4.25. Proposed homologation of boronic esters with the introduction of terminal double bonds as masked carbonyl functionalities.

Soderquist and co-workers demonstrated that α-methoxyvinyllithium (LiAMV) Li-**368** can be used to homologate alkyl borinic esters (Scheme 4.26).[183] In this process, initially generated boronate complex **369** undergoes a BCl_3-mediated alkyl group migration to produce vinyl borinate **370**, which is eventually converted into the corresponding methyl ketones **371** by oxidation with basic hydrogen peroxide.



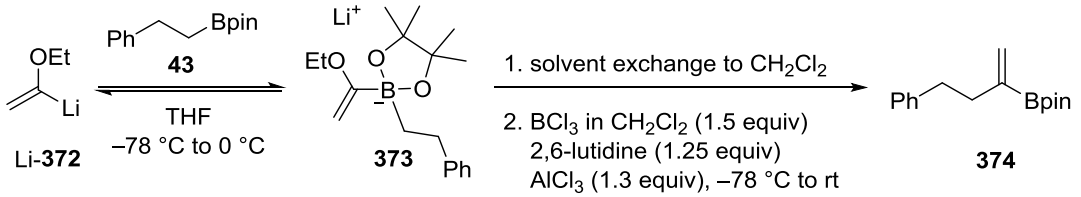
Scheme 4.26. Soderquist's homologation of borinic esters using LiAMV Li-**368**.

The use of boronic esters in an analogous process is unprecedented; it was reasoned that, if boronic esters were reactive under these conditions, versatile vinyl boronates could be rapidly accessed and employed in further iterative homologations. To test this possibility, α-ethoxyvinyllithium Li-**372** was generated *in situ* by treatment of a solution of vinyl ethyl ether in THF with *t*-BuLi at −78 °C and subsequently trapped with phenethyl pinacol boronic ester **43** to give boronate complex **373**, as confirmed by ^{11}B NMR spectroscopy (δ = 4.4 ppm, Scheme 4.27). At this point, a solvent exchange to CH_2Cl_2 was performed, followed by addition of a solution of BCl_3 in CH_2Cl_2 at −78 °C; the resulting reaction mixture was stirred for 30 min at −78 °C and then warmed to room temperature for 2 h to allow the 1,2-metallate rearrangement/elimination sequence. However, the fraction isolated after purification of the crude reaction mixture by chromatography on silica gel was found to be a mixture of desired vinyl boronic ester **374**, isomerised product **375** and starting material **43** in 5:3:2 ratio, as determined by ^1H NMR analysis. A yield of 16% could therefore be calculated for isolated **374**, while isomerised alkene **375** accounted for an 8% yield. Isomerisation was suggested to happen under the reaction conditions, presumably favoured by the combination of Lewis acidic BCl_3 in CH_2Cl_2 and trace amount of HCl generated *in situ* by fortuitous hydrolysis of the boron reagent.[184]



Scheme 4.27. Attempted homologation of boronic ester **43** using α-ethoxyvinyllithium Li-**372** and BCl_3.

Attempt to prevent the undesired isomerisation side-reaction by using milder TMS-OTf to promote the 1,2-migration/elimination step met with failure, leading to the recovery of only unreacted starting boronic ester **43**. The use of $SiCl_4$ as the promoter gave an analogous result to the one obtained using BCl_3, the two Lewis acidic species presumably behaving in a similar fashion in the process. Conditions reported by Ingleson and co-workers for the electrophilic borylation of arenes and heteroarenes were also tested (Scheme 4.28).[185-186] In this case, the active borylating agent was pre-formed *in situ* by treatment of BCl_3 in CH_2Cl_2 with 2,6-lutidine in the presence of $AlCl_3$. However, no desired vinyl boronate **374** was formed under these conditions and only unreacted starting material **43** was reisolated.

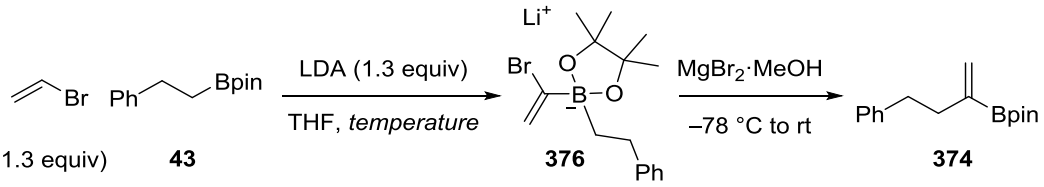


Scheme 4.28. Attempted homologation of boronic ester **43** using α-ethoxyvinyllithium Li-**372** and preactivated BCl_3.

It was argued that, if the generated vinyllithium was attached to a sufficiently good leaving group, the desired 1,2-metallate rearrangement could occur without the need to activate the alkene moiety. To prove this, commercially available vinyl bromide, which undergoes lithiation by treatment with LDA at low temperature,[187-188] was selected as suitable carbenoid precursor (Table 4.4). However, deprotonation of vinyl bromide at −78 °C in the presence of phenethyl pinacol boronic ester **43** only resulted in incomplete boronate complex formation after stirring the reaction mixture at −78 °C for 4 h, as shown by *in situ* ^{11}B NMR analysis (δ = 5.6 ppm). Subsequent addition of $MgBr_2 \cdot MeOH$ to promote the desired 1,2-migration,

followed by warming the reaction mixture to room temperature, gave a mixture of required vinyl boronic ester **374** and starting material **43** in a 40:60 ratio, as revealed by GCMS analysis (Table 4.4, entry 1). Performing the deprotonation step at −95 °C to prevent decomposition of the unstable 1,1-lithiobromoethene[188] only led to a moderate improvement, with a **374**:**43** ratio of 54:46, determined by GCMS analysis (Table 4.4, entry 1).

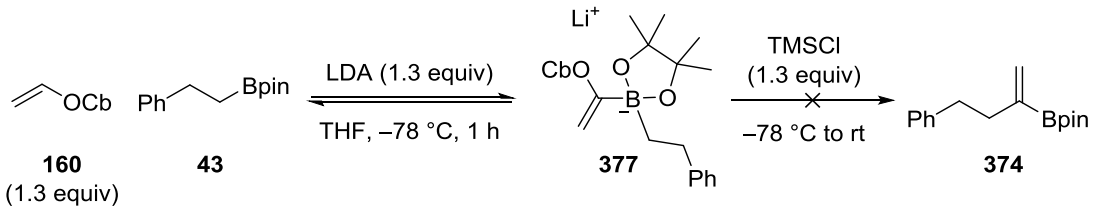
Table 4.4. Attempted homologation of boronic ester **43** using vinyl bromide.



Entry	Temperature	374:43[a]
1	−78 °C	40:60
2	−95 °C	54:46

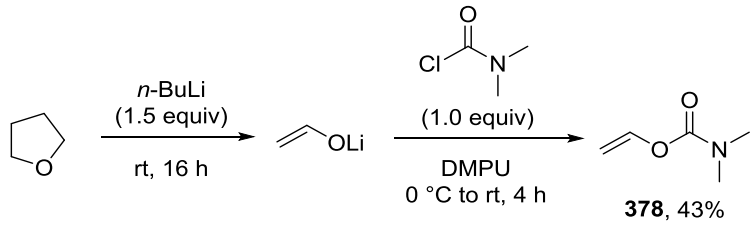
[a] Determined by GCMS analysis.

Since the main problem of the reaction was the high instability of the generated lithiated intermediate, we turned our attention towards the possibility of enhancing the stability of the carbenoid with respect to decomposition, in order to allow complete boronate complex formation. To this aim, vinyl carbamate **160**, which can be lithiated with LDA at −78 °C,[99] was tested as suitable building block for the homologation of boronic ester **43** (Scheme 4.29). Generation of lithiated carbamate Li-**160** in the presence of **43** gave full conversion to boronate complex **377**, as determined by ^{11}B NMR analysis of the reaction mixture (δ = 5.1 ppm). Owing to the diminished leaving group ability of the carbamate with respect to the bromide, addition of TMSCl as an additive was necessary to promote the desired 1,2-metallate rearrangement. However, no required vinyl boronic ester **374** was generated under these conditions and ^{1}H NMR analysis of the crude reaction mixture revealed the presence of starting boronic ester **43** together with unreacted carbamate **160**. This suggests that the 1,2-migration process was too slow to occur and the boronate complex reversed back to reform both the starting materials.



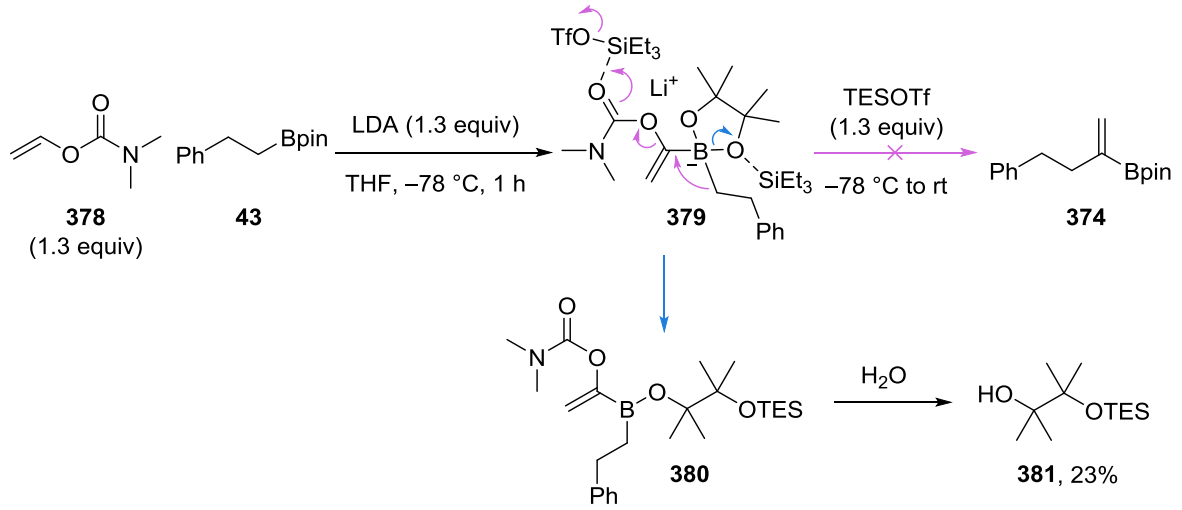
Scheme 4.29. Attempted homologation of boronic ester **43** using vinyl carbamate **160**.

With the aim of reducing the steric hindrance around the boron centre and facilitate the desired 1,2-metallate rearrangement, *N*,*N*-dimethylvinyl carbamate **378** was readily synthesised by deprotonation of THF with *n*-BuLi, followed by trapping with commercially available dimethylcarbamyl chloride (Scheme 4.30).[189]



Scheme 4.30. Synthesis of *N*,*N*-dimethylvinyl carbamate **378**.

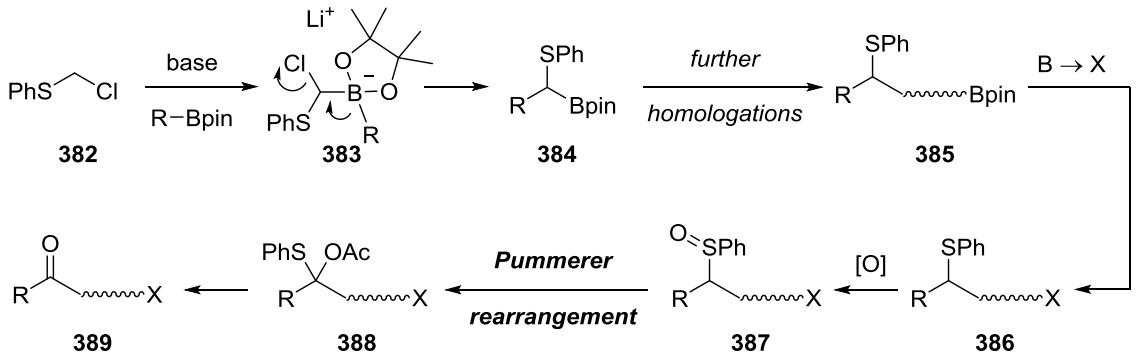
As expected, treatment of a solution of vinyl cabamate **378** and phenethyl pinacol boronic ester **43** in THF with LDA at −78 °C resulted in the complete formation of boronate complex **379**, as confirmed by *in situ* ^{11}B NMR monitoring of the reaction mixture (δ = 4.7 ppm, Scheme 4.31). However, addition of TMSOTf as the activator, followed by warming the reaction mixture to room temperature, gave only starting boronic ester **43**, and no desired product **374** was detected. The isolation of monoprotected diol **381** in 23% yield suggested that the desired 1,2-metallate rearrangement was too slow and a competing ring-opening of the pinacol boronic ester moiety, upon activation with TMSOTf, occurred instead to give intermediate borinic ester **380**, which was eventually hydrolysed during aqueous work-up.



Scheme 4.31. Attempted homologation of boronic ester **43** using *N*,*N*-dimethylvinyl carbamate **378**.

Subsequent attempt of using Tf_2O as a stronger activating agent also met with failure and desired vinyl boronate **374** could not be accessed.

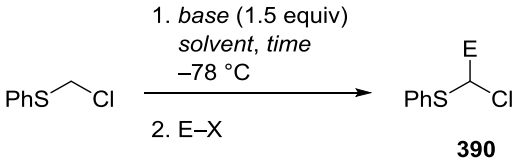
Since the homologation of boronic esters leading to the insertion of terminal double bonds as masked carbonyl functionalities could not be achieved, building blocks bearing other potential masking groups were considered. We were specifically intrigued by the possibility of using a building block **382** that, if employed in a lithiation−borylation reaction with a boronic ester, would allow the synthesis of intermediate thioether **384**; after further iterative homologations, oxidation of sulfide **386** to the corresponding sulfoxide **387** and subsequent Pummerer rearrangement would liberate the required ketone functionality **389** (Scheme 4.32).



Scheme 4.32. Proposed homologation of boronic esters with the introduction of thioethers as masked carbonyl functionalities.

Commercially available chloromethyl phenyl sulfide was initially selected as a suitable carbenoid precursors. However, lithiation−trapping studies immediately made evident the high instability of the generated lithium carbenoid with respect to decomposition (Table 4.5). Deprotonation of chloromethyl phenyl sulfide in THF at −78 °C with *s*-BuLi for 1 h, followed by quenching with an excess of TMSCl, resulted in complete decomposition of the generated lithiated species (Table 4.5, entry 1); the use of LDA as the base did not give a better result in either THF or Et_2O and decomposition of the carbenoid was revealed after quenching the reaction mixture with CD_3OD (Table 4.5, entries 2−3). Performing the deprotonation with LDA for only 5 min, before addition of CD_3OD, also met with failure, and deuterated sulfide **390** was not observed (Table 4.5, entry 4); finally, when NaHMDS was employed as the base, unreacted starting material was recovered after quenching with CD_3OD, indicating that the base was not sufficiently strong to perform the desired deprotonation (Table 4.5, entry 5).

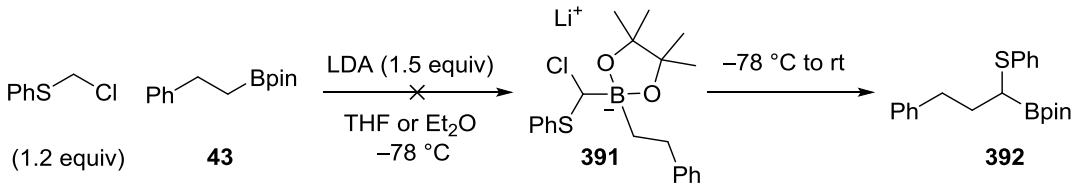
Table 4.5. Attempted lithiation–trapping of chloromethyl phenyl sulfide.



390

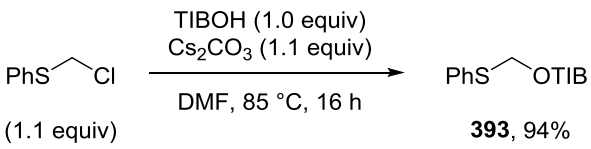
Entry	Base	Solvent	Time	E–X	% Yield 390
1	*s*-BuLi	THF	1 h	TMSCl	0
2	LDA	THF	1 h	CD_3OD	0
3	LDA	Et_2O	1 h	CD_3OD	0
4	LDA	THF	5 min	CD_3OD	0
5	NaHMDS	THF	5 min	CD_3OD	0

Despite the unpromising outset, the homologation of boronic ester **43** with chloromethyl phenyl sulfide was attempted, with the hope that an *in situ* trapping of the generated lithium carbenoid would be sufficiently fast to prevent decomposition (Scheme 4.33). However, deprotonation of chloromethyl phenyl sulfide with LDA in the presence of **43** did not lead to the formation of boronate complex **391**, as confirmed by *in situ* ^{11}B NMR monitoring of the reaction mixture, therefore suggesting that the lithiated species decomposed before being trapped by the boronic ester.



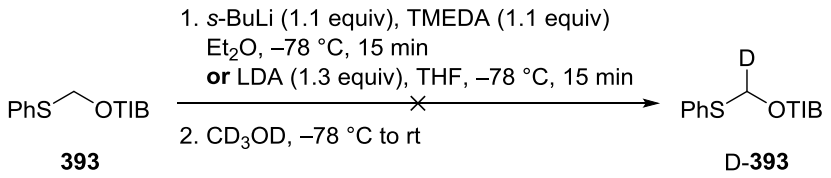
Scheme 4.33. Attempted homologation of boronic ester **43** using chloromethyl phenyl sulfide.

In an attempt to generate a more stable lithium carbenoid with respect to decomposition, sulfide-substituted TIB benzoate **393** was readily synthesised from the corresponding chloride (Scheme 4.34).



Scheme 4.34. Synthesis of sulfide-substituted benzoate **393**.

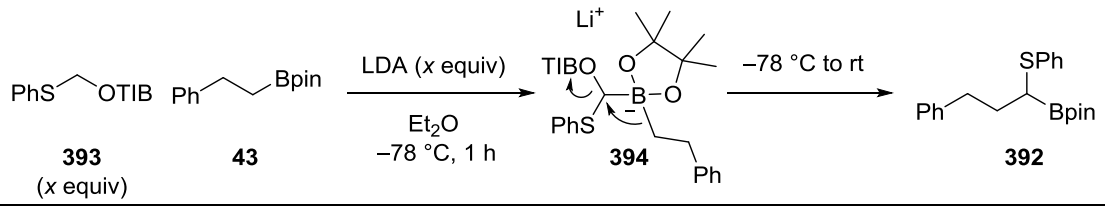
Initial lithiation−deuteration studies on benzoate **393**, using either *s*-BuLi in Et_2O or LDA in THF, revealed the high instability of the corresponding lithiated carbenoid, which was found to decompose at −78 °C in only 15 min (Scheme 4.35).



Scheme 4.35. Lithiation−deuteration studies on benzoate **393**.

In situ trapping of the generated lithiated benzoate with phenethyl pinacol boronic ester **43** was therefore attempted. Pleasingly, treatment of a solution of thioether **393** (1.2 equiv) in Et_2O with LDA (1.5 equiv) at −78 °C for 1 h, followed by warming the reaction mixture to room temperature, gave the desired homologated boronic ester **392**, together with starting material **43**, in an 85:15 ratio, as determined by GCMS analysis (Table 4.6, entry 1). Increasing the amount of LDA employed to 2.0 equiv only led to a partial improvement, with the product to starting material ratio determined by GCMS analysis being **392**:**43** = 90:10 (Table 4.6, entry 2). Finally, using an excess of both carbenoid precursor **393** (2.0 equiv) and base (2.0 equiv) gave complete consumption of starting material, thus proving the high instability of the generated lithium carbenoid with respect to decomposition (Table 4.6, entry 3). Disappointingly, homologated boronic ester **392** was never isolated in high yield after purification by column chromatography, the species presumably being unstable on silica gel.

Table 4.6. Homologation of boronic ester **43** with benzoate **393**.

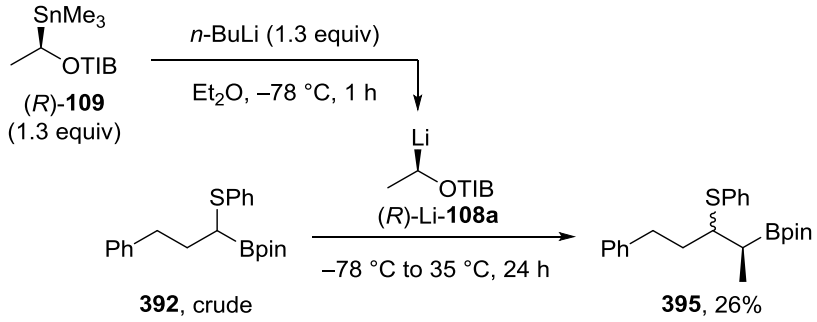


393 (*x* equiv) **43** **394** **392**

Entry	Equiv 393	Equiv LDA	392:43[a]	% Yield 392
1	1.2	1.5	85:15	29
2	1.2	2.0	90:10	n.d.
3	2.0	2.0	100:0	45

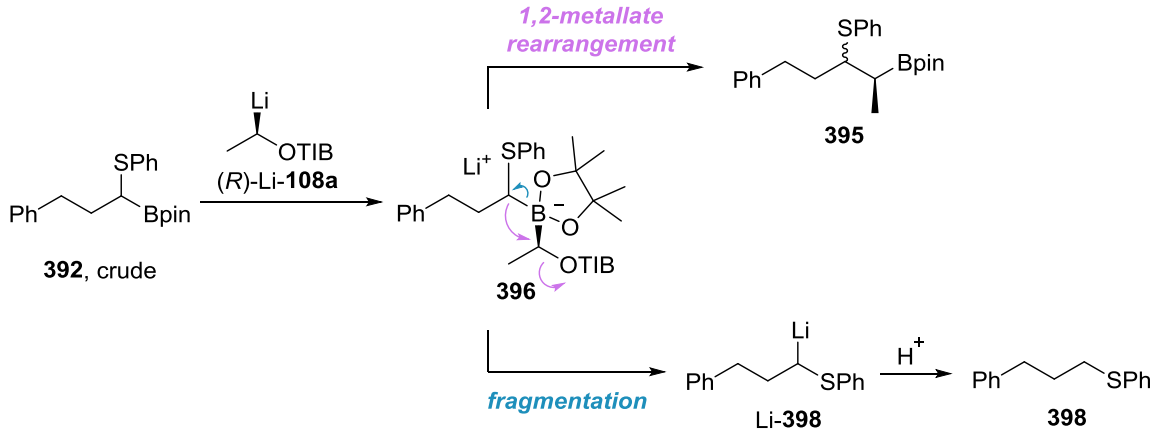
[a] Determined by GCMS analysis; n.d. = not determined.

The instability of boronic ester **392** on silica gel was attributed to the presence of the α-thioether group. It was therefore decided to use crude boronic ester **392** in a subsequent homologation with lithiated carbenoid (*R*)-Li-**108a**, generated *in situ* from α-stannyl benzoate (*R*)-**109**; the process would form β-sulfide boronic ester **395**, which was hoped to be more stable than its precursor **392** on silica gel (Scheme 4.36). However, generation of lithiated benzoate (*R*)-Li-**108a** by lithium−halogen exchange, followed by addition of a solution of crude boronic ester **392** in Et_2O, gave moderate levels of conversion of starting material **392**, and desired homologated product **395** was isolated as a mixture of diastereoisomers (d.r. = 1:1) in only 26% yield over the two steps. Under-homologated boronic ester **392** was also reisolated in 28% yield, indicating either incomplete or reversible boronate complex formation.



Scheme 4.36. Attempted homologation of crude α-thioboronic ester **392** with (*R*)-Li-**108a**.

GCMS analysis of the crude reaction mixture revealed the formation of sulfide **398** as a side-product, although the species was not isolated. This suggested that a fragmentation pathway of boronate complex **396**, leading to stabilised anion **398**, competed with the desired 1,2-metallate rearrangement (Scheme 4.37).



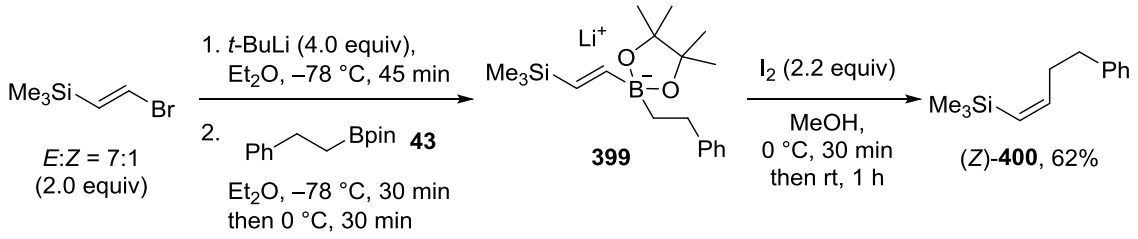
Scheme 4.37. Fragmentation of boronate complex **396** competing with the desired 1,2-metallate rearrangement.

α-Phenylthio boronic ester **392** was therefore shown not to be a suitable substrate for lithiation−borylation reactions. Additionally, homologation of boronic ester **43** with benzoate **393** proved to be not always reproducible, giving variable levels of conversion of starting material **43**, as determined by GCMS analysis. These observations, together with the high number of steps necessary for the final release of the targeted carbonyl functionality, made us hesitant about further attempts to optimise the process. New types of building blocks for the homologation of boronic esters leading to the introduction of masked ketones were to be therefore considered in the future.

4.2.2. Development of a 2-C Building Block for the Introduction of C−C Double Bonds through the Homologation of Boronic Esters

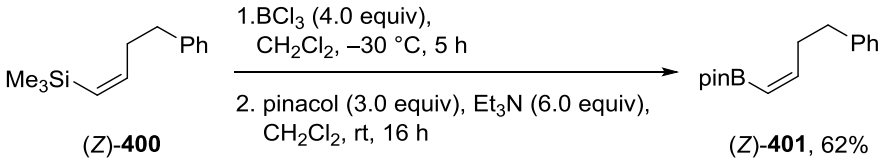
The development of a two-carbon building block enabling the homologation of boronic esters leading to the introduction of C−C double bonds began with exploring the possibility of using a Zweifel olefination reaction. As aforementioned, the required carbenoid precursor must bear a group that can be readily converted into an organolithium; additionally, a functional group, stable under the reaction conditions and able to be eventually transformed into a boronic ester, is necessary to make subsequent iterations possible. Commercially available (2-bromovinyl)trimethylsilane was initially selected as a suitable building block (Scheme 4.38). Lithium−halogen exchange was successfully achieved by treatment of a solution of (2-bromovinyl)trimethylsilane in Et_2O with *t*-BuLi at −78 °C for 45 min; a solution of boronic ester **43** in Et_2O was subsequently added and the complete boronate complex formation was confirmed by *in situ* ^{11}B NMR analysis (δ = 5.5 ppm). Addition of a solution of I_2 in MeOH at 0 °C, followed by warming the reaction mixture to room temperature, allowed

the 1,2-metallate rearrangement/elimination process to take place, to give, after purification by chromatography on silica gel, alkene **400** in 62% yield and as a single *Z*-isomer.



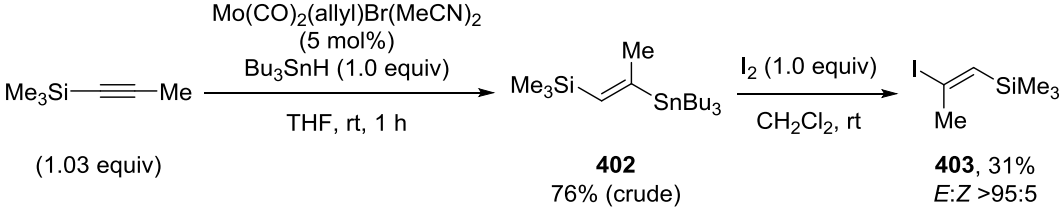
Scheme 4.38. Zweifel olefination of boronic ester **43** with (2-bromovinyl)trimethylsilane.

Prompted by the successful olefination of boronic ester **43**, we were willing to test the subsequent borodesilylation of alkene (*Z*)-**400** to give vinylboronate (*Z*)-**401**. To this aim, conditions reported for the *ipso*-borodesilylation of alkenylsilanes were applied (Scheme 4.39).[190-192] Treatment of a solution of alkene (*Z*)-**400** in CH_2Cl_2 with BCl_3 at low temperature, followed by esterification with pinacol, afforded the desired alkenyl boronate (*Z*)-**401** in 62% yield after chromatographic purification.



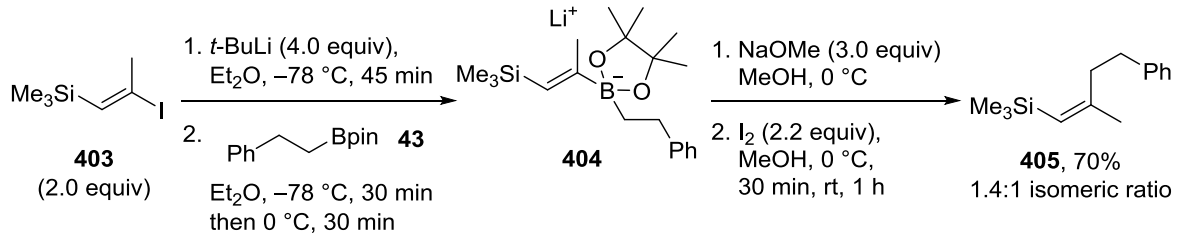
Scheme 4.39. *ipso*-Borodesilylation of vinylsilane (*Z*)-**400**.

With an efficient protocol to homologate boronic esters leading to the introduction of a disubstituted C−C double bond in hand, the next step was exploring the possibility of applying the same methodology to introduce trisubstitued alkenes. In particular, we were interested in the introduction of methyl substituents, since isopropenyl units are ubiquitous in polyketide structures. To this aim, literature known methyl-substituted iodoalkene **403** was identified as a suitable building block and readily accessed by hydrostannylation of commercially available 1-(trimethylsilyl)propyne, followed by iodination (Scheme 4.40).[193]



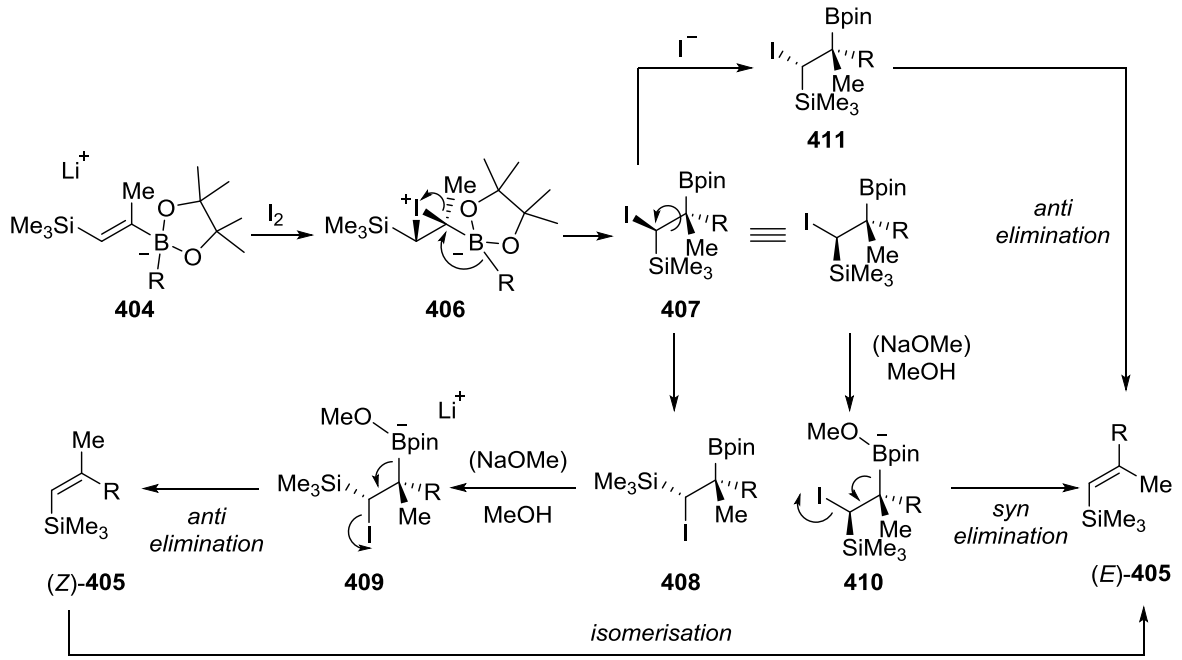
Scheme 4.40. Synthesis of iodoalkene **403**.

Phenethyl pinacol boronic ester **43** was initially subjected to a Zweifel olefination reaction with alkene **403** using the reaction conditions that had previously allowed the introduction of a disubstituted double bond (Scheme 4.41). Iodine−lithium exchange, followed by addition of **43**, resulted in full boronate complex formation, as determined by ^{11}B NMR analysis of the reaction mixture (δ = 6.9 ppm); a subsequent iodine-mediated 1,2-metallate rearrangement/elimination sequence afforded trisubstitued alkene **405** in 70% yield after purification by column chromatography. Surprisingly, the isolated product was found to be a mixture of geometric isomers in a 1.4:1 ratio, as determined by ^{1}H NMR analysis.



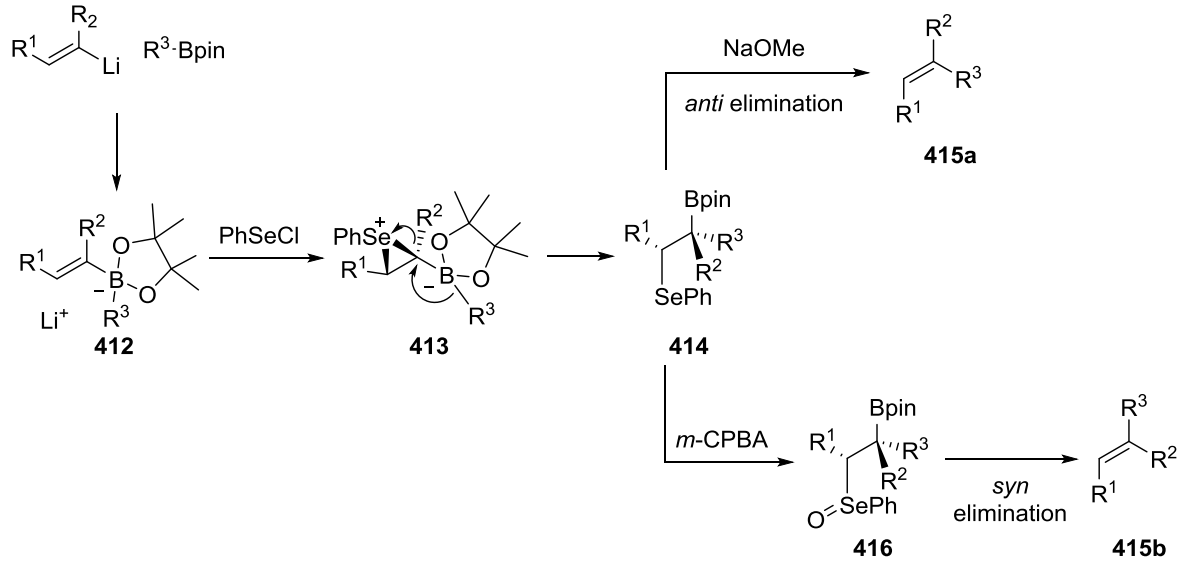
Scheme 4.41. Iodine-mediated Zweifel olefination of boronic ester **43** using alkene **403** leading to a mixture of geometric isomers.

The Zweifel olefination was known to be a stereospecific process, leading to the selective formation of a single geometric isomer through *anti*-elimination of the intermediate β-iodoboronic ester (see § 1.7.3). The possible scenario accounting for the observed diminished stereospecificity in the case of alkene **403** is depicted in Scheme 4.42. One possibility is that a *cis*-elimination of intermediate β-iodoboronic ester **407** competes with the favoured *anti*-elimination, therefore leading to the formation of the opposite geometric isomer; this pathway is nevertheless unlikely, since a *cis*-elimination process would require an eclipsed synperiplanar transition state, which is less favoured that the corresponding staggered antiperiplanar transition state. Another possibility is that an S_N2 reaction occurs at the C−I bond, due to presence of iodide ions in solution, eventually leading to inversion of configuration at the carbon centre; the generated intermediate **411** would then undergo the expected *anti*-elimination to give alkene (*E*)-**405**. Finally, isomerisation of the initially generated alkene (*Z*)-**405** could occur under reaction conditions, leading to a mixture of geometric isomers.



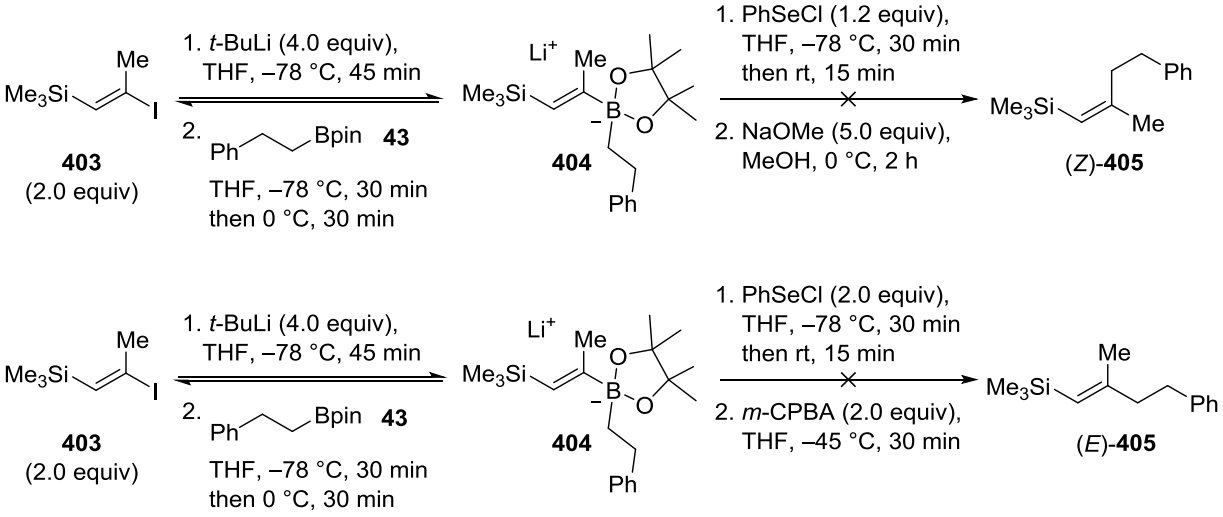
Scheme 4.42. Possible mechanisms accounting for the diminished stereoselectivity observed in the Zweifel olefination of boronic ester **43** with alkene **403**.

It was argued that the use of a different electrophile, other than iodine, to induce the 1,2-metallate rearrangement/elimination sequence would overcome the observed diminished selectivity. Aggarwal and co-workers have recently developed a protocol for the stereodivergent Zweifel olefination of boronic esters with vinyl halides using PhSeCl (Scheme 4.43).[98] In this process, initially generated boronate complex **412** undergoes selenation by addition of PhSeCl to give intermediate **413**, which, after 1,2-metallate rearrangement, affords β-selenoboronic ester **414**; subsequent addition of a solution of NaOMe in MeOH triggers an *anti*-elimination process to give homologated alkene **415** as a single geometric isomer. Alternatively, intermediate β-selenoboronic ester **414** can be oxidised by *m*-CPBA to afford selenoxide **416**; attack of the selenoxide **416** onto the boron centre results in a *syn*-elimination process to give exclusively the other geometric isomer of alkene **415**.



Scheme 4.43. Aggarwal's stereodivergent Zweifel olefination of boronic esters using PhSeCl.

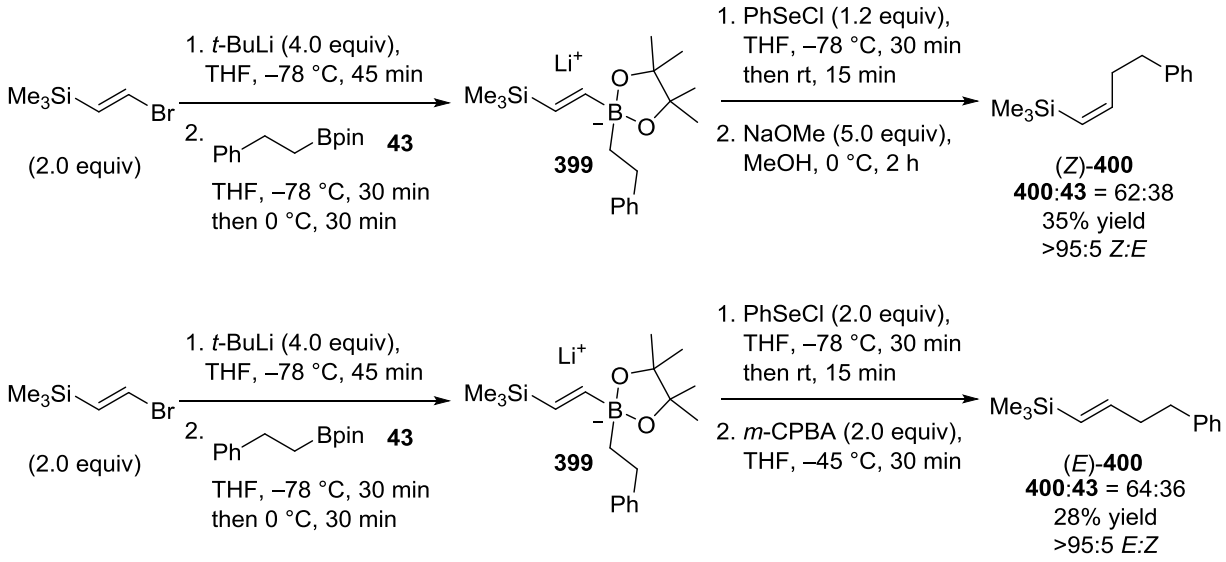
Both sets of reaction conditions were tested in the Zweifel olefination of boronic ester **43** (Scheme 4.44). However, the expected trisubstituted alkene **405** was not formed and only starting boronic ester **43** could be reisolated, despite *in situ* ^{11}B NMR monitoring of the reaction mixture showed full boronate complex formation (δ = 5.8 ppm).



Scheme 4.44. Stereodivergent Zweifel olefination of boronic ester **43** with trisubstituted alkene **403**.

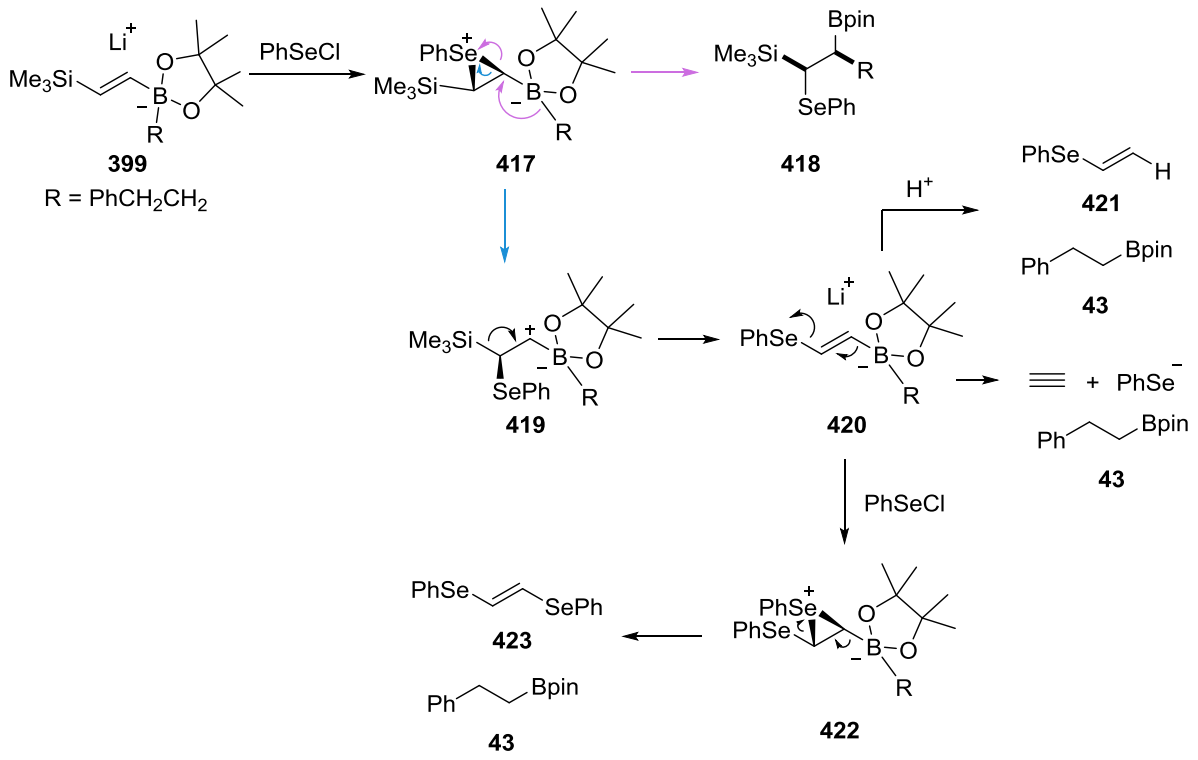
Since silyl-substituted alkenes had never been employed in selenium-mediated Zweifel olefination reactions before, the protocol was tested on disubstituted (2-bromovinyl)trimethylsilane, reasoning that the reduced steric hindrance on the vinylhalide compared to alkene **403** would make the process more facile (Scheme 4.45). In this case, the application of the previously described conditions to accomplish the stereodivergent Zweifel olefination of boronic ester **43** gave access to both the geometric isomers of alkene **400**;

however, despite full boronate complex formation was confirmed by *in situ* ^{11}B NMR spectroscopy (δ = 5.4 ppm), low product to starting material ratio was observed by GCMS analysis of the crude reaction mixture.



Scheme 4.45. Stereodivergent Zweifel olefination of boronic ester **43** with (2-bromovinyl)trimethylsilane.

The considerable amount of starting boronic ester **43** recovered suggested the operation of a mechanism competing with the desired 1,2-metallate rearrangement/elimination pathway (Scheme 4.46). Specifically, breaking (or lengthening) of the C−Se bond could lead to the formation of intermediate **419**, with the forming (or partially forming) carbocation stabilised by the presence of the silicon group in the β position; subsequent elimination of the TMS group would generate β-seleno boronate complex **420**, which would be either protonated upon aqueous work-up to give vinyl selenide **421** and starting boronic ester **43** or would eliminate the selenide to form acetylene. Alternatively, further reaction of intermediate **420** with PhSeCl would give, after elimination, bis(phenylseleno)-alkene **423**.

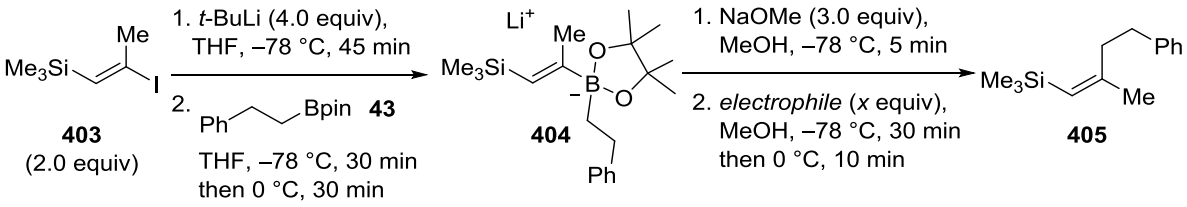


Scheme 4.46. Possible competing elimination pathway accounting for the recovery of starting material **43** in the Zweifel olefination reaction using PhSeCl.

With the knowledge that PhSeCl was not a suitable electrophile to accomplish the Zweifel olefination of boronic ester **43** using trisubstituted alkene **403**, other experiments were conducted, with the aim of identifying new reaction conditions ensuring high stereoselectivity (Table 4.7). Addition of I_2 and NaOMe in THF, thus avoiding the use of MeOH, shut down any reactivity of the boronate complex and no desired product **405** was observed (Table 4.7, entry 1). Not surprisingly, reducing the equivalents of I_2 (1.05 equiv) and performing the 1,2-metallate rearrangement/elimination step at −78 °C instead of 0 °C, gave only moderate product to starting material ratio (**405**:**43** = 74:26, as determined by GCMS analysis), but an increased isomeric ratio of 3.5:1, therefore suggesting that the presence of iodide ions in the reaction mixture might have an effect on the observed low stereoselectivity (Table 4.7, entry 2). However, the use of NIS in the place of I_2, to reduce the amount of iodide ions in solution, gave a similar result, with a 67:33 product to starting material ratio observed by GCMS analysis and an isomeric ratio of 1.8:1 (Table 4.7, entry 3). Finally, iodine monochloride (ICl) was tested as the electrophile (Table 4.7, entries 4–5). The addition of ICl as a solution in MeOH:CH_2Cl_2 (4:1 *v*/*v*) resulted in a moderate product to starting material ratio of 80:20, determined by GCMS analysis, and an isomeric ratio of 2.3:1; attempts to avoid the use of MeOH by adding ICl as a solution in pure CH_2Cl_2 was detrimental and a low product to starting material ratio

was observed (**405**:**43** = 20:80, determined by GCMS analysis) as well as low stereoselectivity (1:1 isomeric ratio, determined by ^{1}H NMR analysis).

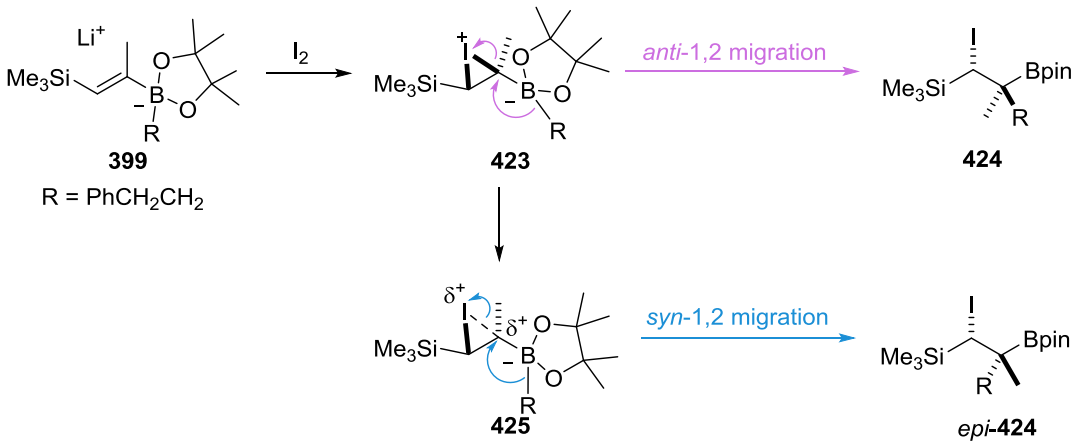
Table 4.7. Zweifel olefination of boronic ester **43** with trisubstitued alkene **403** using various electrophiles.



Entry	Electrophile (equiv)	405:43[a]	isomeric ratio[b]
1[c]	I_2 (2.2 equiv)	–	–
2	I_2 (1.05 equiv)	74:26	3.5:1
3	NIS (1.2 equiv)	67:33	1.8:1
4	ICl (1.3 equiv)	80:20	2.3:1
5[d]	ICl (1.3 equiv)	20:80	1:1

[a] Determined by GCMS analysis of the crude reaction mixture; [b] determined by ^{1}H NMR analysis of the crude reaction mixture; [c] I_2 and NaOMe were added in THF instead of MeOH at 0 °C; [d] ICl was added as a solution in CH_2Cl_2.

The experiments conducted were not sufficient to determine the origin of the observed lack of stereoselectivity in the Zweifel olefination of boronic ester **43** with trisubstituted alkene **403**. The increased isomeric ratio obtained when only one equivalent of I_2 was employed or when NIS was used as the electrophile suggests that the iodide ions present in the reaction mixture might play a role in inducing the observed diminished stereoselectivity; this would presumably happen through an S_N2 process occurring at the C−I bond in the intermediate β-iodoboronic ester leading to inversion of configuration (Scheme 4.42). This pathway is however difficult to prevent, due to the generation of LiI as the by-product of the initial lithium−iodine exchange reaction. Another possibility is that elongation of the C−I bond allows a partial positive charge to build up at the tertiary centre, further stabilised by the β-silicon effect, and this allows a *syn*-migration process to occur (Scheme 4.47). This operating pathway is similar to the one postulated to explain the low diastereoselectivity observed in the trapping of vinyl boronate complexes with PhSeCl to give β-selenoboronic esters.[194] In that case, the undesired competing mechanism was found to be solvent-dependent and could be suppressed by performing the reaction in a 1:1 mixture of THF:trifluoroethanol.

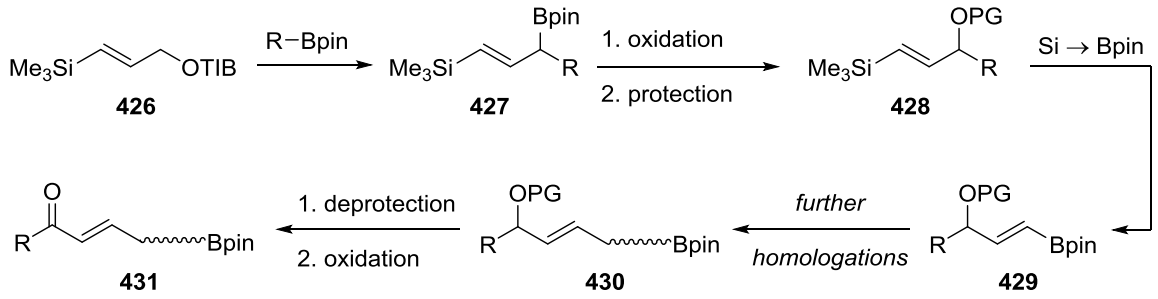


Scheme 4.47. Postulated non-diastereoselective trapping of boronate complex **399** accounting for the observed reduced stereospecificity in the Zweifel olefination of boronic ester **43**.

Further experiments will be therefore conducted in order to confirm the occurrence of these operating pathways. Alternative methodologies to introduce C–C double bonds through the homologation of boronic esters will be also considered.

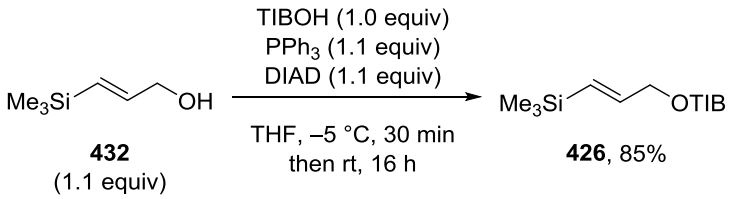
4.2.3. Development of a 3-C Building Block for the Introduction of Enone Functionalities through the Homologation of Boronic Esters

Initial investigations on the development of a 3-carbon building block enabling the introduction of a masked enone functionality focused on the possibility of employing a carbenoid precursor having the required C–C double bond pre-installed. In particular, attention was turned towards allylic benzoate **426**, which, if subjected to lithiation–borylation reaction conditions with a boronic ester, would give access to homologated product **427** (Scheme 4.48). Subsequent oxidation of the boronic ester moiety, followed by protection of the generated alcohol with a suitable protecting group, would yield vinyl silane **428**. *ipso*-Borodesilylation would eventually reintroduce the boronate group, thus making other iterative homologations possible; final deprotection and oxidation of the hydroxy group would release the targeted enone functionality.



Scheme 4.48. Proposed homologation of boronic esters using benzoate **426** leading to the introduction of an enone functionality.

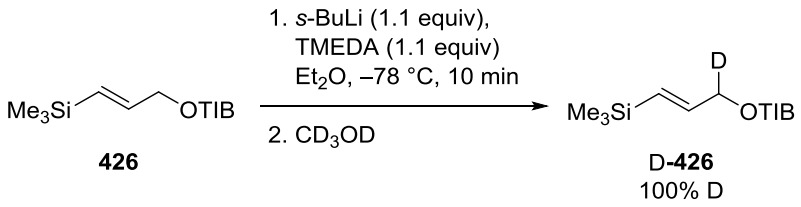
Required benzoate **426** was readily accessed from the corresponding commercially available alcohol **432** through a Mitsunobu reaction (Scheme 4.49).



Scheme 4.49. Synthesis of allylic benzoate **426**.

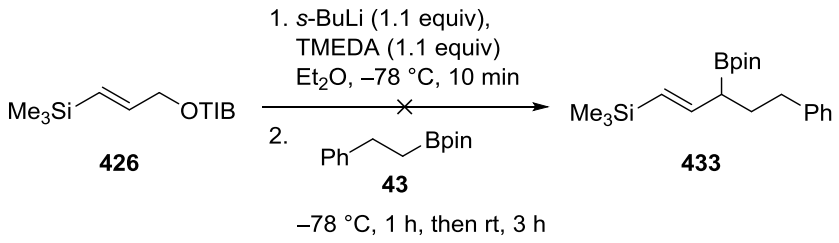
Aggarwal and co-workers showed that secondary allylic carbamates can successfully undergo lithiation−borylation reactions with various boronic esters, displaying excellent α-selectivity in the boronate complex formation step.[195] However, no data was reported on the homologation of boronic esters using primary allylic TIB esters.

A lithiation−deuteration study of benzoate **426** was conducted and it showed that deprotonation by treatment of a solution of **426** in Et_2O with *s*-BuLi in the presence of TMEDA was complete in only 10 min (Scheme 4.50). However, an unidentified side-product was visible on the ^1H NMR recorded on the crude reaction mixture, suggesting partial instability of the generated lithium carbenoid with respect to decomposition.



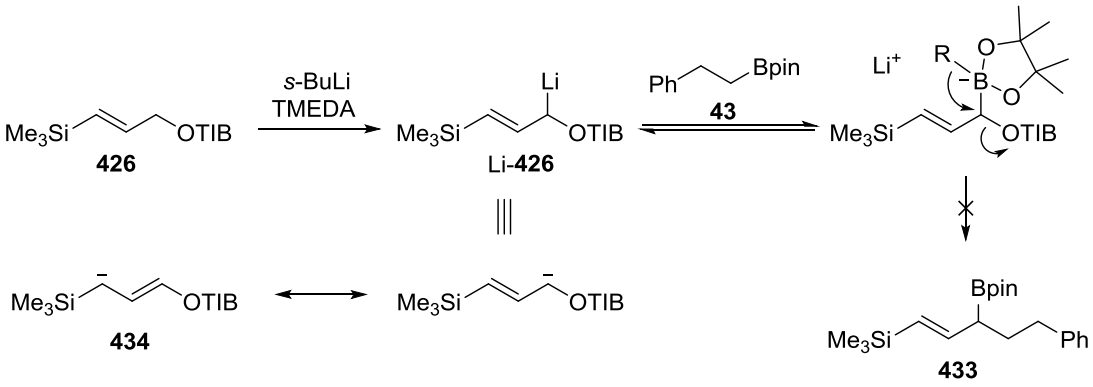
Scheme 4.50. Lithiation−deuteration study on benzoate **426**.

Unfortunately, when benzoate **426** was employed for the homologation of boronic ester **43**, no desired product **433** was observed, and unreacted starting material **43** could instead be reisolated (Scheme 4.51).



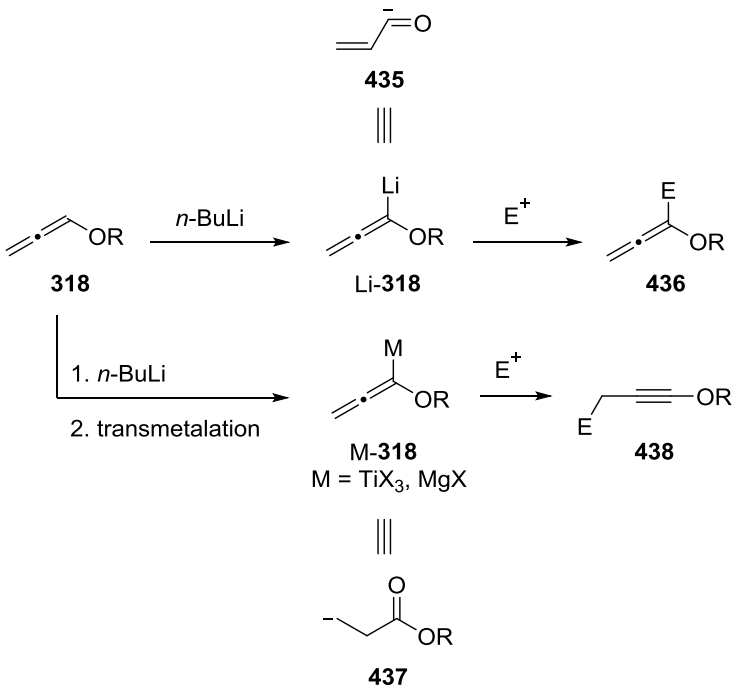
Scheme 4.51. Attempted homologation of boronic ester **43** using benzoate **426**.

This result suggested that the generated lithium carbenoid Li-**426** was trapped by boronic ester **43** in a reversible fashion, and the rapid dissociation of the boronate complex regenerated starting material **43** together with stabilised anion **434**, which presumably underwent decomposition under the reaction conditions (Scheme 4.52).



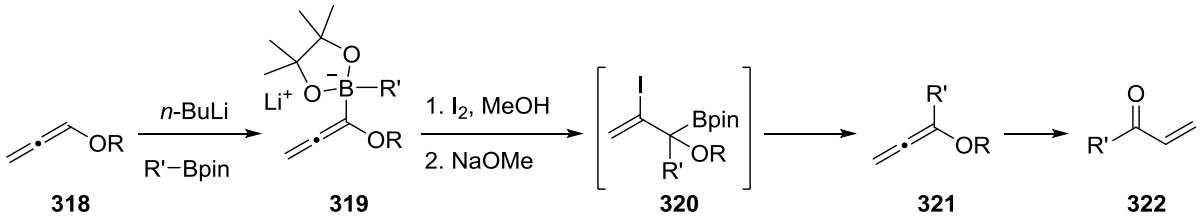
Scheme 4.52. Reversible boronate complex formation in the homologation of boronic ester **43** with benzoate **426**.

With the knowledge that benzoate **426** could not be used as a suitable building block to homologate boronic esters, attention was turned towards a different class of carbenoid precursors. Specifically, we were intrigued about the possibility of using alkoxyallenes, which are known to be versatile building blocks in organic synthesis,[196-197] in a Zweifel olefination reaction to allow the three-carbon homologation of boronates. Alkoxyallenes **318** undergo selective deprotonation at C-1 by treatment with *n*-BuLi to form lithiated intermediate Li-**318**, which can subsequently react with a variety of different electrophiles to access C-1 substituted derivatives **436** (Scheme 4.53).[198] Interestingly, when lithiated intermediate Li-**318** was transmetalated with a less electropositive metal, such as magnesium or titanium, the electrophilic trapping normally occurs at C-3, providing access to functionalised 1-alkoxyalkynes **438**.[199]



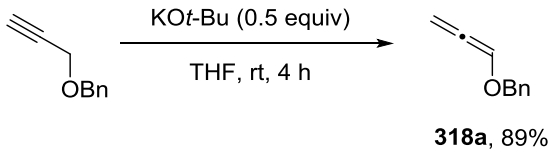
Scheme 4.53. C-1 deprotonation of alkoxyallenes followed by electrophilic trapping.

It was reasoned that trapping of a suitable lithiated alkoxyallene Li-**318** with a boronic ester would give access to boronate complex **319**; upon addition of I_2 and NaOMe, a rapid 1,2-metallate rearrangement would occur, followed by elimination, to afford substituted alkoxyallene **321**, which can be regarded as a terminal α,β-unsaturated carbonyl compound (Scheme 4.54).



Scheme 4.54. Proposed homologation of boronic esters lithiated alkoxyallene Li-**318**.

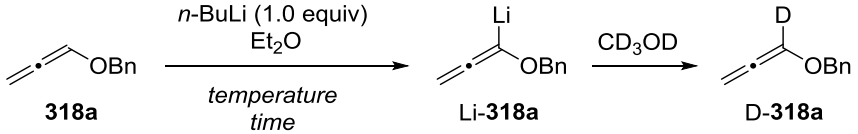
To prove this possibility, benzyloxyallene **318a** was initially identified as a suitable starting material and could be accessed in a straightforward manner by base-promoted isomerisation of commercially available benzyl propargyl ether (Scheme 4.55).[200] The benzyl derivative was selected owing to its low volatility, making the purification more facile; despite the presence of acidic benzylic protons, deprotonation is known to occur selectively at the C-1 position.[200]



Scheme 4.55. Synthesis of benzyloxyallene **318a**.

Lithiation−deuteration studies were conducted in order to optimise the deprotonation conditions (Table 4.8). It was found that full deuterium incorporation was achieved after treatment of a solution of allene **318a** in Et_2O with *n*-BuLi at −42 °C for 30 min, plus additional 10 min at 0 °C, followed by quenching the reaction mixture with an excess of CD_3OD.

Table 4.8. Lithiation−deuteration studies on allene **318a**.

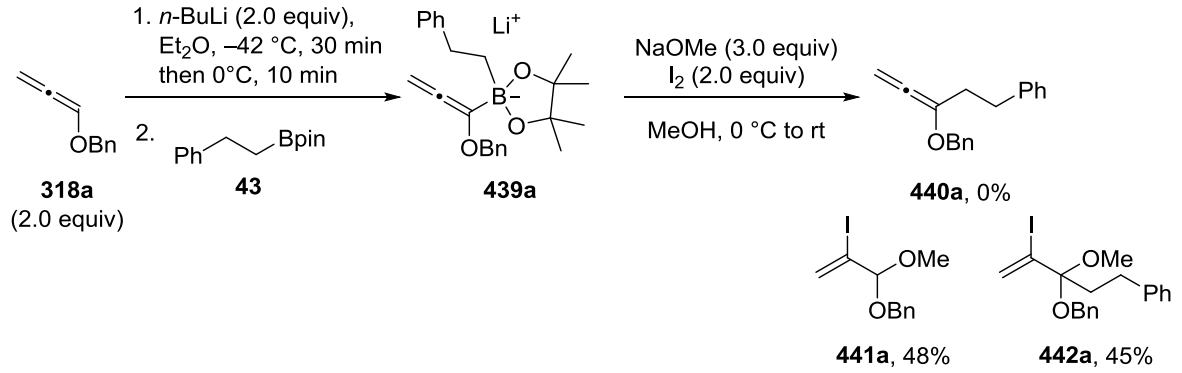


318a Li-**318a** D-**318a**

Entry	Temperature	Time	% D[a]
1	−78 °C	30 min	53
2	−78 °C	1 h	79
3	−42 °C + 0 °C	30 min + 10 min	100

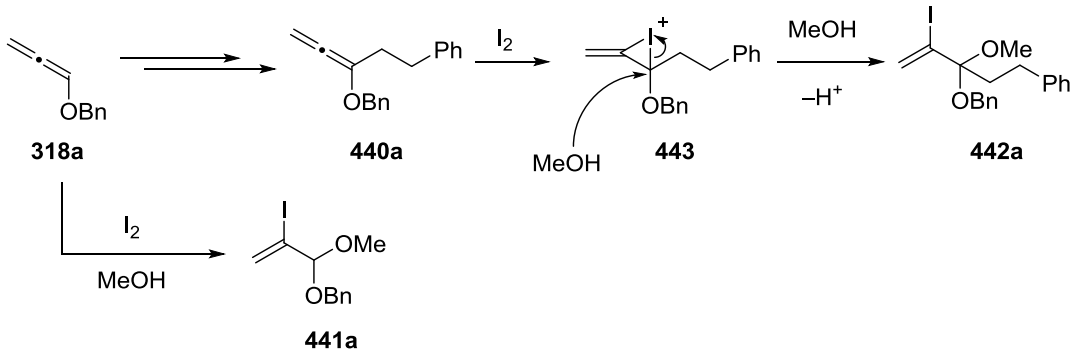
[a] Determined by ^{1}H NMR analysis.

With optimal conditions to deprotonate benzyloxyallene **318a** in hand, the next step was testing the 3-carbon homologation of phenethyl pinacol boronic ester **43** (Scheme 4.56). Trapping of the *in situ* generated lithiated allene Li-**318a** with boronic ester **43** resulted in complete boronate complex formation, as confirmed by ^{11}B NMR analysis of the reaction mixture (δ = 3.2 ppm); however, after I_2-mediated 1,2-metallate rearrangement, followed by elimination, desired substituted allene **440a** was not observed and purification by flash column chromatography only allowed the isolation of vinyl iodides **441a** and **442a** in 48% and 45% yield, respectively.



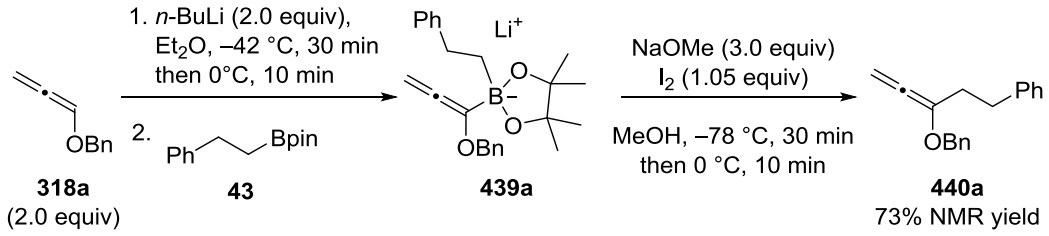
Scheme 4.56. Homologation of boronic ester **43** with alkoxyallene **318a**.

The formation of vinyl iodide **442a** suggested that desired derivatised allene **440a** was initially formed under reaction conditions, but it immediately reacted with the excess of I_2 to form iodonium ion **443**; a subsequent MeOH-promoted ring-opening of intermediate **443** afforded ketal **442a** (Scheme 4.57). The same mechanistic pathway operating on the excess of starting allene **318a** gave access to acetal **441a**.



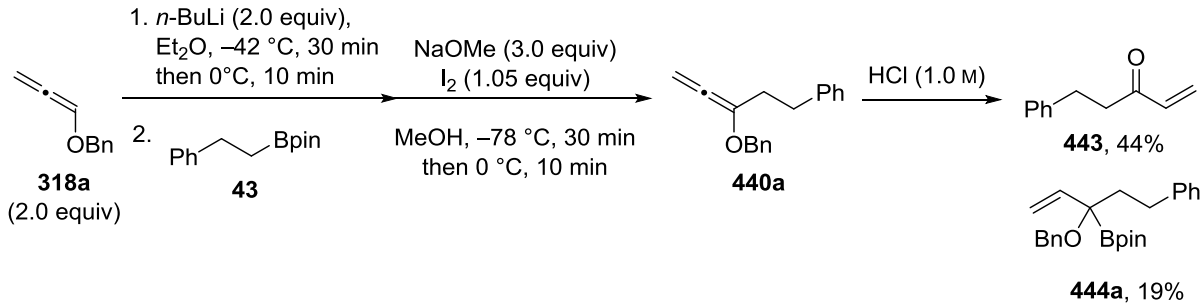
Scheme 4.57. Proposed mechanism for the formation of side-products **441a** and **442a**.

In order to prevent the undesired further reactivity of generated allene **440a**, the sequence was repeated without excess of I_2 (Scheme 4.58). The reaction proceeded smoothly to form desired product **440a** in 73% yield, as determined by ^{1}H NMR analysis of the crude reaction mixture using 1,4-dimethoxybenzene as the internal standard. Unfortunately, allene **440a** was found to be unstable on silica gel, and it could not be isolated after purification by column chromatography.



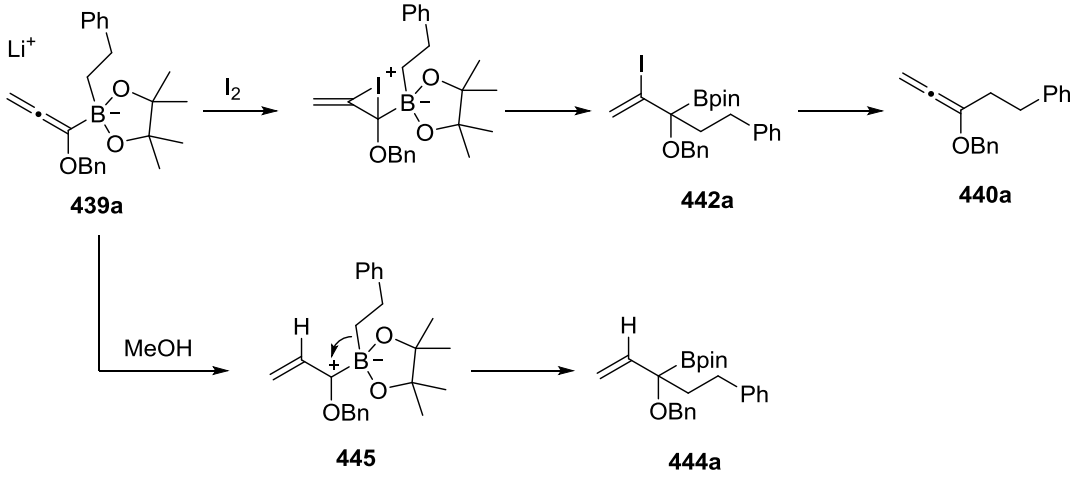
Scheme 4.58. Homologation of boronic ester **43** with alkoxyallene **318a** using no excess of I_2.

To facilitate the isolation process, an acidic wash of a solution of crude allene **440a** was performed to promote its conversion to terminal enone **443** (Scheme 4.59). Pleasingly, these conditions allowed the isolation of desired product **443** in 44% yield after purification by flash column chromatography.



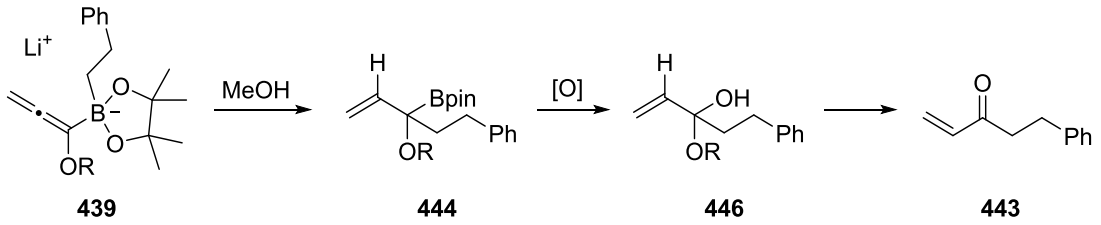
Scheme 4.59. Homologation of boronic ester **43** with alkoxyallene **318a** followed by acidic work-up.

Surprisingly, boronic ester **444a** was also isolated in 19% yield. This suggested that, when the amount of I_2 in solution is not sufficiently high, boronate complex **439** can undergo a proton-mediated 1,2-metallate rearrangement to give alkene **444a** (Scheme 4.60).[201]



Scheme 4.60. Proposed mechanism for the formation of side-product **444a**.

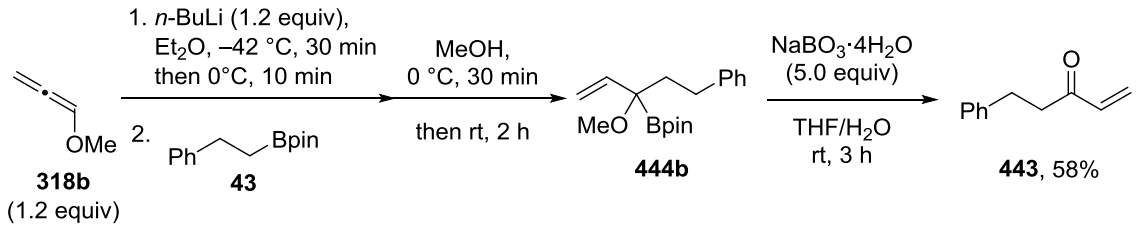
It was reasoned that this reactivity of the generated boronate complex with a proton source could be exploited to achieve a more efficient synthesis of terminal enones, which would be readily accessed by simple oxidation of boronic ester **444** (Scheme 4.61).



439 **444** **446** **443**

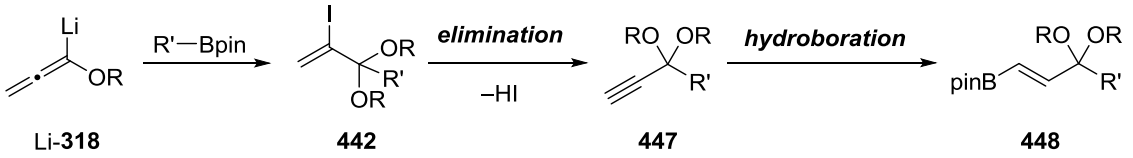
Scheme 4.61. Proposed conversion of boronate complex **439** to enone **443**.

The conversion of boronic ester **444** to terminal enone **443** through a proton-mediated 1,2-metallate rearrangement was therefore attempted (Scheme 4.62). In this case, methoxyallene **318b** was used as the carbenoid precursor (*vide infra*). After generating the intermediate boronate complex using previously described conditions, excess MeOH was added at 0 °C and the reaction mixture was allowed to warm to room temperature over 2 h to give expected alkene **444b**; subsequent oxidation of crude boronic ester **444b** using $NaBO_3 \cdot 4H_2O$ afforded enone **443** in 58% yield after purification by column chromatography.



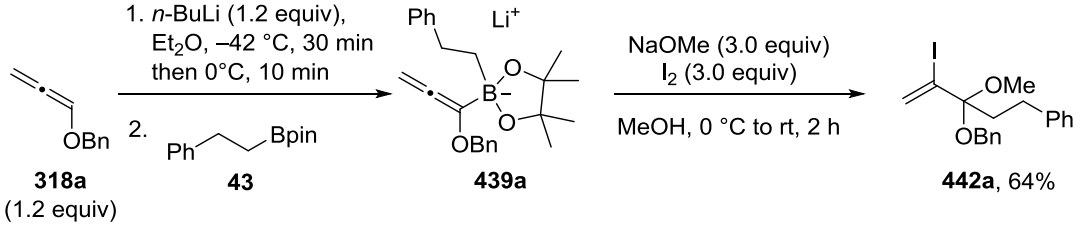
Scheme 4.62. Conversion of boronic ester **43** to enone **443** using methoxyallene **318b**.

With an efficient methodology to perform a 3-carbon homologation of boronic esters leading to the formation of terminal α,β-unsaturated carbonyl compounds, attention was turned towards the possibility of reintroducing the boronate group at the end of the process, in order to enable subsequent iterative homologations. Specifically, side-product **442a** generated in the reaction of boronic ester **43** with lithiated allene Li-**318a** using excess of I_2 looked particularly attractive. It was reasoned that, upon elimination of HI, ketal **442** could be readily converted into alkyne **447**; subsequent hydroboration would lead to the formation of vinyl boronic ester **448**, containing the required masked enone functionality (Scheme 4.63).



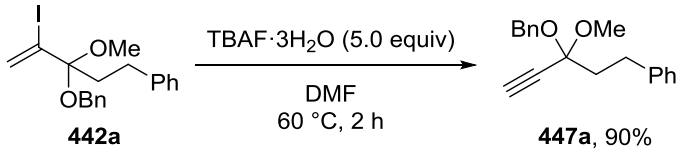
Scheme 4.63. Proposed 3-carbon homologation of boronic ester **43** leading to the formation of vinyl boronate **448** containing a masked enone functionality.

To test this possibility, boronic ester **43** was subjected to Zweifel olefination conditions using allene **318a** in the presence of excess of I_2 (Scheme 4.64). These conditions allowed the formation of vinyl iodide **442a**, which was isolated in 64% yield after purification by column chromatography.



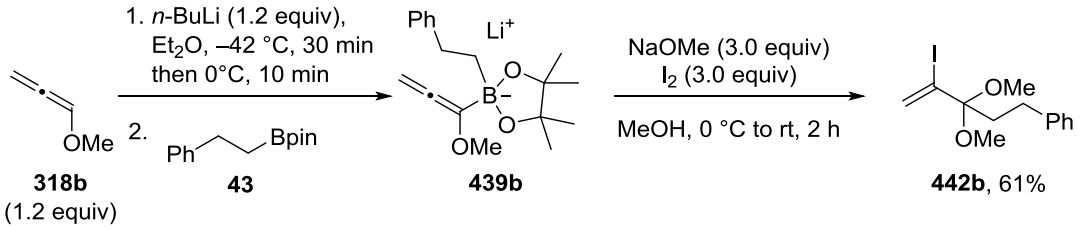
Scheme 4.64. Homologation of boronic ester **43** with benzyloxyallene **318a** using excess of I_2 to form vinyl iodide **442a**.

Subsequent dehydroiodination proceeded smoothly by treatment of a solution of vinyl iodide **442a** in DMF with TBAF·$3H_2O$ to give alkyne **447a** in 90% yield after chromatographic purification (Scheme 4.65).[76]



Scheme 4.65. Dehydroiodination of vinyl iodide **442a** with TBAF·$4H_2O$.

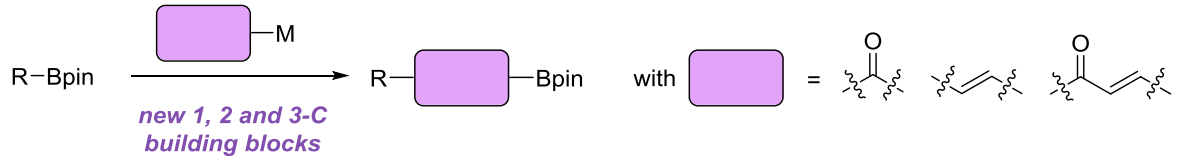
To avoid the formation of stereocentres, that would complicate the assembly-line sequence leading to the formation of diastereoisomers, methoxyallene **318b** was synthesised from commercially available methyl propargyl ether and subsequently employed in the homologation of boronic ester **43** (Scheme 4.66). In this case, vinyl iodide **442a** was isolated in 61% yield, thus demonstrating the analogous reactivity of benzyloxyallene **318a** and methoxyallene **318b**.



Scheme 4.66. Homologation of boronic ester **43** with methoxyallene **318b** using excess of I_2 to form vinyl iodide **442b**.

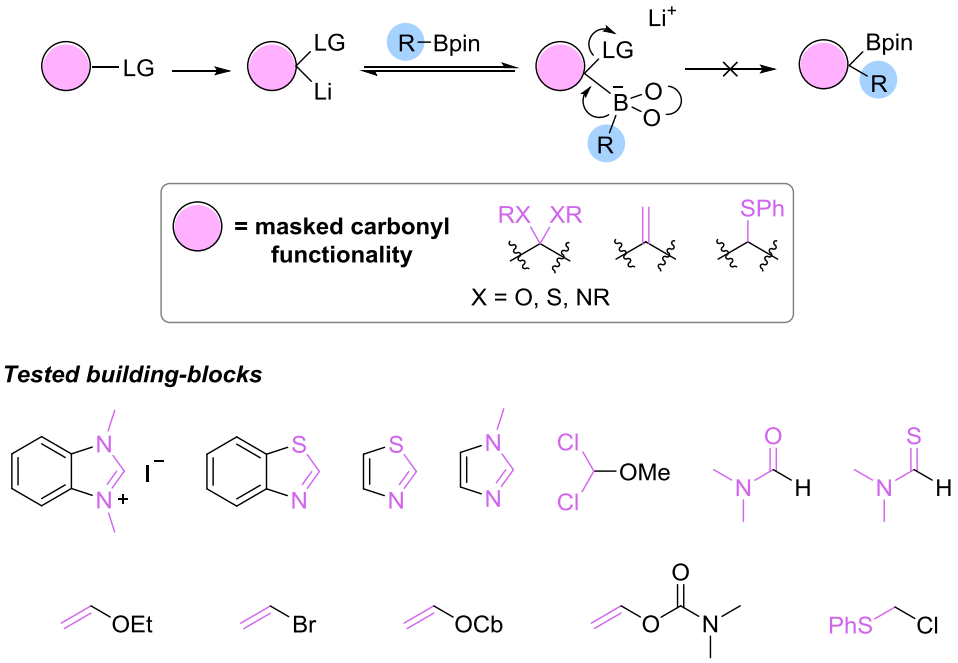
4.3. Conclusions and Future Work

The development of one, two and three-carbon building blocks for the homologation of boronic esters leading to the introduction of useful functional groups has been addressed (Scheme 4.67). In particular, attention focused on the possibility of inserting carbonyl, alkene and enone functionalities; these groups are in fact found to be prominent in numerous polyketide natural products, many of which possess important biological profiles. The use of these building blocks in the Aggarwal's iterative assembly-line synthesis, combined with the ones previously developed within the group, will allow the construction of diversified substituted linear chains of carbon atoms, thus giving potential rapid access to a variety of natural products.



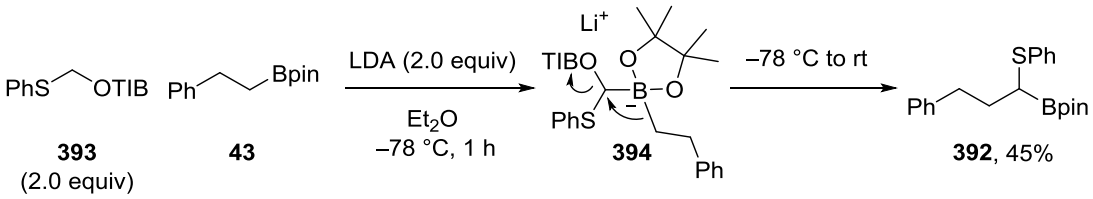
Scheme 4.67. Development of new building blocks for the homologation of boronic esters leading to the introduction of diverse functional groups.

A one-carbon building block to homologate boronic esters leading to the introduction of a masked carbonyl functionality has not been developed yet. Different carbenoid precursors were tested as potential homologating agents, enabling the introduction of various masked ketone groups, but they were all found to be unable to afford the desired product (Scheme 4.68). In most of the cases, the main obstacle proved to be the reversible formation of the intermediate boronate complex, which, instead of undergoing the desired 1,2-metallate rearrangement, reversed back to regenerate the starting boronic ester.



Scheme 4.68. Building blocks tested for the homologation of boronic esters leading to the introduction of masked carbonyl functionalities.

Thioether-substituted benzoate **393** could successfully homologate phenethyl pinacol boronic ester **43**, allowing the introduction of phenyl sulfide as a masked carbonyl group (Scheme 4.69). The relatively low yield of isolated **392** is due to its instability on silica gel.

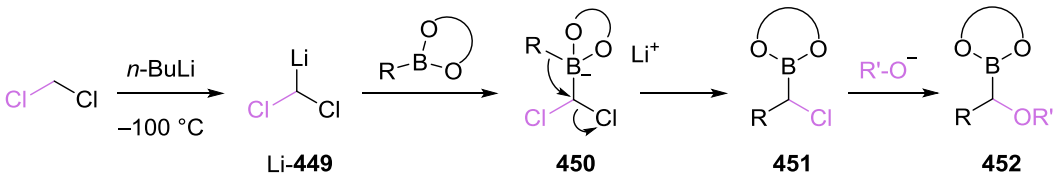


Scheme 4.69. Homologation of boronic ester **43** with thioether-substituted benzoate **393**.

Unfortunately, the reaction was found to be not reproducible, with variable amounts of recovered starting material **43** observed by GCMS analysis. This, together with the difficulties encountered in the attempts to employ homologated boronic ester **392** in a subsequent iteration, prompted us to seek a new and more efficient method to insert masked carbonyl groups through the homologation of boronic esters.

In particular, Matteson and co-workers showed that CH_2Cl_2 can be used as a carbenoid precursor in the homologation of boronic esters.[202] In this process, (dichloromethyl)lithium Li-**449** is generated *in situ* by deprotonation of CH_2Cl_2 with *n*-BuLi at −100 °C and subsequently trapped with a boronic ester to form boronate complex **450**; 1,2-metallate

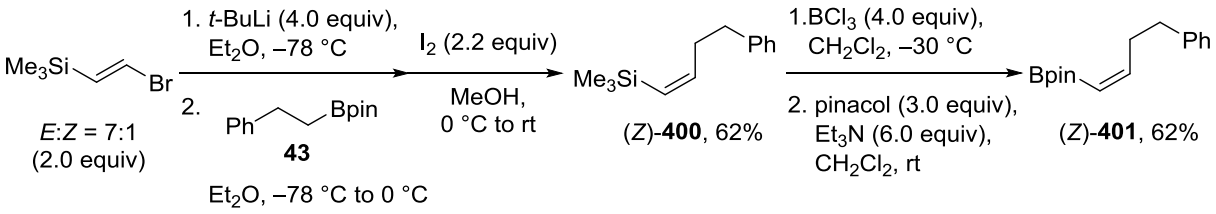
rearrangement affords α-chloro boronic ester **451**, which is eventually converted into α-alkoxy boronic ester **452** by reaction with alkoxide ions (Scheme 4.70).



Scheme 4.70. Matteson's homologation of boronic esters using CH_2Cl_2 as the carbenoid precursor.

This methodology could be optimised and subsequently employed in the iterative homologation of boronic esters to introduce protected alcohols as masked carbonyl functionalities. The alkoxide ion will be carefully chosen in order to allow the selective deprotection of the alcohol at the end of the iterative sequence; final oxidation will unmask the targeted ketone group.

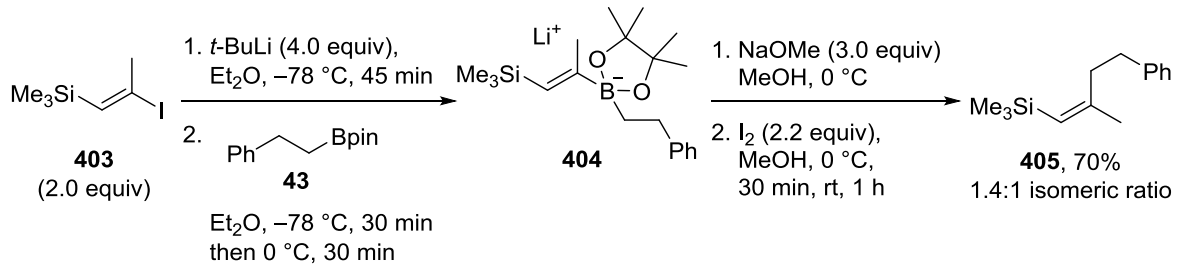
The development of a 2-carbon building block enabling the homologation of boronic esters with the introduction of C−C double bonds has also been addressed. It was found that (trimethylsilyl)vinyllithium, readily accessed from commercially available (2-bromovinyl)trimethylsilane by lithium/halogen exchange, could be successfully employed in the Zweifel olefination of boronic ester **43** to give the corresponding substituted vinyl silane (*Z*)-**400** in good yield (Scheme 4.71). Subsequent borodesilylation allowed the reintroduction of the boronic ester moiety, thus enabling further iterative homologations.



Scheme 4.71. Zweifel olefination of boronic ester **43** with (2-bromovinyl)trimethylsilane and subsequent borodesilylation.

The scope of this process will be probed and a variety of boronic esters, bearing substituents of varying steric hindrance, will be employed in order to define the strenghts and limitations of the methodology.

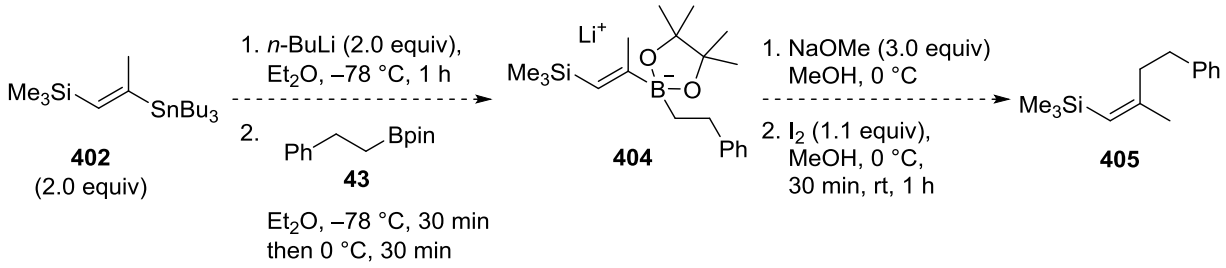
Unfortunately, the protocol was found to be not applicable to the introduction of trisubstitued double bonds, as when alkene **403** was employed as the carbenoid precursor in the same process, the expected homologated vinyl silane **405**, although obtained in good yield, was formed as a mixture of geometric isomers (Scheme 4.72).



Scheme 4.72. Zweifel olefination of boronic ester **43** using trisubstituted alkene **403** giving vinyl silane **405** as a mixture of geometric isomers.

The origin of the observed reduced stereospecificty is still not clear. A possible explanation is that the iodide ions present in the reaction mixture cause an S_N2 reaction to occur at the C–I bond on the generated intermediate β-iodoboronic ester, leading to inversion of configuration. Alternatively, a *syn*-elimination pathway, favoured by the stabilisation of the building positive charge by the silicon group in the β position, might be competing with the expected *anti*-elimination, thus leading to the formation of both the geometric isomers.

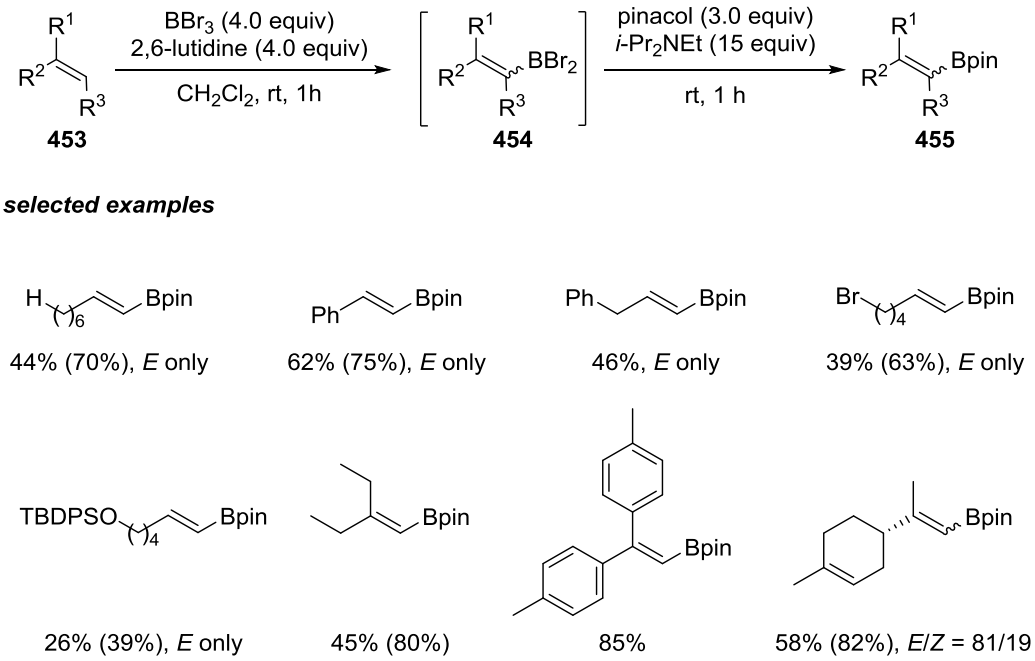
Experiments will be conducted in order to provide further insight into these speculated mechanisms. The Zweifel olefination of boronic ester **43** will be therefore attempted under iodide-free conditions using vinyl stannane **402** as the starting building block, which would generate the required vinyllithium by tin–lithium exchange (Scheme 4.73). The isomeric ratio of trisubstituted alkene **405** will be carefully measured in order to determine the role of iodide ions in decreasing the stereoselectivity of the process.



Scheme 4.73. Proposed Zweifel olefination of boronic ester **43** under iodide-free conditions using vinyl stannane **402**.

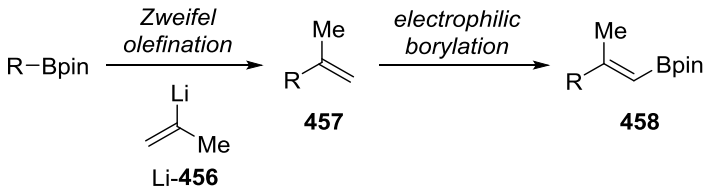
Additionally, the Zweifel olefination of boronic ester **43** with vinyl iodide **403** will be performed in a mixture of THF:trifluoroethanol[194] to determine whether the observed diminished stereoselectivity originates in a non-diastereoselective trapping of the generated boronate complex with iodine. Finally, the possibility of an isomerisation of trisubstituted alkene **405** occurring under the reaction conditions will be addressed.

Alternative methods for the introduction of trisubstituted C−C double bonds through the homologation of boronic esters will also be tested. Hattori and co-workers have recently reported a novel electrophilic borylation of terminal alkenes using BBr_3 in the presence of 2,6-disubstituted pyridines (Scheme 4.74).[203] A variety of alkenes and heteroarenes could be borylated to give the corresponding vinyl boronic esters in good yield. Importantly, α,α-dialkylethylenes were also successfully employed in the process and the corresponding trisubstituted alkenes were formed in good yield, although lower *E*/*Z* selectivity was observed.



Scheme 4.74. Hattori's electrophilic borylation of terminal alkenes with BBr_3.

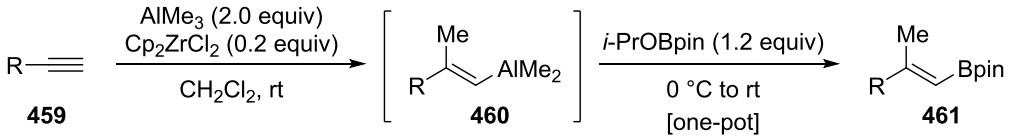
This methodology could be applied to homologate boronic esters to introduce trisubstituted C−C double bonds. Specifically, Zweifel olefination of boronic esters with vinyllithium Li-**456** would afford terminal alkene **457**, which, if subjected to electrophilic borylation, would be converted into desired vinyl boronic ester **458** (Scheme 4.75).



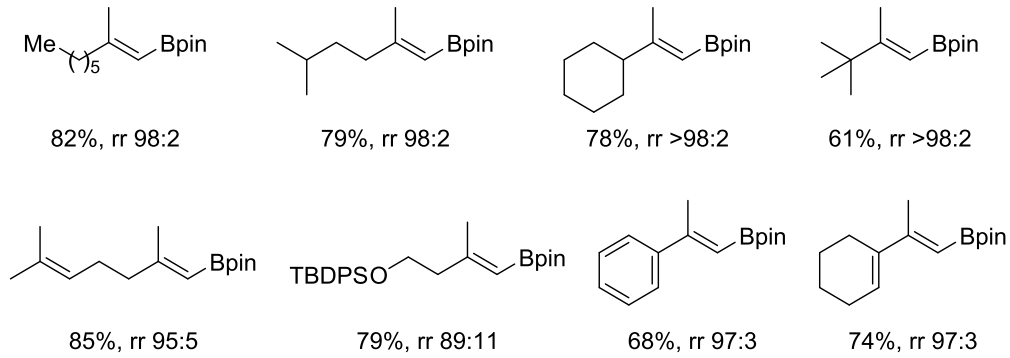
Scheme 4.75. Proposed conversion of boronic esters into trisubstituted vinyl boronates via electrophilic borylation.

Alternatively, the stereo- and regiocontrolled methylboration of terminal alkynes recently developed by Aggarwal and co-workers could be used to convert boronic esters into

trisubstituted vinyl boronates. In this process, terminal alkyne **459** is initially converted into the corresponding alane **460** through a Cp_2ZrCl_2-catalysed Negishi carboalumination using $AlMe_3$; subsequent *in situ* transmetalation of vinyl alane **460** with *i*-PrOBpin affords the desired vinyl boronate **461** in generally good yield and excellent levels of stereo- and regioselectivity (Scheme 4.72).

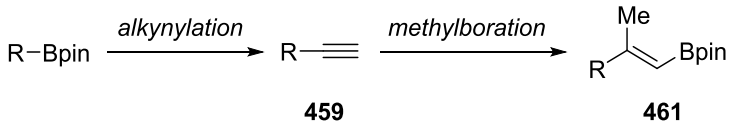


selected examples



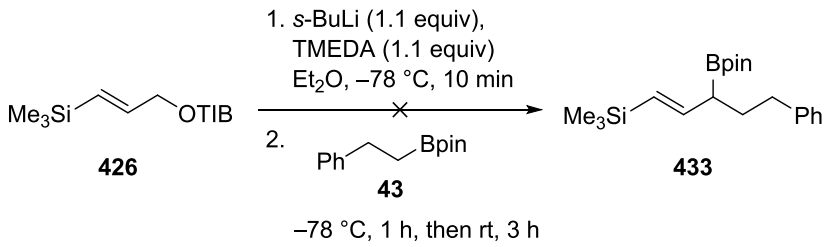
Scheme 4.76. Aggarwal's methylboration of terminal alkynes.

The conversion of boronic esters into terminal alkynes **459** using the conditions developed by Aggarwal and co-workers[99] would give rapid access to the substrate required for the described methylboration, which would afford the targeted trisubstituted vinyl boronates (Scheme 4.77).



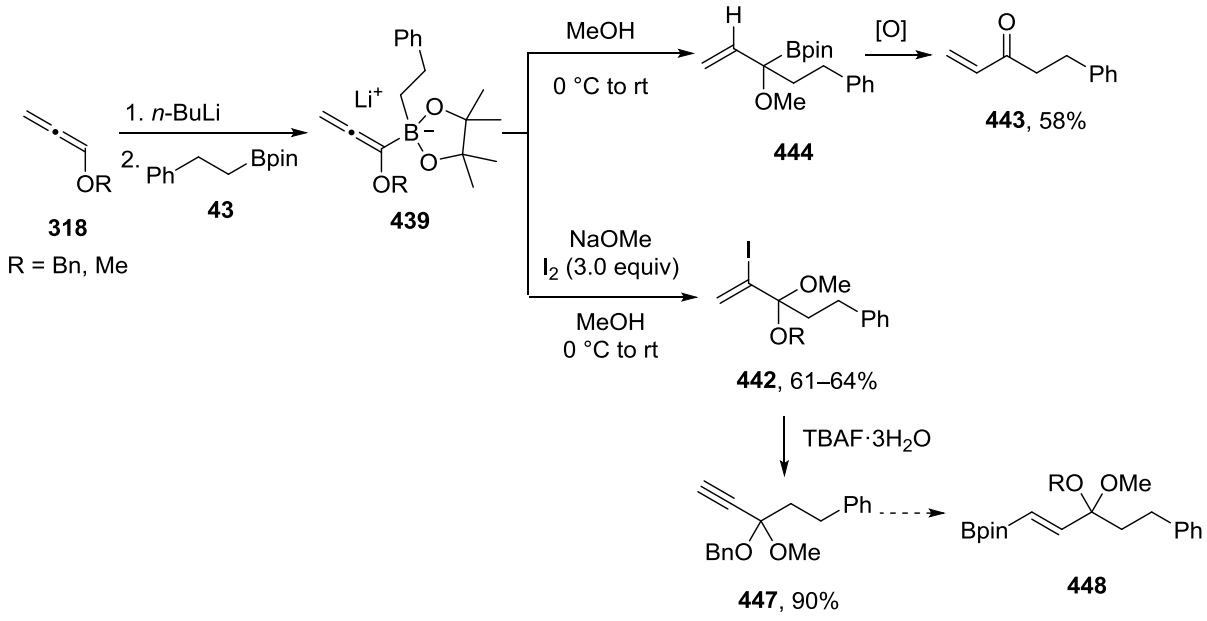
Scheme 4.77. Proposed conversion of boronic esters into trisubstituted vinyl boronates *via* methylboration.

Finally, the 3-carbon homologation of boronic esters allowing the introduction of a masked enone functionality has been examined. Initial investigation showed that allylic benzoate **426** was not a suitable building block to achieve this transformation. In fact, when boronic ester **43** was subjected to lithiation/borylation conditions, no desired homologated product **433** was formed, the formation of the boronate complex presumably being reversible (Scheme 4.78).



Scheme 4.78. Failed homologation of boronic ester **43** using benzoate **426**.

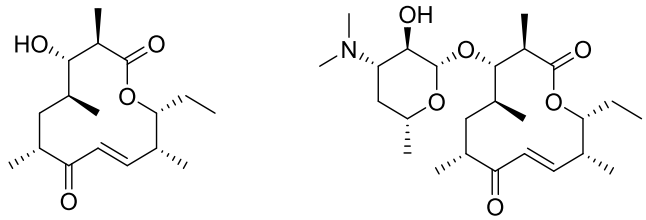
Pleasingly, lithiated alkoxyallenes were found to efficiently react with pinacol boronic esters under Zweifel olefination reaction conditions. In particular, lithiation of alkoxyallenes **318**, followed by trapping with boronic ester **43**, resulted in the complete formation of boronate complex **439** (Scheme 4.79). Upon addition of a proton source, vinyl boronic ester **444** was accessed; subsequent oxidation using $NaBO_3 \cdot 4H_2O$ afforded terminal enone **443** in good yield. Alternatively, treatment of boronate complex **439** with a solution of I_2 in MeOH yielded ketal **442**, which was then subjected to dehydroiodination to give terminal alkyne **447**; subsequent hydroboration will afford the targeted homologated boronic ester **448** containing a masked enone functionality.



Scheme 4.79. 3-Carbon homologation of boronic esters using lithiated alkoxyallenes.

The scope of this protocol will be examined by employing different substituted boronic esters, and the corresponding homologated products, containing terminal or internal masked α,β-unsaturated carbonyl functionalities, will be isolated. The methodology will be also applied to the total synthesis of 10-deoxymethynolide **462**, the 12-membered aglycon of the macrolide

polyketide 10-deoxymethymycin **463**, which displays potent antibiotic activity against gram-positive bacteria (Figure 4.2).[204]



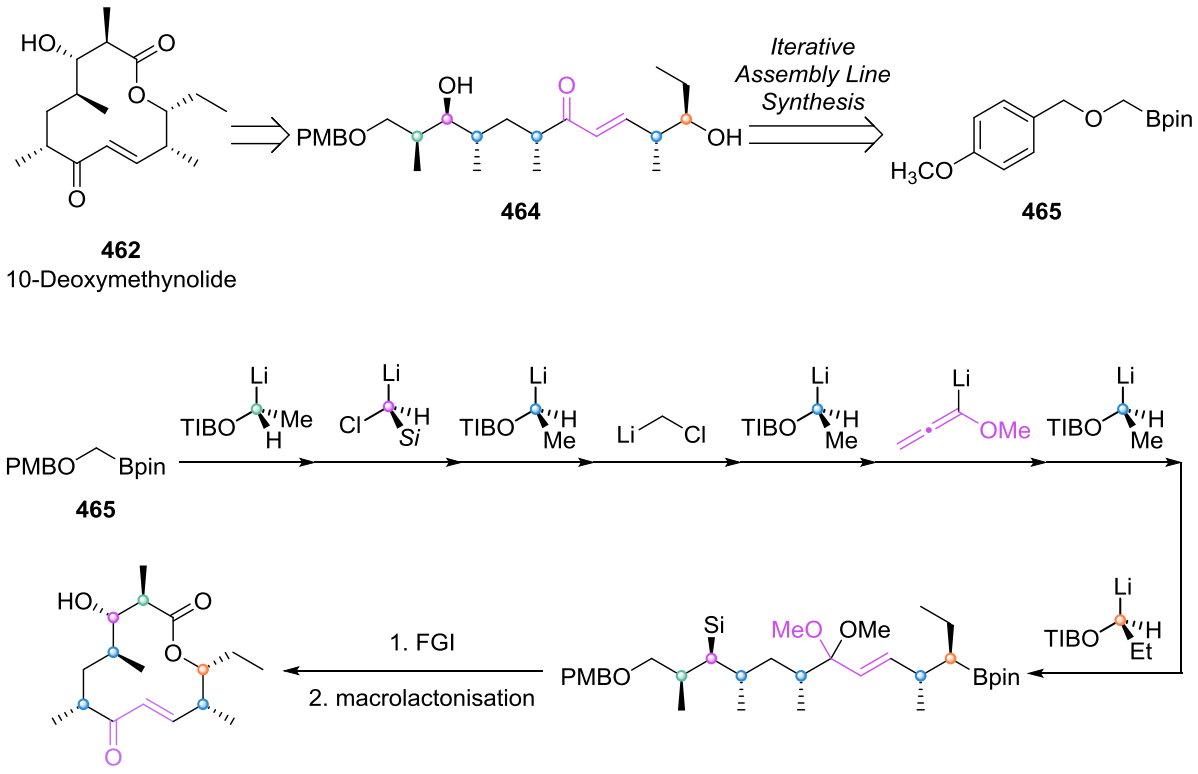
462
10-Deoxymethynolide

463
10-Deoxymethymycin

Figure 4.2. Structures of 10-deoxymethynolide **462** and 10-deoxymethymycin **463**.

To date, only two total syntheses of 10-deoxymethynolide **462** have been reported. In 1998, Pilli and co-workers reported the first synthesis of 10-deoxymethynolide **462** in 17 steps and 12% overall yield using an intramolecular Nozaki-Hiyama-Kishi (NHK) reaction to form the key macrolactone.[205] Ten years later, Kang and co-workers achieved the synthesis of the same target molecule in 13 steps (LLS) and 11% overall yield; key steps in the synthesis involved an asymmetric aldol reaction, a Yamaguchi esterification and ring-closing metathesis for the final cyclisation.[206]

A concise and efficient synthesis of 10-deoxymethynolide **462** is envisaged using the Aggarwal's assembly line synthesis protocol (Scheme 4.80). In particular, advanced intermediate **464** could be accessed through eight iterative homologations starting from boronic ester **465** employing various building blocks, including the recently developed lithiated methoxyallene to introduce the necessary masked enone functionality. Final functional group interconversions and macrolactonisation would give access to the target molecule.



Scheme 4.80. Proposed total synthesis of 10-deoxymethynolide **462** using assembly line synthesis.

5. Experimental

Parts of this section have been adapted from the following articles:

Casoni, G., Myers, E. L., Aggarwal, V. K., *Synthesis* **2016**, *48*, 3241−3253.

Casoni, G., Kucukdisli, M., Fordham, J. M., Burns, M., Myers, E. L., Aggarwal, V. K., *J. Am. Chem. Soc.* **2017**, *139*, 11877−11886.

5.1. General Experimental

All air- and water-sensitive reactions were carried out in oven-dried or flame-dried glassware under a N_2 atmosphere using standard Schlenk techniques. Microwave reactions were performed in a Biotage Initiatio EXP EU microwave synthesiser. Analytical TLC was performed on aluminium backed plates pre-coated (0.25 mm) with Merck Silica Gel 60 F254. Compounds were visualised by exposure to UV-light or stained using $KMnO_4$, *p*-anisaldehyde or phosphomolybdic acid (PMA) followed by heating. Flash column chromatography was performed using Sigma Aldrich silica gel 60 (40-63 μm) or prepacked column (SNAP Ultra columns 10 g, 25 g, 100 g) with automated system (Biotage® IsoleraTM One 3.0). All mixed solvent eluents are reported as *v*/*v* solutions. ^{1}H, ^{13}C, ^{11}B and ^{19}F Nuclear Magnetic Resonance (NMR) spectra were acquired at various field strengths as indicated using JEOL ECS 300, JEOL ECS 400, Varian 400 and Bruker 400 spectrometers. ^{1}H and ^{13}C NMR spectra were referenced internally to the residual non-deuterated solvent signal. ^{1}H and ^{13}C NMR coupling constants are reported in Hertz (Hz). Coupling constants are reported as follows: s = singlet, br. s = broad singlet, d = doublet, t = triplet, q = quartet, quint = quintet, sext = sextet, sept = septet, m = multiplet, dd = doublet of doublet, etc. Assignment of signals in ^{1}H and ^{13}C spectra was performed using COSY, DEPT, HMQC and HMBC experiments where appropriate. ^{13}C signals adjacent to boron are generally not observed due to quadrupolar relaxation. ^{11}B NMR spectra were measured using Norell S-200-QTZ quartz tubes at 128 MHz with complete proton decoupling. ^{19}F NMR spectra were recorded at 376 MHz. High resolution mass spectra were recorded on Bruker Daltonics MicroTOF II by using Electron Spray Ionisation (ESI). GC-MS was performed on an Agilent 6890 apparatus. All IR data were obtained on a Perkin-Elmer Spectrum One FT-IR spectrometer. Optical rotations were measured on a Bellingham and Stanley Ltd. ADP220 polarimeter. Melting point ranges were determined with a Kofler hot-stage microscope apparatus and are reported uncorrected. Enantiomeric excess of boronic esters was determined after oxidation to the corresponding

alcohols. Chiral HPLC was performed using Daicel Chiralpak IA and IB columns (4.6 mm × 250 mm, 5 μm) fitted with the respective guard (4 mm × 10 mm) and monitored by DAD (Diode Array Detector) on an Agilent 1100 system equipped with HP Chemstation/OpenLab software using. Waters HPLC system (Waters system fluidics organiser, Waters 2545 gradient module, and Waters 2998 photodiode array detector) was used for preparative reverse phase separation. Chiral gas chromatography (Chiral GC) was performed on an Agilent 7890A using a Chiraldex β-DP 120 column (30m × 0.25mm × 0.25 μm) and a Chiraldex β-DM 120 column (30m × 0.25mm × 0.25μm).

5.2. Materials and Reagents

All reagents were used as received unless otherwise stated. Anhydrous Et_2O, THF, CH_3CN, toluene and CH_2Cl_2 were dried using a purification column composed of activated alumina. Anhydrous Et_2O was stored over 3 Å molecular sieves. TMEDA, Et_3N, HMDS and DCME were distilled over CaH_2 and stored in a Young's tube under N_2. Diisopropylamine was dried over NaOH before distillation and stored in a Young's tube under N_2. Organolithiums (*n*-BuLi, *s*-BuLi, and *t*-BuLi) reagents were periodically titrated using *N*-benzylbenzamide.[207] *i*-PrMgCl·LiCl was titrated using I_2.[208] LDA and LiHMDS solutions were freshly prepared from the corresponding distilled amines and *n*-BuLi immediately before use. Basic silica gel was prepared by adding trimethylamine (2.0 mL) to a slurry of SiO_2 (~100 g) in Et_2O.

5.3. General Procedures Chapter 2

General procedure for the lithiation/borylation of 1,1-dimethyl-2-phenylazetidin-1-ium trifluoromethanesulfonate 211 to give γ-dimethylamino tertiary boronic esters (GP1)

To a solution of diisopropylamine (2.0 equiv) in anhydrous THF (2.0 M) was added *n*-BuLi (2.0 equiv) at −78 °C. After stirring for 30 min, the solution was added dropwise to a mixture of azetidinium salt **211** (1.0 equiv) and the boronic ester (1.2 equiv) in dry THF (0.03 M) at −78 °C. The reaction mixture was stirred at −78 °C for 1 h, then was allowed to warm to room temperature. The solvent was removed *in vacuo* and the crude residue was taken up with H_2O and extracted with CH_2Cl_2 (3 times). The combined organic layers were dried over $MgSO_4$ and the solvent was removed *in vacuo* to afford the crude tertiary boronic ester, which was purified by flash chromatography on silica gel (EtOAc:Et_3N = 100:0.5) to afford the pure γ-dimethylamino tertiary boronic ester.

General procedure for the lithiation/borylation of 1,1-dimethyl-2-phenylazetidin-1-ium trifluoromethanesulfonate 211 with *in situ* oxidation (GP2a)

To a solution of diisopropylamine (2.0 equiv) in anhydrous THF (2.0 M) was added *n*-BuLi (2.0 equiv) at −78 °C. After stirring for 30 min the solution was added dropwise to a mixture of azetidinium salt **211** (1.0 equiv) and the boronic ester (1.2 equiv) in dry THF (0.03 M) at −78 °C. The reaction mixture was stirred at −78 °C for 1 h, then was allowed to warm to room temperature. The reaction mixture was cooled to 0 °C and a 2:1 mixture of aq. NaOH (2.0 M) and 30% H_2O_2 (3.0 mL in total) was added under vigorous stirring. The cooling bath was removed and the reaction mixture was stirred at room temperature for 1 h. The solvent was removed *in vacuo* and the residue was partitioned between H_2O and CH_2Cl_2. The phases were separated and the aqueous layer was re-extracted with CH_2Cl_2 (2 times). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The residue was purified by flash chromatography on silica gel (EtOAc:Et_3N = 100:0.5) to afford the pure tertiary alcohol.

General procedure for the lithiation/borylation of 1,1-dimethyl-2-phenylazetidin-1-ium trifluoromethanesulfonate 211 with *in situ* oxidation at low temperature (GP2b)

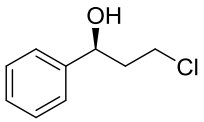
To a solution of diisopropylamine (2.0 equiv) in anhydrous THF (2.0 M) was added *n*-BuLi (2.0 equiv) at −78 °C. After stirring for 30 min the solution was added dropwise to a mixture of azetidinium salt **211** (1.0 equiv) and the boronic ester (1.2 equiv) in dry THF (0.03 M) at −78 °C. The reaction mixture was stirred at −78 °C for 1 h, then was allowed to warm to room temperature. The reaction mixture was cooled to −40 °C and a 2:1 mixture of aq. NaOH (2.0 M) and 30% H_2O_2 (3.0 mL in total) was added under vigorous stirring. The cooling bath was removed and the reaction mixture was stirred at room temperature for 1 h. The solvent was removed *in vacuo* and the residue was partitioned between H_2O and CH_2Cl_2. The phases were separated and the aqueous layer was re-extracted with CH_2Cl_2 (2 times). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The residue was purified by flash chromatography on silica gel (EtOAc:Et_3N = 100:0.5) to afford the pure tertiary alcohol.

General procedure for the lithiation/borylation of 1,1-dimethyl-2-phenylazetidin-1-ium trifluoromethanesulfonate with *in situ* protodeboronation (GP3)

To a solution of diisopropylamine (2.0 equiv) in anhydrous THF (2.0 M) was added *n*-BuLi (2.0 equiv) at −78 °C. After stirring for 30 min the solution was added dropwise to a mixture of azetidinium salt **211** (1.0 equiv) and the boronic ester (1.2 equiv) in dry THF (0.03 M) at −78 °C. The reaction mixture was stirred at −78 °C for 1 h and then was allowed to warm to room temperature. CsF (1.5 equiv) was added at room temperature, followed by H_2O (1.1 equiv), and the reaction mixture was stirred at room temperature for 1 h. The solvent was removed *in vacuo* and the residue was partitioned between H_2O and CH_2Cl_2. The phases were separated and the aqueous layer was re-extracted with CH_2Cl_2 (2 times). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The residue was purified by flash chromatography on silica gel (EtOAc:Et_3N = 100:0.5) to afford the pure protodeboronated product.

5.4. Single Compounds Chapter 2

(*S*)-3-Chloro-1-phenylpropan-1-ol ((*S*)-207)



Following a literature reported procedure,[142] $Cu(OAc)_2 \cdot H_2O$ (0.12 g, 0.60 mmol) and (*S*)-P-Phos (0.15 g, 0.20 mmol) were weighted under air and dissolved in toluene (66 mL). The reaction mixture was stirred at room temperature for 20 min, then a solution of phenylsilane (3.0 mL, 24 mmol) in toluene (32 mL) was added. The mixture was cooled to −20 °C and a solution of 3-chloro-1-phenylpropan-1-one (3.4 g, 20 mmol) in toluene (32 mL) was added under vigorous stirring. The flask was stoppered and the reaction mixture was stirred for 24 h at the above temperature. Upon completion, the mixture was treated with 10% HCl (130 mL) and the organic product was extracted with Et_2O (3 × 150 mL). The combined organic layers were washed with H_2O, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography on silica gel (hexane:EtOAc = 90:10) afforded alcohol (*S*)-**207** (2.5 g, 73%) as a white solid.

[The racemate was synthesised as follows: according to a literature reported procedure,[132] $NaBH_4$ (5.68 g, 150 mmol) was added in small portions at 0 °C to a stirred solution of 3-chloro-1-propiophenone (8.4 g, 50 mmol) in MeOH (104 mL). The mixture was stirred at room temperature for 18 h and then was quenched with H_2O (90 mL). The solvent was removed *in vacuo* and the residue was extracted with Et_2O (3 × 50 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure to give the title compound as a colourless oil (8.4 g, 98% yield). The product was used in the next step without further purification.]

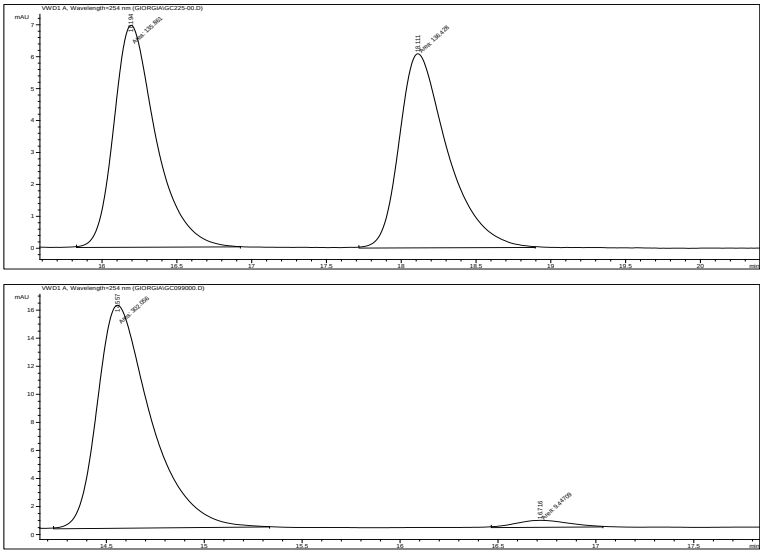
^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.37–7.26 (m, 5H, Ar-H), 4.93 (dd, J_1 = 11.3 Hz, J_2 = 6.4 Hz, 1H, C*H*-OH), 3.73 (ddd, J_1 = 14.5 Hz, J_2 = 10.8 Hz, J_3 = 7.6 Hz, 1H, CH_2-Cl), 3.55 (m, 1H, CH_2-Cl), 2.23 (m, 1H, CH_2-CH), 2.10 (m, 1H, CH_2-CH), 2.03 (br. s, 1H, OH).

^{13}C NMR ($CDCl_3$, 101 MHz) δ: 143.8 (Ar-C), 128.8 (2C, Ar-C), 128.1 (Ar-C), 125.9 (2C, Ar-C), 71.5 (CH), 41.8 (CH_2), 41.6 (CH_2).

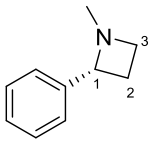
$[\alpha]^{24}_D$: −23 (*c* 1.0, $CHCl_3$). [Lit. value for (*S*): −24.1 (*c* 1.1 $CHCl_3$)].[209]

All analytical data matched that previously reported in the literature.[132]

Chiral HPLC: Daicel Chiralcel-IB column (25 cm), hexane:isopropanol = 98:2, 1.0 mL/min, room temperature, 254 nm: t_R = 16.2 minutes (major), 18.1 minutes (minor), e.r. = 97:3.



(*R*)-1-Methyl-2-phenylazetidine ((*R*)-210)



Following a literature reported procedure,[127] to a solution of (*S*)-3-chloro-1-phenylpropan-1-ol (*S*)-**207** (3.10 g, 18.2 mmol) in dry CH_2Cl_2 (18 mL), a solution of $SOCl_2$ (4.00 mL, 54.6 mmol) in dry CH_2Cl_2 (5.5 mL) was added dropwise at room temperature. After stirring for 1 h, the reaction mixture was poured into H_2O (20 mL) and aq. NaOH (15% *w*/*v*) was added slowly to neutralise the excess of HCl until the pH of the solution was 7. The aqueous phase was extracted with CH_2Cl_2 (3 × 30 mL) and the combined organic layers were dried over $MgSO_4$, filtered and the solvent was evaporated under reduced pressure to afford 1-phenyl-1,3-dichloropropane which was employed in the next step without further purification.

To a solution of 1-phenyl-1,3-dichloropropane and Et_3N (5.10 mL, 36.4 mmol) in EtOH (23 mL) in a sealed flask, a solution of $MeNH_2$ (33% *w*/*v* in EtOH, 23 mL) was added at room temperature. The reaction mixture was heated at 70 °C for 16 h and then allowed to cool to ambient temperature. The solvent was removed *in vacuo* and HCl (2.0 M, 30 mL) was added. The aqueous phase was extracted with CH_2Cl_2 (3 × 40 mL) and subsequently basified by addition of aq. NaOH (15% *w*/*v*) until the pH of the solution was >12. The basic aqueous phase was extracted with CH_2Cl_2 (3 × 50 mL), the combined organic layers were dried over $MgSO_4$, filtered and the solvent was removed *in vacuo*. The crude mixture was purified by flash column chromatography on silica gel (EtOAc:Et_3N = 100:0.5) to afford azetidine (*R*)-**210** (1.34 g, 50% over two steps) as a colourless oil.

[The racemate was synthesised as above, replacing (*S*)-**207** with racemic **207**.]

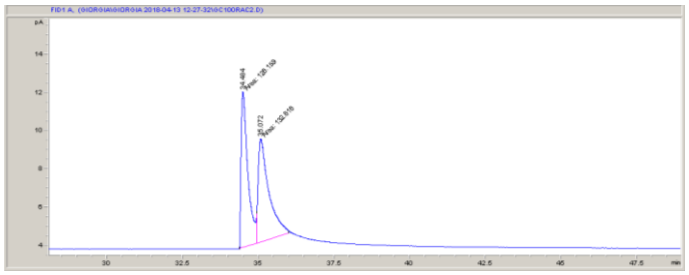
^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.38–7.30 (m, 4H, Ar-H), 7.26–7.22 (m, 1H, Ar-H), 3.87 (t, J = 8.4 Hz, 1H, 1-H), 3.45 (m, 1H, 3-H), 2.85 (dt, J_1 = 9.6 Hz, J_2 = 7.1 Hz, 1H, 3-H), 2.33 (s, 3H, CH_3), 2.26 (m, 1H, 2-H), 2.14 (quint, J = 8.9 Hz, 1H, 2-H).

^{13}C NMR ($CDCl_3$, 101 MHz) δ: 143.0 (Ar-C), 128.5 (2C, Ar-C), 127.4 (Ar-C), 126.7 (2C, Ar-C), 71.3 (1-C), 53.1 (3-C), 44.6 (CH_3), 27.0 (2-C).

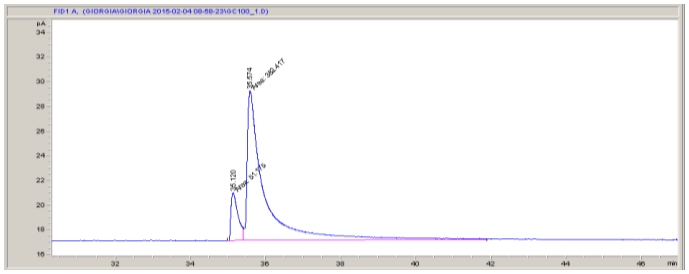
$[\alpha]^{24}_D$: +105 (*c* 0.6, $CHCl_3$). [Lit. value for (*S*): −117 (*c* 0.55 $CHCl_3$)].[127]

All analytical data matched that previously reported in the literature.[127]

Chiral GC: Chiraldex β-DM column, injector T = 250 °C, detector T = 300 °C, inject at T = 90 °C then hold constant for 40 min, He carrier gas at 1.0 mL min^{-1}: t_R = 35.1 minutes (minor), 35.6 minutes (major), e.r. = 88:12.

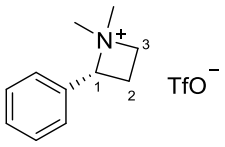


#	Time	Area	Height	Width	Area%	Symmetry
1	34.485	105.8	7.9	0.2226	51.823	0.449
2	35.072	98.3	4.4	0.3698	48.177	0.3



#	Time	Area	Height	Width	Area%	Symmetry
1	35.12	51.2	3.9	0.2206	11.803	0
2	35.574	382.4	12.1	0.5258	88.197	0.188

(*R*)-1,1-Dimethyl-2-phenylazetidin-1-ium trifluoromethanesulfonate ((*R*)-211)



Following a modified literature reported procedure,[130] azetidine (*R*)-**210** (272 mg, 1.85 mmol) was dissolved in dry Et_2O (15 mL). After cooling to 0 °C, methyl trifluoromethane sulfonate (440 µL, 3.89 mmol) was added. The mixture was stirred for 1 h at 0 °C, then all the volatiles were removed under vacuum to afford azetidinium triflate (*R*)-**211** (575 mg, 99%) as a thick orange oil.

[The racemate was synthesised as above, replacing (*R*)-**210** with racemic **210**.]

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.52–7.47 (m, 5H, Ar-H), 5.84 (dd, J_1 = 10.5 Hz, J_2 = 8.6 Hz, 1H, 1-H), 4.59 (ps q, J = 9.3 Hz, 1H, 3-H) 4.07 (ps td, J_1 = 10.0 Hz, J_2 = 3.5 Hz, 1H, 3-H), 3.29 (s, 3H, CH_3), 3.24 (m, 1H, 2-H), 2.78 (m, 1H, 2-H), 2.59 (s, 3H, CH_3).

^{13}C NMR ($CDCl_3$, 101 MHz) δ: 131.9 (Ar-C), 129.9 (2C, Ar-C), 129.7 (2C, Ar-C), 128.8 (Ar-C), 120.7 (q, $^1J_{C-F}$ = 320 Hz, CF_3), 79.1 (1-C), 62.6 (3-C), 52.5 (CH_3), 45.7 (CH_3), 19.0 (2-C).

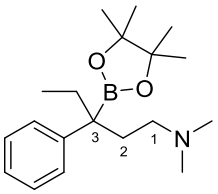
^{19}F NMR ($CDCl_3$, 376 MHz) δ: –78.3.

IR (neat) ν_{max}: 1465, 1254, 1223, 1152, 1028, 975, 830, 770, 756, 706 cm^{-1}.

HRMS (ESI) calculated for $C_{11}H_{16}N$ $(M)^+$: 162.1277, found: 162.1283.

$[\alpha]^{24}_D$: −3 (*c* 1.2, $CHCl_3$).

***N*,*N*-Dimethyl-3-phenyl-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pentan-1-amine (213a)**



According to general procedure GP1, diisopropylamine (561 µL, 4.00 mmol), *n*-BuLi (2.5 mL, 4.0 mmol), 1,1-dimethyl-2-phenylazetidin-1-ium trifluoromethanesulfonate (**211**) (623 mg, 2.00 mmol) and 2-ethyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (375 mg, 2.40 mmol) in anhydrous THF (35 mL) afforded, after purification by flash column chromatography on silica gel (EtOAc:Et_3N = 100:0.5) γ-dimethylamino boronic ester **213a** (438 mg, 69%) as a colourless oil.

R_f: 0.23 (CH_2Cl_2:MeOH:Et_3N = 99.5:0.5:0.5).

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.32–7.29 (m, 2H, Ar-H), 7.27–7.23 (m, 2H, Ar-H), 7.11 (tt, J_1 = 6.8 Hz, J_2 = 1.3 Hz, 1H, Ar-H), 2.20 (s, 6H, N-(CH_3)$_2$), 2.19–2.13 (m, 2H, 1-H), 2.04–1.91 (m, 2H, 2-H), 1.91–1.75 (m, 2H, C*H*$_2$-CH_3), 1.20 (s, 6H, C-CH_3 × 2), 1.17 (s, 6H, C-CH_3 × 2), 0.70 (t, *J* = 7.4 Hz, 3H, CH_2-C*H*$_3$).

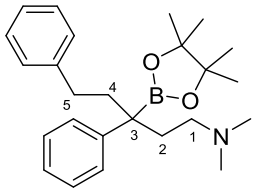
^{13}C NMR ($CDCl_3$, 101 MHz) δ: 145.5 (Ar-C), 128.1 (2C, Ar-C), 127.67 (2C, Ar-C), 125.1 (Ar-C), 83.2 (2C, B-O-C × 2), 56.5 (1-C), 46.0 (2C, N-(CH_3)$_2$), 31.9 (2-C), 29.9 (3-C), 28.1 (*C*H_2-CH_3), 25.0 (2C, C-*C*H_3 × 2), 25.0 (2C, C-*C*H_3 × 2), 9.3 (CH_2-*C*H_3).

^{11}B NMR ($CDCl_3$, 128 MHz) δ: 31.8.

IR (neat) ν_{max}: 2973, 2936, 1460, 1370, 1350, 1308, 1260, 1143, 1031, 167, 851, 759 cm^{-1}.

HRMS (ESI) calculated for $C_{19}H_{33}BNO_2$ $(M+H)^+$: 318.2602, found: 318.2608.

***N*,*N*-dimethyl-3,5-diphenyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pentan-1-amine (213b)**



According to general procedure GP1, diisopropylamine (140 µL, 1.00 mmol), *n*-BuLi (625 µL, 1.00 mmol), 1,1-dimethyl-2-phenylazetidin-1-ium trifluoromethanesulfonate (**211**) (156 mg, 0.500 mmol) and 4,4,5,5-tetramethyl-2-phenethyl-1,3,2-dioxaborolane (139 mg, 0.600 mmol) in anhydrous THF (12 mL) afforded, after purification by flash column chromatography on silica gel (EtOAc:Et_3N = 100:0.5) γ-dimethylamino boronic ester **213b** (97 mg, 50%) as a pale yellow solid.

R_f: 0.24 (CH_2Cl_2:MeOH:Et_3N = 99.5:0.5:0.5).

^{1}H NMR (CD_3OD, 400 MHz) δ: 7.39 (d, *J* = 7.6 Hz, 2H, Ar-H), 7.31 (t, *J* = 7.5 Hz, 2H, Ar-H), 7.23 (t, *J* = 7.5 Hz, 2H, Ar-H), 7.18–7.09 (m, 4H, Ar-H), 2.42–2.37 (m, 2H, 5-H), 2.30–2.26 (m, 2H, 1-H), 2.23 (s, 6H, N-$(CH_3)_2$), 2.13–2.02 (m, 4H, 2-H + 4-H), 1.26 (s, 6H, C-CH_3 × 2), 1.25 (s, 6H, C-CH_3 × 2).

^{13}C NMR (CD_3OD, 101 MHz) δ: 146.1 (Ar-C), 144.4 (Ar-C), 129.4 (2C, Ar-C), 129.2 (2C, Ar-C), 129.2 (2C, Ar-C), 128.5 (2C, Ar-C), 126.7 (Ar-C), 126.5 (Ar-C), 84.7 (2C, B-O-C × 2), 57.4 (1-C), 45.8 (2C, N-$(CH_3)_2$), 39.4 (2-C), 33.1 (5-C), 32.8 (4-C), 25.3 (4C, C-*C*H_3 × 4); *carbon attached to boron not observed due to quadrupolar relaxation.*

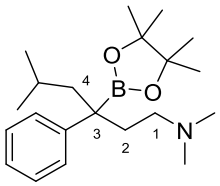
^{11}B NMR (CD_3OD, 128 MHz) δ: 31.6, 13.0.

IR (neat) ν_{max}: 2936, 1459, 1138, 1111, 1096, 1079, 1069, 1052, 1022, 988, 839, 757 cm^{-1}.

HRMS (ESI) calculated for $C_{25}H_{37}BNO_2$ $(M+H)^+$: 394.2916, found: 394.2933.

M.P.: 51–53 ºC.

***N*,*N*,5-trimethyl-3-phenyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hexan-1-amine (213c)**



According to general procedure GP1, diisopropylamine (140 µL, 1.00 mmol), *n*-BuLi (625 µL, 1.00 mmol), 1,1-dimethyl-2-phenylazetidin-1-ium trifluoromethanesulfonate (**211**) (156 mg, 0.500 mmol) and 2-isobutyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (111 mg, 0.600 mmol) in anhydrous THF (12 mL) afforded after purification by flash column chromatography on silica gel (EtOAc:Et_3N = 100:0.5) γ-dimethylamino boronic ester **213c** (80 mg, 46%) as a colourless oil.

R_f: 0.32 (EtOAc:Et_3N = 100:0.5).

^{1}H NMR (CD_3OD, 400 MHz) δ: 7.39 (d, *J* = 8.0 Hz, 2H, Ar-H), 7.26 (t, *J* = 7.6 Hz, 2H, Ar-H), 7.12 (t, *J* = 7.3 Hz, 1H, Ar-H), 2.19 (s, 6H, N-$(CH_3)_2$), 2.17–1.99 (m, 4H, 1-H + 2-H), 1.77 (m, 2H, 4-H), 1.56 (sept, *J* = 6.5 Hz, 1H, CH), 1.21 (s, 6H, C-CH_3 × 2), 1.19 (s, 6H, C-CH_3 × 2), 0.82 (d, *J* = 6.7 Hz, 3H, CH-C*H*$_3$), 0.78 (d, *J* = 6.7 Hz, 3H, CH-C*H*$_3$).

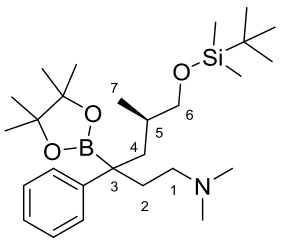
^{13}C NMR (CD_3OD, 101 MHz) δ: 146.5 (Ar-C), 129.1 (2C, Ar-C), 128.6 (2C, Ar-C), 126.3 (Ar-C), 84.7 (2C, B-O-C x 2), 57.1 (1-C), 45.6 (2C, N-$(CH_3)_2$), 45.5 (4-C), 33.0 (2-C), 26.8 (CH), 25.3 (2C, C-*C*H_3 × 2), 25.2 (2C, C-*C*H_3 × 2), 24.9 (CH-CH_3), 24.6 (CH-CH_3); *carbon attached to boron not observed due to quadrupolar relaxation.*

^{11}B NMR (CD_3OD, 128 MHz) δ: 32.4, 19.2, 16.1.

IR (neat) ν_{max}: 2952, 1447, 1371, 1143, 701 cm^{-1}.

HRMS (ESI) calculated for $C_{21}H_{37}BNO_2$ $(M+H)^+$: 346.2916, found: 346.2911.

(5*R*)-6-((*tert*-Butyldimethylsilyl)oxy)-*N*,*N*,5-trimethyl-3-phenyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hexan-1-amine (213d)



According to general procedure GP1, diisopropylamine (140 µL, 1.00 mmol), *n*-BuLi (625 µL, 1.00 mmol), 1,1-dimethyl-2-phenylazetidin-1-ium trifluoromethanesulfonate (**211**) (156 mg, 0.500 mmol) and (*R*)-*tert*-butyldimethyl(2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2yl)propoxy)silane (189 mg, 0.600 mmol) in anhydrous THF (12 mL) afforded after purification by flash column chromatography on silica gel (EtOAc:Et_3N = 100:0.5) γ-dimethylamino boronic ester **213d** (79.5 mg, 46%, 1:1 d.r.) as a colourless oil.

R_f: 0.30 (EtOAc:Et_3N = 100:0.5).

^{1}H NMR (CD_3OD, 400 MHz) δ: 7.39 (d, *J* = 7.8 Hz, 2H, Ar-H), 7.37 (d, *J* = 7.8 Hz, 2H, Ar-H), 7.26 (m, 4H, Ar-H), 7.12 (t, *J* = 7.3 Hz, 2H, Ar-H), 3.28 (m, 2H, 6-H diast. a), 3.14 (dd, J_1 = 9.5 Hz, J_2 = 7.1 Hz, 2H, 6-H diast. b), 2.38–2.25 (m, 2H, 1-H diast. a + diast. b), 2.22 (s, 12H, N-$(CH_3)_2$ diast. a + diast. b), 2.17–2.00 (m, 6H, 1-H diast. a + diast. b + 2-H × 2 diast. a + diast. b), 1.98–1.86 (m, 2H, 5-H diast. a + diast. b), 1.67–1.47 (m, 4H, 4-H x 2 diast. a + diast. b), 1.25 (s, 6H, C-CH_3 × 2 diast. a), 1.23 (s, 6H, C-CH_3 × 2 diast. a), 1.20 (s, 6H, C-CH_3 × 2 diast. b), 1.18 (s, 6H, C-CH_3 × 2 diast. b), 0.88 (s, 9H, Si-C-$(CH_3)_3$ diast. a), 0.86 (s, 9H, Si-C-$(CH_3)_3$ diast. b), 0.83 (d, *J* = 6.2 Hz, 3H, 6'-H diast. a), 0.65 (d, *J* = 6.6 Hz, 3H, 6'-H diast. b), −0.01 (s, 6H, Si-$(CH_3)_2$ diast. a), −0.03 (s, 6H, Si-$(CH_3)_2$ diast. b).

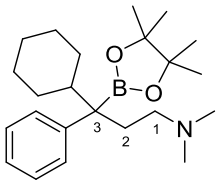
^{13}C NMR (CD_3OD, 101 MHz) δ: 146.7 (Ar-C), 146.6 (Ar-C), 129.1 (2C, Ar-C), 129.1 (2C, Ar-C), 128.8 (Ar-C), 128.7 (2C, Ar-C), 128.6 (2C, Ar-C), 128.5 (Ar-C), 84.7 (4C, B-O-C × 2 diast. a + diast. b), 70.2 (6-C diast. a), 70.2 (6-C diast. b), 57.7 (1-C diast. a), 57.2 (1-C diast. b), 45.7 (4C, N-$(CH_3)_2$ diast. a + diast. b), 41.0 (4-C diast. a), 39.5 (4-C diast. b), 34.5 (5-C diast. a), 34.3 (5-C diast. b), 34.0 (2-C diast. a), 32.4 (2-C diast. b), 26.5 (3C, Si-C-$(CH_3)_3$ diast. a), 26.5 (3C, Si-C-$(CH_3)_3$ diast. b), 26.4 (2C, Si-C-CH_3 diast. a + diast. b), 25.4 (2C, C-CH_3 × 2 diast. a), 25.4 (2C, C-CH_3 x 2 diast. a), 25.2 (2C, C-CH_3 × 2 diast. b), 25.0 (2C, C-CH_3 × 2 diast. b), 19.1 (7-C diast. a), 19.1 (7-C diast. b), –6.1 (2C, Si-CH_3 diast. a), –5.2 (2C, Si-CH_3, diast. b); *carbon attached to boron not observed due to quadrupolar relaxation.*

^{11}B NMR (CD_3OD, 128 MHz) δ: 32.8, 15.4.

IR (neat) ν_{max}: 2954, 2929, 1253, 1143, 1083, 834, 774, 700 cm^{-1}.

HRMS (ESI) calculated for $C_{27}H_{51}BNO_3Si$ $(M+H)^+$: 476.3731, found: 476.3725.

3-Cyclohexyl-*N*,*N*-dimethyl-3-phenyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propan-1-amine (213e)



According to general procedure GP1, diisopropylamine (140 µL, 1.00 mmol), *n*-BuLi (625 µL, 1.00 mmol), 1,1-dimethyl-2-phenylazetidin-1-ium trifluoromethanesulfonate (**211**) (159 mg, 0.510 mmol) and 2-cyclohexyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (126 mg, 0.600 mmol) in anhydrous THF (12 mL) afforded after purification by flash column chromatography on silica gel (EtOAc:Et_3N = 100:0.5) γ-dimethylamino boronic ester **213e** (84 mg, 44%) as a colourless oil.

R_f: 0.24 (CH_2Cl_2:MeOH:Et_3N = 99.5:0.5:0.5).

^{1}H NMR (CD_3OD, 400 MHz) δ: 7.35 (d, *J* = 7.5 Hz, 2H, Ar-H), 7.24 (t, *J* = 7.5 Hz, 2H, Ar-H), 7.13 (t, *J* = 7.3 Hz, 1H, Ar-H), 2.24–2.10 (m, 2H, 3-H + *c*-Hex-H), 2.17 (s, 6H, N-$(CH_3)_2$), 2.02–1.93 (m, 2H, 1-H + *c*-Hex-H), 1.89 (m, 1H, *c*-Hex-H), 1.76–1.48 (m, 5H, *c* Hex-H × 3 + 2-H × 2), 1.33 (s, 6H, C-CH_3 × 2), 1.32 (s, 6H, C-CH_3 × 2), 1.29–0.91 (m, 5H, *c*-Hex-H × 5).

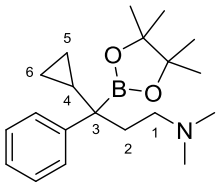
^{13}C NMR (CD_3OD, 101 MHz) δ: 144.8 (Ar-C), 130.2 (2C, Ar-C), 128.7 (2C, Ar-C), 126.5 (Ar-C), 84.8 (2C, B-O-C x 2), 58.3 (1-C), 48.0 (2-C), 45.5 (2C, N-$(CH_3)_2$), 33.9 (*c*-Hex-C), 31.5 (*c*-Hex-C), 30.2 (*c*-Hex-C), 28.4 (*c*-Hex-C), 28.2 (*c*-Hex-C), 28.0 (*c*-Hex-C), 25.7 (2C, C-*C*H_3 × 2), 25.4 (2C, C-*C*H_3 × 2); *carbon attached to boron not observed due to quadrupolar relaxation.*

^{11}B NMR (CD_3OD, 128 MHz) δ: 33.3.

IR (neat) ν_{max}: 2926, 2852, 1450, 1371, 1350, 1300, 1269, 1141, 1036, 852 cm^{-1}.

HRMS (ESI) calculated for $C_{23}H_{39}BNO_2$ $(M+H)^+$: 372.3073, found: 372.3091.

3-Cyclopropyl-*N*,*N*-dimethyl-3-phenyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propan-1-amine (213f)



According to general procedure GP1, diisopropylamine (140 µL, 1.00 mmol), *n*-BuLi (625 µL, 1.00 mmol), 1,1-dimethyl-2-phenylazetidin-1-ium trifluoromethanesulfonate (**211**) (156 mg, 0.500 mmol) and 2-cyclopropyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (101 mg, 0.600 mmol) in anhydrous THF (12 mL) afforded after purification by flash column chromatography on silica gel (EtOAc:Et_3N = 100:0.5) γ-dimethylamino boronic ester **213f** (108 mg, 66%) as a colourless oil.

R_f: 0.31 (EtOAc:Et_3N = 100:0.5).

^{1}H NMR (CD_3OD, 400 MHz) δ: 7.42 (dd, J_1 = 7.9 Hz, J_2 = 1.2 Hz, 2H, Ar-H), 7.26 (t, J = 7.5 Hz, 2H, Ar-H), 7.13 (t, J = 7.3 Hz, 1H, Ar-H), 2.35 (t, J = 8.2 Hz, 2H, 1-H), 2.20 (s, 6H, N-$(CH_3)_2$), 2.01 (m, 2H, 2-H), 1.22 (s, 6H, C-CH_3 × 2), 1.20 (s, 6H, C-CH_3 × 2), 1.03 (m, 1H, 4-H), 0.59–0.48 (m, 3H, 5-H/6-H), 0.32 (m, 1H, 5-H/6-H).

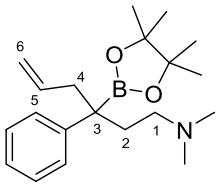
^{13}C NMR (CD_3OD, 101 MHz) δ: 146.9 (Ar-C), 129.0 (2C, Ar-C), 128.9 (2C, Ar-C), 126.4 (Ar-C), 84.7 (2C, B-O-C x 2), 57.5 (1-C), 45.5 (2C, N-$(CH_3)_2$), 36.1 (2-C), 25.2 (2C, C-*C*H_3 × 2), 25.1 (2C, C-*C*H_3 × 2), 18.1 (4-C), 4.1 (5-C/6-C), 3.4 (5-C/6-C); *carbon attached to boron not observed due to quadrupolar relaxation.*

^{11}B NMR (CD_3OD, 128 MHz) δ: 31.7.

IR (neat) ν_{max}: 2976, 1371, 1306, 1142, 853, 700 cm^{-1}.

HRMS (ESI) calculated for $C_{20}H_{33}BNO_2$ $(M+H)^+$: 330.2603, found: 330.2607.

***N*,*N*-Dimethyl-3-phenyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hex-5-en-1-amine (213g)**



According to general procedure GP1, diisopropylamine (140 µL, 1.00 mmol), *n*-BuLi (625 µL, 1.00 mmol), 1,1-dimethyl-2-phenylazetidin-1-ium trifluoromethanesulfonate (**211**) (155 mg, 0.500 mmol) and 2-allyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (101 mg, 0.600 mmol) in anhydrous THF (12 mL) afforded after purification by flash column chromatography on silica gel (EtOAc:Et_3N = 100:0.5) γ-dimethylamino boronic ester **213g** (67 mg, 45%) as a colourless oil.

R_f: 0.32 (EtOAc:Et_3N = 100:0.5).

^{1}H NMR (CD_3OD, 400 MHz) δ: 7.32–7.24 (m, 4H, Ar-H), 7.11 (ps t, J = 7.2 Hz, 1H, Ar-H), 5.62 (tdd, J_1 = 17.3 Hz, J_2 = 10.2 Hz, J_3 = 7.2 Hz, 1H, 5-H), 5.03 (dd, J_1 = 17.1 Hz, J_2 = 2.2 Hz, 1H, 6-H_{trans}), 4.95 (dd, J_1 = 10.2 Hz, J_2 = 2.2 Hz, 1H, 6-H_{cis}), 2.57 (d, J = 7.2 Hz, 2H, 4-H), 2.26–2.17 (m, 2H, 1-H), 2.19 (s, 6H, N-$(CH_3)_2$), 2.02–1.97 (m, 2H, 2-H), 1.20 (s, 6H, C-CH_3 × 2), 1.19 (s, 6H, C-CH_3 × 2).

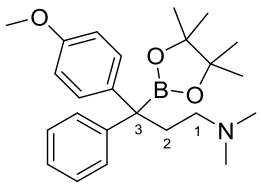
^{13}C NMR (CD_3OD, 101 MHz) δ: 146.0 (Ar-C), 136.9 (5-C), 129.1 (2C, Ar-C), 128.4 (2C, Ar-C), 126.3 (6-C), 117.3 (Ar-C), 84.6 (2C, B-O-C x 2), 56.8 (1-C), 45.8 (2C, N-$(CH_3)_2$), 40.5 (4-C), 32.3 (2-C), 25.4 (2C, C-*C*H_3 × 2), 25.3 (2C, C-*C*H_3 × 2); *carbon attached to boron not observed due to quadrupolar relaxation.*

^{11}B NMR (CD_3OD, 128 MHz) δ: 30.7.

IR (neat) ν_{max}: 2975, 1457, 1371, 1143, 1057, 700 cm^{-1}.

HRMS (ESI) calculated for $C_{20}H_{33}BNO_2$ $(M+H)^+$: 330.2603, found: 330.2604.

3-(4-Methoxyphenyl)-*N*,*N*-dimethyl-3-phenyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propan-1-amine (213k)



According to general procedure GP1, diisopropylamine (140 µL, 1.00 mmol), *n*-BuLi (625 µL, 1.00 mmol), 1,1-dimethyl-2-phenylazetidin-1-ium trifluoromethanesulfonate (**211**) (153 mg, 0.500 mmol) and 2-(4-methoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (141 mg, 0.600 mmol) in anhydrous THF (12 mL) afforded after purification by flash column chromatography on silica gel (EtOAc:Et_3N = 100:0.5) γ-dimethylamino boronic ester **213k** (145 mg, 75%) as a yellow oil.

R_f: 0.31 (EtOAc:Et_3N = 100:0.5).

^{1}H NMR (CD_3OD, 400 MHz) δ: 7.26–7.10 (m, 7H, Ar-H), 6.80 (d, *J* = 8.7 Hz, 2H, Ar-H), 3.76 (s, 3H, O-CH_3), 2.36–2.28 (m, 2H, 1-H), 2.20 (s, 6H, N-$(CH_3)_2$), 2.10 (ps t, *J* = 7.8 Hz, 2H, 2-H), 1.15 (s, 6H, C-CH_3 × 2), 1.14 (s, 6H, C-CH_3 × 2).

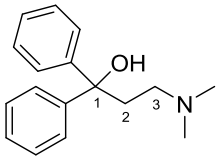
^{13}C NMR (CD_3OD, 101 MHz) δ: 159.1 (Ar-C), 147.8 (Ar-C), 139.2 (Ar-C), 131.3 (2C, Ar-C), 130.3 (2C, Ar-C), 128.8 (2C, Ar-C), 126.5 (Ar-C), 114.3 (2C, Ar-C), 84.8 (2C, B-O-C x 2), 58.8 (1-C), 55.6 (O-CH_3), 45.4 (2C, N-$(CH_3)_2$), 35.9 (2-C), 24.9 (2C, C-*C*H_3 × 2), 24.9 (2C, C-*C*H_3 × 2); *carbon attached to boron not observed due to quadrupolar relaxation.*

^{11}B NMR (CD_3OD, 128 MHz) δ: 31.5, 13.2.

IR (neat) ν_{max}: 2969, 1509, 1461, 1341, 1297, 1245, 1181, 1141, 1035, 852, 827 cm^{-1}.

HRMS (ESI) calculated for $C_{24}H_{35}BNO_3$ $(M+H)^+$: 396.2709, found: 396.2718.

3-(Dimethylamino)-1,1-diphenylpropan-1-ol (217i)



According to general procedure GP2a, diisopropylamine (140 µL, 1.00 mmol), *n*-BuLi (625 µL, 1.00 mmol), 1,1-dimethyl-2-phenylazetidin-1-ium trifluoromethanesulfonate (**211**) (153 mg, 0.490 mmol) and 4,4,5,5-tetramethyl-2-phenyl-1,3,2-dioxaborolane (123 mg, 0.600 mmol) in anhydrous THF (12 mL), afforded after purification by flash chromatography on silica gel (EtOAc:Et_3N = 100:0.5) tertiary alcohol **217i** (88 mg, 70%) as a white solid.

R_f: 0.22 (CH_2Cl_2:MeOH:Et_3N = 99:1:0.5).

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.50 (pd, *J* = 8.0 Hz, 4H, Ar-H), 7.32 (ps t, *J* = 7.4 Hz, 4H, Ar-H), 7.20 (ps t, *J* = 7.2 Hz, 2H, Ar-H), 2.42 (s, 4H, 2-H + 3-H), 2.23 (s, 6H, N-$(CH_3)_2$).

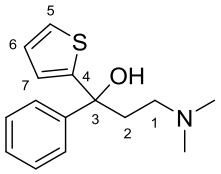
^{13}C NMR ($CDCl_3$, 101 MHz) δ: 148.1 (2C, Ar-C), 128.0 (4C, Ar-C), 126.3 (2C, Ar-C), 125.8 (4C, Ar-C), 79.2 (1-C), 56.3 (3-C), 45.1 (2C, N-$(CH_3)_2$), 36.0 (2-C).

IR (neat) ν_{max}: 2830, 2783, 1446, 1204, 1064, 1019, 963, 891, 841, 1777, 751, 716 cm^{-1}.

HRMS (ESI) calculated for $C_{17}H_{22}NO$ $(M+H)^+$: 256.1696, found: 256.1697.

M.P.: 157–159 ºC.

3-(Dimethylamino)-1-phenyl-1-(thiophen-2-yl)propan-1-ol (217j)



According to general procedure GP2b, diisopropylamine (140 µL, 1.00 mmol), *n*-BuLi (625 µL, 1.00 mmol), 1,1-dimethyl-2-phenylazetidin-1-ium trifluoromethanesulfonate (**211**) (156 mg, 0.500 mmol) and 4,4,5,5-tetramethyl-2-(thiophen-2-yl)-1,3,2-dioxaborolane (126 mg, 0.600 mmol) in anhydrous THF (12 mL), afforded after purification by flash chromatography on silica gel (EtOAc:Et_3N = 100:0.5) tertiary alcohol **217j** (64 mg, 49%) as a white solid.

R_f: 0.39 (EtOAc:Et_3N = 100:0.5).

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.56 (d, *J* = 7.4 Hz, 2H, Ar-H), 7.33 (t, *J* = 7.6 Hz, 2H, Ar-H), 7.22 (t, *J* = 7.1 Hz, 1H, Ar-H), 7.18 (d, *J* = 5.0 Hz, 1H, 5-H), 6.92 (t, *J* = 3.6 Hz, 1H, 6-H), 6.89 (d, *J* = 3.5 Hz, 1H, 7-H), 2.52 (m, 1H, 1-H), 2.47–2.30 (m, 3H, 1-H + 2-H), 2.24 (s, 6H, N-$(CH_3)_2$).

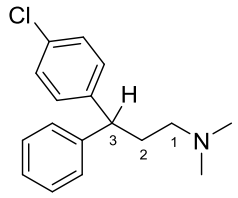
^{13}C NMR ($CDCl_3$, 101 MHz) δ: 154.4 (4-C), 147.4 (Ar-C), 128.2 (2C, Ar-C), 126.8 (Ar-C), 126.6 (6-C), 125.5 (2C, Ar-C), 124.3 (5-C), 122.8 (7-C), 78.5 (3-C), 56.6 (1-C), 45.2 (2C, N-$(CH_3)_2$), 38.1 (2-C).

IR (neat) ν_{max}: 2779, 1178, 1068, 847, 699 cm^{-1}.

HRMS (ESI) calculated for $C_{15}H_{20}NOS$ $(M+H)^+$: 262.1260, found: 262.1267.

M.P.: 115–117 ºC.

3-(4-Chlorophenyl)-*N*,*N*-dimethyl-3-phenylpropan-1-amine (218l)



According to general procedure GP3, diisopropylamine (120 µL, 0.876 mmol), *n*-BuLi (565 µL, 1.00 mmol), 1,1-dimethyl-2-phenylazetidin-1-ium trifluoromethanesulfonate (**211**) (137 mg, 0.438 mmol), 2-(4-chlorophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (138 mg, 0.581 mmol), CsF (99.8 mg, 0.657 mmol) and H_2O (9.0 µL, 0.48 mmol) in anhydrous THF (8 mL), afforded after purification by flash chromatography on silica gel (EtOAc:Et_3N = 100:0.5) protodeboronated compound **218l** (85 mg, 71%) as a colourless oil.

R_f: 0.24 (CH_2Cl_2:MeOH:Et_3N = 99.5:0.5:0.5).

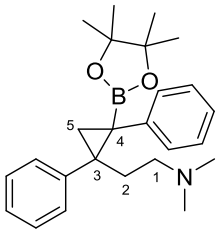
^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.26–7.24 (m, 8H, Ar-H), 7.15 (m, 1H, Ar-H), 3.93 (t, *J* = 6.0 Hz, 1H, 3-H), 2.27–2.20 (m, 4H, 1-H + 2-H), 2.19 (s, 6H, N-$(CH_3)_2$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ: 145.5 (Ar-C), 145.0 (Ar-C), 132.9 (Ar-C), 130.4 (2C, Ar-C), 129.6 (2C, Ar-C), 129.5 (2C, Ar-C), 128.7 (2C, Ar-C), 127.5 (Ar-C), 59.1 (1-C), 49.9 (3-C), 45.4 (2C, N-$(CH_3)_2$), 34.0 (2-C).

IR (neat) ν_{max}: 2942, 2765, 1489, 1092, 1014, 821, 698 cm^{-1}.

HRMS (ESI) calculated for $C_{17}H_{21}Cl$ $(M+H)^+$: 274.1357, found: 274.1363.

2-(1,2-Diphenyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclopropyl)-*N*,*N*-dimethylethan-1-amine (220)



According to general procedure GP1, diisopropylamine (140 µL, 1.00 mmol), *n*-BuLi (625 µL, 1.00 mmol), 1,1-dimethyl-2-phenylazetidin-1-ium trifluoromethanesulfonate (**211**) (155 mg, 0.500 mmol) and 4,4,5,5-tetramethyl-2-(1-phenylvinyl)-1,3,2-dioxaborolane (138 mg, 0.600 mmol) in anhydrous THF (12 mL) afforded after purification by flash column chromatography on silica gel (EtOAc:Et_3N = 100:0.5) cyclopropane **220** (47 mg, 24%) as a colourless oil.

R_f: 0.30 (EtOAc:Et_3N = 100:0.5).

^{1}H NMR (CD_3OD, 400 MHz) δ: 7.06–6.78 (m, 10H, Ar-H), 2.54 (td, J_1 = 12.4 Hz, J_2 = 4.4 Hz, 1H, 1-H), 2.32 (td, J_1 = 11.5 Hz, J_2 = 4.4 Hz, 1H, 1-H), 2.17 (s, 6H, N-$(CH_3)_2$), 2.20–2.10 (m, 1H, 2-H), 1.99 (bs, 1H, 5-H), 1.87 (td, J_1 = 12.3 Hz, J_2 = 4.3 Hz, 1H, 2-H), 1.36 (d, J = 4.8 Hz, 1H, 5-H), 1.26 (s, 6H, C-CH_3 × 2), 1.22 (s, 6H, C-CH_3 × 2).

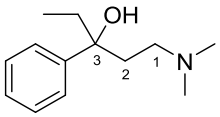
^{13}C NMR (CD_3OD, 101 MHz) δ: 141.4 (Ar-C), 141.3 (Ar-C), 131.4 (2C, Ar-C), 130.6 (2C, Ar-C), 128.6 (2C, Ar-C), 128.1 (2C, Ar-C), 126.8 (Ar-C), 125.8 (Ar-C), 85.0 (2C, B-O-C × 2), 58.7 (1-C), 45.3 (2C, N-$(CH_3)_2$), 37.6 (3-C), 36.8 (2-C), 25.3 (2C, C-*C*H_3 × 2), 25.2 (2C, C-*C*H_3 × 2), 20.4 (5-C); *carbon attached to boron not observed due to quadrupolar relaxation.*

^{11}B NMR ($CDCl_3$, 96 MHz) δ: 30.7, 21.1.

IR (neat) ν_{max}: 2976, 1599, 1448, 1372, 1144, 849, 766, 697 cm^{-1}.

HRMS (ESI) calculated for $C_{25}H_{35}BNO_2$ $(M+H)^+$: 392.2760, found: 392.2768.

1-(Dimethylamino)-3-phenylpentan-3-ol (217a)



According to general procedure GP2a, diisopropylamine (140 µL, 1.00 mmol), *n*-BuLi (625 µL, 1.00 mmol), 1,1-dimethyl-2-phenylazetidin-1-ium trifluoromethanesulfonate (**211**) (156 mg, 0.500 mmol) and 2-ethyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (94 mg, 0.60 mmol) in anhydrous THF (6 mL), afforded after purification by flash chromatography on silica gel (CH_2Cl_2:MeOH:Et_3N = 100:0.5:0.5) tertiary alcohol **217a** (60 mg, 58%) as a white solid.

R_f: 0.25 (EtOAc:Et_3N = 100:1).

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.41–7.39 (m, 2H, Ar-H), 7.34–7.30 (m, 2H, Ar-H), 7.20 (ps tt, J_1 = 8.4 Hz, J_2 = 0.9 Hz, 1H, Ar-H), 2.28 (td, J_1 = 12.5 Hz, J_2 = 2.6 Hz, 1H, 1-H), 2.19 (m, 1H, 1-H), 2.18 (s, 6H, N-$(CH_3)_2$), 2.08 (ddd, J_1 = 14.7 Hz, J_2 = 12.0 Hz, J_3 = 3.12 Hz, 1H, 2-H), 1.84–1.74 (m, 3H, C*H*$_2$-CH_3 + 2-H), 0.72 (t, J = 7.3 Hz, 3H, CH_2-C*H*$_3$).

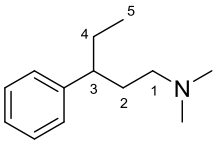
^{13}C NMR ($CDCl_3$, 101 MHz) δ: 147.0 (Ar-C), 128.0 (2C, Ar-C), 126.1 (Ar-C), 125.9 (2C, Ar-C), 78.2 (3-C), 56.2 (1-C), 45.2 (2C, N-$(CH_3)_2$), 37.2 (2-C), 36.7 (*C*H_2-CH_3), 7.7 (CH_2-*C*H_3).

IR (neat) ν_{max}: 2936, 2823, 2781, 1464, 1445, 1174, 1042, 1024, 773, 758 cm^{-1}.

HRMS (ESI) calculated for $C_{13}H_{22}NO$ $(M+H)^+$: 208.1696, found: 208.1702.

M.P.: 39–41 ºC.

***N*,*N*-Dimethyl-3-phenylpentan-1-amine (218a)**



Following a modified literature procedure,[94] *N*,*N*-dimethyl-3-phenyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2yl)pentan-1-amine (**213a**) (64 mg, 0.20 mmol) was dissolved in dry THF (2 mL) and TBAF·$3H_2O$ (95 mg, 0.30 mmol) was added at room temperature. The reaction mixture was allowed to stir at 65 °C for 2 h, then H_2O (5 mL) was added. The mixture was partitioned between H_2O and CH_2Cl_2 and the aqueous phase was extracted with CH_2Cl_2 (2 × 5 mL). The combined organic layers were dried over $MgSO_4$ and solvent was removed under reduced pressure. The crude residue was purified by flash chromatography on silica gel (EtOAc:Et_3N = 100:0.5) to afford **218a** (28 mg, 73%) as a colourless oil.

R_f: 0.20 (EtOAc:Et_3N = 100:0.5).

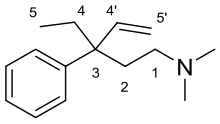
^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.30 (m, 2H, Ar-H), 7.22–7.15 (m, 3H, Ar-H), 2.47 (sept, J = 5.0 Hz, 1H, 3-H), 2.21 (m, 1H, 1-H), 2.21 (s, 6H, N-$(CH_3)_2$), 2.09 (td, J_1 = 10.3 Hz, J_2 = 5.1 Hz, 1H, 1-H), 1.87 (m, 1H, 2-H), 1.80–1.65 (m, 2H, 2-H + 4-H), 1.59 (m, 1H, 4-H), 0.78 (t, J = 7.4 Hz, 3H, 5-H).

^{13}C NMR ($CDCl_3$, 101 MHz) δ: 145.4 (Ar-C), 128.4 (2C, Ar-C), 127.8 (2C, Ar-C), 126.13 (Ar-C), 58.1 (1-C), 46.0 (3-C), 45.5 (2C, N-$(CH_3)_2$), 34.3 (2-C), 30.0 (4-C), 12.2 (5-C).

IR (neat) ν_{max}: 2929, 1453, 1042, 755, 700 cm^{-1}.

HRMS (ESI) calculated for $C_{13}H_{22}N$ $(M+H)^+$: 192.1747, found: 192.1755.

3-Ethyl-*N*,*N*-dimethyl-3-phenylpent-4-en-1-amine (221a)



Following a literature procedure,[210] *n*-BuLi (1.50 mmol, 940 µL) was added dropwise to neat tetravinyltin (140 µL, 0.750 mmol) at room temperature under a N_2 atmosphere. The reaction mixture was stirred for 30 min; the white solid formed was allowed to settle and the colourless solution was removed by syringe under N_2. The solid (vinyl lithium) was washed with dry pentane (3 × 1 mL), every time adding and removing the solvent by syringe under N_2, then it was dissolved in dry THF (1 mL). *N*,*N*-Dimethyl-3-phenyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2yl)pentan-1-amine (**213a**) (95 mg, 0.30 mmol) was dissolved in dry THF (3 mL) and the vinyl lithium solution was added dropwise at −78 °C. The reaction mixture was stirred for 30 min at −78 °C, then it was warmed to −42 °C and stirred for additional 20 min. After that time, ^{11}B NMR analysis of the crude reaction mixture showed complete boronate complex formation. The solution was cooled to −78 °C and a solution of I_2 (381 mg, 1.50 mmol) in dry MeOH (2.4 mL) was added dropwise. After stirring for 15 min at −78 °C a suspension of MeONa (126 mg, 3.00 mmol) in dry MeOH (1.2 mL) was added. The reaction mixture was allowed to warm to room temperature and stirred for 1 h, then sat. aq. $Na_2S_2O_3$ (10 mL) was added. The layers were separated, the organic layer was washed with brine (2 × 5 mL) and the combined aqueous layers were extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude residue was purified by flash column chromatography on silica gel (EtOAc:Et_3N = 100:0.5) to afford alkene **221a** (34 mg, 52%) as a colourless oil.

R_f: 0.20 (EtOAc:Et_3N = 100:0.5).

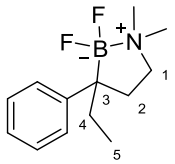
^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.31−7.28 (m, 4H, Ar-H), 7.18 (m, 1H, Ar-H), 5.91 (dd, J_1 = 17.7 Hz, J_2 = 11.0 Hz, 1H, 4'-H), 5.20 (dd, J_1 = 10.9 Hz, J_2 = 1.0 Hz, 1H, 5'-H_{cis}), 5.11 (dd, J_1 = 17.7 Hz, J_2 = 1.0 Hz, 1H, 5'-H_{trans}), 2.19 (s, 6H, N-$(CH_3)_2$), 2.10 (m, 2H, 1-H), 1.97 (m, 2H, 2-H), 1.80 (qd, J_1 = 13.8 Hz, J_2 = 7.2 Hz, 2H, 4-H), 0.72 (t, J = 7.4 Hz, 3H, 5-C).

^{13}C NMR ($CDCl_3$, 101 MHz) δ: 145.7 (Ar-C), 145.2 (4'-C), 128.2 (2C, Ar-C), 127.4 (2C, Ar-C), 126.0 (Ar-C), 113.2 (5'-C), 55.2 (1-C), 47.0 (3-C), 45.7 (2C, N-$(CH_3)_2$), 34.5 (2-C), 30.3 (4-C), 8.6 (5-C).

IR (neat) ν_{max}: 2937, 2815, 2763, 1462, 1041, 912, 759, 699 cm^{-1}.

HRMS (ESI) calculated for $C_{15}H_{24}N$ $(M+H)^+$: 218.1903, found: 2218.1910.

3-Ethyl-2,2-difluoro-1,1-dimethyl-3-phenyl-1λ⁴,2λ⁴-azaborolidine (223a)



Following a literature reported procedure,[55] to a rapidly stirred solution of *N*,*N*-dimethyl-3-phenyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2yl)pentan-1-amine **213a** (95 mg, 0.30 mmol) in MeOH (3 mL) was added dropwise a solution of KHF_2 (105 mg, 1.35 mmol) in H_2O (700 µL) at room temperature. The resulting reaction mixture was stirred for 30 min, then all the volatiles were removed under reduced pressure. The residue was dissolved in a mixture of MeOH:H_2O (1:1 *v*/*v*, 6 mL) and evaporated to dryness. This evaporation–dissolution cycle was repeated 6 times, after which ^{1}H NMR analysis of an aliquot of the reaction mixture showed no presence of pinacol (δ = 1.14 ppm) in CD_3CN. The solid residue was then triturated with dry acetone (5 mL); the liquid phase was carefully decanted and the residual inorganic salts were additionally washed with acetone (3 × 1 mL). The combined washings were collected and concentrated *in vacuo* to give a 2:1 mixture of tetrafluoroborate salt **222a** and azaborolidine **223a** (82% overall yield).

A portion of the mixture (45 mg) was dissolved in dry CH_3CN (3 mL) and the solution was heated at reflux for 5 h. The reaction mixture was then filtered through a pad of SiO_2 and washed with CH_2Cl_2 to give azaborolidine **223a** (26 mg, 68%) as a white solid.

R_f: 0.66 (EtOAc:Et_3N = 100:0.5).

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.29 (m, 4H, Ar-H), 7.12 (m, 1H, Ar-H), 3.00 (m, 1H, 1-H), 2.90 (m, 1H, 1-H), 2.61 (s, 3H, N-CH_3), 2.39 (s, 3H, N-CH_3), 2.30 (quint, *J* = 7.6 Hz, 1H, 2-H), 1.89 (m, 2H, 4-H), 1.59 (quint, *J* = 6.9 Hz, 1H, 2-H), 0.57 (t, *J* = 7.2 Hz, 3H, 5-H).

^{13}C NMR ($CDCl_3$, 101 MHz) δ: 147.7 (Ar-C), 137.7 (4C, Ar-C), 124.4 (Ar-C), 60.4 (1-C), 46.8 (d, *J* = 9.1 Hz, N-CH_3), 46.6 (d, *J* = 10.1 Hz, N-CH_3), 30.9 (4-C), 29.6 (2-C), 9.1 (5-C); *carbon attached to boron not observed due to quadrupolar relaxation.*

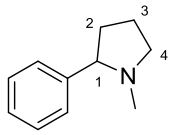
^{11}B NMR ($CDCl_3$, 96 MHz) δ: 7.4 (t, *J* = 67.4 Hz).

^{19}F NMR ($CDCl_3$, 282 MHz) δ: −152.4 (m), −157.3 (m).

IR (neat) ν_{max}: 2959, 2927, 1467, 1053, 950, 755, 724, 701, 658 cm^{-1}.

HRMS (ESI) calculated for $C_{13}H_{20}BF_2NNa$ $(M+Na)^+$: 262.1551, found: 262.1551.

1-Methyl-2-phenylpyrrolidine (226)



Following a literature reported procedure,[140] commercially available 2-phenylpyrrolidine (3.40 mmol, 500 mg) was suspended in H_2O (4 mL) in a microwave test tube and formic acid (3.70 mmol, 141 µL) and formaldehyde (35% solution in H_2O, 3.70 mmol, 320 µL) were added at room temperature. The tube was sealed and it was heated using microwave radiation at 150 °C for 5 min. The reaction mixture was allowed to cool to room temperature, then it was basified to pH 14 using aq. NaOH (2.0 M) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was removed *in vacuo*. The crude material was purified by Kugelrohr distillation to afford the pure tertiary amine (396 mg, 72%) as a colourless oil.

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.36–7.29 (m, 4H, Ar-H), 7.23 (m, 1H, Ar-H), 3.24 (td, J_1 = 9.4 Hz, J_2 = 1.8 Hz, 1H, 4-H), 3.03 (t, J = 8.8 Hz, 1H, 1-H), 2.28 (q, J = 9.3 Hz, 1H, 4-H), 2.17 (m, 1H, 2-H), 2.17 (s, 3H, CH_3), 1.95 (m, 1H, 3-H), 1.78 (m, 2H, 2-H + 3-H).

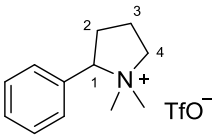
^{13}C NMR ($CDCl_3$, 101 MHz) δ: 143.4 (Ar-C), 128.5 (2C, Ar-C), 127.6 (2C, Ar-C), 127.1 (Ar-C), 71.8 (1-C), 57.2 (4-C), 40.6 (CH_3), 35.3 (2-C), 22.6 (3-C).

IR (neat) ν_{max}: 2968, 2775, 1454, 1044, 754, 699 cm^{-1}.

HRMS (ESI) calculated for $C_{11}H_{16}N$ $(M+H)^+$: 162.1277, found: 162.1272.

All analytical data matched that previously reported in the literature.[140]

1,1-Dimethyl-2-phenylpyrrolidin-1-ium trifluoromethanesulfonate (227)



Following a modified procedure reported by Couty,[130] pyrrolidine **226** (358 mg, 2.22 mmol) was dissolved in dry Et_2O (19 mL) and trifluoromethanesulfonate (500 µL, 4.45 mmol) was added at 0 °C. The mixture was stirred for 1 h at room temperature, then all the volatiles were removed under vacuum to afford pyrrolidinium triflate **227** (721 g, >99%) as a purple oil.

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.50 (d, J = 6.6 Hz, 2H, Ar-H), 7.45 (t, J = 8.6 Hz, 3H, Ar-H), 4.87 (dd, J_1 = 11.5 Hz, J_2 = 7.8 Hz, 1H, 1-H), 3.82 (t, J = 7.7 Hz, 2H, 4-H), 3.07 (s, 3H, CH_3), 2.69 (s, 3H, CH_3), 2.60 (m, 1H, 2-H), 2.49 (m, 1H, 2-H), 2.31 (b quint, J = 7.1 Hz, 2H, 3-H).

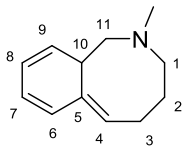
^{13}C NMR ($CDCl_3$, 101 MHz) δ: 131.4 (Ar-C), 130.9 (2C, Ar-C), 129.5 (2C, Ar-C), 128.4 (Ar-C), 120.7 (q, $^1J_{C-F}$ = 320 Hz, CF_3), 78.7 (1-C), 65.8 (4-C), 50.6 (CH_3), 45.2 (CH_3), 26.1 (2-C), 19.3 (3-C).

^{19}F NMR ($CDCl_3$, 376 MHz) δ: −78.4.

IR (neat) ν_{max}: 2972, 1475, 1256, 1152, 754, 706, 635 cm^{-1}.

HRMS (ESI) calculated for $C_{12}H_{18}N$ $(M)^+$: 176.1434, found: 176.1440.

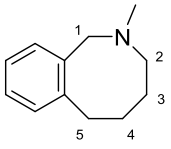
(*Z*)-2-Methyl-1,2,3,4,5,10a-hexahydrobenzo[*c*]azocine (229)



To a solution of diisopropylamine (140 µL, 1.00 mmol) in anhydrous THF (500 µL) was added *n*-BuLi (625 µL, 1.00 mmol) at −78 °C. After stirring for 20 min at −78 °C and 10 min at room temperature, the solution was added dropwise to a mixture of pyrrolidinium salt **227** (163 mg, 0.50 mmol) and 2-ethyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (94 mg, 0.60 mmol) in dry THF (12 mL) at −78 °C. The reaction mixture was stirred at −78 °C for 1 h, then was allowed to warm to room temperature. The solvent was removed *in vacuo* and the crude residue was taken up with H_2O (5 mL) and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure to afford crude **229**, which was purified by flash chromatography on silica gel (EtOAc:Et_3N = 100:0.5) to afford the pure azocine **229** (42 mg, 48%) as a colourless oil.

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 6.05 (d, J = 9.5 Hz, 1H, 6-H), 5.94 (dd, J_1 = 9.4 Hz, J_2 = 5.3 Hz, 1H, 8-H), 5.77–5.68 (m, 3H, 4-H, 7-H, 9-H), 3.51 (br. s, 1H, 10-H), 2.70–2.46 (m, 4H, 1-H × 2, 3-H, 11-H), 2.42 (s, 3H, CH_3), 2.21 (m, 1H, 3-H), 2.04 (m, 1H, 11-H), 1.87 (m, 1H, 2-H), 1.47 (m, 1H, 2-H).

(*Z*)-2-Methyl-1,2,3,4,5,10a-hexahydrobenzo[*c*]azocine (**229**) was found to rapidly rearrange at room temperature to give 2-methyl-1,2,3,4,5,6-hexahydrobenzo[*c*]azocine (**230**) which could be fully characterised.



R_f: 0.54 (EtOAc:Et_3N = 100:0.5).

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.18 (m, 4H, Ar-H), 3.78 (s, 2H, 1-H), 2.85 (t, J = 5.8 Hz, 2H, 5-H), 2.46 (t, J = 4.8 Hz, 2H, 2-H), 2.39 (s, 3H, CH_3), 1.71 (quint, J = 5.8 Hz, 2H, 4-H), 1.61 (quint, J = 5.6 Hz, 2H, 3-H).

^{13}C NMR ($CDCl_3$, 101 MHz) δ: 142.1 (Ar-C), 134.5 (Ar-C), 131.0 (Ar-C), 129.6 (Ar-C), 127.8 (Ar-C), 126.0 (Ar-C), 55.9 (1-C), 54.1 (2-C), 43.6 (CH_3), 33.1 (5-C), 31.0 (4-C), 23.7 (3-C).

IR (neat) ν_{max}: 2922, 1448, 1044, 753, 613 cm^{-1}.

HRMS (ESI) calculated for $C_{12}H_{18}N$ $(M+H)^+$: 176.1434, found: 176.1430.

5.5. General Procedures Chapter 3

General procedure for the synthesis of *syn* and *anti* 1-(*p*-tolylsulfinyl) 2,4,6-triisopropylbenzoates by transmetalation (GP4)

To a stirred solution of 2,4,6-triisopropylbenzoate (1.0 equiv) and TMEDA (1.2−1.5 equiv) in anhydrous Et_2O (0.3 M) was added *s*-BuLi (1.3 M in cyclohexane/hexane, 1.2−1.5 equiv) dropwise at −78 °C under N_2 atmosphere. After stirring for the required time at −78 °C, a solution of freshly prepared $MgBr_2 \cdot Et_2O$* (1.5 equiv in Et_2O − 0.8 M) was added at −78 °C and the reaction mixture was stirred for 2 h at that temperature. At this point, a solution of (1*R*,2*S*,5*R*)-(−)-menthyl (*S*)-*p*-toluenesulfinate (1.5 equiv) in anhydrous THF (1.0 M) was added dropwise at −78 °C. The mixture was stirred for additional 1 h at that temperature before being warmed to room temperature and stirred overnight. The reaction mixture was then diluted with EtOAc and sat. aq. NH_4Cl, the phases were separated and the aqueous phase was extracted with EtOAc (3 times). The combined organic layers were washed with brine, dried over $MgSO_4$ and the solvent was evaporated under reduced pressure. In many cases separation of the desired diastereoisomers from the menthol by-product was facilitated by silylation of menthol:[211] to a solution of the crude mixture in anhydrous CH_2Cl_2 (0.5 M) was added Et_3N (1.5 equiv). TMSCl (1.3 equiv) was added dropwise at room temperature, the resulting mixture was stirred for 20 min, diluted with Et_2O and washed with H_2O. The organic layer was dried over $MgSO_4$ and the solvent was removed under reduced pressure to give a crude residue, which was purified by flash silica gel column chromatography (hexane:EtOAc) to afford the *syn* (less polar) and the *anti* (more polar) diastereoisomers.

The racemates were synthesised as described above but using racemic methyl 4-methylbenzenesulfinate **466** as the starting material.

* A solution of $MgBr_2 \cdot Et_2O$ was prepared as follows: Mg turnings (4.0 equiv) were charged in a Schlenk tube in a N_2 atmosphere and anhydrous Et_2O (0.8 M with respect to dibromoethane) was added. The solution was cooled to 0 °C and dibromoethane (1.5 equiv) was added dropwise. The ice bath was removed and the reflux was initiated after a few minutes. After gas evolution ceased, the reaction mixture was stirred for additional 30 min.

General procedure for the synthesis of *syn* and *anti* 1-(*p*-tolylsulfinyl) 2,4,6-triisopropylbenzoates by alkylation (GP5)

(*p*-Tolylsulfinyl)methyl 2,4,6-triisopropylbenzoate (*R*) or (*S*)-**256** (1.0 equiv) and the alkylating agent (1.1−2.0 equiv) in an oven dried Schlenk tube were dissolved in anhydrous THF (0.2 M) under a N_2 atmosphere. For substrate **255n**, HMPA (2.0 equiv) was added at this stage. The reaction mixture was cooled to −78 °C and the base (2.0 equiv) was added dropwise. The mixture was stirred at −78 °C for 30 min, then the cooling bath was removed and the solution was stirred at room temperature for 30 min. The reaction mixture was quenched with sat. aq. NH_4Cl and diluted with EtOAc. The layers were separated and the aqueous phase was extracted with EtOAc (3 times). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude residue was purified by flash silica gel column chromatography (hexane:EtOAc) to give the *syn* (less polar) and the *anti* (more polar) diastereoisomers.

The racemates were synthesised as described above but using racemic sulfoxide *rac*-**256** as the starting material.

General procedure for the stereocontrolled homologation of boronic esters using *α*-sulfinyl benzoates: *in situ* procedure using *t*-BuLi (GP6)

t-BuLi (1.7 M in pentane, 2.00 equiv) was added dropwise to a mixture of sulfoxide (1.05−1.10 equiv) and pinacol boronic ester (1.00 equiv) in anhydrous THF (0.1 M with respect to the boronic ester) at −78 °C under N_2 atmosphere and the resulting solution was stirred at this temperature for 1 h. After warming to room temperature, the reaction mixture was heated at 66 °C for 3 h, cooled to room temperature, diluted with Et_2O and sat. aq. NH_4Cl was added. The phases were separated and the aqueous phase was extracted with Et_2O (3 times). The combined organic layers were dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. Purification of the crude reaction mixture by flash silica gel column chromatography (hexane:Et_2O) afforded the desired homologated boronic ester. A small portion of the boronic ester was oxidised to the corresponding alcohol following general procedures GP8 to determine the e.r.

For substrate **255r**, after stirring the reaction mixture at −78 °C for 1 h, acetic acid (1.00 equiv) was added to quench the excess of the reactive organolithium and the 1,2-metallate rearrangement was performed at room temperature for 16 h.

When the separation of the homologated boronic ester from the unreacted starting boronic ester was not possible the mixture was oxidised (see GP8) and the corresponding alcohol was isolated clean.

The racemates were synthesised as described above but using the corresponding racemic sulfoxides as the starting materials.

General procedure for the stereocontrolled homologation of boronic esters using α-sulfinyl benzoates: *in situ* procedure using *i*-PrMgCl·LiCl (GP7a)

i-PrMgCl·LiCl (1.3 M in THF, 1.2 equiv) was added dropwise to a mixture of sulfoxide (1.3 equiv) and pinacol boronic ester (1.0 equiv) in anhydrous CH_2Cl_2 (0.1 M with respect to the boronic ester) at −78 °C under N_2 atmosphere and the resulting solution was stirred at this temperature for 1 h. After being warmed to room temperature, the reaction mixture was heated at 40 °C for 3 h, cooled to room temperature, diluted with Et_2O and sat. aq. NH_4Cl was added. The phases were separated and the aqueous phase was extracted with Et_2O (3 times). The combined organic layers were dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The crude mixture was purified by flash silica gel column chromatography (hexane:Et_2O) to afford the desired homologated boronic ester. A small portion of the boronic ester was oxidised to the corresponding alcohol following general procedures GP8 to determine the e.r.

When the separation of the homologated boronic ester from the unreacted starting boronic ester was not possible the mixture was oxidised (see GP8) and the corresponding alcohol was isolated.

The racemates were synthesised as described above but using the corresponding racemic sulfoxides as the starting materials.

General procedure for the stereocontrolled homologation of boronic esters using α-sulfinyl benzoates: *ex situ* procedure using *i*-PrMgCl·LiCl (GP7b)

i-PrMgCl·LiCl (1.3 M in THF, 1.2 equiv) was added dropwise to a solution of sulfoxide (1.3 equiv) in anhydrous CH_2Cl_2 (0.13 M) at −78 °C under N_2 atmosphere and the resulting solution was stirred at this temperature for 30 min. A solution of the pinacol boronic ester (1.0 equiv) in CH_2Cl_2 (0.5 M) was then added slowly and the resulting mixture was stirred at −78 °C for additional 45 min. After being warmed to room temperature, the reaction mixture was heated at 40 °C for 3 h, cooled to room temperature, diluted with Et_2O and sat. aq. NH_4Cl

was added. The phases were separated and the aqueous phase was extracted with Et_2O (3 times). The combined organic layers were dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The crude mixture was purified by flash silica gel column chromatography (hexane:Et_2O) to afford the desired homologated boronic ester. A small portion of the boronic ester was oxidised to the corresponding alcohol following general procedures GP8 to determine the e.r.

When the separation of the homologated boronic ester from the unreacted starting boronic ester was not possible the mixture was oxidised (see GP8) and the corresponding alcohol was isolated clean.

The racemates were synthesised as described above but using the corresponding racemic sulfoxides as the starting materials.

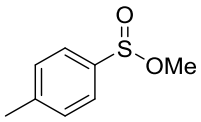
General procedure for the stereospecific oxidation of boronic esters using H_2O_2/NaOH (GP8)

Pinacol boronic ester (1.0 equiv) was dissolved in THF (5.0 mL) and the solution was cooled to 0 °C. A solution of aq. NaOH (2.0 M) and 30% H_2O_2 (2/1 *v*/*v*, 3.0 mL) was added dropwise. The solution was stirred vigorously for 2 h at room temperature, then it was diluted with H_2O (10 mL) and Et_2O (10 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3 × 10 mL). The organic layers were combined, dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash silica gel column chromatography (hexane:EtOAc) to afford the desired alcohol.

5.6. Single Compounds Chapter 3

5.6.1. Preparation of α-Sulfinyl Benzoates

Methyl 4-methylbenzenesulfinate (466)



Following a literature reported procedure,[212] solid *N*-bromosuccinimide powder (12.6 g, 70.8 mmol) was added in one portion to a solution of 4-methylbenzenethiol (150 mg, 1.07 mmol) in a mixture of MeOH:CH_2Cl_2 (1/1 *v*/*v*, 86 mL) at 0 °C. The ice bath was removed and after 1 h the mixture was poured into a solution of saturated $NaHCO_3$ (50 mL) at 0 °C. The biphasic mixture was transferred into a separating funnel and shaken until discoloration. The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude residue was purified by column chromatography on silica gel (hexane:Et_2O = 90:10) to afford pure methyl sulfinate ester **466** (5.56 g, 93%) as a colourless oil.

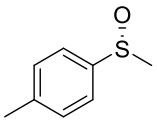
^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.57 (d, 2H, *J* = 8.2 Hz, Ar-H), 7.32 (d, *J* = 7.9 Hz, 2H, Ar-H), 3.44 (s, 3H, O-CH_3), 2.41 (s, 3H, CH_3).

^{13}C NMR ($CDCl_3$, 101 MHz) δ: 142.7 (Ar-C), 140.9 (Ar-C), 129.6 (2C, Ar-C x 2), 125.3 (2C, Ar-C x 2), 49.3 (O-CH_3), 21.4 (CH_3).

IR (neat) ν_{max}: 2941, 1129, 1080, 959, 812, 676, 626 cm^{-1}.

All analytical data matched that previously reported in the literature.[213]

(*R*)-1-Methyl-4-(methylsulfinyl)benzene (258)



MeMgBr (3.0 M in Et_2O, 9.50 mL, 28.6 mmol) was added dropwise to a solution of (−)-menthyl (*S*)-*p*-toluenesulfinate **117** (6.0 g, 20.4 mmol) in dry toluene (60 mL) at 0 °C. The reaction mixture was stirred at room temperature for 2 h, then it was quenched with sat. aq. NH_4Cl (50 mL). The phases were separated and the aqueous phase was extracted with Et_2O (3 × 50 mL). The combined organic phases were washed with water (50 mL), with brine (50 mL), dried over $MgSO_4$ and the solvent was evaporated under reduced pressure. The crude residue was purified by flash column chromatography on silica gel (CH_2Cl_2:MeOH = 100:0 → 95:5) to yield sulfoxide **258** (2.35 g, 75%) as a colourless solid.

[The racemate was synthesised as follows: a mixture of methyl *p*-tolyl sulfide (691 mg, 5.00 mmol) and H_2O_2 (30%, 540 µL, 5.50 mmol) was heated at 60 °C for 16 h. The reaction mixture was cooled to room temperature and diluted with CH_2Cl_2 (5 mL) and H_2O (5 mL). The phases were separated and the organic phase was washed with water (5 mL), with brine (5 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The crude residue was purified by flash column chromatography on silica gel (EtOAc) to afford methyl *p*-tolyl sulfoxide *rac*-**258** (619 mg, 80%) as a colourless solid.]

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.53 (d, *J* = 8.2 Hz, 2H, Ar-H), 7.32 (d, *J* = 8.4 Hz, 2H, Ar-H), 2.70 (s, 3H, S-CH_3), 2.41 (s, 3H, C-CH_3).

^{13}C NMR ($CDCl_3$, 101 MHz) δ: 142.6 (Ar-C), 141.7 (Ar-C), 130.2 (2C, Ar-C), 123.7 (2C, Ar-C), 44.1 (S-CH_3), 21.5 (C-*C*H_3).

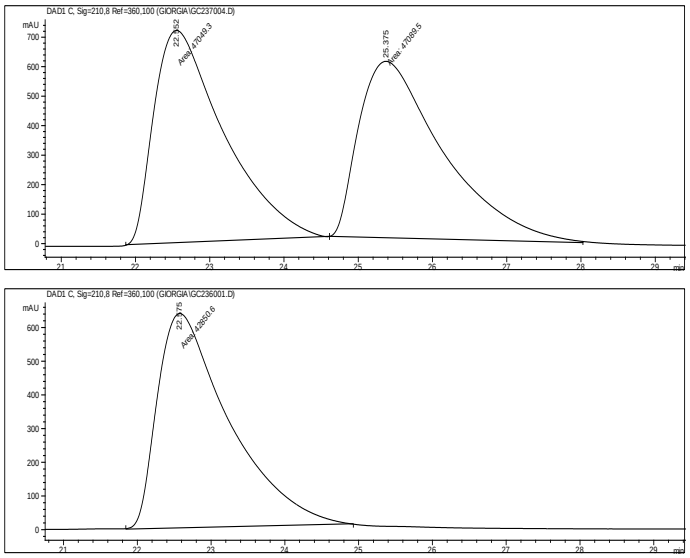
IR (neat) ν_{max}: 3468, 2996, 1494, 1087, 1038, 1014, 952, 811, 684 cm^{-1}.

HRMS (ESI) calculated for $C_8H_{10}NaOS$ $(M+Na)^+$: 177.0345, found: 177.0350.

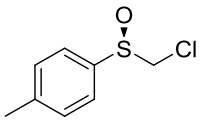
$[\alpha]^{20}_D$: +173 (*c* 1.0, $CHCl_3$). [Lit. value for (*R*): +150.4 (*c* 1.17 acetone)].[214]

All analytical data matched that previously reported in the literature.[214]

Chiral HPLC: Daicel Chiralcel-OD-H column (25 cm), hexane:isopropanol = 92:8, 0.5 mL/min, room temperature, 210.8 nm: t_R = 22.5 minutes (major), 25.3 minutes (minor), e.r. >99:1.



(*R*)-1-((Chloromethyl)sulfinyl)-4-methylbenzene (257)



Following a literature reported procedure,[147] to a solution of methyl *p*-tolyl sulfoxide **258** (2.00 g, 13.0 mmol) in dry CH_2Cl_2 (13 mL) was added K_2CO_3 (1.08 g, 7.78 mmol), followed by NCS (3.46 g, 25.9 mmol). The resulting suspension was stirred for 40 h at room temperature. The reaction mixture was diluted with Et_2O (50 mL) and aq. NaI (4% *w*/*v*, 50 mL). The phases were separated and the organic phase was washed with aq. $Na_2S_2O_3$ (10% *w*/*v*, 50 mL), dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude residue was purified by flash column chromatography on silica gel (pentane:EtOAc = 75:25) to give sulfoxide **257** (1.79 g, 73%) as a colourless solid. Recrystallisation from AcOEt:hexane afforded enantiopure sulfoxide **257** (926 mg, 38%) as a colourless solid.

[The racemate was synthesised as follows: sulfoxide *rac*-**258** (600 mg, 3.52 mmol) was dissolved in dry THF (20 mL) and chloroiodomethane (515 µL, 7.05 mmol) was added. The solution was cooled to −78 °C and *n*-BuLi (1.6 M in hexane, 4.40 mL, 7.05 mmol) was added dropwise. The reaction mixture was stirred at −78 °C for 30 min, then NH_4Cl (20 mL) was added. After stirring for additional 30 min at −78 °C the reaction mixture was warmed to room temperature and diluted with Et_2O (20 mL). The phases were separated and the aqueous phase was extracted with Et_2O (3 × 20 mL). The combined organic phases were washed with brine (20 mL), dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude residue was purified by flash column chromatography on silica gel (pentane:EtOAc = 75:25) to afford sulfoxide *rac*-**257** (363 mg, 55%) as a colourless solid.]

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.59 (d, J_1 = 8.2 Hz, 2H, Ar-H), 7.36 (d, J = 8.4 Hz, 2H, Ar-H), 4.36 (s, 2H, CH_2), 2.44 (s, 3H, CH_3).

^{13}C NMR ($CDCl_3$, 101 MHz) δ: 142.88 (Ar-C), 137.70 (Ar-C), 130.04 (2C, Ar-C × 2), 124.83 (2C, Ar-C × 2), 61.24 (CH_2), 21.51 (CH_3).

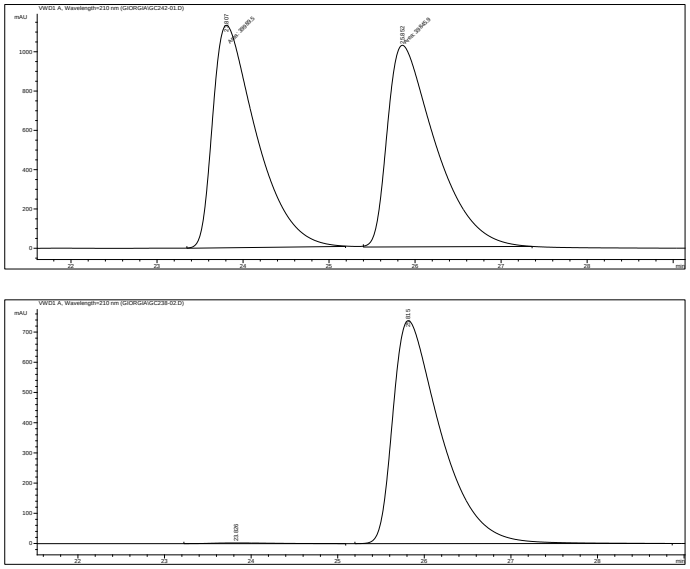
IR (neat) ν_{max}: 2921, 1493, 1146, 1080, 1040, 1016, 809, 738 cm^{-1}.

HRMS (ESI) calculated for $C_8H_9ClNaOS$ $(M+Na)^+$: 210.9955, found: 210.9961.

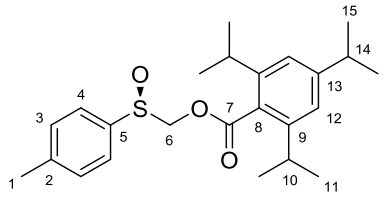
$[\alpha]^{23}_D$: −178 (*c* 1.0, $CHCl_3$). [Lit. value for (*R*): −239.0 (*c* 1.0 acetone)].[147]

All analytical data matched that previously reported.[215]

Chiral HPLC: Daicel Chiralcel-IB column (25 cm), hexane:isopropanol = 90:10, 0.5 mL/min, room temperature, 210.8 nm: t_R = 23.8 minutes (minor), 25.8 minutes (major), e.r. >99:1.



(*R*)-(*p*-Tolylsulfinyl)methyl 2,4,6-triisopropylbenzoate ((*R*)-256)



KOH (39 mg, 0.69 mmol) was added to a solution of 2,4,6-triisopropylbenzoic acid (171 mg, 0.689 mmol) in dry DMF (900 µL) at room temperature and the resulting mixture was stirred for 30 min. Chloromethyl *p*-tolyl sulfoxide **257** (100 mg, 0.530 mmol) was added and the reaction mixture was heated using microwave irradiation at 150 °C for 6 h. The solution was then allowed to cool to room temperature and was diluted with sat. aq. NH_4Cl (3 mL) and EtOAc (3 mL). The phases were separated and the aqueous phase was extracted with EtOAc (2 × 3 mL). The combined organic phases were washed with water (3 × 3 mL), with aq. NaOH (1.0 M, 2 × 3 mL), washed with brine (3 × 3 mL), dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude residue was purified by flash column chromatography on silica gel (pentane:EtOAc = 75:25) to afford sulfoxide (*R*)-**256** (200 mg, 94%) as a viscous colourless oil that turned into a colourless solid upon standing at room temperature.

[The racemate was synthesised as above, replacing **257** with *rac*-**257**.]

R_f: 0.32 (pentane:EtOAc = 80:20).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.64 (d, *J* = 8.2 Hz, 2H, Ar-H), 7.37 (d, *J* = 8.2 Hz, 2H, Ar-H), 7.02 (s, 2H, Ar-H), 5.28 (d, *J* = 10.4 Hz, 1H, 6-H), 5.00 (d, *J* = 10.4 Hz, 1H, 6-H), 2.90 (sept, *J* = 7.5 Hz, 1H, 14-H), 2.90 (sept, *J* = 6.9 Hz, 2H, 10H), 2.44 (s, 3H, 1-H), 1.25 (d, *J* = 6.9 Hz, 12H, CH_3 × 4), 1.23 (d, *J* = 6.9 Hz, 6H, CH_3 × 2).

^{13}C NMR (101 MHz, $CDCl_3$): δ 169.8 (CO), 151.1 (Ar-C), 145.4 (2C, Ar-C × 2), 142.5 (Ar-C), 137.4 (Ar-C), 130.3 (2C, Ar-C × 2), 128.6 (Ar-C), 124.8 (2C, Ar-C × 2), 121.1 (2C, Ar-C × 2), 83.4 (6-C), 34.6 (14-C), 31.8 (2C, 10-C), 24.4 (2C, CH-*C*H_3 × 2), 24.3 (2C, CH-*C*H_3 × 2), 24.1 (2C, CH-*C*H_3 × 2), 21.6 (1-C).

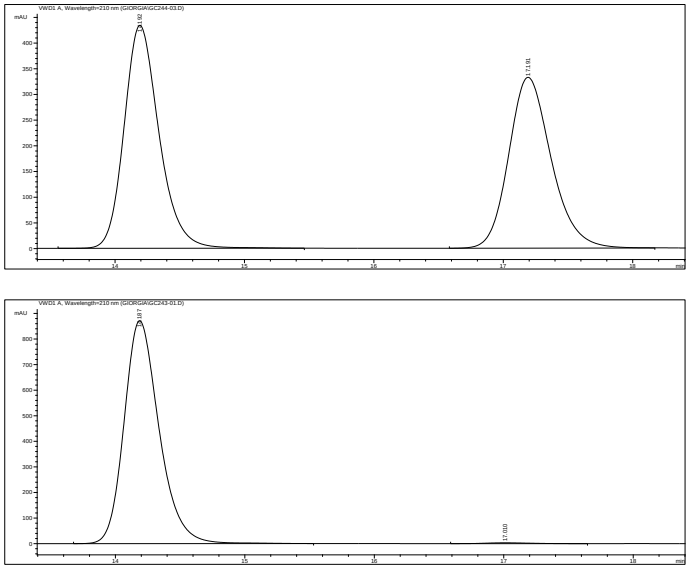
IR (neat) ν_{max}: 2961, 1745, 1227, 1035, 816 cm^{-1}.

HRMS (ESI) calculated for $C_{24}H_{32}O_3Sna$ $(M+Na)^+$: 423.1964, found 423.1974.

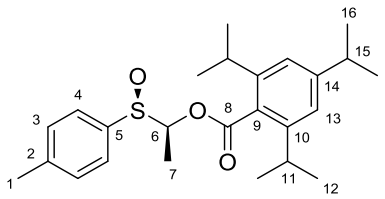
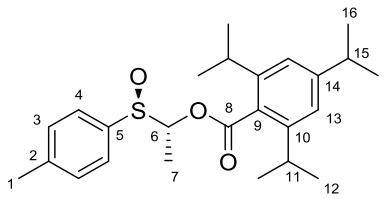
M.P.: 90–92 °C.

$[\alpha]^{22}_D$: −123 (*c* 0.9, $CHCl_3$).

Chiral HPLC: Daicel Chiralcel-IA column (25 cm), hexane:isopropanol = 95:5, 1.0 mL/min, room temperature, 210.8 nm: t_R = 14.2 minutes (major), 17.0 minutes (minor), e.r. >99:1.



(*R*)-1-((*R*)-*p*-Tolylsulfinyl)ethyl 2,4,6-triisopropylbenzoate (*syn*-255a) and (*S*)-1-((*R*)-*p*-tolylsulfinyl)ethyl 2,4,6-triisopropylbenzoate (*anti*-255a)

NaHMDS (1.0 M in THF, 8.9 mL, 8.9 mmol), was added dropwise to a solution of sulfoxide (*R*)-**256** (3.1 g, 7.7 mmol) and MeI (0.53 mL, 8.5 mmol) in anhydrous THF (40 mL) at −78 °C. The reaction mixture was stirred for 30 min at −78 °C before being warmed to room temperature and then stirred for additional 30 min at this temperature. The reaction mixture was then diluted with sat. aq. NH_4Cl (30 mL), the phases were separated and the aqueous phase was extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with brine (60 mL), dried over $MgSO_4$ and the solvent was evaporated under reduced pressure. The crude residue (d.r. = 55:45) was purified by flash column chromatography (pentane:EtOAc = 90:10) to afford the two diastereoisomers *syn*-**255a** (less polar, 1.4 g, 44%) and *anti*-**255a** (more polar, 1.7 g, 54%) as colourless solids.

[The racemates were synthesised as above, replacing (*R*)-**256** with *rac*-**256**.]

***syn*-255a**

R_f: 0.29 (pentane:EtOAc = 90:10).

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.63 (d, *J* = 8.2 Hz, 2H, Ar-H), 7.37 (d, *J* = 8.0 Hz, 2H, Ar-H), 7.04 (s, 2H, Ar-H), 5.79 (q, *J* = 6.4 Hz, 1H, 6-H), 2.90 (app sept, J_{app} = 6.8 Hz, 3H, 15-H + 11-H), 2.44 (s, 3H, 1-H), 1.40 (d, *J* = 6.4 Hz, 3H, 7-H), 1.29–1.24 (m, 18H, CH_3 × 6).

^{13}C NMR ($CDCl_3$, 101 MHz) δ: 169.9 (CO), 150.9 (Ar-C), 145.2 (2C, Ar-C × 2), 141.7 (Ar-C), 137.5 (Ar-C), 130.0 (2C, Ar-C × 2), 128.7 (Ar-C), 124.4 (2C, Ar-C × 2), 121.0 (2C, Ar-C × 2), 89.0 (6-C), 34.5 (15-C), 31.6 (2C, 11-C), 24.2 (2C, CH-*C*H_3 × 2), 24.1 (2C, CH-*C*H_3 × 2), 23.9 (2C, CH-*C*H_3 × 2), 21.4 (1-C), 9.1 (7-C).

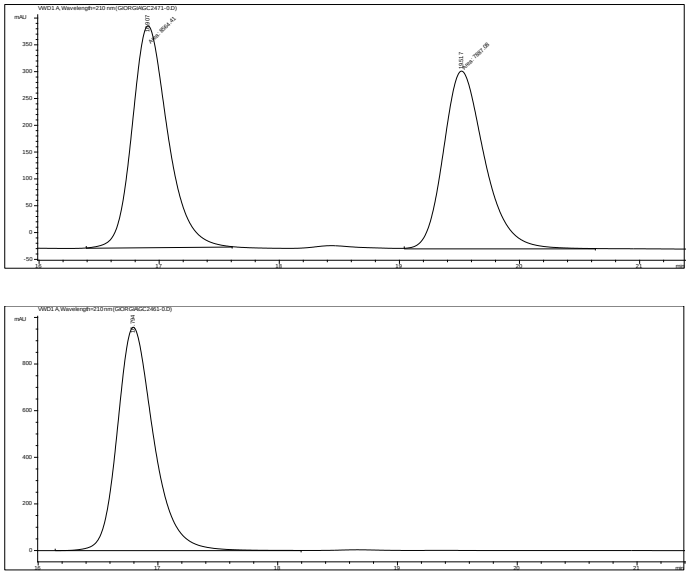
IR (neat) ν_{max}: 2962, 1735, 1228, 1087, 1060, 1041, 874, 811 cm^{-1}.

HRMS (ESI) calculated for $C_{25}H_{34}NaOS$ $(M+Na)^+$: 437.2121, found: 437.2109.

M.P.: 117−119 ºC.

$[\alpha]^{23}_D$: −43 (*c* 1.0, $CHCl_3$).

Chiral HPLC: Daicel Chiralcel-IA column (25 cm), hexane:isopropanol = 95:5, 0.5 mL/min, room temperature, 210.8 nm: t_R = 16.9 minutes (major), 19.5 minutes (minor), e.r. >99:1.



***anti*-255a**

R_f: 0.20 (pentane:EtOAc = 90:10).

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.54 (d, *J* = 9.0 Hz, 2H, Ar-H), 7.32 (d, *J* = 8.0 Hz, 2H, Ar-H), 7.01 (s, 2H, Ar-H), 6.07 (q, *J* = 6.4 Hz, 1H, 6-H), 2.90 (sept, *J* = 6.8 Hz, 1H, 15-H), 2.78 (sept, *J* = 6.8 Hz, 2H, 11-H), 2.41 (s, 3H, 1-H), 1.39 (d, *J* = 6.4 Hz, 3H, 7-H), 1.26–1.24 (m, 12H, 12-H), 1.19 (d, *J* = 6.0 Hz, 6H, 16-H).

^{13}C NMR ($CDCl_3$, 101 MHz) δ: 169.0 (CO), 150.7 (Ar-C), 145.1 (2C, Ar-C × 2), 142.1 (Ar-C), 136.0 (Ar-C), 129.8 (2C, Ar-C × 2), 128.8 (Ar-C), 125.6 (2C, Ar-C × 2), 120.9 (2C, Ar-C × 2), 85.0 (6-C), 34.4 (15-C), 31.5 (2C, 11-C), 24.5 (2C, CH-*C*H_3 × 2), 23.9 (2C, CH-*C*H_3 × 2), 23.9 (2C, CH-*C*H_3 × 2), 21.4 (1-C), 13.1 (7-C).

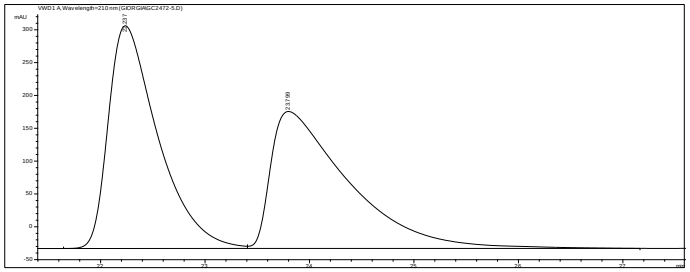
IR (neat) ν_{max}: 2962, 1735, 1228, 1087, 1060, 1041, 874, 811 cm^{-1}.

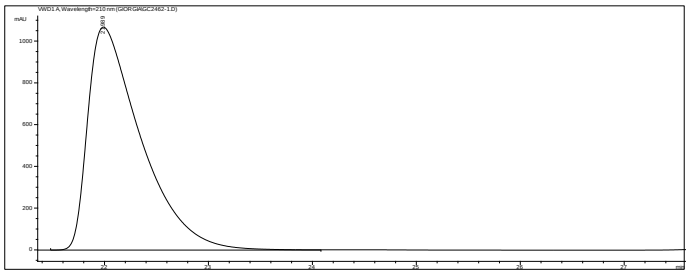
HRMS (ESI) calculated for $C_{25}H_{34}NaOS$: 437.212087, found: 437.210910.

M.P.: 95–97 ºC.

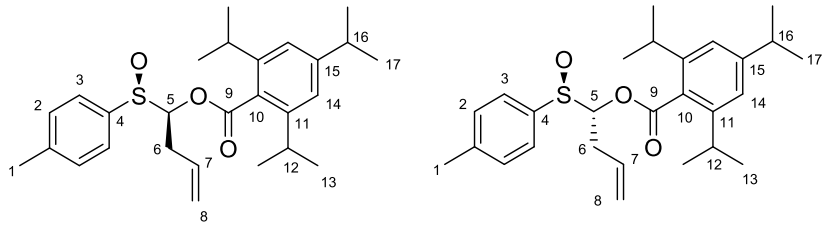
$[\alpha]^{21}_D$: −29 (*c* 1.0, $CHCl_3$).

Chiral HPLC: Daicel Chiralcel-IB column (25 cm), hexane:isopropanol = 98:2, 0.5 mL/min, room temperature, 210.8 nm: t_R = 22.2 minutes (major), 23.8 minutes (minor), e.r. >99:1.





(*R*)-1-((*R*)-*p*-Tolylsulfinyl)but-3-en-1-yl 2,4,6-triisopropylbenzoate (*syn*-255b) and (S)-1-((*R*)-*p*-tolylsulfinyl)but-3-en-1-yl 2,4,6-triisopropylbenzoate (*anti*-255b)



To a solution of bis(trimethylsilyl)amine (0.89 mL, 4.2 mmol) in anhydrous THF (0.70 mL) *n*-BuLi (1.6 M in hexane, 2.6 mL, 4.2 mmol) was added dropwise at −78 °C. After stirring for 20 min at 0 °C, the solution was added dropwise to a solution of sulfoxide (*R*)-**256** (1.5 g, 3.8 mmol) and allyl iodide (0.40 mL, 4.4 mmol) in anhydrous THF (21 mL) at −78 °C. The reaction mixture was stirred for 30 min at −78 °C before being warmed to room temperature and then stirred for additional 30 min at this temperature. The reaction mixture was then diluted with sat. aq. NH_4Cl (20 mL), the phases were separated and the aqueous phase was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$ and the solvent was evaporated under reduced pressure. The crude residue (d.r. = 86:14) was purified by flash column chromatography (pentane:EtOAc = 90:10) to afford the *syn* diastereoisomer *syn*-**255b** (less polar, 205 mg, 12%) as a colourless solid and the *anti* diastereosiomer *anti*-**255b** (more polar, 1.2 g, 74%) as a dense, colourless oil.

[The racemates were synthesised as above, replacing (*R*)-**256** with *rac*-**256**.]

***syn*-255b**

R_f: 0.21 (hexane:EtOAc = 90:10).

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.67 (d, *J* = 8.0 Hz, 2H, Ar-H), 7.38 (d, *J* = 8.0 Hz, 2H, Ar-H), 7.04 (s, 2H, Ar-H), 5.75 (dd, J_1 = 10.0 Hz, J_2 = 3.0 Hz, 1H, 5-H), 5.67 (m, 1H, 7-H), 5.11–5.06 (m, 2H, 8-H), 2.91 (app sept, J_{app} = 6.6 Hz, 3H, 12-H + 16-H), 2.72 (m, 1H, 6-H), 2.44 (s, 3H, 1-H), 2.42 (m, 1H, 6-H), 1.28–1.23 (m, 18H, CH_3 × 6).

^{13}C NMR ($CDCl_3$, 101 MHz) δ: 170.1 (CO), 150.7 (Ar-C), 145.1 (2C, Ar-C × 2), 141.6 (Ar-C), 137.2 (Ar-C), 131.3 (Ar-C), 130.0 (2C, Ar-C × 2), 128.7 (7-C), 124.3 (2C, Ar-C × 2), 120.9 (2C, Ar-C × 2), 119.2 (8-C), 91.3 (5-C), 34.3 (16-C), 31.4 (6-C), 27.7 (2C, 12-C), 24.3 (2C, CH-*C*H_3 × 2), 24.1 (2C, CH-*C*H_3 × 2), 23.8 (2C, CH-*C*H_3 × 2), 21.3 (1-C).

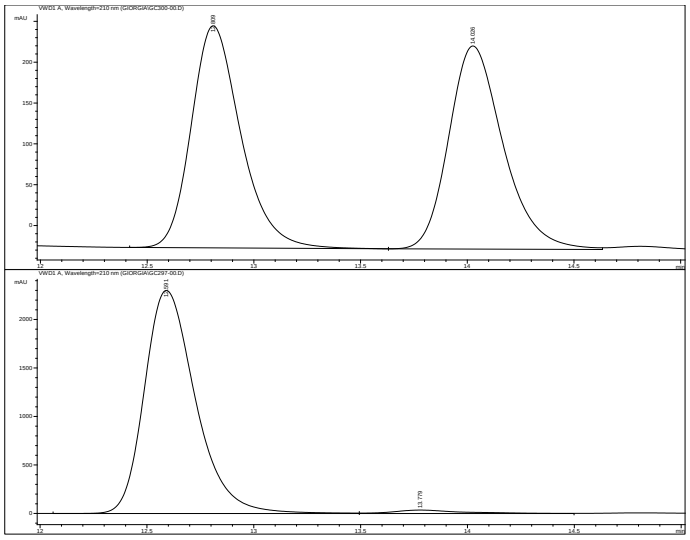
IR (neat) ν_{max}: 2961, 1740, 1230, 1056, 1038, 877, 809 cm^{-1}.

HRMS (ESI) calculated for $C_{27}H_{36}NaO_3S$ $(M+Na)^+$: 463.2277, found: 463.2276.

M.P.: 85−87 ºC.

$[\alpha]^{22}_D$: −86 (*c* 0.5, $CHCl_3$).

Chiral HPLC: (Daicel Chiralcel-IA column (25 cm), hexane:isopropanol = 95:5, 0.5 mL/min, room temperature, 210.8 nm): t_R = 12.8 minutes (major), 14.0 minutes (minor), e.r. = 98:2.



***anti*-255b**

R_f: 0.17 (hexane:EtOAc = 90:10).

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.55 (d, *J* = 8.1 Hz, 2H, Ar-H), 7.32 (d, *J* = 8.1 Hz, 2H, Ar-H), 7.02 (s, 2H, Ar-H), 6.07 (dd, J_1 = 8.9 Hz, J_2 = 3.6 Hz, 1H, 5-H), 5.78 (m, 1H, 7-H), 5.15 (m, 2H, 8-H), 2.90 (sept, *J* = 7.0 Hz, 1H, 16-H), 2.83 (sept, *J* = 6.7 Hz, 2H, 12-H × 2), 2.70 (m, 1H, 6-H), 2.42 (s, 3H, 1-H), 2.08 (m, 1H, 6-H), 1.26–1.18 (m, 18H, CH_3 × 6).

^{13}C NMR ($CDCl_3$, 101 MHz) δ: 169.1 (CO), 150.6 (Ar-C), 145.2 (2C, Ar-C × 2), 142.1 (Ar-C), 136.0 (Ar-C), 131.3 (Ar-C), 129.8 (2C, Ar-C × 2), 128.8 (7-C), 125.4 (2C, Ar-C × 2), 120.9 (2C, Ar-C × 2), 119.5 (8-C), 87.2 (5-C), 34.3 (16-C), 31.8 (6-C), 31.3 (2C, 12-C), 24.4 (2C, CH-*C*H_3 × 2), 24.0 (2C, CH-*C*H_3 × 2), 23.8 (2C, CH-*C*H_3 × 2), 21.4 (1-C).

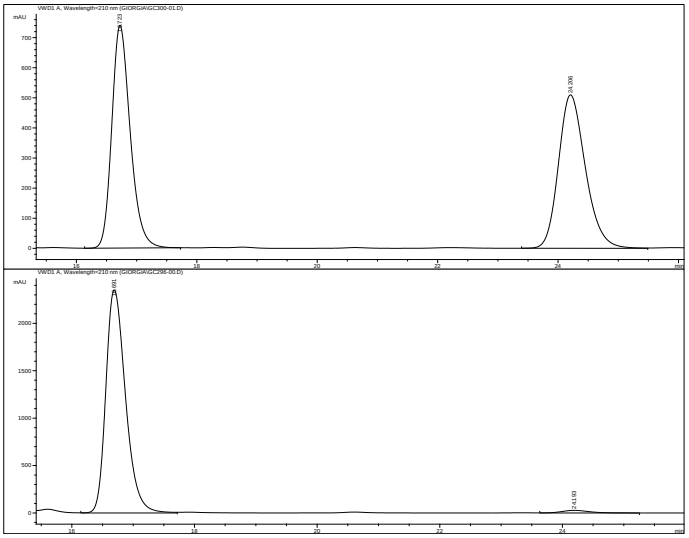
IR (neat) ν_{max}: 2961, 1740, 1230, 1056, 1038, 877, 809 cm^{-1}.

HRMS (ESI) calculated for $C_{27}H_{36}NaO_3S$: 463.2277, found: 463.2276.

M.P.: 85–87 ºC.

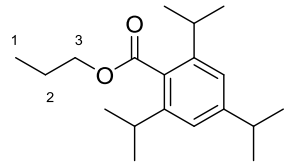
$[\alpha]^{20}_D$: −22 (*c* 1.0, $CHCl_3$).

Chiral HPLC: (Daicel Chiralcel-IA column (25 cm), hexane:isopropanol = 95:5, 0.5 mL/min, room temperature, 210.8 nm): t_R = 16.7 minutes (major), 24.2 minutes (minor), e.r. = 98.5:1.5



5.6.2. Preparation of Triisopropylbenzoates

Propyl 2,4,6-triisopropylbenzoate (108c)



Following a modified literature reported procedure,[99] to a solution of 2,4,6-triisopropylbenzoic acid (5.0 g, 20 mmol) in $CHCl_3$ (50 mL) was added a solution of NaOH (2.4 g, 60 mmol) and *n*-Bu_4NHSO_4 (0.55 g, 1.6 mmol) in deionised H_2O (50 mL). 4-Bromo-1-butene (5.5 mL, 60 mmol) was added to the biphasic mixture under vigorous stirring and the resulting reaction mixture was stirred at room temperature for 16 h. The phases were separated, the organic phase was dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The resulting oil was dissolved in hexane:EtOAc = 90:10 and filtered through a plug of silica. The solution was concentrated under reduced pressure to afford the pure benzoate (6.0 g, 99%) as a colourless oil.

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.01 (s, 2H, Ar-H), 4.27 (t, *J* = 6.7 Hz, 2H, 3-H), 2.93–2.84 (m, 3H, C*H*$(CH_3)_2$ × 3), 1.77 (sest, *J* = 7.1 Hz, 2H, 2-H), 1.25 (d, *J* = 6.8 Hz, 18H, CH_3 × 6), 1.01 (t, *J* = 7.4 Hz, 3H, 1-H).

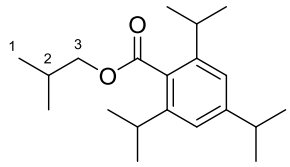
^{13}C NMR ($CDCl_3$, 101 MHz) δ: 171.0 (CO), 150.0 (Ar-C), 144.7 (2C, Ar-C × 2), 130.7 (Ar-C), 120.8 (2C, Ar-C × 2), 66.6 (3-C), 34.4 (*C*H-$(CH_3)_2$), 31.5 (2C, *C*H-$(CH_3)_2$ × 2), 24.1 (4C, CH_3 × 4), 24.0 (2C, CH_3 × 2), 21.98 (2-C), 10.55 (1-C).

IR (neat) ν_{max}: 2961, 1724, 1461, 1249, 1136, 1074, 876 cm^{-1}.

HRMS (ESI) calculated for $C_{19}H_{30}NaO_2$ $(M+Na)^+$: 313.2138, found: 313.2136.

All analytical data matched that previously reported in the literature.[99]

Isobutyl 2,4,6-triisopropylbenzoate (108d)



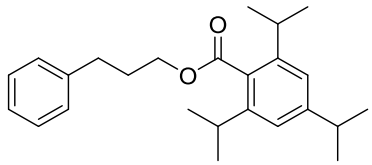
Following a literature reported procedure,[216] to a solution of *i*-butyl alcohol (1.6 mL, 17 mmol) and Et_3N (1.4 mL, 10 mmol) in anhydrous PhMe (10 mL) in a sealable microwave vial equipped with a magnetic stirring bar was added 2,4,6-triisopropylbenzoyl chloride (2.0 g, 7.7 mmol). The vial was sealed and the resulting reaction mixture was heated using microwave irradiation at 150 °C for 2 h. The reaction mixture was cooled to room temperature and filtered through a plug of silica washing with Et_2O. The solvent was removed under reduced pressure and the crude reaction mixture was purified by chromatography on silica gel (petroleum ether:Et_2O = 95:5) to afford benzoate **108d** as a colourless oil (1.8 g, 75%).

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.01 (s, 2H, Ar-H), 4.08 (d, *J* = 6.6 Hz, 2H, 3-H), 2.86 (m, 3H, C*H*$(CH_3)_2$ × 3), 2.03 (hept, *J* = 6.7 Hz, 1H, 2-H), 1.24 (d, *J* = 6.8 Hz, 18H, CH_3 × 6), 0.99 (d, *J* = 6.7 Hz, 6H, 1-H × 2).

^{13}C NMR ($CDCl_3$, 101 MHz) δ: 171.1 (CO), 150.0 (Ar-C), 144.7 (2C, Ar-C × 2), 130.8 (Ar-C), 120.81 (2C, Ar-C × 2), 71.3 (3-C), 34.4 (*C*H-$(CH_3)_2$), 31.5 (2C, *C*H-$(CH_3)_2$ × 2), 27.7 (2-C), 24.2 (4C, CH_3 × 4), 24.0 (2C, CH_3 × 2), 19.3 (2C, 1-C × 2) ppm

All analytical data matched that previously reported in the literature.[216]

3-Phenylpropyl 2,4,6-triisopropylbenzoate (108f)



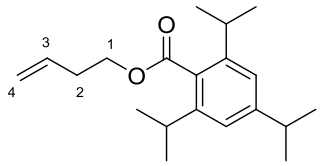
Following a literature reported procedure,[216] to a solution of 3-phenylpropan-1-ol (1.85 mL, 13.3 mmol) and Et_3N (2.23 mL, 16.0 mmol) in anhydrous PhMe (12 mL) in a sealable microwave vial equipped with a magnetic stirring bar was added 2,4,6-triisopropylbenzoyl chloride (3.2 g, 12 mmol). The vial was sealed and the resulting reaction mixture was heated using microwave irradiation at 150 °C for 1 h. The reaction mixture was cooled to room temperature and filtered through a plug of silica washing with Et_2O. The solvent was removed under reduced pressure and the crude reaction mixture was purified by chromatography on silica gel (hexane:Et_2O = 98:2) to afford benzoate **108f** as a colourless oil (1.85 g, 42%).

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.30 (app t, J_{app} = 7.6 Hz, 2H, Ar-H), 7.20 (app t, J = 8.6 Hz, 3H, Ar-H), 7.02 (s, 2H, Ar-H), 4.33 (t, J = 6.5 Hz, 2H, O-CH_2), 2.88 (hept, J = 6.9 Hz, 3H, C*H*(CH_3)$_2$ × 3), 2.75 (t, J = 7.5 Hz, 2H, Ph-CH_2), 2.06 (q, J = 8.5 Hz, 2H, CH_2), 1.27 (d, J = 6.8 Hz, 12H, CH_3 × 4), 1.25 (d, J = 6.8 Hz, 6H, CH_3 × 2).

^{13}C NMR ($CDCl_3$, 101 MHz) δ: 171.0 (CO), 150.1 (Ar-C), 144.7 (2C, Ar-C × 2), 141.1 (Ar-C), 130.6 (Ar-C), 128.5 (2C, Ar-C × 2), 128.4 (2C, Ar-C × 2), 126.1 (Ar-C), 120.9 (2C, Ar-C × 2), 64.3 (O-CH_2), 34.4 (Ph-CH_2), 32.3 (*C*H-(CH_3)$_2$), 31.5 (2C, *C*H-(CH_3)$_2$ × 2), 30.4 (CH_2), 24.2 (4C, CH_3 × 4), 23.9 (2C, CH_3 × 2).

All analytical data matched that previously reported in the literature.[216]

But-3-en-1-yl 2,4,6-triisopropylbenzoate (108b)



To a solution of 2,4,6-triisopropylbenzoic acid (5.00 g, 20.1 mmol) in $CHCl_3$ (50 mL) was added a solution of NaOH (2.42 g, 60.4 mmol) and *n*-Bu_4NHSO_4 (0.55 g, 1.6 mmol) in deionised H_2O (50 mL). 4-Bromo-1-butene (6.13 mL, 60.4 mmol) was added to the biphasic mixture under vigorous stirring and the resulting reaction mixture was stirred at room temperature for 16 h. The phases were separated, the organic phase was dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The resulting oil was dissolved in pentane:EtOAc = 90:10 and filtered through a plug of silica. The solution was concentrated under reduced pressure to afford the pure benzoate **108b** (4.93 g, 81%) as a colourless oil.

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.03 (s, 2H, Ar-H), 5.86 (m, 1H, 3-H), 5.17 (dq, J_1 = 17.2 Hz, J_2 = 1.6 Hz, 1H, 4-H$_{trans}$), 5.11 (dq, J_1 = 10.3 Hz, J_2 = 1.2 Hz, 1H, 4-H$_{cis}$), 4.40 (t, J = 6.8 Hz, 2H, 1-H), 2.89 (sept, J = 6.8 Hz, 3H, C*H*$(CH_3)_2$ × 3), 2.52 (qt, J_1 = 6.7 Hz, J_2 = 1.4 Hz, 2H, 2-H), 1.26 (d, J = 6.9 Hz, 18H, CH_3 × 6).

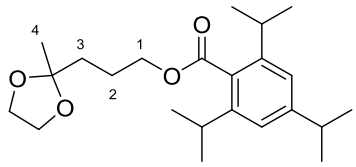
^{13}C NMR ($CDCl_3$, 101 MHz) δ: 170.8 (CO), 150.1 (Ar-C), 144.7 (2C, Ar-C × 2), 134.0 (3-C), 130.5 (Ar-C), 120.8 (2C, Ar-C × 2), 117.3 (4-C), 64.0 (1-C), 34.4 (*C*H-$(CH_3)_2$), 33.1 (2-C), 31.4 (2C, *C*H-$(CH_3)_2$ × 2), 24.1 (2C, CH_3 × 2), 23.9 (4C, CH_3 × 4).

IR (neat) ν_{max}: 2961, 2930, 2871, 1725, 1607, 1461, 1248, 1134, 1102, 1074, 917, 876 cm^{-1}.

HRMS (ESI) calculated for $C_{20}H_{31}O_2$ $(M+H)^+$: 303.2319, found: 303.2319.

All analytical data matched that previously reported in the literature.[217]

3-(2-Methyl-1,3-dioxolan-2-yl)propyl 2,4,6-triisopropylbenzoate (108g)



Following a modified literature reported procedure,[218] to a solution of 2,4,6-triisopropylbenzoic acid (2.00 g, 8.05 mmol) and Cs_2CO_3 (3.94 g, 12.1 mmol) in CH_3CN (90 mL) was added 5-chloro-2-pentanone ethylene ketal (1.47 g, 8.90 mmol) and the resulting reaction mixture was stirred at 82 °C for 24 h. After cooling to room temperature, the precipitate was filtered off and the filtrate was concentrated under reduced pressure. The residue was dissolved in $CHCl_3$ (50 mL) and washed with aq. $NaHCO_3$ (20% *w*/*v*, 3 × 30 mL). The organic phases were combined, dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. Purification by flash silica gel column chromatography (hexane:Et_2O = 70:30) afforded the pure benzoate **108g** (2.82 g, 93%) as a colourless oil.

R_f: 0.33 (hexane:EtOAc = 80:20).

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.01 (s, 2H, Ar-H), 4.33 (t, *J* = 6.2 Hz, 2H, 1-H), 3.94 (m, 4H, O-CH_2 × 2), 2.87 (sept, *J* = 6.7 Hz, 3H, C*H*(CH_3)$_2$ × 3), 1.89–1.81 (m, 2H, 2-H), 1.79–1.75 (m, 2H, 3-H), 1.33 (s, 3H, 4-H), 1.25 (d, *J* = 6.8 Hz, 18H, CH_3 × 6).

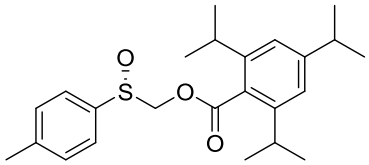
^{13}C NMR ($CDCl_3$, 101 MHz) δ: 171.0 (CO), 150.0 (Ar-C), 144.7 (2C, Ar-C × 2), 130.6 (Ar-C), 120.8 (2C, Ar-C × 2), 109.6 (O-C-O), 65.0 (1-C), 64.7 (2C, O-CH_2 × 2), 35.7 (3-C), 34.4 (*C*H-(CH_3)$_2$), 31.5 (2C, *C*H-(CH_3)$_2$ × 2), 24.1 (4C, CH_3 × 4), 23.9 (2C, CH_3 × 2), 23.9 (2-C), 23.4 (4-C).

IR (neat) ν_{max}: 2961, 1722, 1462, 1250, 1137, 1068, 877, 754 cm^{-1}.

HRMS (ESI) calculated for $C_{23}H_{36}NaO_4$ $(M+Na)^+$: 399.2506, found: 399.2503.

5.6.3. Preparation of α-Sulfinyl Benzoates by transmetalation

(*S*)-(*p*-Tolylsulfinyl)methyl 2,4,6-triisopropylbenzoate ((*S*)-256)

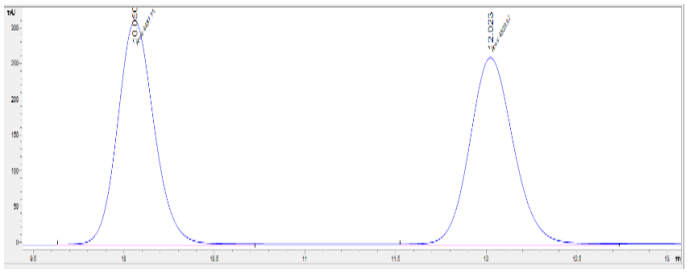


Following GP4, methyl 2,4,6-triisopropylbenzoate (5.00 g, 19.1 mmol), TMEDA (3.71 mL, 24.8 mmol), *s*-BuLi (1.30 M in cyclohexane/hexane, 19.1 mL, 24.8 mmol – lithiation time = 30 min), Mg turnings (1.37 g, 57.2 mmol), dibromoethane (2.46 mL, 28.6 mmol) and (1*R*,2*S*,5*R*)-(−)-menthyl (*S*)-*p*-toluenesulfinate (8.15 g, 28.6 mmol) afforded after purification by flash column chromatography (hexane:EtOAc = 100:0 → 80:20) sulfoxide (*S*)-**256** (5.09 g, 67%) as a colourless solid.

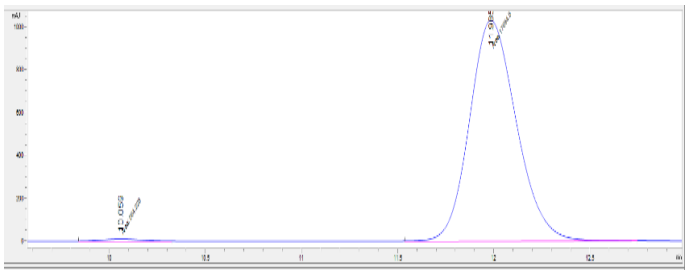
[α]$^{24}_{D}$: +134 (*c* 1.0, $CHCl_3$).

Spectral data matched that previously described in this report.

Chiral HPLC: (Daicel Chiralcel-IA column (25 cm) with guard, hexane:isopropanol = 95:5, 1.0 mL/min, room temperature, 210.8 nm): t_R = 10.1 minutes (minor), 12.0 minutes (major), e.r. = 99:1

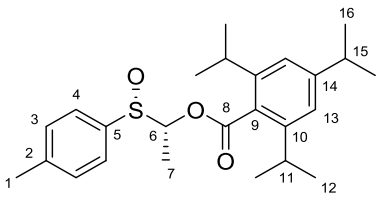
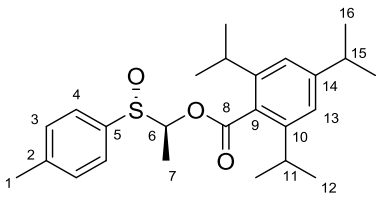


#	Time	Type	Area	Height	Width	Area%	Symmetry
1	10.06	MM	4487.7	316.6	0.2363	49.768	0.863
2	12.023	MM	4529.7	264.4	0.2855	50.232	0.873



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	10.059	MM	264.2	14.5	0.3035	1.471	0.841
2	11.985	MM	17694.5	1032.1	0.2857	98.529	0.819

(*S*)-1-((*S*)-*p*-Tolylsulfinyl)ethyl 2,4,6-triisopropylbenzoate (*ent-syn*-255a) and (*R*)-1-((*S*)-*p*-tolylsulfinyl)ethyl 2,4,6-triisopropylbenzoate (*ent-anti*-255a)

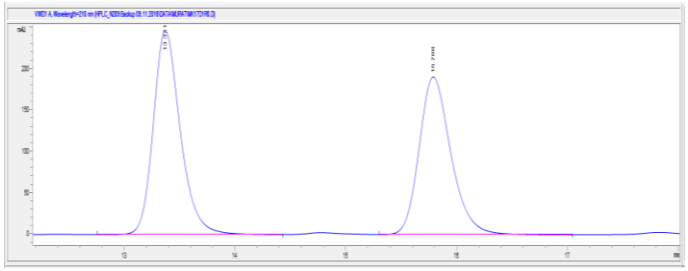
Following GP4, ethyl benzoate **108a** (2.45 g, 8.86 mmol), TMEDA (1.59 mL, 10.64 mmol), *s*-BuLi (1.3 M in cyclohexane/hexane, 8.18 mL, 10.6 mmol – lithiation time = 1 h), Mg turnings (869 mg, 36.2 mmol), dibromoethane (1.17 mL, 13.3 mmol), (1*R*,2*S*,5*R*)-(−)-menthyl (*S*)-*p*-toluenesulfinate (3.91 g, 13.3 mmol), Et_3N (1.85 mL, 13.3 mmol) and TMSCl (1.46 mL, 11.6 mmol) afforded after purification by flash column chromatography (hexane:EtOAc = 95:5) the *syn* diastereoisomer *ent-syn*-**255a** (less polar, 1.49 g, 41%) as a colourless solid and the *anti* diastereoisomer *ent-anti*-**255a** (more polar, 1.48 g, 40%) as a colourless solid.

Spectral data matched that previously described in this report.

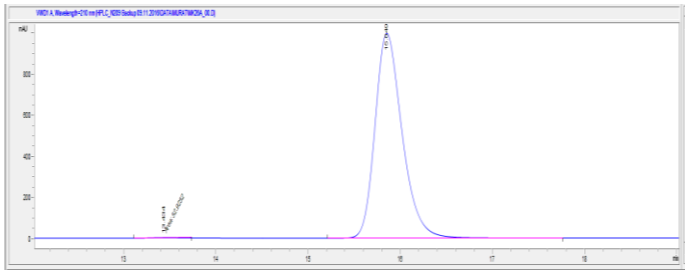
***syn*-255a**

$[\alpha]^{24}_D$: +86 (*c* 1.0, $CHCl_3$).

Chiral HPLC: Daicel Chiralcel-IA column (25 cm), hexane:isopropanol = 96:4, 0.5 mL/min, room temperature, 210.8 nm: t_R = 13.4 minutes (minor), 15.8 minutes (major), e.r. >99:1.



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	13.371	BB	4170.1	246.7	0.2569	52.406	0.754
2	15.788	VB	3787.2	190.2	0.3037	47.594	0.76

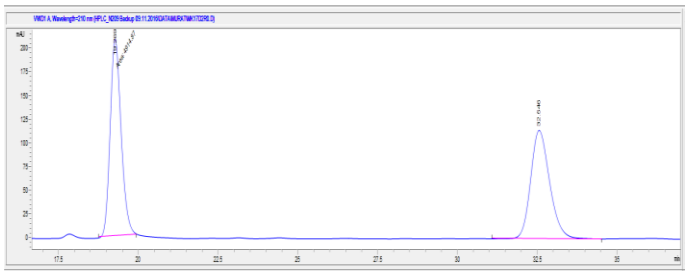


#	Time	Type	Area	Height	Width	Area%	Symmetry
1	13.434	MM	52.9	2.5	0.3529	0.260	1.502
2	15.849	BB	20277.3	994.3	0.3122	99.740	0.719

***anti*-255a**

$[\alpha]^{21}_{D}$: +30 (*c* 1.0, $CHCl_3$).

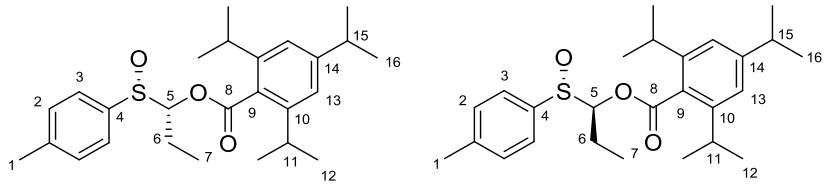
Chiral HPLC: Daicel Chiralcel-IA column (25 cm), hexane:isopropanol = 96:4, 0.5 mL/min, room temperature, 210.8 nm: t_R = 19.3 minutes (minor), 32.5 minutes (major), e.r. = 99:1.



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	19.269	MM	4914.9	206.8	0.3961	51.009	0.802
2	32.546	BB	4720.5	114.1	0.6356	48.991	0.775

#	Time	Type	Area	Height	Width	Area%	Symmetry
1	19.569	BB	184.3	7.6	0.3712	0.931	0.882
2	33.45	BB	19596.8	447.3	0.6655	99.069	0.647

(*S*)-1-((*S*)-*p*-Tolylsulfinyl)propyl 2,4,6-triisopropylbenzoate (*syn*-255c) and (*R*)-1-((*S*)-*p*-tolylsulfinyl)propyl 2,4,6-triisopropylbenzoate (*anti*-255c)



Following GP4, propyl 2,4,6-triisopropylbenzoate (2.9 g, 10 mmol), TMEDA (1.8 mL, 12 mmol), *s*-BuLi (1.30 M in cyclohexane/hexane, 9.2 mL, 12.0 mmol − lithiation time = 1 h), Mg turnings (972 mg, 40.0 mmol), dibromoethane (1.3 mL, 15 mmol) and (1*R*,2*S*,5*R*)-(−)-menthyl (*S*)-*p*-toluenesulfinate (4.40 g, 15.0 mmol), afforded after purification by flash column chromatography (hexane:EtOAc = 95:5 → 90:10) the *syn* diastereoisomer *syn*-**255c** (less polar, 1.10 g, 26%) as a colourless solid and the *anti* diastereoisomer *anti*-**255c** (more polar, 1.37 g, 32%) as a colourless oil that turned into a waxy colourless solid upon standing at room temperature.

[The racemates were synthesised as above, replacing (1*R*,2*S*,5*R*)-(−)-menthyl (*S*)-*p*-toluenesulfinate with racemic sulfinate **466**.]

***syn*-255c**

R_f: 0.19 (hexane:EtOAc = 95:5).

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.66 (d, *J* = 8.0 Hz, 2H, Ar-H), 7.36 (d, *J* = 8.0 Hz, 2H, Ar-H), 7.04 (s, 2H, Ar-H), 5.62 (dd, J_1 = 9.8 Hz, J_2 = 3.2 Hz, 1H, 5-H), 2.92 (app sest, *J* = 6.7 Hz, 3H, 11-H × 2 + 15-H), 2.44 (s, 3H, 1-H), 2.01 (sept, *J* = 7.6 Hz, 1H, 6-H), 1.71 (m, 1H, 6-H), 1.29 (d, *J* = 6.8 Hz, 6H, CH_3 × 2), 1.26 (d, *J* = 6.9 Hz, 6H, CH_3 × 2), 1.25 (d, *J* = 6.6 Hz, 6H, CH_3 × 2), 0.95 (t, *J* = 7.4 Hz, 3H, 7-H).

^{13}C NMR ($CDCl_3$, 101 MHz) δ: 170.5 (CO), 150.8 (Ar-C), 145.2 (2C, Ar-C × 2), 141.5 (Ar-C), 137.6 (Ar-C), 130.0 (2C, Ar-C × 2), 128.9 (Ar-C), 124.4 (2C, Ar-C × 2), 121.0 (2C, Ar-C × 2), 93.8 (5-C), 34.4 (15-C), 31.6 (2C, 11-C × 2), 24.4 (2C, CH-*C*H_3 × 2), 24.2 (2C, CH-*C*H_3 × 2), 23.9 (2C, CH-*C*H_3 × 2), 21.5 (1-C), 16.7 (6-C), 9.4 (7-C).

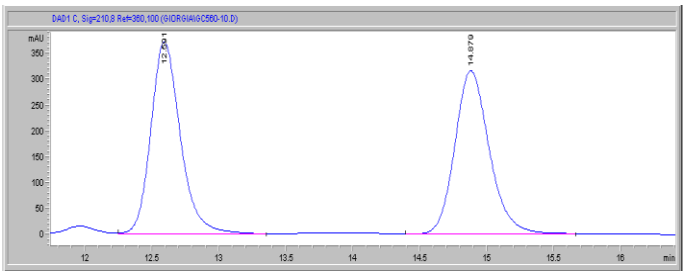
IR (neat) ν_{max}: 3675, 2988, 2972, 2901, 1394, 1057, 892 cm^{-1}.

HRMS (ESI) calculated for $C_{26}H_{36}NaO_3S$ $(M+Na)^+$: 451.2277, found: 451.2278.

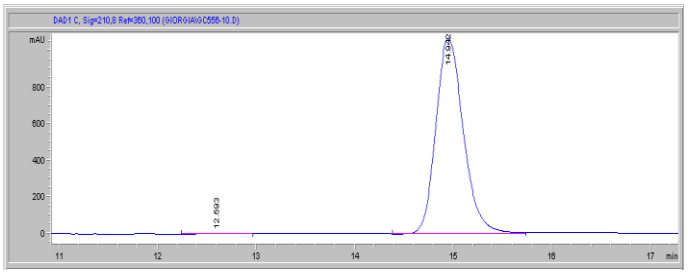
M.P.: 87−89 °C.

[α]$^{22}_{D}$: +92 (*c* 1.0, $CHCl_3$).

Chiral HPLC: Daicel Chiralcel-IA column (25 cm), hexane:isopropanol = 95:5, 0.5 mL/min, room temperature, 210.8 nm: t_R = 12.6 minutes (minor), 14.9 minutes (major), e.r. >99:1.



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.591	VB	0.2358	5728.54346	371.64734	50.3389
2	14.879	VB	0.2729	5651.41113	315.64185	49.6611



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.593	VV	0.2472	82.40370	4.08701	0.3928
2	14.942	VV	0.3018	2.08966e4	1070.01074	99.6072

***anti*-255c**

R$_f$: 0.16 (hexane:EtOAc = 95:5).

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.55 (d, *J* = 8.1 Hz, 2H, Ar-H), 7.31 (d, *J* = 8.0 Hz, 2H, Ar-H), 7.02 (s, 2H, Ar-H), 5.93 (dd, J_1 = 8.5 Hz, J_2 = 4.1 Hz, 1H, 5-H), 2.90 (sept, *J* = 6.9 Hz, 1H, 15-H), 2.84 (sept, *J* = 6.8 Hz, 2H, 11-H × 2), 2.41 (s, 3H, 1-H), 1.94 (m, 1H, 6-H), 1.45 (sept, *J* = 8.0 Hz, 1H, 6-H), 1.25 (d, *J* = 6.9 Hz, 6H, CH_3 × 2), 1.25 (d, *J* = 6.8 Hz, 6H, CH_3 × 2), 1.20 (d, *J* = 6.8 Hz, 6H, CH_3 × 2), 1.06 (t, *J* = 7.4 Hz, 3H, 7-H).

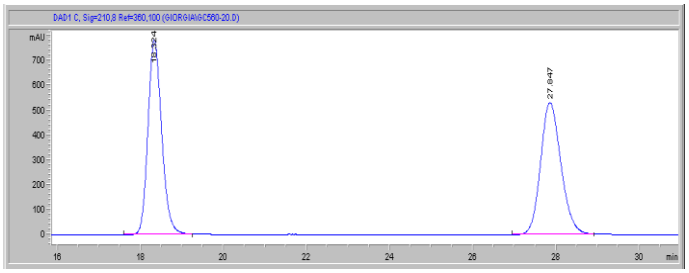
^{13}C NMR ($CDCl_3$, 101 MHz) δ: 169.4 (CO), 150.6 (Ar-C), 145.1 (2C, Ar-C × 2), 142.0 (Ar C), 136.4 (Ar-C), 129.8 (2C, Ar-C × 2), 129.0 (Ar-C), 125.5 (2C, Ar-C × 2), 121.0 (2C, Ar-C × 2), 89.9 (5-C), 34.4 (15-C), 31.6 (2C, 11-C × 2), 24.6 (2C, CH-*C*H_3 × 2), 24.1 (2C, CH-*C*H_3 × 2), 23.9 (2C, CH-*C*H_3 × 2), 21.5 (1-C), 21.0 (6-C), 9.8 (7-C).

IR (neat) ν_{max}: 3675, 2968, 1742, 1231, 1065, 752 cm^{-1}.

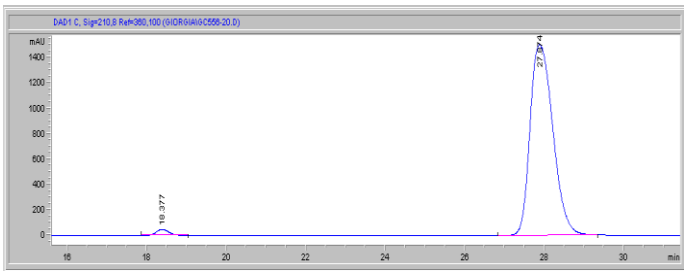
HRMS (ESI) calculated for $C_{26}H_{36}NaO_3S$ $(M+Na)^+$: 451.2277, found: 451.2278.

[α]$^{22}_{D}$: +20 (*c* 1.0, $CHCl_3$).

Chiral HPLC: Daicel Chiralcel-IA column (25 cm), hexane:isopropanol = 95:5, 0.5 mL/min, room temperature, 210.8 nm: t_R = 18.3 minutes (minor), 27.8 minutes (major), e.r. = 98:2.

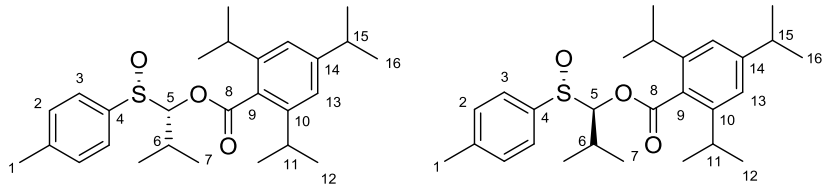


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.324	BB	0.3436	2262.10059	100.87549	50.2338
2	27.847	BB	0.5185	2241.04517	66.61805	49.7662



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.377	VV	0.3384	1096.58911	48.74957	1.8001
2	27.874	VB	0.4838	5.98218e4	1504.76941	98.1999

(*S*)-2-Methyl-1-((*S*)-*p*-tolylsulfinyl)propyl 2,4,6-triisopropylbenzoate (*syn*-255d) and (*R*)-2-methyl-1-((*S*)-*p*-tolylsulfinyl)propyl 2,4,6-triisopropylbenzoate (*anti*-255d)



Following GP4, isobutyl 2,4,6-triisopropylbenzoate (0.51 g, 1.7 mmol), TMEDA (300 µL, 2.01 mmol), *s*-BuLi (1.30 M in cyclohexane/hexane, 1.50 mL, 2.01 mmol – lithiation time = 1.5 h), Mg turnings (163 mg, 6.72 mmol), dibromoethane (220 µL, 2.52 mmol), (1*R*,2*S*,5*R*)-(−)-menthyl (*S*)-*p*-toluenesulfinate (0.74 g, 2.5 mmol), Et_3N (350 µL, 2.52 mmol) and TMSCl (280 µL, 2.18 mmol) afforded after purification by flash column chromatography (hexane:EtOAc = 90:10) a 1.8:1 mixture of the *syn* diastereoisomer *syn*-**255d** and the *anti* diastereoisomer *anti*-**255d** (488 mg, 66% overall yield, 36:64 d.r.). A portion of the mixture (450 mg) was further purified by reverse phase HPLC (CH_3CN:H_2O = 85:15, isocratic) to afford the *syn* diastereoisomer *syn*-**255d** (less polar, 112 mg, 15%) as a colourless solid and the *anti* diastereoisomer *anti*-**255d** (more polar, 215 mg, 29%) as a thick colourless oil.

[The racemates were synthesised as above, replacing (1*R*,2*S*,5*R*)-(−)-menthyl (*S*)-*p*-toluenesulfinate with racemic sulfinate **466**.]

***syn*-255d**

R_f: 0.29 (hexane:EtOAc = 90:10).

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.73 (d, *J* = 7.8 Hz, 2H, Ar-H), 7.35 (d, *J* = 7.8 Hz, 2H, Ar-H), 7.04 (s, 2H, Ar-H), 5.72 (d, *J* = 4.9 Hz, 1H, 5-H), 2.94–2.81 (m, 3H, 11-H × 2 + 15-H), 2.54 (app sest, J_{app} = 6.8 Hz, 1H, 6-H), 2.43 (s, 3H, 1-H), 1.26 (d, *J* = 6.9 Hz, 12H, CH_3 × 4), 1.22 (d, *J* = 6.8 Hz, 6H, CH_3 × 2), 1.14 (d, *J* = 6.8 Hz, 3H, 7-H), 0.96 (d, *J* = 6.9 Hz, 3H, 7-H).

^{13}C NMR ($CDCl_3$, 101 MHz) δ: 170.1 (CO), 150.7 (Ar-C), 145.2 (2C, Ar-C × 2), 141.7 (Ar-C), 138.2 (Ar-C), 129.9 (2C, Ar-C × 2), 128.7 (Ar-C), 125.3 (2C, Ar-C × 2), 121.0 (2C, Ar-C × 2), 95.8 (5-C), 34.4 (15-C), 31.4 (2C, 11-C × 2), 26.5 (6-C), 24.4 (2C, CH-*C*H_3 × 2), 24.3 (2C, CH-*C*H_3 × 2), 23.9 (2C, CH-*C*H_3 × 2), 21.4 (1-C), 20.1 (7-C), 17.5 (7-C).

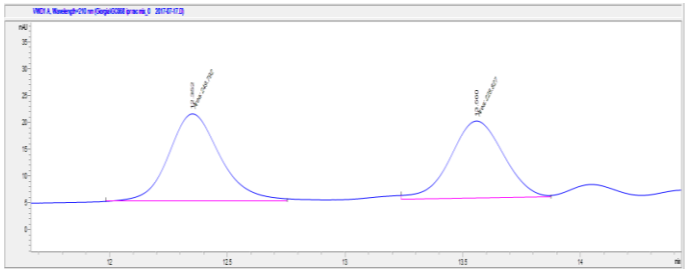
IR (neat) ν_{max}: 2961, 1729, 1236, 1060, 1042, 812 cm^{-1}.

HRMS (ESI) calculated for $C_{27}H_{38}NaO_3S$ $(M+Na)^+$: 465.2434, found: 465.2439.

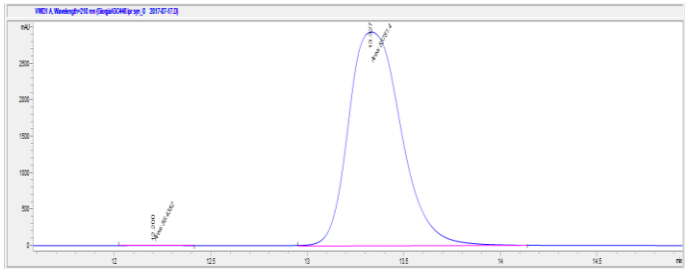
M.P.: 87–89 ºC.

[α]$^{22}_{D}$: +41 (*c* 0.9, $CHCl_3$).

Chiral HPLC: Daicel Chiralcel-IA column (25 cm), hexane:isopropanol = 95:5, 0.5 mL/min, room temperature, 210.8 nm: t_R = 12.3 minutes (minor), 13.6 minutes (major), e.r. >99:1.



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	12.352	MM	249.8	16.3	0.2551	52.190	0.831
2	13.56	MM	228.8	14.5	0.2635	47.810	0.968



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	12.2	MM	56.4	3.3	0.2818	0.101	0.486
2	13.327	MM	55781.4	2950.3	0.3151	99.899	0.724

***anti*-155d**

R*f*: 0.29 (hexane:EtOAc = 90:10).

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.66 (d, *J* = 8.0 Hz, 2H, Ar-H), 7.35 (d, *J* = 8.0 Hz, 2H, Ar-H), 7.04 (s, 2H, Ar-H), 5.89 (d, *J* = 3.5 Hz, 1H, 5-H), 3.03 (sept, *J* = 6.7 Hz, 2H, 11-H × 2), 2.90 (sept, *J* = 6.9 Hz, 1H, 15-H), 2.43 (s, 3H, 1-H), 1.95 (m, 1H, 6-H), 1.26 (d, *J* = 6.9 Hz, 12H, CH_3 × 4), 1.23 (d, *J* = 6.8 Hz, 6H, CH_3 × 2), 1.06 (app t, *J* = 6.4 Hz, 6H, 7-H × 2).

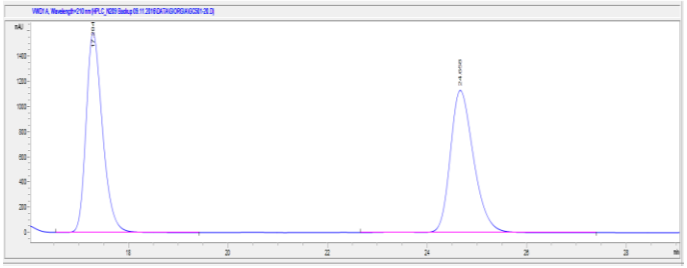
^{13}C NMR ($CDCl_3$, 101 MHz) δ: 169.6 (CO), 150.5 (Ar-C), 145.5 (2C, Ar-C × 2), 142.3 (Ar-C), 138.3 (Ar-C), 130.1 (2C, Ar-C × 2), 129.2 (Ar-C), 125.7 (2C, Ar-C × 2), 121.0 (2C, Ar-C × 2), 94.5 (5-C), 34.4 (15-C), 31.3 (2C, 11-C × 2), 28.6 (6-C), 24.5 (4C, CH-*C*H_3 × 4), 23.9 (2C, CH-*C*H_3 × 2), 21.5 (1-C), 19.5 (7-C), 17.3 (7-C).

IR (neat) ν_{max}: 2962, 1740, 1461, 1230, 1063, 1048, 877, 810 cm^{-1}.

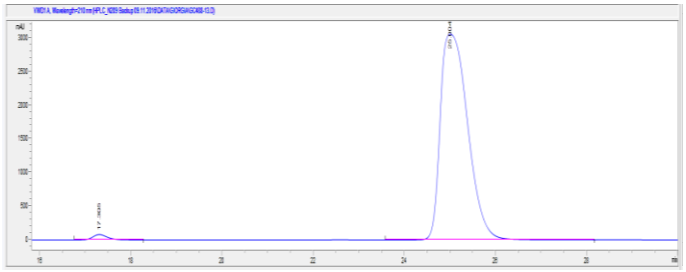
HRMS (ESI) calculated for $C_{27}H_{38}NaO_3S$ $(M+Na)^+$: 465.2434, found: 465.2439.

[α]$^{22}_{D}$: +173 (*c* 1.0, $CHCl_3$).

Chiral HPLC: Daicel Chiralcel-IA column (25 cm), hexane:isopropanol = 95:5, 0.5 mL/min, room temperature, 210.8 nm: t_R = 17.3 minutes (minor), 24.7 minutes (major), e.r. = 98:2.

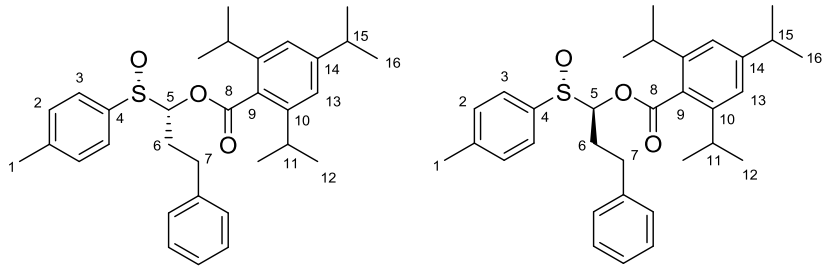


#	Time	Type	Area	Height	Width	Area%	Symmetry
1	17.284	VB	36487	1588.4	0.351	49.768	0.707
2	24.658	VB R	36827.8	1131.6	0.4988	50.232	0.731



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	17.305	BB	1819.8	81.7	0.3414	1.396	0.763
2	25.004	BB	128499.8	3085.6	0.6577	98.604	0.532

(*S*)-3-Phenyl-1-((*S*)-*p*-tolylsulfinyl)propyl 2,4,6-triisopropylbenzoate (*syn*-255f) and (*R*)-3-phenyl-1-((*S*)-*p*-tolylsulfinyl)propyl 2,4,6-triisopropylbenzoate (*anti*-255f)



Following GP4, 3-phenylpropyl 2,4,6-triisopropylbenzoate (1.0 g, 2.7 mmol), TMEDA (485 µL, 3.24 mmol), *s*-BuLi (1.30 M in cyclohexane/hexane, 2.50 mL, 3.24 mmol − lithiation time = 2 h), Mg turnings (263 mg, 10.8 mmol), dibromoethane (350 µL, 4.05 mmol), (1*R*,2*S*,5*R*)-(−)-menthyl (*S*)-*p*-toluenesulfinate (1.19 g, 4.05 mmol), Et_3N (560 µL, 4.05 mmol) and TMSCl (450 µL, 3.51 mmol) afforded after purification by flash column chromatography (hexane:EtOAc = 95:5) the *syn* diastereoisomer *syn*-**255f** (less polar, 500 mg, 37%) as a colourless solid and the *anti* diastereoisomer *anti*-**255f** (more polar, 581 mg, 43%) as a colourless solid.

[The racemates were synthesised as above, replacing (1*R*,2*S*,5*R*)-(−)-menthyl (*S*)-*p*-toluenesulfinate with racemic sulfinate **466**.]

***syn*-255f**

R_f: 0.29 (hexane:EtOAc = 95:5).

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.60 (d, *J* = 8.2 Hz, 2H, Ar-H), 7.34 (d, *J* = 8.0 Hz, 2H, Ar-H), 7.21–7.15 (m, 3H, Ar-H), 7.07 (s, 2H, Ar-H), 6.94 (d, *J* = 6.3 Hz, 2H, Ar-H), 5.64 (dd, J_1 = 9.7 Hz, J_2 = 2.9 Hz, 1H, 5-H), 2.96 (m, 3H, 11-H × 2 + 15-H), 2.78 (m, 1H, 7-H), 2.51 (m, 1H, 7-H), 2.45 (s, 3H, 1-H), 2.29 (m, 1H, 6-H), 1.99 (m, 1H, 6-H), 1.33–1.27 (m, 18H, CH_3 × 6).

^{13}C NMR ($CDCl_3$, 101 MHz) δ: 170.4 (CO), 150.9 (Ar-C), 145.2 (2C, Ar-C × 2), 141.5 (Ar-C), 139.9 (Ar-C), 137.4 (Ar-C), 130.0 (2C, Ar-C × 2), 128.8 (Ar-C), 128.4 (2C, Ar-C × 2), 128.1 (2C, Ar-C × 2), 126.2 (Ar-C), 124.2 (2C, Ar-C × 2), 121.0 (2C, Ar-C × 2), 92.0 (5-C), 34.5 (15-C), 31.7 (2C, 11-C), 30.8 (7-C), 24.6 (6-C), 24.4 (2C, CH-*C*H_3 × 2), 24.3 (2C, CH-*C*H_3 × 2), 23.9 (2C, CH-*C*H_3 × 2), 21.4 (1-C).

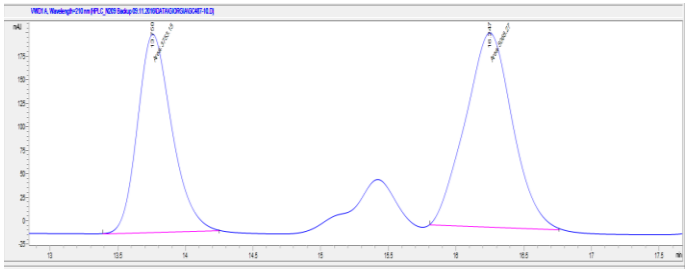
IR (neat) ν_{max}: 2960, 1731, 1239, 1060, 1048, 1027, 813, 756 cm^{-1}.

HRMS (ESI) calculated for $C_{32}H_{40}NaO_3S$ $(M+Na)^+$: 527.2590, found: 527.2574.

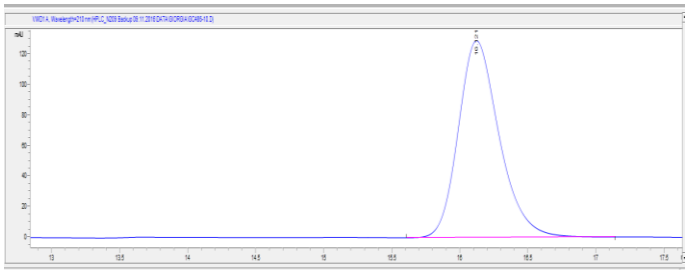
M.P.: 99–101 ºC.

[α]$^{22}_D$: +123 (*c* 0.9, $CHCl_3$).

Chiral HPLC: Daicel Chiralcel-IA column (25 cm), hexane:isopropanol = 95:5, 0.5 mL/min, room temperature, 210.8 nm: t_R = 13.8 minutes (minor), 16.2 minutes (major), e.r. >99:1.



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	13.758	MM	3753.1	211.7	0.2955	42.546	0.778
2	16.247	MM	5068.3	207.9	0.4064	57.454	1.045



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	16.121	BB	2697.5	129.3	0.3176	100.000	0.76

***anti*-255f**

R$_f$: 0.21 (hexane:EtOAc = 95:5).

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.53 (d, *J* = 8.1 Hz, 2H, Ar-H), 7.31–7.26 (m, 4H, Ar-H), 7.21 (t, *J* = 7.2 Hz, 1H, Ar-H), 7.09 (d, *J* = 7.2 Hz, 2H, Ar-H), 7.07 (s, 2H, Ar-H), 6.08 (dd, J_1 = 8.8 Hz, J_2 = 3.4 Hz, 1H, 5-H), 2.96 (app sept, *J* = 6.8 Hz, 3H, 11-H × 2 + 15-H), 2.78 (m, 2H, 7-H), 2.41 (s, 3H, 1-H), 2.21 (m, 1H, 6-H), 1.71 (m, 1H, 6-H), 1.30–1.25 (m, 18H, CH_3 × 6).

^{13}C NMR ($CDCl_3$, 101 MHz) δ: 169.2 (CO), 150.8 (Ar-C), 145.2 (2C, Ar-C × 2), 142.1 (Ar-C), 139.9 (Ar-C), 136.1 (Ar-C), 129.9 (2C, Ar-C × 2), 128.9 (Ar-C), 128.6 (2C, Ar-C × 2), 128.2 (2C, Ar-C × 2), 126.4 (Ar-C), 125.5 (2C, Ar-C × 2), 121.0 (2C, Ar-C × 2), 87.8 (5-C), 34.4 (15-C), 31.7 (2C, 11-C × 2), 31.6 (7-C), 29.2 (6-C), 24.7 (2C, CH-*C*H_3 × 2), 24.1 (2C, CH-*C*H_3 × 2), 23.9 (2C, CH-*C*H_3 × 2), 21.5 (1-C).

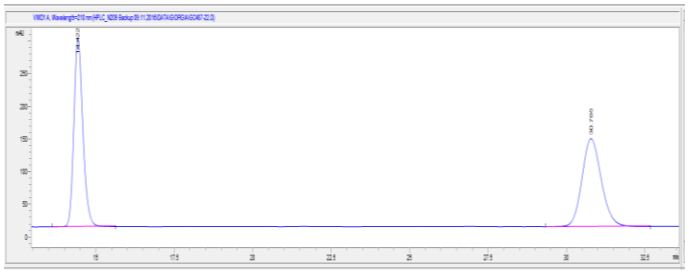
IR (neat) ν_{max}: 2962, 1734, 1460, 1229, 1067, 1042, 880, 815 cm^{-1}.

HRMS (ESI) calculated for $C_{32}H_{40}NaO_3S$ $(M+Na)^+$: 527.2590, found: 527.2574.

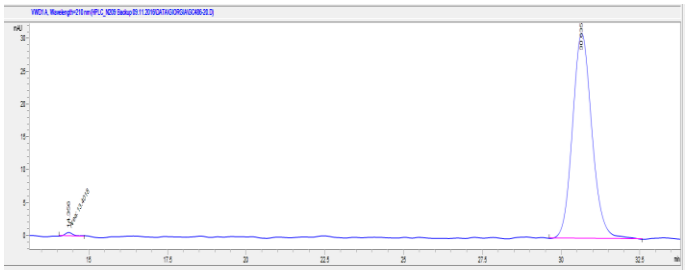
M.P.: 91–93 ºC.

[α]$^{22}_{D}$: +11 (*c* 1.0, $CHCl_3$).

Chiral HPLC: Daicel Chiralcel-IA column (25 cm), hexane:isopropanol = 95:5, 0.7 mL/min, room temperature, 210.8 nm: t_R = 14.4 minutes (minor), 30.8 minutes (major), e.r. >99:1.

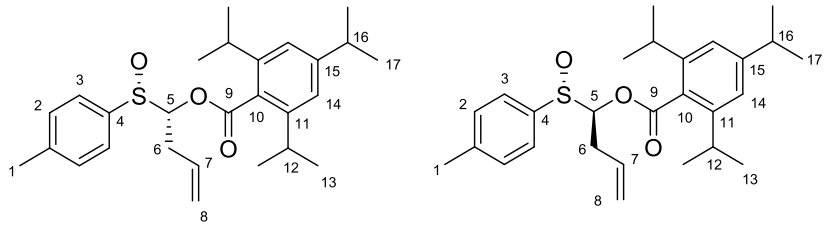


#	Time	Type	Area	Height	Width	Area%	Symmetry
1	14.422	BB	5742.7	288.1	0.3039	49.932	0.781
2	30.785	BB	5758.4	134.2	0.6621	50.068	0.844



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	14.356	MM	13.4	6E-1	0.3722	0.990	0.585
2	30.635	BB	1340.4	31.2	0.6603	99.010	0.857

(*S*)-1-((*S*)-*p*-Tolylsulfinyl)but-3-en-1-yl 2,4,6-triisopropylbenzoate (*ent-syn*-255b) and (*R*)-1-((*S*)-*p*-tolylsulfinyl)but-3-en-1-yl 2,4,6-triisopropylbenzoate (*ent-anti*-255b)



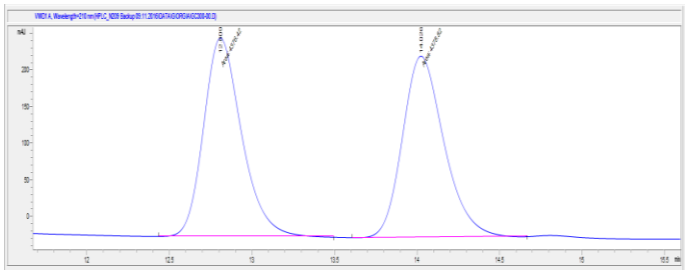
Following GP4, homoallylic benzoate **108b** (700 mg, 2.31 mmol), TMEDA (417 µL, 2.78 mmol), *s*-BuLi (1.35 M in cyclohexane/hexane, 2.00 mL, 2.78 mmol – lithiation time = 1 h), Mg turnings (225 mg, 9.24 mmol), dibromoethane (300 µL, 3.47 mmol), (1*R*,2*S*,5*R*)-(−)-menthyl (*S*)-*p*-toluenesulfinate (1.36 g, 4.62 mmol), Et_3N (485 µL, 3.47 mmol) and TMSCl (380 µL, 3.00 mmol) afforded after purification by flash column chromatography (hexane:EtOAc = 95:5) the *syn* diastereoisomer *ent-syn*-**255b** (less polar, 285 mg, 28%) as a colourless solid and the *anti* diastereoisomer *ent-anti*-**255b** (more polar, 395 mg, 39%) as a dense colourless oil.

Spectral data matched that previously described in this report.

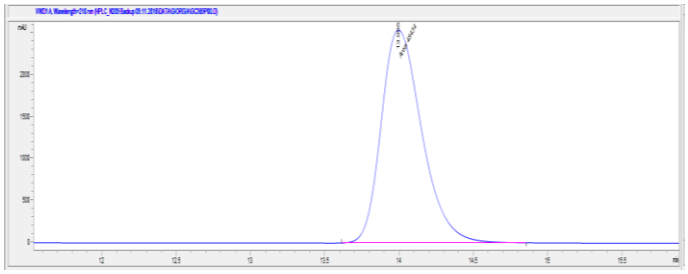
***ent-syn*-255b**

[α]$^{22}_{D}$: +163 (*c* 0.3, $CHCl_3$).

Chiral HPLC: Daicel Chiralcel-IA column (25 cm), hexane:isopropanol = 95:5, 0.5 mL/min, room temperature, 210.8 nm: t_R = 12.8 minutes (minor), 14.0 minutes (major), e.r. >99:1.



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	12.809	MM	4376.4	271.8	0.2684	49.986	0.774
2	14.026	MM	4378.8	248.4	0.2938	50.014	0.785

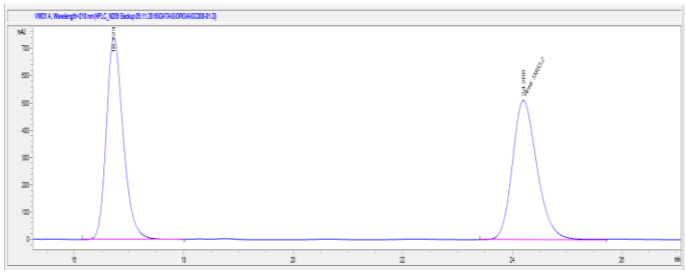


#	Time	Type	Area	Height	Width	Area%	Symmetry
1	13.995	MM	48434	2553.6	0.3161	100.000	0.715

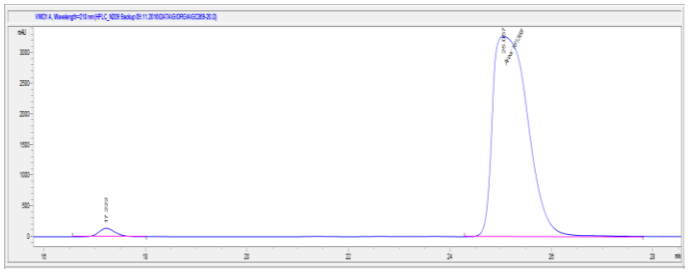
***ent-anti*-255b**

[α]$^{25}_{D}$: +8 (*c* 1.0, $CHCl_3$).

Chiral HPLC: Daicel Chiralcel-IA column (25 cm), hexane:isopropanol = 95:5, 0.5 mL/min, room temperature, 210.8 nm: t_R = 16.7 minutes (minor), 24.2 minutes (major), e.r. = 98:2.

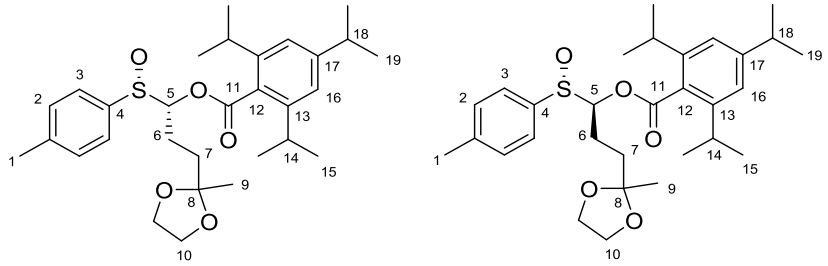


#	Time	Type	Area	Height	Width	Area%	Symmetry
1	16.723	BB	15799.6	740.3	0.3262	49.915	0.753
2	24.206	MM	15853.2	509	0.5191	50.085	0.775



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	17.222	BB	3126.2	138.3	0.3452	1.901	0.798
2	25.057	MM	161368.1	3304.9	0.8138	98.099	0.46

(*S*)-3-(2-Methyl-1,3-dioxolan-2-yl)-1-((*S*)-*p*-tolylsulfinyl)propyl 2,4,6-triisopropylbenzoate (*syn*-255g) and (*R*)-3-(2-methyl-1,3-dioxolan-2-yl)-1-((*S*)-*p*-tolylsulfinyl)propyl 2,4,6-triisopropylbenzoate (*anti*-255g)



Following GP4, ketal benzoate **108g** (1.45 g, 3.85 mmol), TMEDA (870 µL, 5.78 mmol), *s*-BuLi (1.30 M in cyclohexane/hexane, 4.40 mL, 5.78 mmol – lithiation time = 2 h), Mg turnings (374 mg, 15.5 mmol), dibromoethane (500 µL, 5.78 mmol) and (1*R*,2*S*,5*R*)-(−)-menthyl (*S*)-*p*-toluenesulfinate (1.70 g, 5.78 mmol), afforded after purification by flash column chromatography (hexane:EtOAc = 75:25 → 70:30) the *syn* diastereoisomer *syn*-**255g** (less polar, 367 mg, 19%) as a colourless solid and the *anti* diastereoisomer *anti*-**255g** (more polar, 659 mg, 33%) as a colourless oil that turned into a waxy colourless solid upon standing at room temperature.

[The racemates were synthesised as above, replacing (1*R*,2*S*,5*R*)-(−)-menthyl (*S*)-*p*-toluenesulfinate with racemic sulfinate **466**.]

***syn*-255g**

R*f*: 0.24 (hexane:EtOAc = 75:25).

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.66 (d, *J* = 8.0 Hz, 2H, Ar-H), 7.36 (d, *J* = 7.9 Hz, 2H, Ar-H), 7.04 (s, 2H, Ar-H), 5.78 (dd, J_1 = 10.2 Hz, J_2 = 2.1 Hz, 1H, 5-H), 3.83 (m, 2H, 10-H), 3.72–3.60 (m, 2H, 10-H), 2.99–2.88 (m, 3H, 14-H × 2 and 18-H), 2.43 (s, 3H, 1-H), 2.05 (m, 1H, 6-H), 1.83–1.73 (m, 2H, 7-H), 1.64 (m, 1H, 6-H), 1.29 (d, *J* = 6.8 Hz, 6H, CH_3 × 2), 1.26 (d, *J* = 6.9 Hz, 12H, CH_3 × 4), 1.16 (s, 3H, 9-H).

^{13}C NMR ($CDCl_3$, 101 MHz) δ: 170.4 (CO), 150.8 (Ar-C), 145.2 (2C, Ar-C × 2), 141.4 (Ar-C), 137.6 (Ar-C), 129.9 (2C, Ar-C × 2), 128.9 (Ar-C), 124.3 (2C, Ar-C × 2), 121.0 (2C, Ar-C × 2), 109.3 (8-C), 92.5 (5-C), 64.7 (10-C), 64.4 (10-C), 34.4 (18-C), 33.6 (7-C), 31.5 (2C, 14-C × 2), 24.4 (2C, CH-*C*H_3 × 2), 24.2 (2C, CH-*C*H_3 × 2), 23.9 (9-C), 23.9 (CH-*C*H_3), 23.9 (CH-*C*H_3), 21.4 (1-C), 17.6 (6-C).

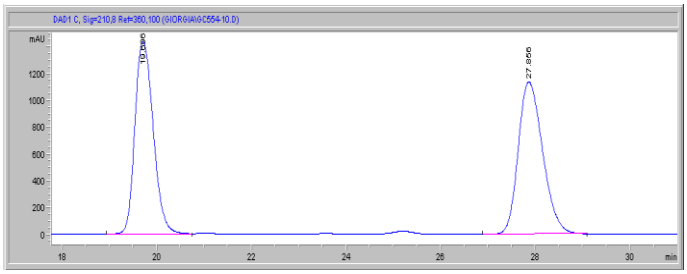
IR (neat) ν_{max}: 3675, 2988, 2901, 1394, 1250, 1066, 1057, 892 cm^{-1}.

HRMS (ESI) calculated for $C_{30}H_{42}NaO_5S$ $(M+Na)^+$: 537.2645, found: 537.2641.

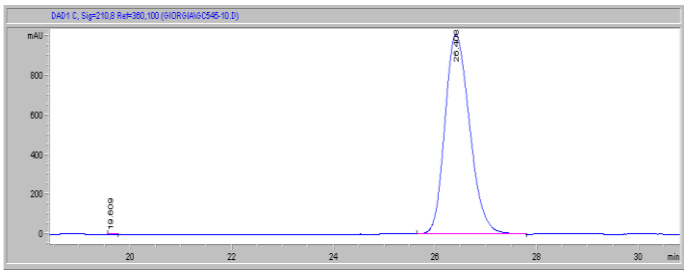
M.P.: 71–73 ºC.

$[\alpha]^{22}_D$: +64 (*c* 0.7, $CHCl_3$).

Chiral HPLC: Daicel Chiralcel-IA column (25 cm), hexane:isopropanol = 95:5, 0.5 mL/min, room temperature, 210.8 nm: t_R = 19.7 minutes (minor), 27.8 minutes (major), e.r. >99:1.



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.696	VB	0.4219	3.92311e4	1439.80762	48.9997
2	27.856	BB	0.5563	4.08329e4	1133.42981	51.0003



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.860	VV	0.3266	115.64310	4.28786	0.3392
2	26.408	BB	0.5242	3.39788e4	1005.62115	99.6608

***anti*-255g**

R_f: 0.18 (hexane:EtOAc = 75:25).

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.56 (d, *J* = 7.8 Hz, 2H, Ar-H), 7.31 (d, *J* = 7.9 Hz, 2H, Ar-H), 7.01 (s, 2H, Ar-H), 6.09 (dd, J_1 = 8.2 Hz, J_2 = 4.2 Hz, 1H, 5-H), 3.92 (m, 2H, 10-H), 3.84 (m, 2H, 10-H), 2.90 (sept, *J* = 6.9 Hz, 1H, 18-H), 2.82 (sept, *J* = 6.8 Hz, 2H, 14-H × 2), 2.41 (s, 3H, 1-H), 2.04 (m, 1H, 6-H), 1.84 (m, 2H, 7-H), 1.58 (m, 1H, 6-H), 1.26–1.20 (m, 21H, CH_3 × 6 + 9-H).

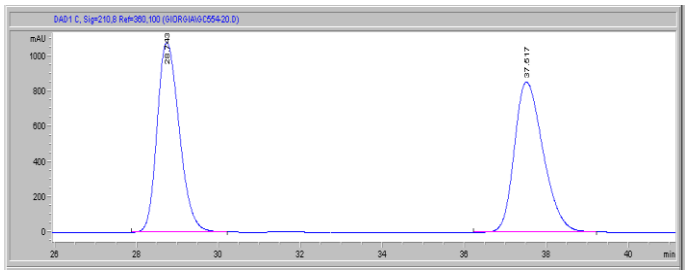
^{13}C NMR ($CDCl_3$, 101 MHz) δ: 169.20 (CO), 150.6 (Ar-C), 145.1 (2C, Ar-C × 2), 142.0 (Ar-C), 136.4 (Ar-C), 129.8 (2C, Ar-C × 2), 128.9 (Ar-C), 125.5 (2C, Ar-C × 2), 120.9 (2C, Ar-C × 2), 109.2 (8-C), 88.4 (5-C), 64.7 (10-C), 64.7 (10-C), 34.4 (14-C), 34.3 (7-C), 31.5 (2C, 18-C × 2), 24.6 (2C, CH-*C*H_3 × 2), 24.1 (2C, CH-*C*H_3 × 2), 23.9 (CH_3), 23.9 (CH_3), 23.9 (CH_3), 22.5 (6-C), 21.4 (1-C).

IR (neat) ν_{max}: 3675, 2962, 1736, 1230, 1040, 812 cm^{-1}.

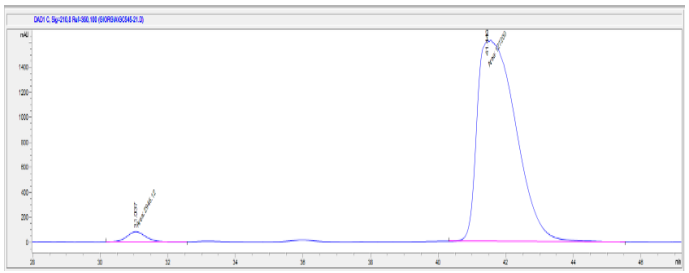
HRMS (ESI) calculated for $C_{30}H_{42}NaO_5S$ $(M+Na)^+$: 537.2645, found: 537.2641.

[α]$^{22}_{D}$: +47 (*c* 1.0, $CHCl_3$).

Chiral HPLC: Daicel Chiralcel-IA column (25 cm), hexane:isopropanol = 95:5, 0.5 mL/min, room temperature, 210.8 nm: t_R = 28.7 minutes (minor), 37.5 minutes (major), e.r. = 98:2.



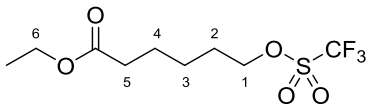
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	28.743	PB	0.5717	4.04683e4	1078.54944	49.3256
2	37.517	VB	0.7090	4.15750e4	852.47467	50.6744



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	31.037	MM	2946.1	78.9	0.6226	2.264	0.842
2	41.446	MM	127199.8	1604.6	1.3212	97.736	0.364

5.6.4. Preparation of Triflates

Ethyl 6-(((trifluoromethyl)sulfonyl)oxy)hexanoate (467)



To a solution of trifluoromethanesulfonic anhydride (1.2 mL, 7.4 mmol) in CH_2Cl_2 (10 mL) at −10 °C was added a solution of ethyl 6-hydroxyhexanoate (1.0 mL, 6.2 mmol) in CH_2Cl_2 (2.0 mL). The reaction mixture was stirred at −10 °C for 20 min, then was warmed to room temperature and stirred for further 40 min. H_2O (10 mL) was added, the phases were separated and the aqueous phase was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic phases were dried over $MgSO_4$ and the solvent was removed under reduced pressure. Filtration of the crude reaction mixture through a plug of SiO_2 eluting with CH_2Cl_2 gave triflate **467** (1.24 g, 70%) as a colourless oil.

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 4.53 (t, *J* = 6.4 Hz, 2H, 1-H), 4.12 (q, *J* = 7.1 Hz, 2H, 6-H), 2.32 (t, *J* = 10.0 Hz, 2H, 5-H), 1.84 (m, 2H, 2-H), 1.67 (m, 2H, 4-H), 1.48 (m, 2H, 3-H), 1.25 (t, *J* = 7.1 Hz, 3H, CH_3).

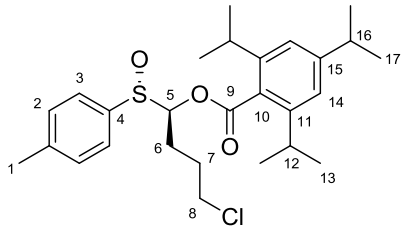
^{13}C NMR ($CDCl_3$, 101 MHz) δ: 173.5 (CO), 118.6 (q, $^1J_{C–F}$ = 320 Hz, CF_3), 77.2 (1-C), 60.5 (6-C), 33.9 (5-C), 28.9 (2-C), 24.6 (4-C), 24.1 (3-C), 14.1 (CH_3).

^{19}F NMR ($CDCl_3$, 376 MHz) δ: −74.8.

All analytical data matched that previously reported in the literature.[219]

5.6.5. Preparation of α-Sulfinyl Benzoates by alkylation

(*R*)-4-Chloro-((*S*)-*p*-tolylsulfinyl)butyl 2,4,6-triisopropylbenzoate (*anti*-255n)



Following GP5, ((*S*)-*p*-tolylsulfinyl)methyl 2,4,6-triisopropylbenzoate (*S*)-**256** (1.0 g, 2.5 mmol), 1-chloro-3-iodopropane (1.0 g, 5.0 mmol), *i*-Pr_2NH (700 µL, 5.00 mmol), *n*-BuLi (1.6 M in hexane, 3.1 mL, 5.0 mmol) and HMPA (870 µL, 5.00 mmol) afforded after purification by flash column chromatography (hexane:EtOAc = 90:10) the *syn* diastereoisomer *syn*-**255n** (less polar, mixed with impurity) and the *anti* diastereoisomer *anti*-**255n** (more polar, 482 mg, 40%) as a colourless solid.

[The racemate was synthesised as above, replacing (*S*)-**256** with racemic benzoate *rac*-**256**.]

R_f: 0.21 (hexane:EtOAc = 80:20).

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.56 (d, *J* = 8.0 Hz, 2H, Ar-H), 7.32 (d, *J* = 8.0 Hz, 2H, Ar-H), 7.03 (s, 2H, Ar-H), 6.02 (dd, J_1 = 8.4 Hz, J_2 = 3.4 Hz, 1H, 5-H), 3.49 (m, 2H, 8-H), 2.91 (sept, *J* = 6.9 Hz, 1H, 16-H), 2.84 (sept, *J* = 6.8 Hz, 2H, 12-H × 2), 2.42 (s, 3H, 1-H), 2.06–1.90 (m, 3H, 7-H × 2 + 6-H), 1.60 (m, 1H, 6-H), 1.26 (d, *J* = 6.8 Hz, 12H, CH_3 × 4), 1.21 (d, *J* = 6.8 Hz, 6H, CH_3 × 2).

^{13}C NMR ($CDCl_3$, 101 MHz) δ: 169.2 (CO), 150.8 (Ar-C), 145.2 (2C, Ar-C × 2), 142.3 (Ar-C), 136.1 (Ar-C), 130.0 (2C, Ar-C × 2), 128.7 (Ar-C), 125.5 (2C, Ar-C × 2), 121.0 (2C, Ar-C × 2), 87.6 (5-C), 43.8 (8-C), 34.4 (16-C), 31.6 (2C, 12-C × 2), 28.3 (7-C), 25.2 (6-C), 24.5 (2C, CH-*C*H_3 × 2), 24.1 (2C, CH-*C*H_3 × 2), 23.9 (2C, CH-*C*H_3 × 2), 21.5 (1-C).

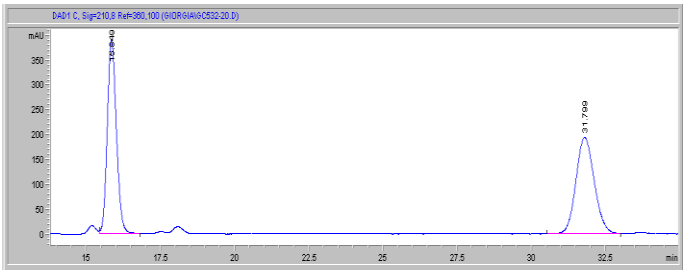
IR (neat) ν_{max}: 3675, 2965, 1741, 1229, 1073, 1040 cm^{-1}.

HRMS (ESI) calculated for $C_{27}H_{37}ClNaO_3S$ $(M+Na)^+$: 499.2044, found: 499.2044.

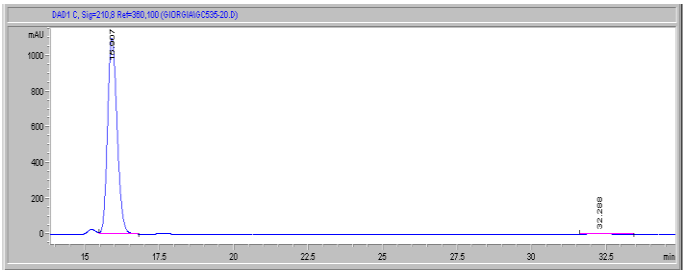
M.P.: 95–97 °C.

[α]$^{22}_D$: −15 (*c* 1.0, $CHCl_3$).

Chiral HPLC: Daicel Chiralcel-IA column (25 cm), hexane:isopropanol = 95:5, 0.7 mL/min, room temperature, 210.8 nm: t_R = 15.8 minutes (major), 31.8 minutes (minor), e.r. = 99:1.

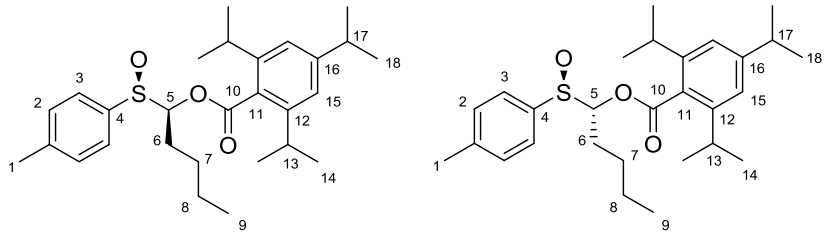


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.849	VB	0.3323	8411.31055	392.06799	50.1070
2	31.799	VV	0.6194	8375.37891	194.12285	49.8930



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.907	VB	0.3548	2.45615e4	1098.77454	98.7785
2	32.288	VV	0.5321	303.72989	6.89234	1.2215

(*R*)-1-((*R*)-*p*-Tolylsulfinyl)pentyl 2,4,6-triisopropylbenzoate (*syn*-255p) and (*S*)-1-((*R*)-*p*-tolylsulfinyl)pentyl 2,4,6-triisopropylbenzoate (*anti*-255p)



Following GP5, ((*S*)-*p*-tolylsulfinyl)methyl 2,4,6-triisopropylbenzoate (*R*)-**256** (601 mg, 1.50 mmol), butyl trifluoromethanesulfonate (260 μL, 1.65 mmol), NaHMDS (1.0 M in THF, 1.60 mL, 1.58 mmol) afforded after purification by flash column chromatography (hexane:EtOAc = 95:5) the *syn* diastereoisomer *syn*-**255p** (less polar, 290 mg, 42%) as a colourless solid and the *anti* diastereoisomer *anti*-**255p** (more polar, 246 mg, 36%) as a colourless solid.

[The racemates were synthesised as above, replacing (*S*)-**256** with racemic benzoate *rac*-**256**.]

***syn*-255p**

R_f: 0.24 (hexane:EtOAc = 95:5).

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.65 (d, *J* = 8.1 Hz, 2H, Ar-H), 7.37 (d, *J* = 8.0 Hz, 2H, Ar-H), 7.05 (s, 2H, Ar-H), 5.67 (dd, J_1 = 10.2 Hz, J_2 = 2.8 Hz, 1H, 5-H), 2.93 (app sept, *J* = 7.0 Hz, 3H, 13-H × 2 + 17-H), 2.44 (s, 3H, 1-H), 2.00 (m, 1H, 6-H), 1.61 (m, 1H, 6-H), 1.41 (m, 1H, 7-H), 1.34–1.16 (m, 3H, 7-H + 8-H × 2), 1.29 (d, *J* = 6.8 Hz, 6H, CH_3 × 2), 1.26 (d, *J* = 6.7 Hz, 12H, CH_3 × 4), 0.80 (t, *J* = 7.4 Hz, 3H, 9-H).

^{13}C NMR ($CDCl_3$, 101 MHz) δ: 170.5 (CO), 150.8 (Ar-C), 145.2 (2C, Ar-C × 2), 141.5 (Ar-C), 137.5 (Ar-C), 130.0 (2C, Ar-C × 2), 128.9 (Ar-C), 124.4 (2C, Ar-C × 2), 120.9 (2C, Ar-C × 2), 92.5 (5-C), 34.4 (17-C), 31.6 (2C, 13-C × 2), 26.9 (7-C), 24.4 (2C, CH-*C*H_3 × 2), 24.2 (2C, CH-*C*H_3 × 2), 23.9 (CH-*C*H_3), 23.9 (CH-*C*H_3), 22.6 (6-C), 22.2 (8-C), 21.4 (1-C), 13.7 (9-C).

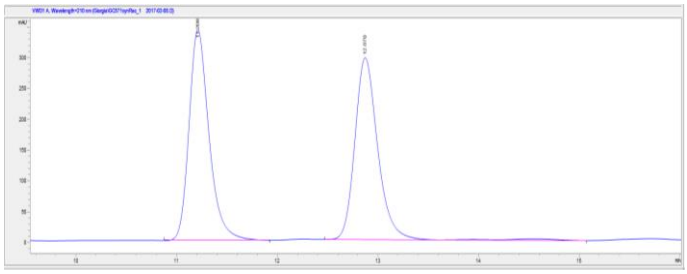
IR (neat) ν_{max}: 2960, 1735, 1461, 1232, 1046, 753 cm^{-1}.

HRMS (ESI) calculated for $C_{28}H_{40}NaO_3S$ $(M+Na)^+$: 479.2590, found: 479.2580.

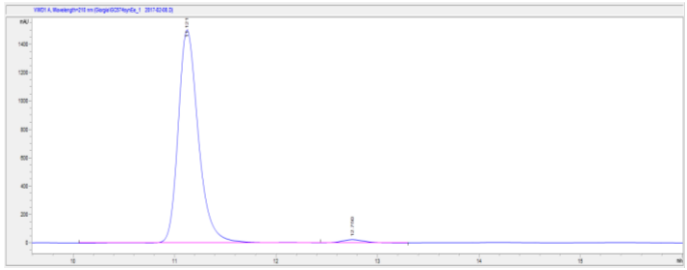
M.P.: 104−106 ºC.

$[\alpha]^{22}_D$: −126 (*c* 1.3, $CHCl_3$).

Chiral HPLC: Daicel Chiralcel-IA column (25 cm), hexane:isopropanol = 95:5, 0.5 mL/min, room temperature, 210.8 nm: t_R = 11.2 minutes (major), 12.9 minutes (minor), e.r. = 98:2.



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	11.208	BB	4710	341.9	0.2084	49.954	0.746
2	12.87	BV R	4718.6	295	0.2397	50.046	0.769



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	11.121	VV R	20929.9	1507.5	0.2112	98.281	0.74
2	12.75	VB E	366.1	22.8	0.2386	1.719	0.88

***anti*-255p**

R*f*: 0.18 (hexane:EtOAc = 95:5).

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.55 (d, *J* = 8.2 Hz, 2H, Ar-H), 7.31 (d, *J* = 8.0 Hz, 2H, Ar-H), 7.03 (s, 2H, Ar-H), 6.00 (m, 1H, 5-H), 2.94–2.82 (m, 3H, 13-H × 2 + 17-H), 2.42 (s, 3H, 1-H), 1.85 (m, 1H, 6-H), 1.47–1.39 (m, 3H, 6-H + 7-H × 2), 1.35–1.29 (m, 2H, 8-H), 1.25 (d, *J* = 6.9 Hz, 12H, CH_3 × 4), 1.21 (d, *J* = 6.8 Hz, 6H, CH_3 × 2), 0.85 (t, *J* = 7.4 Hz, 3H, 9-H).

^{13}C NMR ($CDCl_3$, 101 MHz) δ: 169.3 (CO), 150.6 (Ar-C), 145.1 (2C, Ar-C × 2), 142.0 (Ar-C), 136.5 (Ar-C), 129.8 (2C, Ar-C × 2), 129.0 (Ar-C), 125.5 (2C, Ar-C × 2), 121.0 (2C, Ar-C × 2), 88.5 (5-C), 34.4 (17-C), 31.5 (2C, 13-C × 2), 27.3 (7-C), 27.1 (6-C), 24.6 (2C, CH-*C*H_3 × 2), 24.1 (2C, CH-*C*H_3 × 2), 23.9 (CH-*C*H_3), 23.9 (CH-*C*H_3), 22.2 (8-C), 21.5 (1-C), 13.7 (9-C).

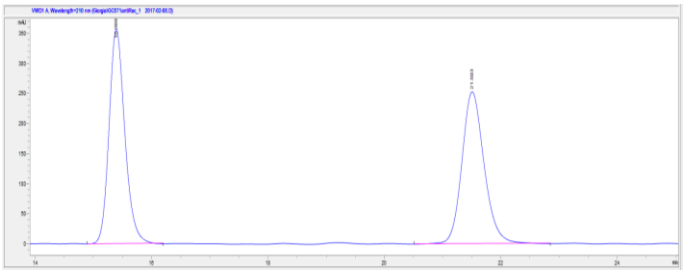
IR (neat) ν_{max}: 3675, 2968, 2901, 1736, 1394, 1230, 1066, 1044, 879 cm^{-1}.

HRMS (ESI) calculated for $C_{28}H_{40}NaO_3S$ $(M+Na)^+$: 479.2590, found: 479.2580.

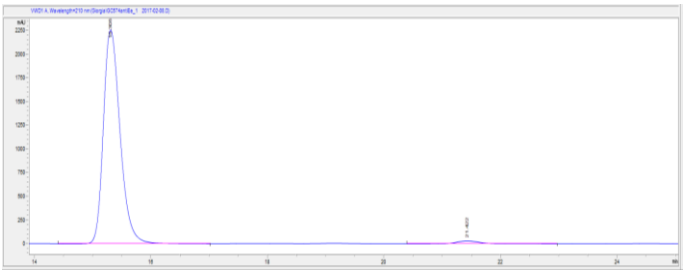
M.P.: 112−114 ºC.

[α]^{22}D: −14 (*c* 1.3, $CHCl_3$).

Chiral HPLC: Daicel Chiralcel-IA column (25 cm), hexane:isopropanol = 95:5, 0.5 mL/min, room temperature, 210.8 nm: t_R = 15.4 minutes (major), 21.5 minutes (minor), e.r. = 98:2.

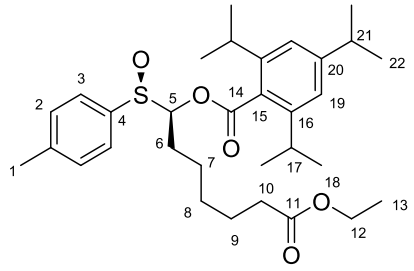


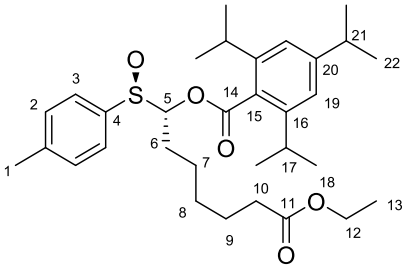
#	Time	Type	Area	Height	Width	Area%	Symmetry
1	15.389	BB	6718.7	356.7	0.2867	50.042	0.801
2	21.503	BB	6707.5	252.4	0.4062	49.958	0.823



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	15.305	VV R	44930.7	2259.3	0.3074	98.105	0.717
2	21.422	BV R	867.8	30.9	0.4038	1.895	0.774

(*R*)-7-Ethoxy-7-oxo-1-((*R*)-*p*-tolylsulfinyl)heptyl 2,4,6-triisopropylbenzoate (*syn*-255q) and (*S*)-7-ethoxy-7-oxo-1-((*R*)-*p*-tolylsulfinyl)heptyl 2,4,6-triisopropylbenzoate (*anti*-255q)





Following GP5, ((*S*)-*p*-tolylsulfinyl)methyl 2,4,6-triisopropylbenzoate (*R*)-**256** (600 mg, 1.50 mmol), ethyl hexanoate trifluoromethanesulfonate (575 mg, 1.95 mmol) and NaHMDS (1.0 M in THF, 2.25 mL, 2.25 mmol) afforded after purification by flash column chromatography (hexane:EtOAc = 85:15) the *syn* diastereoisomer *syn*-**255q** (less polar, 239 mg, 29%) as a thick colourless oil and the *anti* diastereoisomer *anti*-**255q** (more polar, 217 mg, 27%) as a thick colourless oil which was found to contain 5% of *syn*-**255q**. Further subsequent purification by reverse phase HPLC (CH_3CN:H_2O = 30:70 → 85:15) afforded pure *anti*-**255q**, which was used for characterisation.

[The racemates were synthesised as above, replacing (*S*)-**256** with racemic benzoate *rac*-**256**.]

***syn*-255q**

R_f: 0.18 (hexane:EtOAc = 85:15).

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.64 (d, *J* = 7.8 Hz, 2H, Ar-H), 7.37 (d, *J* = 7.6 Hz, 2H, Ar-H), 7.04 (s, 2H, Ar-H), 5.66 (dd, J_1 = 9.6 Hz, J_2 = 2.2 Hz, 1H, 5-H), 4.09 (q, *J* = 7.0 Hz, 2H, 12-H), 2.92 (quint, *J* = 6.4 Hz, 3H, 17-H × 2 + 21-H), 2.44 (s, 3H, 1-H), 2.20 (t, *J* = 7.4 Hz, 2H, 10-H), 1.99 (m, 1H, 6-H), 1.64–1.41 (m, 5H, 6-H + 7-H × 2 + 9-H × 2), 1.30–1.21 (m, 23H, CH_3 × 7 + 8-H × 2).

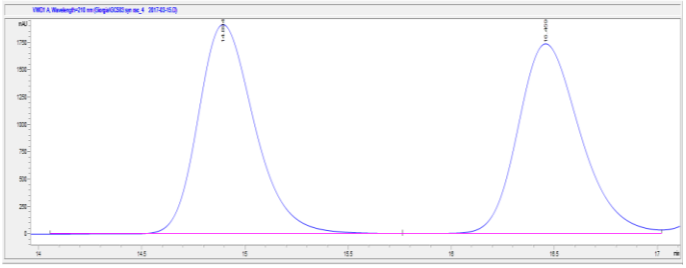
^{13}C NMR ($CDCl_3$, 101 MHz) δ: 173.4 (Ar-CO), 170.4 (Et-CO), 150.8 (Ar-C), 145.1 (2C, Ar-C × 2), 141.6 (Ar-C), 137.5 (Ar-C), 130.0 (2C, Ar-C × 2), 128.8 (Ar-C), 124.3 (2C, Ar-C × 2), 121.0 (2C, Ar-C × 2), 92.5 (5-C), 60.2 (12-C), 34.4 (21-C), 34.0 (10-C), 31.6 (2C, 17-C × 2), 28.6 (8-C), 24.6 (9-C), 24.5 (7-C), 24.4 (2C, CH-*C*H_3 × 2), 24.2 (2C, CH-*C*H_3 × 2), 23.9 (2C, CH-*C*H_3 × 2), 22.8 (6-C), 21.4 (1-C), 14.2 (13-C).

IR (neat) ν_{max}: 2960, 1731, 1461, 1233, 1044, 811 cm^{-1}.

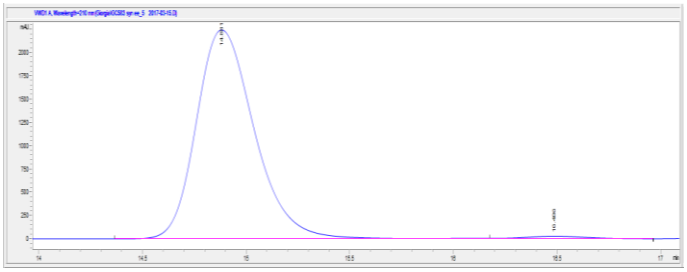
HRMS (ESI) calculated for $C_{32}H_{46}NaO_5S$ $(M+Na)^+$: 565.2958, found: 565.2955.

[α]$^{22}_{D}$: −93 (*c* 0.7, $CHCl_3$).

Chiral HPLC: Daicel Chiralcel-IA column (25 cm), hexane:isopropanol = 90:10, 0.5 mL/min, room temperature, 210.8 nm: t_R = 14.9 minutes (major), 16.5 minutes (minor), e.r. = 99:1.



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	14.894	VV R	36853.7	1923.7	0.2964	49.880	0.753
2	16.459	VV	37031.4	1747.2	0.3266	50.120	0.77



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	14.881	BV R	43441.2	2235.5	0.2995	98.746	0.74
2	16.486	VB E	551.9	27.1	0.3079	1.254	0.924

***anti*-255q**

R_f: 0.16 (hexane:EtOAc = 85:15).

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.53 (d, *J* = 8.0 Hz, 2H, Ar-H), 7.31 (d, *J* = 8.0 Hz, 2H, Ar-H), 7.02 (s, 2H, Ar-H), 5.99 (dd, J_1 = 8.5 Hz, J_2 = 4.1 Hz, 1H, 5-H), 4.11 (q, *J* = 7.2 Hz, 2H, 12-H), 2.90 (sept, *J* = 6.9 Hz, 1H, 21-H), 2.84 (sept, *J* = 6.8 Hz, 2H, 17-H × 2), 2.42 (s, 3H, 1-H), 2.25 (t, *J* = 7.5 Hz, 2H, 10-H), 1.85 (m, 1H, 6-H), 1.56 (quint, *J* = 7.5 Hz, 2H, 9-H), 1.50–1.31 (m, 5H, 6-H + 7-H × 2 + 8-H × 2), 1.26–1.20 (m, 21H, CH_3 × 7).

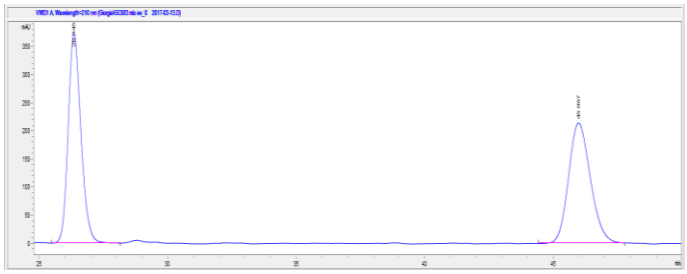
^{13}C NMR ($CDCl_3$, 101 MHz) δ: 173.4 (Ar-CO), 169.3 (1), 150.7 (Ar-C), 145.1 (2C, Ar-C × 2), 142.1 (Ar-C), 136.3 (Ar-C), 129.9 (2C, Ar-C × 2), 128.9 (Ar-C), 125.5 (2C, Ar-C × 2), 121.0 (2C, Ar-C × 2), 88.7 (5-C), 60.2 (12-C), 34.4 (21-C), 34.1 (10-C), 31.6 (2C, 17-C × 2), 28.7 (8-C), 27.2 (6-C), 25.1 (7-C), 24.6 (9-C), 24.6 (2C, CH-*C*H_3 × 2), 24.1 (2C, CH-*C*H_3 × 2), 23.9 (2C, CH-*C*H_3 × 2), 21.5 (1-C), 14.2 (13-C).

IR (neat) ν_{max}: 2961, 1733, 1230, 1088, 1038, 810 cm^{-1}.

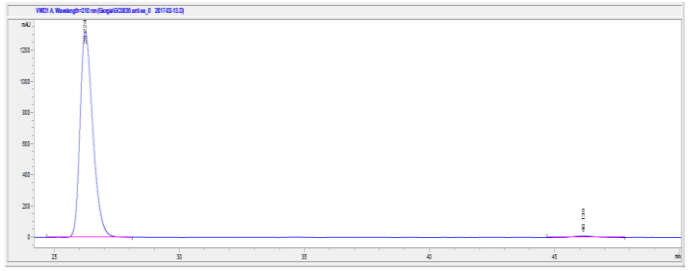
HRMS (ESI) calculated for $C_{32}H_{46}NaO_5S$ $(M+Na)^+$: 565.2958, found: 565.2955.

[α]$^{22}_{D}$: −9 (*c* 0.8, $CHCl_3$).

Chiral HPLC: Daicel Chiralcel-IA column (25 cm), hexane:isopropanol = 95:5, 0.5 mL/min, room temperature, 210.8 nm: t_R = 26.3 minutes (major), 46.0 minutes (minor), e.r. = 99:1.



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	26.345	BV R	12879.4	372.5	0.5147	50.479	0.784
2	45.987	BB	12634.9	214.2	0.8556	49.521	0.816



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	26.224	VV R	46882.7	1324.3	0.5379	98.654	0.664
2	46.139	VV R	639.8	10.2	0.734	1.346	0.903

5.6.6. Epimerisation of *anti*-255a to *syn*-255a

Representative Procedure Using TMPMgCl·LiCl

A stirred solution of a 50:50 mixture of *syn*- and *anti*-**255a** (20.7 mg, 0.05 mmol) in dry THF (0.5 mL) under N_2 was treated with TMPMgCl·LiCl (1.0 M in THF/toluene, 0.750 mL, 0.075 mmol) at −78 °C. The resulting mixture was stirred for 30 min at −78 °C before the proton source (0.50 mmol, 10 equiv) was added. The quenched reaction mixture was warmed to room temperature, H_2O (5 mL) and Et_2O (5 mL) were added, the phases were separated and the aqueous phase was extracted with Et_2O (3 × 5 mL). The combined organic layers were dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The d.r. and the yield of each diastereoisomer were determined by ^{1}H NMR using 1,4-dimethoxybenzene as the internal standard.

Procedure Using KO*t*-Bu/*t*-BuOH

A stirred solution of a 50:50 mixture of *syn*- and *anti*-**255a** (20.7 mg, 0.05 mmol) in dry THF (0.50 mL) under N_2 was treated with KO*t*-Bu (1.0 M in *t*-BuOH, 0.750 mL, 0.075 mmol) at −78 °C. The resulting mixture was stirred for 30 min at −78 °C before it was warmed to room temperature. H_2O (5 mL) and Et_2O (5 mL) were added, the phases were separated and the aqueous phase was extracted with Et_2O (3 × 5 mL). The combined organic layers were dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The d.r. and the yield of each diastereoisomer were determined by ^{1}H NMR using 1,4-dimethoxybenzene as the internal standard.

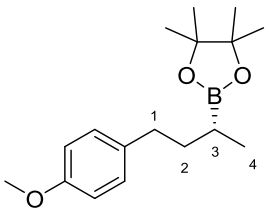
Procedure Using NaDMSO/DMSO

NaDMSO was freshly prepared according to a modified literature procedure.[220] A dry schlenk tube was charged with NaH (60% dispersion in mineral oil, 8.0 mg, 0.2 mmol). Pentane (1.0 mL) was added, the suspension was swirled for few minutes, decanted and the solvent was removed with a syringe. The procedure was repeated for three times to remove all the mineral oil, then NaH was dried under high vacuum before being suspended in dry DMSO (1.0 mL). The resulting suspension was heated at 60 °C for 40 minutes. Completion of the reaction was shown by disappearance of solid NaH and cessation of gas evolution to give a pale yellow solution. The flask was cooled to room temperature and a 50:50 mixture of *syn*- and *anti*-**255a** (42 mg, 0.1 mmol) in DMSO:THF (2/1 *v*/*v*, 1.0 mL in total) under N_2 was added slowly. The resulting mixture was stirred for 1 h at room temperature before H_2O (5 mL) and Et_2O (5 mL) were added. The phases were separated and the aqueous phase was extracted with Et_2O

(3 × 5 mL). The combined organic layers were dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The d.r. and the yield of each diastereoisomer were determined by ^1H NMR using 1,4-dimethoxybenzene as the internal standard.

5.6.7. Homologation of Boronic Esters

(*R*)-2-(4-(4-Methoxyphenyl)butan-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (284a)



Following GP6, methyl sulfoxide *ent-syn*-**255a** (87 mg, 0.21 mmol), boronic ester **283** (52 mg, 0.20 mmol) and *t*-BuLi (1.7 M in pentane, 235 µL, 0.400 mmol) afforded after purification by flash column chromatography (hexane:Et_2O = 95:5) the homologated boronic ester **284a** (45.4 mg, 78%) as a colourless oil.

Following GP7a, methyl sulfoxide *ent-syn*-**255a** (108 mg, 0.260 mmol), boronic ester **283** (52 mg, 0.20 mmol) and *i*-PrMgCl·LiCl (1.14 M in THF, 210 µL, 0.240 mmol) afforded after purification by flash column chromatography (hexane:Et_2O = 95:5) the homologated boronic ester **284a** (33.6 mg, 58%) as a colourless oil.

[The racemate was synthesised as above, replacing enantioenriched α-sulfinyl benzoate *ent-syn*-**255a** with racemic α-sulfinyl benzoate *rac-syn*-**255a**.]

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.10 (dt, J_1 = 8.7 Hz, J_2 = 2.9 Hz, 2H, Ar-H), 6.81 (dt, J_1 = 8.6 Hz, J_2 = 3.0 Hz, 2H, Ar-H), 3.78 (s, 3H, O-CH_3), 2.60−2.53 (m, 2H, 1-H), 1.75 (m, 1H, 2-H), 1.56 (m, 1H, 2-H), 1.25 (s, 12H, C-CH_3 × 4), 1.10−1.00 (m, 4H, 3-H + 4-H).

^{13}C NMR ($CDCl_3$, 101 MHz) δ: 157.5 (Ar-C), 135.2 (Ar-C), 129.3 (2C, Ar-C × 2), 113.6 (2C, Ar-C × 2), 82.8 (2C, B-O-C × 2), 55.2 (O-CH_3), 35.5 (1-C), 34.4 (2-C), 24.8 (2C, C-CH_3 × 2), 24.8 (2C, C-CH_3 × 2), 15.4 (4-C); *carbon attached to boron not observed due to quadrupolar relaxation.*

^{11}B NMR ($CDCl_3$, 128 MHz) δ: 34.3.

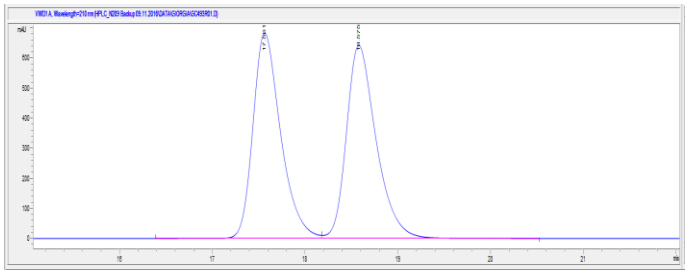
IR (neat) ν_{max}: 2977, 2931, 1612, 1512, 1463, 1380, 1370, 1314, 1243, 1142, 1112, 1038, 967, 863, 848, 822, 687, 670, 561 cm^{-1}.

HRMS (ESI) calculated for $C_{17}H_{27}BO_3$ $(M+H)^+$: 291.2132, found: 291.2123.

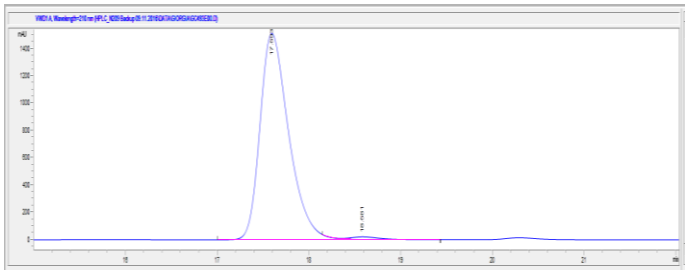
$[\alpha]^{23}_D$: −19 (*c* 0.7, $CHCl_3$). [Lit. value for (*R*):[93] −8.2 (*c* 0.98, $CHCl_3$); for (*S*):[92] +7.6 (*c* 1.7, $CHCl_3$)].

All analytical data matched that previously reported in the literature.[92]

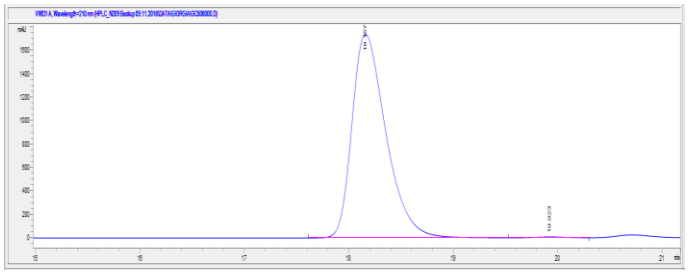
Chiral HPLC: Daicel Chiralcel-IB column (25 cm), hexane:isopropanol = 95:5, 0.5 mL/min, room temperature, 210.8 nm: t_R = 17.6 minutes (major), 18.6 minutes (minor), e.r. = 99:1 (Li), >99:1 (Mg).



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	17.561	VV R	14130.3	681.3	0.3133	49.783	0.695
2	18.575	VB	14253.7	640.7	0.3352	50.217	0.668

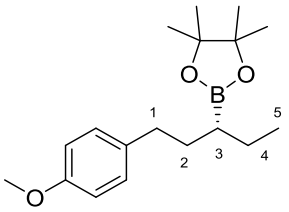


#	Time	Type	Area	Height	Width	Area%	Symmetry
1	17.593	BV R	32696.8	1506.2	0.3304	98.566	0.658
2	18.581	VB E	475.7	20.4	0.3442	1.434	0.702



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	18.157	BV R	39056.7	1736.5	0.3439	99.666	0.617
2	19.923	VV E	131	6.6	0.3132	0.334	0.901

(*R*)-2-(1-(4-Methoxyphenyl)pentan-3-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (284c)



Following GP6, ethyl sulfoxide *syn*-**255c** (90 mg, 0.21 mmol), boronic ester **283** (52 mg, 0.20 mmol) and *t*-BuLi (1.7 M in pentane, 235 µL, 0.400 mmol) afforded after purification by flash column chromatography (hexane:Et_2O = 95:5) the homologated boronic ester **284c** (37.1 mg, 61%) as a colourless oil.

Following GP7a, ethyl sulfoxide *syn*-**255c** (111 mg, 0.260 mmol), boronic ester **283** (52 mg, 0.20 mmol) and *i*PrMgCl·LiCl (1.3 M in THF, 210 µL, 0.240 mmol) afforded after purification by flash column chromatography (hexane:Et_2O = 95:5) the homologated boronic ester **284c** (29.8 mg, 49%) as a colourless oil.

[The racemate was synthesised as above, replacing enantioenriched α-sulfinyl benzoate *syn*-**255c** with racemic α-sulfinyl benzoate *rac*-*syn*-**255c**.]

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.10 (d, *J* = 8.6 Hz, 2H, Ar-H), 6.82 (d, *J* = 8.5 Hz, 2H, Ar-H), 3.78 (s, 3H, O-CH_3), 2.61–2.48 (m, 2H, 1-H), 1.72 (m, 1H, 2-H), 1.62 (m, 1H, 2-H), 1.51–1.43 (m, 2H, 4-H), 1.27 (s, 12H, C-CH_3 × 4), 0.98 (m, 1H, 3-H), 0.22 (t, *J* = 7.4 Hz, 3H, 5-H).

^{13}C NMR ($CDCl_3$, 101 MHz) δ: 157.6 (Ar-C), 135.2 (Ar-C), 129.2 (2C, Ar-C × 2), 113.6 (2C, Ar-C × 2), 82.9 (2C, B-O-C × 2), 55.2 (O-CH_3), 34.7 (1-C), 33.4 (2-C), 24.8 (2C, C-*C*H_3 × 2), 24.8 (2C, C-*C*H_3 × 2), 24.1 (4-C), 13.6 (5-C); *carbon attached to boron not observed due to quadrupolar relaxation.*

^{11}B NMR ($CDCl_3$, 128 MHz) δ: 33.6.

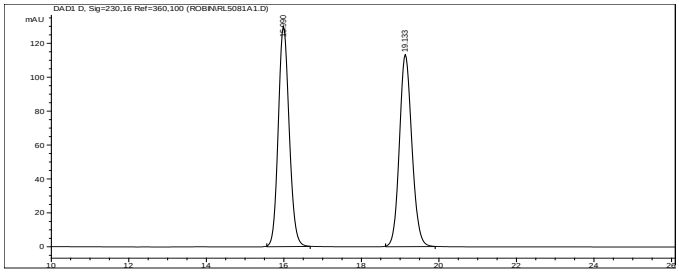
IR (neat) ν_{max}: 2976, 2927, 1511, 1371, 1313, 1244, 1142, 1038, 966, 852, 824 cm^{-1}.

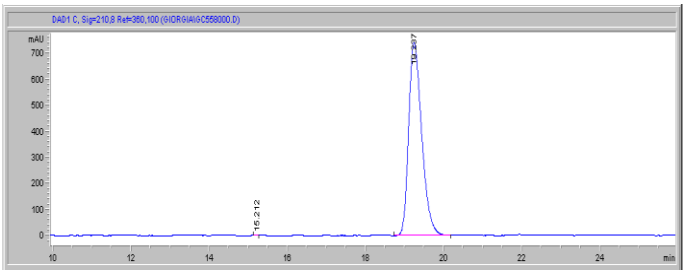
HRMS (ESI) calculated for $C_{18}H_{29}BNaO_3$ $(M+Na)^+$: 327.2105, found: 327.2099.

$[\alpha]^{23}_D$: −9 (*c* 0.7, $CHCl_3$)). [Lit. value for (*R*):[93] −9.6 (*c* 1.05, $CHCl_3$); for (*S*):[92] +9.4 (*c* 1.6, $CHCl_3$)].

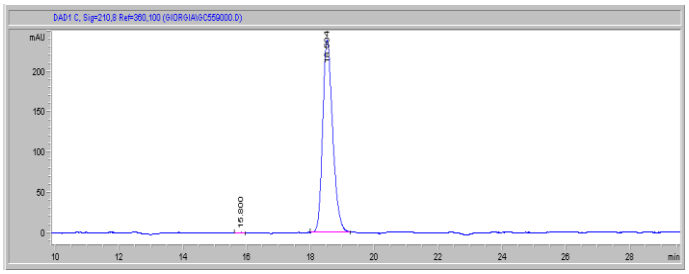
All analytical data matched that previously reported in the literature.[92]

Chiral HPLC: Daicel Chiralcel-IB column (25 cm), hexane:isopropanol = 97:3, 0.7 mL/min, room temperature, 210.8 nm: t_R = 16.0 minutes, 19.1 minutes, e.r. >99:1 (Li), e.r. >99:1 (Mg).



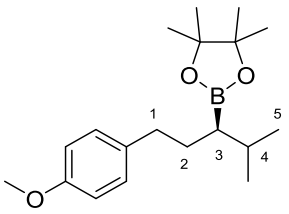


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.212	VV	0.0972	8.73743	1.11776	0.0506
2	19.237	VV	0.3579	1.72745e4	741.09216	99.9494



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.800	VV	0.1758	15.85568	1.12918	0.3029
2	18.504	VB	0.3288	5218.14941	238.96301	99.6971

(*R*)-2-(1-(4-Methoxyphenyl)-4-methylpentan-3-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (284d)



Following GP6, isopropyl sulfoxide *anti*-**255d** (93 mg, 0.21 mmol), boronic ester **283** (52 mg, 0.20 mmol) and *t*-BuLi (1.7 M in pentane, 235 µL, 0.400 mmol) afforded after purification by flash column chromatography (hexane:Et_2O = 97:3) the homologated boronic ester **284d** (34.1 mg, 54%) as a colourless solid.

Following GP7a, isopropyl sulfoxide *anti*-**255d** (95.0 mg, 0.22 mmol), boronic ester **283** (43.3 mg, 0.17 mmol) and *i*-PrMgCl·LiCl (1.14 M in THF, 170 µL, 0.20 mmol) afforded after purification by flash column chromatography (hexane:Et_2O = 97:3) the homologated boronic ester **284d** (4.00 mg, 8%) as a colourless solid.

[The racemate was synthesised as above, replacing enantioenriched α-sulfinyl benzoate *anti*-**255d** with racemic α-sulfinyl benzoate *rac-anti*-**255d**.]

R_f: 0.26 (hexane:Et_2O = 97:3).

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.12 (d, *J* = 8.5 Hz, 2H, Ar-H), 6.82 (d, *J* = 8.5 Hz, 2H, Ar-H), 3.79 (s, 3H, O-CH_3), 2.58 (m, 1H, 1-H), 2.46 (m, 1H, 1-H), 1.80–1.59 (m, 3H, 2-H + 4-H), 1.28 (s, 12H, C-CH_3 × 4), 0.93 (d, *J* = 6.8 Hz, 6H, 5-H × 2), 0.91 (m, 1H, 3-H).

^{13}C NMR ($CDCl_3$, 101 MHz) δ: 157.68 (Ar-C), 135.4 (Ar-C), 129.3 (2C, Ar-C × 2), 113.8 (2C, Ar-C × 2), 83.0 (2C, B-O-C × 2), 55.3 (O-CH_3), 35.2 (1-C), 31.8 (2-C), 29.7 (4-C), 25.2 (2C, C-*C*H_3 × 2), 25.0 (2C, C-*C*H_3 × 2), 22.4 (5-C), 21.8 (5-C); *carbon attached to boron not observed due to quadrupolar relaxation.*

^{11}B NMR ($CDCl_3$, 128 MHz) δ: 33.7.

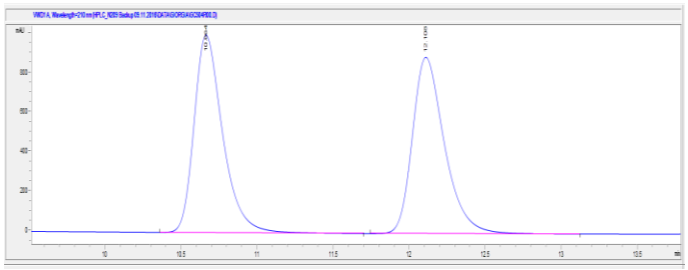
IR (neat) ν_{max}: 2952, 2857, 1512, 1312, 1297, 1235, 1141, 1041, 874, 824, 515 cm^{-1}.

HRMS (ESI) calculated for $C_{19}H_{31}BNaO_3$ $(M+Na)^+$: 341.2262, found: 341.2261.

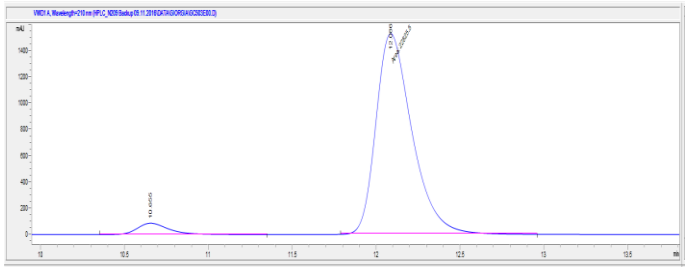
M.P.: 35–37 °C.

[α]$^{23}_D$: +3 (*c* 1.1, $CHCl_3$).

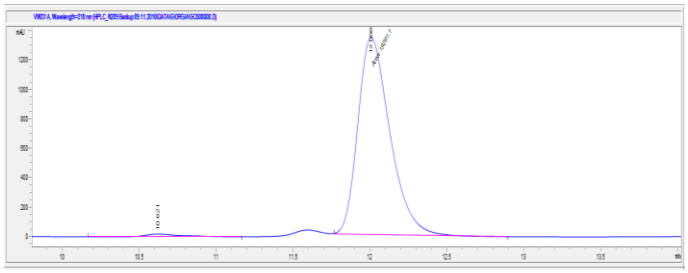
Chiral HPLC: Daicel Chiralcel-IB column (25 cm), hexane:isopropanol = 90:10, 0.5 mL/min, room temperature, 210.8 nm: t_R = 10.7 minutes (minor), 12.1 minutes (major), e.r. = 95:5 (Li), e.r. = 98:2 (Mg).



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	10.664	BB	13086.7	1001.5	0.1976	49.961	0.675
2	12.108	BB	13107.1	894	0.222	50.039	0.677

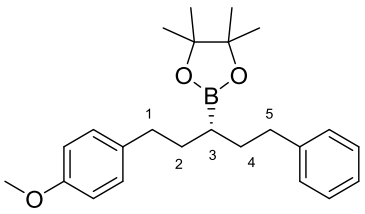


#	Time	Type	Area	Height	Width	Area%	Symmetry
1	10.655	BB	1130.7	87.1	0.1967	4.720	0.689
2	12.086	MM	22825.5	1535.5	0.2478	95.280	0.668



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	10.621	BV	298.9	18.4	0.2313	1.526	0.497
2	12.006	MM	19291.1	1336.4	0.2406	98.474	0.687

(*R*)-2-(1-(4-Methoxyphenyl)-5-phenylpentan-3-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (284f)



Following GP6, phenyl ethyl sulfoxide *syn*-**255f** (106 mg, 0.210 mmol), boronic ester **283** (52 mg, 0.20 mmol) and *t*-BuLi (1.7 M in pentane, 235 µL, 0.400 mmol) afforded after purification by flash column chromatography (hexane:Et_2O = 95:5) the homologated boronic ester **284f** (61.7 mg, 81%) as a colourless oil.

Following GP7a, phenyl ethyl sulfoxide *syn*-**255f** (131 mg, 0.260 mmol), boronic ester **283** (52 mg, 0.20 mmol) and *i*-PrMgCl·LiCl (1.14 M in THF, 210 µL, 0.240 mmol) afforded after purification by flash column chromatography (hexane:Et_2O = 95:5) the homologated boronic ester **284f** (61.7 mg, 71%) as a colourless oil.

[The racemate was synthesised as above, replacing enantioenriched α-sulfinyl benzoate *syn*-**255f** with racemic α-sulfinyl benzoate *rac*-*syn*-**255f**.]

R_f: 0.31 (hexane:Et_2O = 90:10).

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.30–7.26 (m, 2H, Ar-H), 7.21–7.17 (m, 3H, Ar-H), 7.11 (d, *J* = 8.6 Hz, 2H, Ar-H), 6.83 (d, *J* = 8.6 Hz, 2H, Ar-H), 3.80 (s, 3H, O-CH_3), 2.70–2.51 (m, 4H, 1-H + 5-H), 1.86–1.64 (m, 4H, 2-H + 4-H), 1.30 (s, 12H, C-CH_3 × 4), 1.14 (m, 1H, 3-H).

^{13}C NMR ($CDCl_3$, 101 MHz) δ: 157.6 (Ar-C), 143.0 (Ar-C), 135.0 (Ar-C), 129.2 (2C, Ar-C × 2), 128.4 (2C, Ar-C × 2), 128.2 (2C, Ar-C × 2), 125.5 (Ar-C), 113.6 (2C, Ar-C × 2), 83.0 (2C, B-O-C × 2), 55.2 (O-CH_3), 35.6 (5-C), 34.6 (1-C), 33.6 (2-C), 33.4 (4-C), 24.9 (4C, C-*C*H_3 × 4); *carbon attached to boron not observed due to quadrupolar relaxation.*

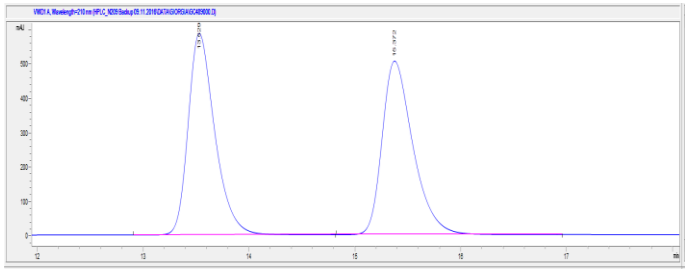
^{11}B NMR ($CDCl_3$, 128 MHz) δ: 33.5.

IR (neat) ν_{max}: 2977, 2926, 1511, 1379, 1316, 1243, 1142, 1037, 821 cm^{-1}.

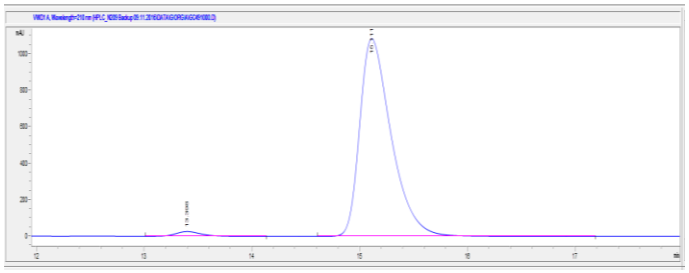
HRMS (ESI) calculated for $C_{24}H_{33}BNaO_3$ $(M+Na)^+$: 403.2419, found: 403.2412.

$[\alpha]^{23}_D$: −6 (*c* 0.5, $CHCl_3$).

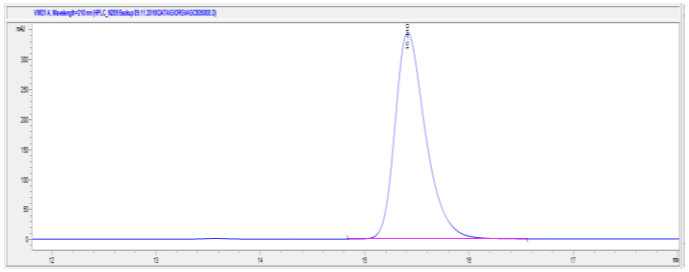
Chiral HPLC: Daicel Chiralcel-IB column (25 cm), hexane:isopropanol = 90:10, 0.7 mL/min, room temperature, 210.8 nm: t_R = 13.5 minutes (minor), 15.3 minutes (major), e.r. = 98:2 (Li), e.r. >99:1 (Mg).



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	13.529	BB	10227.8	586.2	0.2647	49.976	0.679
2	15.372	BB	10237.6	505.4	0.3077	50.024	0.637

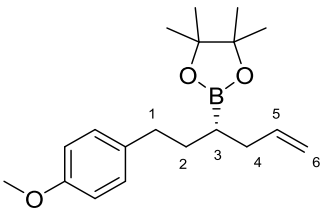


#	Time	Type	Area	Height	Width	Area%	Symmetry
1	13.398	BB	426.3	26	0.2497	1.897	0.775
2	15.111	BB	22040.9	1085.9	0.3067	98.103	0.577



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	15.41	BB	6947.7	343.1	0.309	100.000	0.668

(*S*)-2-(1-(4-Methoxyphenyl)hex-5-en-3-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (284b)



Following GP6, allylic sulfoxide *ent-syn*-**255b** (93 mg, 0.21 mmol), boronic ester **283** (52 mg, 0.20 mmol) and *t*-BuLi (1.7 M in pentane, 235 µL, 0.400 mmol) afforded after purification by flash column chromatography (hexane:Et_2O = 95:5) the homologated boronic ester **284b** (53.6 mg, 85%) as a colourless oil.

Following GP7a, allylic sulfoxide *ent-syn*-**255b** (115 mg, 0.26 mmol), boronic ester **283** (52.4 mg, 0.20 mmol) and *i*-PrMgCl·LiCl (1.14 M in THF, 210 µL, 0.24 mmol) afforded after purification by flash column chromatography (hexane:Et_2O = 95:5) the homologated boronic ester **284b** (43.9 mg, 69%) as a colourless oil.

[The racemate was synthesised as above, replacing enantioenriched α-sulfinyl benzoate *ent-syn*-**255b** with racemic α-sulfinyl benzoate *rac-ent-syn*-**255b**.]

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.09 (dt, J_1 = 8.6 Hz, J_2 = 2.9 Hz, 2H, Ar-H), 6.81 (dt, J_1 = 8.6 Hz, J_2 = 2.9 Hz, 2H, Ar-H), 5.80 (m, 1H, 5-H), 5.03 (dq, J_1 = 17.1 Hz, J_2 = 2.0 Hz, 1H, 6-H$_{trans}$), 4.95 (dq, J_1 = 10.1 Hz, J_2 = 1.0 Hz, 1H, 6-H$_{cis}$), 3.78 (s, 3H, O-CH_3), 2.55 (m, 2H, 1-H), 2.19 (m, 2H, 4-H), 1.68 (m, 2H, 2-H), 1.25 (s, 12H, C-CH_3 × 4), 1.13 (m, 1H, 3-H).

^{13}C NMR ($CDCl_3$, 101 MHz) δ: 157.6 (Ar-C), 138.4 (5-C), 135.0 (Ar-C), 129.2 (2C, Ar-C × 2), 114.9 (6-C), 113.7 (2C, Ar-C × 2), 83.0 (2C, B-O-C × 2), 55.2 (O-CH_3), 35.4 (1-C), 34.5 (3-C), 33.2 (2-C), 24.9 (2C, C-*C*H_3 × 2), 24.8 (2C, C-*C*H_3 × 2); *carbon attached to boron not observed due to quadrupolar relaxation*.

^{11}B NMR ($CDCl_3$, 128 MHz) δ: 33.3.

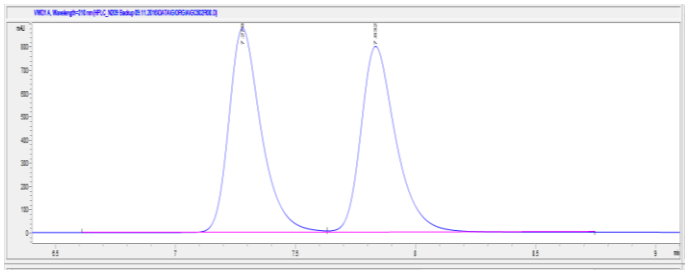
IR (neat) ν_{max}: 2977, 2924, 1511, 1318, 1142, 1038, 823 cm^{-1}.

HRMS (ESI) calculated for $C_{19}H_{29}BNaO_3$ $(M+Na)^+$: 339.2105, found: 339.2109.

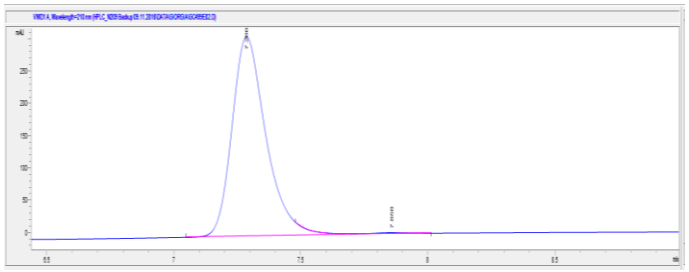
[α]$^{23}_D$: −16 (*c* 0.8, $CHCl_3$). [Lit. Value for (*R*):[92] +0.12 (*c* 1.0, $CHCl_3$)].

All analytical data matched that previously reported in the literature.[92]

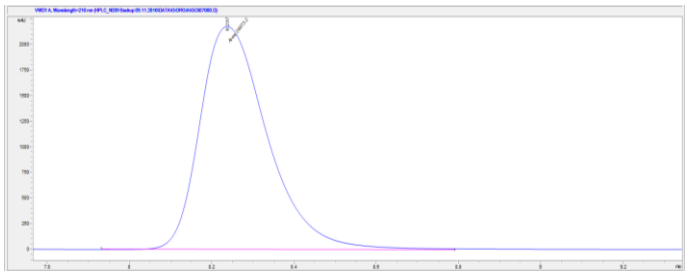
Chiral HPLC: Daicel Chiralcel-IB column (25 cm), hexane:isopropanol = 90:10, 0.8 mL/min, room temperature, 210.8 nm: t_R = 7.3 minutes, 7.8, e.r. = 99:1 (Li), e.r. >99:1 (Mg).



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	7.278	BV	8222.7	878.2	0.1413	50.349	0.685
2	7.832	VB	8108.8	799.8	0.1532	49.651	0.679

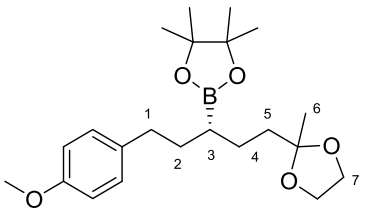


#	Time	Type	Area	Height	Width	Area%	Symmetry
1	7.286	BV R	2887.9	310.3	0.1392	99.000	0.701
2	7.858	VB E	29.2	1.8	0.2201	1.000	2.73



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	8.237	MM	24973.2	2185.5	0.1904	100.000	0.656

(*S*)-2-(1-(4-Methoxyphenyl)-5-(2-methyl-1,3-dioxolan-2-yl)pentan-3-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (284g)



Following GP6, ketal sulfoxide *syn*-**255g** (108 mg, 0.210 mmol), boronic ester **283** (52 mg, 0.20 mmol) and *t*-BuLi (1.7 M in pentane, 235 µL, 0.400 mmol) afforded after purification by flash column chromatography (hexane:Et_2O = 75:25) the homologated boronic ester **284g** (54.3 mg, 70%) as a colourless oil.

Following GP7a, ketal sulfoxide *syn*-**255g** (134 mg, 0.260 mmol), boronic ester **283** (52 mg, 0.20 mmol) and *i*-PrMgCl·LiCl (1.14 M in THF, 210 µL, 0.240 mmol) afforded after purification by flash column chromatography (hexane:Et_2O = 75:25) the homologated boronic ester **284g** (48.9 mg, 63%) as a colourless oil.

[The racemate was synthesised as above, replacing enantioenriched α-sulfinyl benzoate *syn*-**255g** with racemic α-sulfinyl benzoate *rac*-*syn*-**255g**.]

R_f: 0.18 (hexane:Et_2O = 80:20).

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.09 (d, *J* = 8.5 Hz, 2H, Ar-H), 6.81 (d, *J* = 8.5 Hz, 2H, Ar-H), 3.95−3.87 (m, 4H, 7-H × 2), 3.77 (s, 3H, O-CH_3), 2.61−2.47 (m, 2H, 1-H), 1.77−1.46 (m, 6H, 2-H + 4-H + 5-H), 1.31 (s, 3H, 6-H), 1.25 (s, 12H, C-CH_3 × 4), 1.00 (m, 1H, 3-H).

^{13}C NMR ($CDCl_3$, 101 MHz) δ: 157.6 (Ar-C), 135.1 (Ar-C), 129.2 (2C, Ar-C × 2), 113.6 (2C, Ar-C × 2), 110.1 (O-C-O), 82.9 (2C, B-O-C × 2), 64.5 (2C, 7-C × 2), 55.2 (O-CH_3), 38.3 (5-C), 34.6 (1-C), 33.6 (2-C), 25.5 (4-C), 24.8 (2C, C-*C*H_3 × 2), 24.8 (2C, C-*C*H_3 × 2), 23.6 (6-C); *carbon attached to boron not observed due to quadrupolar relaxation*.

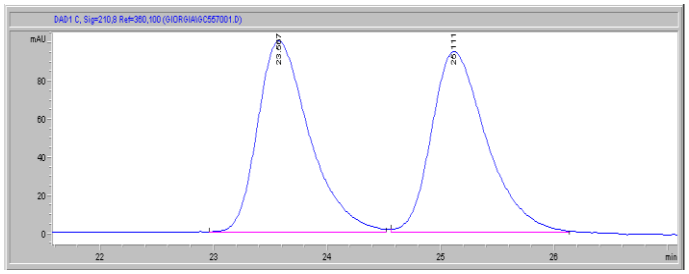
^{11}B NMR ($CDCl_3$, 128 MHz) δ: 33.7.

IR (neat) ν_{max}: 2978, 2932, 1511, 1372, 1316, 1244, 1142, 1037, 848, 825 cm^{-1}.

HRMS (ESI) calculated for $C_{22}H_{35}BNaO_5$ $(M+Na)^+$: 413.2474, found: 413.2475.

$[\alpha]^{23}_D$: −3 (*c* 0.6, $CHCl_3$).

Chiral HPLC: Daicel Chiralcel-IB column (25 cm), hexane:isopropanol = 95:5, 0.7 mL/min, room temperature, 210.8 nm: t_R = 23.6 minutes (major), 25.1 minutes (minor), e.r. = 99:1 (Li), e.r. = 99:1 (Mg).



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
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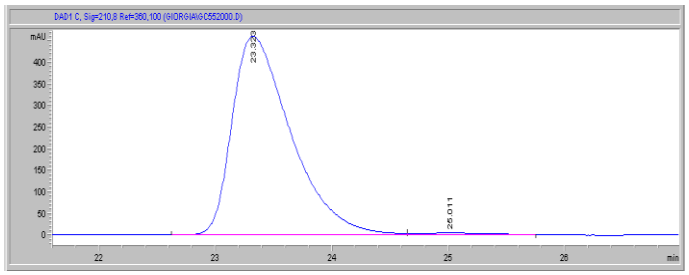
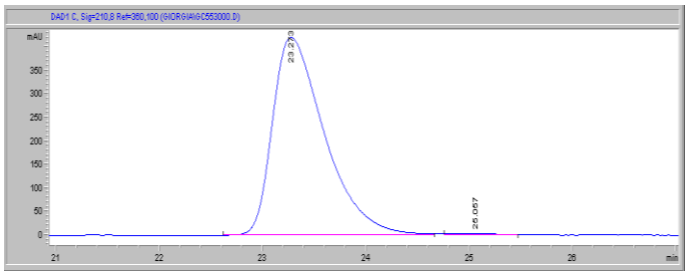
2	25.111	BV	0.4994	3213.07983	94.80626	49.9606

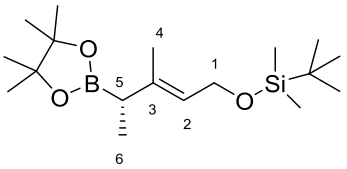


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	23.323	VB	0.5300	1.61917e4	460.73987	98.6724
2	25.011	BV	0.5090	217.85738	5.19751	1.3276



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	23.273	VB	0.5233	1.47985e4	421.79361	99.1386
2	25.057	BV	0.3655	128.57690	4.24386	0.8614

(*S*,*E*)-*tert*-Butyldimethyl((3-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pent-2-en-1-yl)oxy)silane (286ac)



Following GP6, methyl sulfoxide *anti*-**255a** (87 mg, 0.21 mmol), boronic ester **285c** (63 mg, 0.20 mmol) and *t*-BuLi (1.7 M in pentane, 235 µL, 0.400 mmol) afforded after purification by flash column chromatography (hexane:Et_2O = 97:3) the homologated boronic ester **286ac** (20.8 mg, 31%) as a colourless oil.

Following GP7a, methyl sulfoxide *anti*-**255a** (108 mg, 0.260 mmol), boronic ester **285c** (63 mg, 0.20 mmol) and *i*-PrMgCl·LiCl (1.25 M in THF, 190 µL, 0.240 mmol) afforded after purification by flash column chromatography (hexane:Et_2O = 97:3) the homologated boronic ester **286ac** (49.1 mg, 73%) as a colourless oil.

[The racemate was synthesised as above, replacing enantioenriched α-sulfinyl benzoate *syn*-**255a** with racemic α-sulfinyl benzoate *rac*-*syn*-**255a**.]

R_f: 0.26 (hexane:Et_2O = 97:3).

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 5.27 (t, *J* = 6.4 Hz, 1H, 2-H), 4.21 (d, *J* = 6.3 Hz, 2H, 1-H), 1.80 (q, *J* = 7.3 Hz, 1H, 5-H), 1.65 (s, 3H, CH_3), 1.22 (s, 12H, C-CH_3 × 4), 1.09 (d, *J* = 7.4 Hz, 3H, 6-H), 0.89 (s, 9H, Si-C-$(CH_3)_3$), 0.06 (s, 6H, Si-$(CH_3)_2$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ: 139.2 (2-C), 122.7 (3-C), 83.1 (2C, B-O-C × 2), 60.6 (1-C), 26.0 (3C, Si-C-*C*H_3)$_3$), 24.7 (2C, C-*C*H_3 × 2), 24.6 (2C, C-*C*H_3 × 2), 18.4 (Si-C), 16.7 (4-C), 14.1 (6-C), **−**5.0 (2C, Si-$(CH_3)_2$); *carbon attached to boron not observed due to quadrupolar relaxation*.

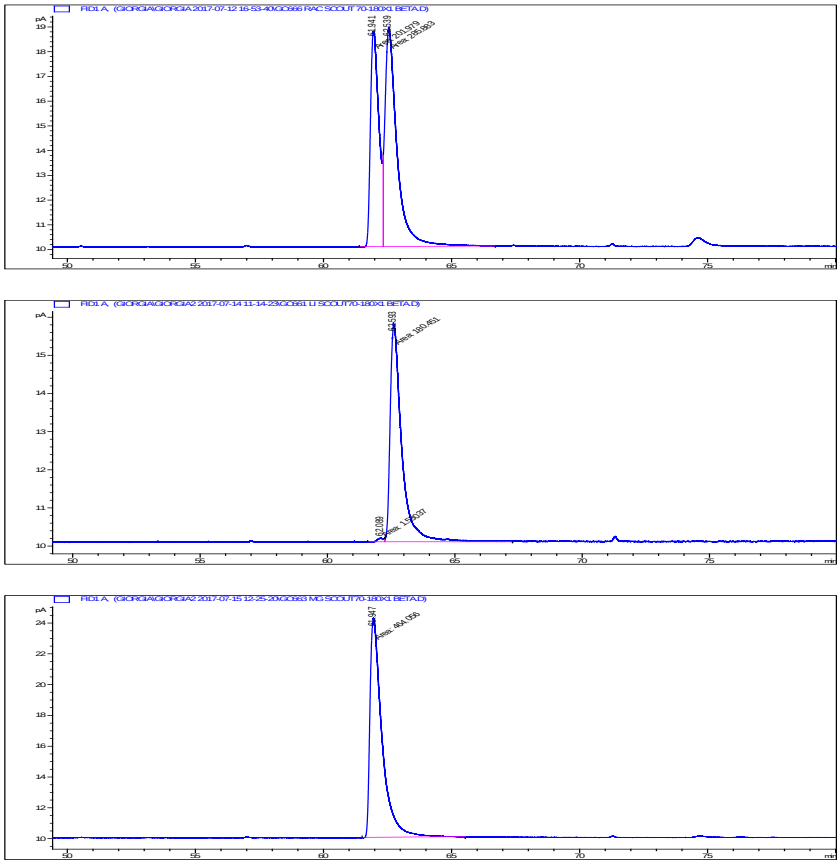
^{11}B NMR ($CDCl_3$, 128 MHz) δ: 32.8.

IR (neat) ν_{max}: 2956, 2929, 1462, 1347, 1317, 1253, 1144, 834, 774 cm^{-1}.

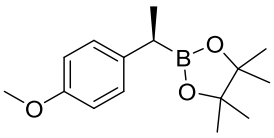
HRMS (ESI) calculated for $C_{18}H_{37}BNaO_3Si$ $(M+Na)^+$: 363.2501, found: 363.2512.

[α]$^{23}_D$: −95 (*c* 0.8, $CHCl_3$).

Chiral GC: Chiraldex β-DM column, injector T = 250 °C, detector T = 300 °C, inject at T = 70 °C for 3 min, then ramp (1 °C min^{-1}) until 180 °C then hold for 5 min, He carrier gas at 1.0 mL min^{-1}: t_R = 61.9 min (minor), 62.5 min (major), total analysis time 120 min; e.r. = 99:1 (Li), e.r. >99:1 (Mg).



(*R*)-2-(1-(4-Methoxyphenyl)ethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (286ad)



Following GP6, methyl sulfoxide *ent-anti*-**255a** (87 mg, 0.21 mmol), 4-methoxyphenyl pinacol boronic ester **285d** (47 mg, 0.20 mmol), and *t*-BuLi (1.7 M in pentane, 235 µL, 0.400 mmol) afforded after purification by flash column chromatography (hexane:Et_2O = 95:5) the homologated boronic ester **286ad** (23.1 mg, 44%) as a colourless oil. A solution of $MgBr_2$·MeOH* (1.0 M, 300 µL, 0.300 mmol) was added prior to warm the reaction mixture to 66 °C.

* 1.0 M $MgBr_2$·MeOH solution was prepared in advance by adding anhydrous MeOH to solid $MgBr_2$. Reaction without addition of $MgBr_2$·MeOH gave the desired homologated alcohol in 56% yield but only 85:15 e.r. due to reversible "ate" complex formation.[66]

Following GP7a, methyl sulfoxide *ent-anti*-**255a** (108 mg, 0.260 mmol), boronic ester **285d** (47 mg, 0.20 mmol) and *i*-PrMgCl·LiCl (1.25 M in THF, 190 µL, 0.240 mmol) afforded after purification by flash column chromatography (hexane:Et_2O = 95:5) the homologated boronic ester **286ad** (37 mg, 71%) as a colourless oil.

[The racemate was synthesised as above, replacing enantioenriched α-sulfinyl benzoate *ent-anti*-**255a** with racemic α-sulfinyl benzoate *rac-ent-anti*-**255a**.]

Spectral data matched that previously reported.[221]

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.14 (d, *J* = 8.6 Hz, 2H, Ar-H), 6.82 (d, *J* = 8.6 Hz, 2H, Ar-H), 3.78 (s, 3H, O-CH_3), 2.38 (q, *J* = 7.6 Hz, 1H, C*H*-CH_3), 1.30 (d, *J* = 7.5 Hz, 3H, CH-C*H*$_3$), 1.22 (s, 6H, C-CH_3 x 2), 1.20 (s, 6H, C-CH_3 x 2).

^{13}C NMR ($CDCl_3$, 101 MHz) δ: 157.2 (Ar-C), 137.0 (Ar-C), 128.6 (2C, Ar-C × 2), 113.7 (2C, Ar-C × 2), 83.2 (2C, B-O-C × 2), 55.2 (O-CH_3), 24.6 (2C, C-*C*H_3 × 2), 24.6 (2C, C-*C*H_3 × 2), 17.3 (CH-*C*H_3); *carbon attached to boron not observed due to quadrupolar relaxation*.

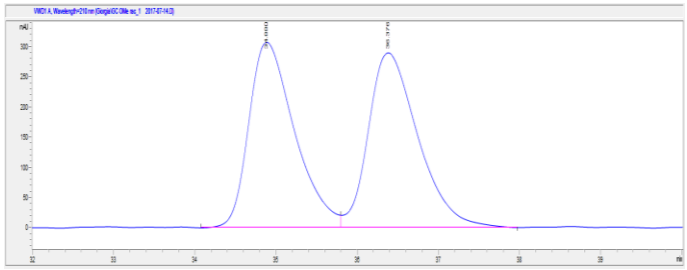
^{11}B NMR ($CDCl_3$, 128 MHz) δ: 32.8.

IR (neat) ν_{max}: 2977, 1509, 1353, 1318, 1242, 1141, 1038, 845, 828 cm^{-1}.

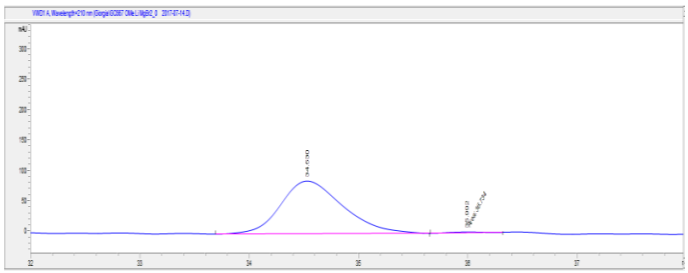
HRMS (ESI) calculated for $C_{15}H_{24}BO_3$ $(M+H)^+$: 263.1816, found: 263.1822.

[α]$^{23}_{D}$: −10 (*c* 0.1, $CHCl_3$). [Lit. value for (*R*)[74]: −120.3 (*c* 1.0, $CHCl_3$); for (*S*)[217]: +13 (*c* 1.0, $CHCl_3$)].

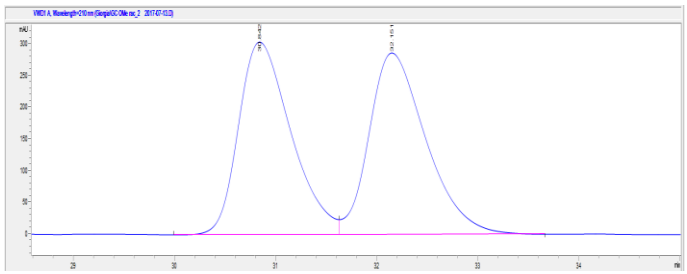
Chiral HPLC: Daicel Chiralcel-IB column (25 cm), hexane:isopropanol = 99:1, 0.7 mL/min, room temperature, 210.8 nm: t_R = 34.5 minutes (major), 36.0 minutes (minor), e.r. = 99:1 (Li), e.r. = 97:3 (Mg).



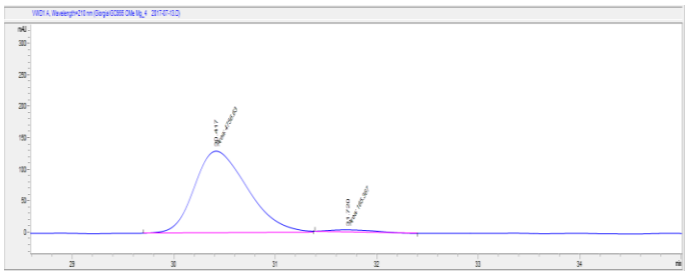
#	Time	Type	Area	Height	Width	Area%	Symmetry
1	34.88	BV	12053.2	307.6	0.5915	49.438	0.609
2	36.376	VB	12327.3	289.8	0.6478	50.562	0.631



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	34.53	BB	3437.3	86.8	0.579	98.943	0.727
2	35.992	MM	36.7	1.6	0.3842	1.057	1.638

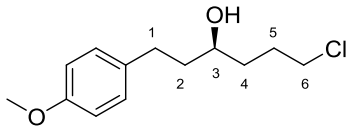


#	Time	Type	Area	Height	Width	Area%	Symmetry
1	30.842	BV	10973.8	304.3	0.547	49.449	0.643
2	32.151	VB	11218.3	286.6	0.5818	50.551	0.643



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	30.417	MM	4756.6	130.1	0.6092	96.640	0.682
2	31.72	MM	165.4	4.6	0.6052	3.360	0.515

(*R*)-6-Chloro-1-(4-methoxyphenyl)hexan-3-ol (284n)



Following GP6, chloropropyl sulfoxide *anti*-**255n** (100 mg, 0.210 mmol), boronic ester **283** (52 mg, 0.20 mmol), *t*-BuLi (1.7 M in pentane, 235 µL, 0.400 mmol) and acetic acid (11 µL), afforded after purification by flash column chromatography (hexane:Et_2O = 95:5) a mixture of the desired homologated boronic ester and starting boronic ester **283**. Following GP8, oxidation of the mixture using H_2O_2/NaOH (1/1 *v*/*v*, 1 mL) afforded after purification by flash column chromatography (hexane:EtOAc = 80:20) the alcohol **284n** (20.3 mg, 42%) as a colourless solid.

Following GP7b, chloropropyl sulfoxide *anti*-**255n** (124 mg, 0.260 mmol), boronic ester **283** (52 mg, 0.20 mmol) and *i*-PrMgCl·LiCl (1.14 M in THF, 210 µL, 0.240 mmol) afforded after purification by flash column chromatography (hexane:Et_2O = 95:5) a mixture of the desired homologated boronic ester and starting boronic ester **283**. Following GP8, oxidation of the mixture using H_2O_2/NaOH (1/1 *v*/*v*, 1 mL) afforded after purification by flash column chromatography (hexane:EtOAc = 80:20) the alcohol **284n** (27.0 mg, 56%) as a colourless solid.

[The racemate was synthesised as above, replacing enantioenriched α-sulfinyl benzoate *anti*-**255n** with racemic α-sulfinyl benzoate *rac*-*anti*-**255n**.]

R_f: 0.16 (hexane:EtOAc = 80:20).

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.12 (d, *J* = 8.6 Hz, 2H, Ar-H), 6.84 (d, *J* = 8.6 Hz, 2H, Ar-H), 3.79 (s, 3H, O-CH_3), 3.65 (m, 1H, 3-H), 3.57 (t, *J* = 6.0 Hz, 2H, 6-H), 2.73 (m, 1H, 1-H), 2.63 (m, 1H, 1-H), 1.96 (m, 1H, 5-H), 1.89–1.64 (m, 4H, 5-H + 2-H × 2 + 4-H), 1.56 (m, 1H, 4-H), 1.48 (bs, 1H, OH).

^{13}C NMR ($CDCl_3$, 101 MHz) δ: 157.8 (Ar-C), 133.8 (Ar-C), 129.3 (2C, Ar-C × 2), 113.9 (2C, Ar-C × 2), 70.7 (3-C), 55.3 (O-CH_3), 45.2 (6-C), 39.4 (2-C), 34.6 (4-C), 31.1 (1-C), 28.8 (5-C).

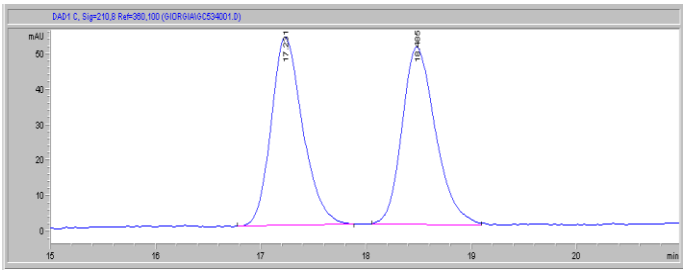
IR (neat) ν_{max}: 3675, 2988, 2972, 2901, 1394, 1074, 1066, 1057, 892, 879 cm^{-1}.

HRMS (ESI) calculated for $C_{13}H_{19}ClNaO_2$ $(M+Na)^+$: 265.0966, found: 265.0976.

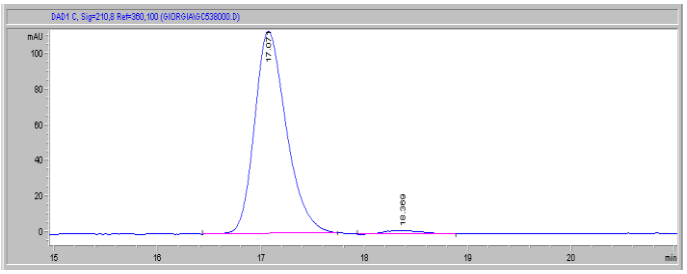
M.P.: 37–39 °C.

[α]$^{23}_{D}$: −8 (*c* 0.5, $CHCl_3$).

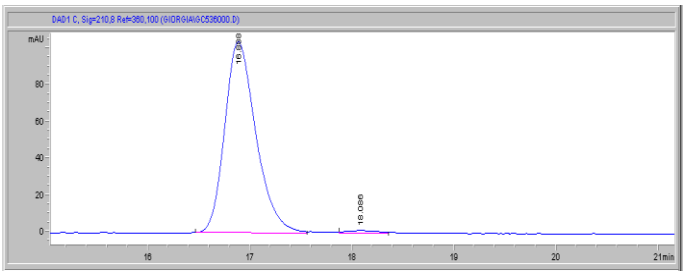
Chiral HPLC: Daicel Chiralcel-IB column (25 cm), hexane:isopropanol = 95:5, 0.7 mL/min, room temperature, 210.8 nm: t_R = 17.2 minutes (major), 18.5 minutes (minor), e.r. = 98:2 (Li), e.r. = 99:1 (Mg).



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.231	PB	0.3161	1110.17432	53.05347	50.0516
2	18.485	BB	0.3226	1107.88672	49.98637	49.9484

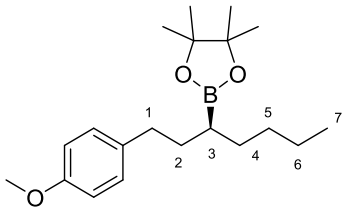


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.071	VB	0.3207	2444.90698	113.78085	97.9217
2	18.369	PV	0.2860	51.89127	2.16219	2.0783



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.888	BB	0.3186	2201.40137	104.13776	98.5457
2	18.086	BV	0.2309	32.48722	1.76329	1.4543

(*S*)-2-(1-(4-Methoxyphenyl)pentan-3-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (284p)



Following GP6, butyl sulfoxide *syn*-**255p** (96 mg, 0.21 mmol), boronic ester **283** (52 mg, 0.20 mmol) and *t*-BuLi (1.7 M in pentane, 235 µL, 0.400 mmol) afforded after purification by flash column chromatography (hexane:Et_2O = 98:2) the homologated boronic ester **284p** (43.2 mg, 65%) as a colourless oil.

Following GP7a, ethyl sulfoxide *syn*-**255p** (119 mg, 0.260 mmol), boronic ester **283** (52 mg, 0.20 mmol) and *i*-PrMgCl·LiCl (1.14 M in THF, 210 µL, 0.240 mmol) afforded after purification by flash column chromatography (hexane:Et_2O = 98:2) the homologated boronic ester **284p** (46.2 mg, 70%) as a colourless oil.

[The racemate was synthesised as above, replacing enantioenriched α-sulfinyl benzoate *syn*-**255p** with racemic α-sulfinyl benzoate *rac*-*syn*-**255p**.]

R_f: 0.28 (hexane:Et_2O = 98:2).

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.10 (dt, J_1 = 8.6 Hz, J_2 = 2.9 Hz, 2H, Ar-H), 6.81 (dt, J_1 = 8.6 Hz, J_2 = 2.9 Hz, 2H, Ar-H), 3.78 (s, 3H, O-CH_3), 2.61–2.48 (m, 2H, 1-H), 1.70 (m, 1H, 2-H), 1.62 (m, 1H, 2-H), 1.49−1.36 (m, 2H, 4-H), 1.32–1.23 (m, 4H, 5-H + 6-H), 1.26 (s, 12H, C-CH_3 × 4), 1.03 (m, 1H, 3-H), 0.88 (t, J = 7.0 Hz, 3H, 7-H).

^{13}C NMR ($CDCl_3$, 101 MHz) δ: 157.6 (Ar-C), 135.3 (Ar-C), 129.2 (2C, Ar-C × 2), 113.6 (2C, Ar-C × 2), 82.9 (2C, B-O-C × 2), 55.2 (O-CH_3), 34.7 (1-C), 33.8 (2-C), 31.5 (4-C), 30.9 (5-C), 24.9 (2C, C-*C*H_3 × 2), 24.8 (2C, C-*C*H_3 × 2), 23.0 (6-C), 14.1 (7-C); *carbon attached to boron not observed due to quadrupolar relaxation*.

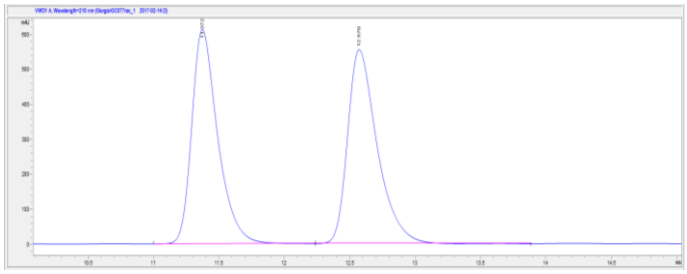
^{11}B NMR ($CDCl_3$, 128 MHz) δ: 33.8.

IR (neat) ν_{max}: 2923, 2856, 1512, 1379, 1314, 1244, 1143, 1039, 967, 824 cm^{-1}.

HRMS (ESI) calculated for $C_{20}H_{33}BNaO_3$ $(M+Na)^+$: 355.2419, found: 355.2422.

$[\alpha]^{23}_D$: +6 (*c* 0.5, $CHCl_3$).

Chiral HPLC: Daicel Chiralcel-IB column (25 cm), hexane:isopropanol = 95:5, 0.7 mL/min, room temperature, 210.8 nm: t_R = 11.4 minutes (minor), 12.6 minutes (major), e.r. = 97:3 (Li), e.r. = 98:2 (Mg).



#	Time	Type	Area	Height	Width	Area%	Symmetry
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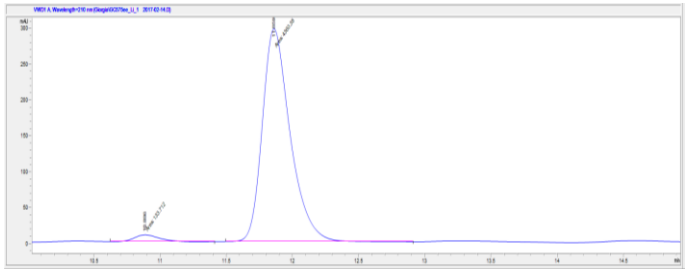
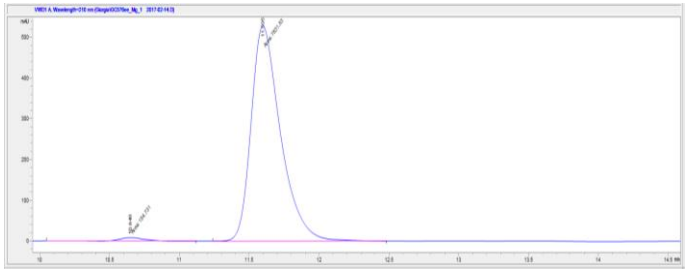
2	12.57	BV R	8701.2	553.2	0.2392	50.801	0.599

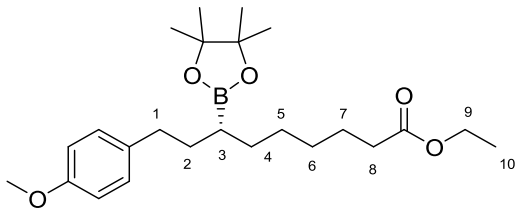


#	Time	Type	Area	Height	Width	Area%	Symmetry
1	10.886	MM	133.7	9.7	0.2297	2.975	0.731
2	11.859	MM	4360.4	296.8	0.2448	97.025	0.697



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	10.648	MM	154.7	8.9	0.2906	1.937	1.111
2	11.595	MM	7831.5	531.7	0.2455	98.063	0.645

Ethyl (*S*)-9-(4-methoxyphenyl)-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nonanate (284q)



Following GP7b, ethyl sulfoxide *anti*-**255q** (71 mg, 0.13 mmol), boronic ester **283** (26 mg, 0.10 mmol) and *i*-PrMgCl·LiCl (1.14 M in THF, 105 µL, 0.120 mmol) afforded after purification by flash column chromatography (hexane:Et_2O = 85:15) the homologated boronic ester **284q** (25.4 mg, 61%) as a colourless oil.

[The racemate was synthesised as above, replacing enantioenriched α-sulfinyl benzoate *anti*-**255q** with racemic α-sulfinyl benzoate *rac*-*anti*-**255q**.]

R_f: 0.30 (hexane:Et_2O = 85:15).

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.08 (d, *J* = 8.6 Hz, 2H, Ar-H), 6.80 (d, *J* = 8.6 Hz, 2H, Ar-H), 4.10 (q, *J* = 7.1 Hz, 2H, 10-H), 3.77 (s, 3H, O-CH_3), 2.59–2.57 (m, 2H, 1-H), 2.26 (t, *J* = 7.5 Hz, 2H, 8-H), 1.74–1.66 (m, 1H, 2-H), 1.64–1.56 (m, 3H, 2-H + 7-H), 1.47–1.36 (m, 2H, 4-H), 1.31–1.21 (m, 19H, C-CH_3 × 4, 5-H, 6-H, 10-H), 1.03 (m, 1H, 3-H).

^{13}C NMR ($CDCl_3$, 101 MHz) δ: 173.9 (CO), 157.6 (Ar-C), 135.1 (Ar-C), 129.2 (2C, Ar-C × 2), 113.6 (2C, Ar-C × 2), 82.9 (2C, B-O-C × 2), 60.1 (10-C), 55.2 (O-CH_3), 34.7 (1-C), 34.3 (8-C), 33.7 (2-C), 31.0 (4-C), 29.4 (6-C), 28.8 (5-C), 24.9 (7-C), 24.8 (2C, C-*C*H_3 × 2), 24.8 (2C, C-*C*H_3 × 2), 14.2 (11-C); *carbon attached to boron not observed due to quadrupolar relaxation*.

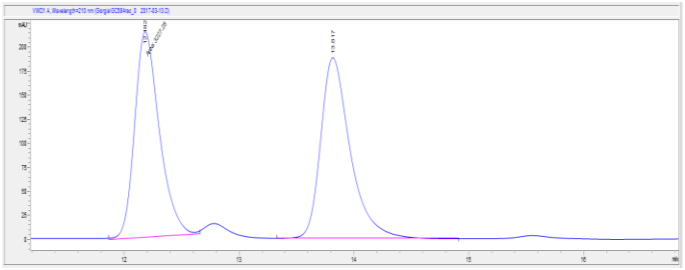
^{11}B NMR ($CDCl_3$, 128 MHz) δ: 34.2.

IR (neat) ν_{max}: 2927, 1733, 1512, 1379, 1314, 1244, 1143, 1036, 967, 824 cm^{-1}.

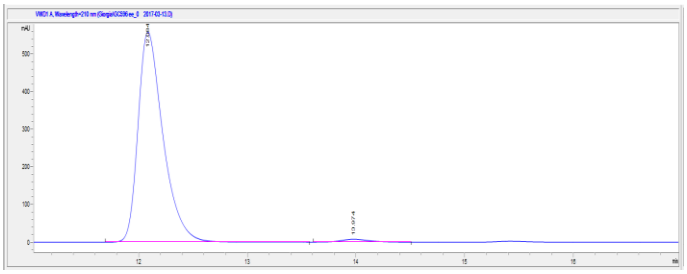
HRMS (ESI) calculated for $C_{24}H_{39}BNaO_5$ $(M+Na)^+$: 441.2787, found: 441.2792.

$[\alpha]^{23}_D$: −6 (*c* 0.8, $CHCl_3$).

Chiral HPLC: Daicel Chiralcel-IB column (25 cm), hexane:isopropanol = 90:10, 0.7 mL/min, room temperature, 210.8 nm: t_R = 12.2 minutes (major), 13.8 minutes (minor), e.r. = 99:1.



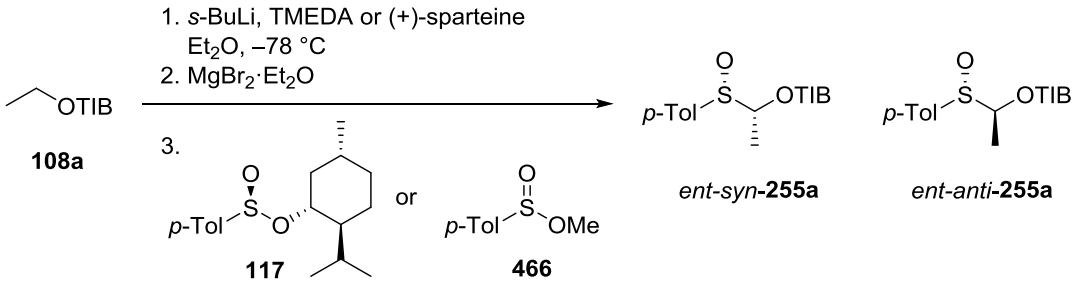
#	Time	Type	Area	Height	Width	Area%	Symmetry
1	12.182	MM	3227.3	214.5	0.2508	48.898	0.722
2	13.817	BB	3372.8	188.2	0.2699	51.102	0.65



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	12.084	BV R	8893.1	557.3	0.2412	98.544	0.611
2	13.974	BB	131.4	7.7	0.2415	1.456	0.769

5.6.8. Determination of the Absolute Configuration of α-Sulfinyl Benzoates

The stereochemistry of the sulfoxide–metal exchange is well established in the literature.[80] While inversion of configuration at sulfur occurs with sulfoxide−metal exchange,[153] the generated metal carbenoid reacts with boronic esters with retention of configuration. When ethyl benzoate **108a** was lithiated with *s*-BuLi in the presence of TMEDA and trapped with racemic methyl tolylsulfinate **466** after transmetalation to the corresponding magnesiated species, all four stereoisomers were obtained (Figure 5.1A). Replacing racemic methyl tolylsulfinate **466** with enantiomeriacally pure Andersen's sulfinate **117** gave two major stereoisomers of benzoate **255a** with *S*-configuration at the sulfur atom (Figure 5.1B). On the other hand, enantioselective lithiation of ethyl benzoate **108a** using (+)-sparteine in the place of TMEDA, followed by transmetalation and trapping of the generated magnesium carbenoid with racemic methyl tolylsulfinate **466** gave two major stereoisomers of benzoate **255a** with *R*-configuration at the carbon centre (Figure 5.1C). The less polar compound on TLC was therefore identified as the *syn* diastereomer *ent-syn*-**255a**, while the more polar compound was revealed to be the *anti* diastereomer *ent-anti*-**255a**.



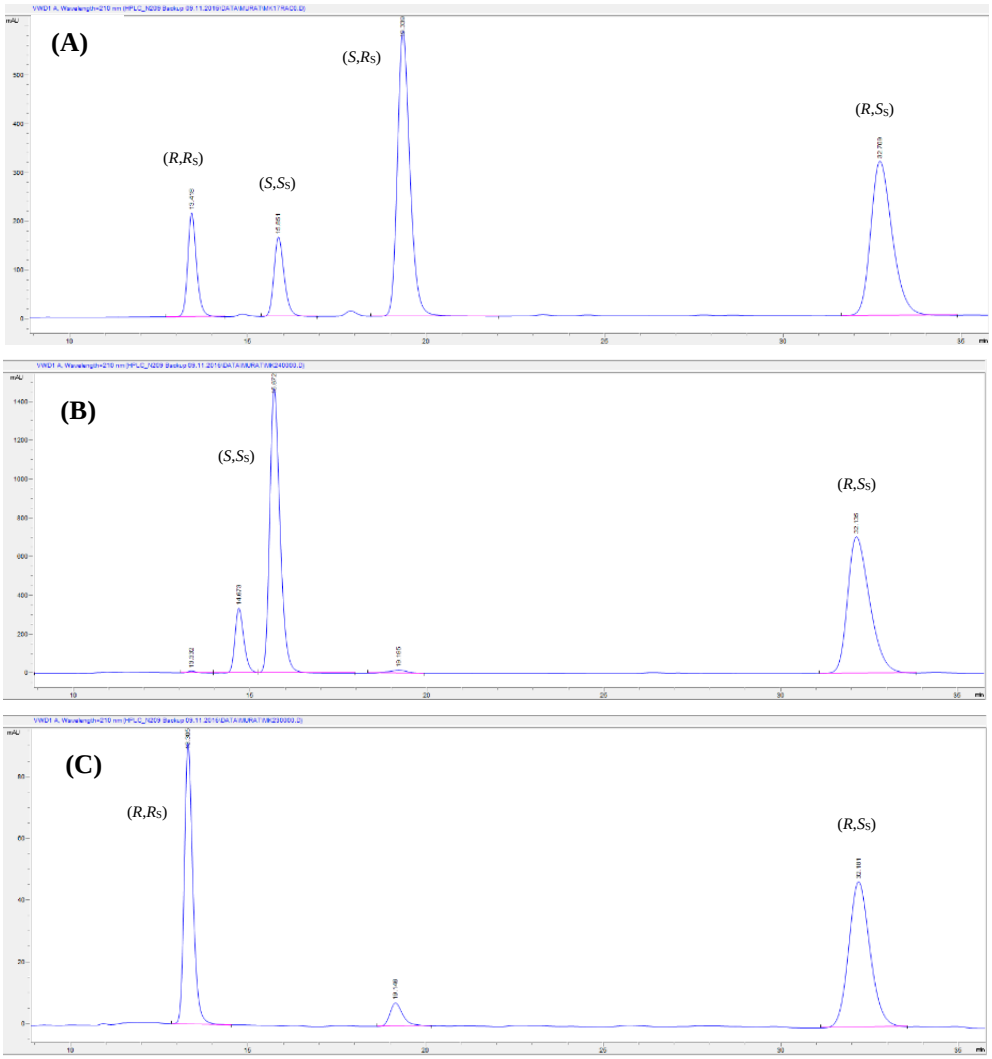
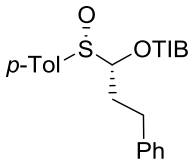
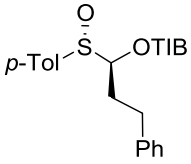
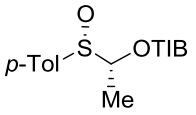
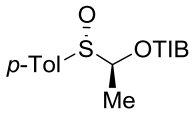
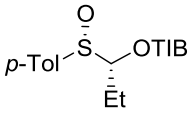
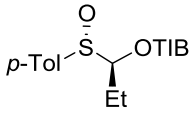
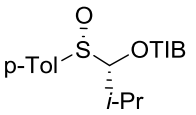
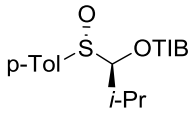
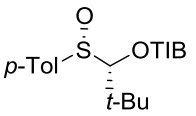
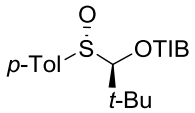
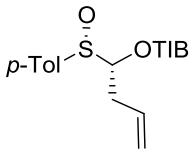
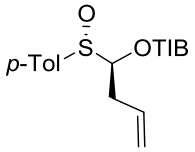
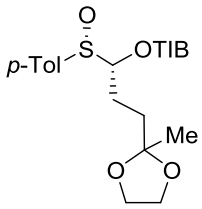
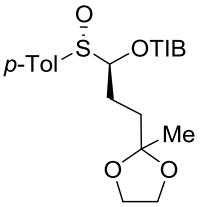
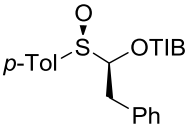
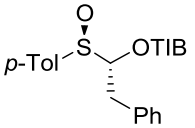


Figure 5.1. (A): Reaction using TMEDA and racemic methyl sulfinate **466**; (B) reaction using TMEDA and Andersen's sulfinate **117**; (C): reaction using (+)-sparteine and racemic methyl sulfinate **466**.

The same experiment using (+)-sparteine was done starting from homoallylic benzoate **108b** and the opposite enantiomer of Andersen's sulfinate *ent*-**117** to generate *ent*-*syn*-**255b** as the major diastereomer (less polar) with only minor amount of *ent*-*anti*-**255b** (more polar).

After comparison of the chemical shifts for the α-sulfinyl proton (^{1}H NMR) and α-sulfinyl carbon (^{13}C NMR), the trends have been used to assign the stereochemistry of sulfoxides **255a-r** as *syn* or *anti*.

syn-**255** (less polar)		*anti*-**255** (more polar)	
	α-H 5.64 ppm α-C 92.0 ppm		α-H 6.08 ppm α–C 87.8 ppm
	α-H 5.79 ppm α-C 89.0 ppm		α-H 6.07 ppm α-C 85.0 ppm
	α-H 5.62 ppm α-C 93.8 ppm		α-H 5.93 ppm α-C 89.9 ppm
	α-H 5.72 ppm α-C 95.8 ppm		α-H 5.89 ppm α-C 94.5 ppm
	α-H 5.61 ppm α-C 98.6 ppm		α-H 5.66 ppm α-C 95.7 ppm
	α-H 5.75 ppm α-C 91.3 ppm		α-H 6.07 ppm α-C 87.2 ppm
	α-H 5.78 ppm α-C 92.5 ppm		α-H 6.09 ppm α-C 88.4 ppm
	α-H 5.99 ppm α-C n.d.		α-H 6.37 ppm α-C 88.3 ppm

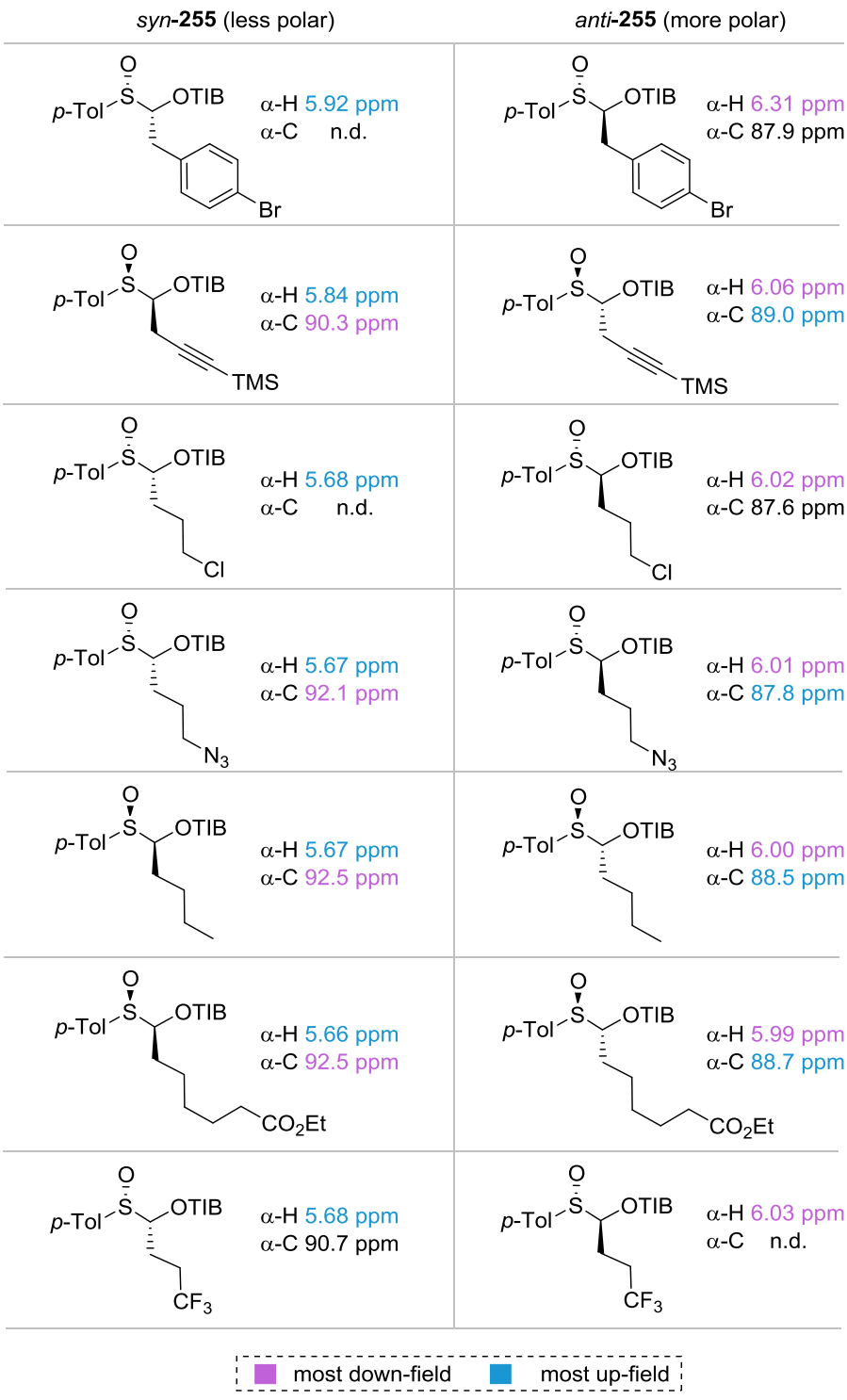
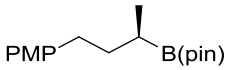


Figure 5.2. Correlation between the chemical shifts α-proton and carbon of sulfinyl benzoates and the relative configuration of compounds **255**.

Furthermore, four known compounds have been synthesised and the optical rotation value of each compound was compared with the values reported in the literature.

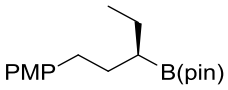


(*R*)-**284a**

$[\alpha]^{23}_{D}$: −19 (*c* 0.7, $CHCl_3$)

For (*R*): −8.2 (*c* 0.98, $CHCl_3$)[93]

For (*S*): +7.6 (*c* 1.7, $CHCl_3$)[92]

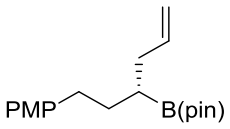


(*R*)-**284c**

$[\alpha]^{23}_{D}$: −9 (*c* 0.7, $CHCl_3$)

For (*R*): −9.6 (*c* 1.05, $CHCl_3$)[93]

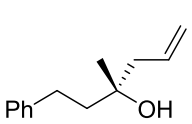
For (*S*): +9.4 (*c* 1.6, $CHCl_3$)[92]



(*S*)-**284b**

$[\alpha]^{23}_{D}$: −16 (*c* 0.8, $CHCl_3$)

For (*R*): +0.12 (*c* 1.05, $CHCl_3$)[92]



(*R*)-**287ab**

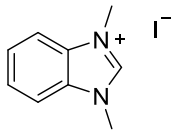
$[\alpha]^{23}_{D}$: +18 (*c* 0.8, $CHCl_3$)

For (*R*): +57 (*c* 1.0, $CHCl_3$)[72]

For (*S*): −58 (*c* 1.0, $CHCl_3$)[222]

5.7. Single Compounds Chapter 4

1,3-Dimethyl-1*H*-benzo[*d*]imidazole-3-ium iodide (330a)



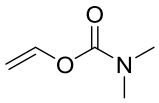
Following a literature reported procedure,[223] benzimidazole (2.0 g, 17 mmol) was charged in a round-bottomed flask equipped with a condenser and aq. KOH (5.0 N, 20 mL) was added, followed by MeOH (10 mL). Methyl iodide (12 mL, 19 mmol) was added dropwise at room temperature and the resulting reaction mixture was stirred at 45 °C for 16 h. After cooling to room temperature, the precipitated solid was filtered and dried *in vacuo* to give iodide **330a** (2.7 g, 59%).

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 9.66 (s, 1H, N-CH-N), 8.05 (dd, J_1 = 6.3 Hz, J_2 = 3.2 Hz, 2H, Ar-H), 7.74 (dd, J_1 = 6.3 Hz, J_2 = 3.2 Hz, 2H, Ar-H), 4.11 (s, 6H, CH_3 × 2).

^{13}C NMR ($CDCl_3$, 101 MHz) δ: 143.6 (N-CH-N), 132.1 (2C, Ar-C × 2), 126.9 (2C, Ar-C × 2), 113.9 (2C, Ar-C × 2), 33.7 (2C, CH_3 × 2).

All analytical data matched that previously reported in the literature.[223]

Vinyl dimethylcarbamate (378)



Following a modified literature reported procedure,[189] a solution of *n*-BuLi (1.6 M in hexane, 9.4 mL, 15 mmol) in THF (12 mL) was stirred at room temperature overnight. The solution was cooled to 0 °C and a solution of dimethylcarbamoyl chloride (0.92 mL, 10 mmol) in anhydrous DMPU (11 mL) was added. The reaction mixture was stirred at room temperature for 4 h and then sat. aq. NH_4Cl (20 mL) and Et_2O (20 mL) were added. The phases were separated and the aqueous phase was extracted with Et_2O (2 × 20 mL). The combined organic phases were dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure without heating. Purification by flash column chromatography on SiO_2 (hexane:Et_2O = 50:50) afforded cabamate **378** (495 mg, 43%) as a colourless oil.

R_f: 0.83 (hexane:EtOAc = 50:50).

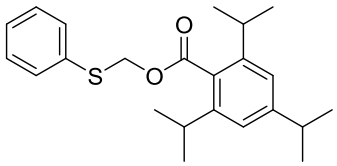
^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.20 (dd, J_1 = 14.0, J_2 = 6.3 Hz, 1H, CH), 4.77 (dd, J_1 = 14.0, J_2 = 1.5 Hz, 1H, CH_{2trans}), 4.43 (dd, J_1 = 6.3, J_2 = 1.5 Hz, 1H, CH_{2cis}), 2.97 (s, 3H, CH_3), 2.94 (s, 3H, CH_3).

^{13}C NMR ($CDCl_3$, 101 MHz) δ: 153.7 (CO), 142.6 (CH), 95.0 (CH_2), 36.5 (CH_3), 35.9 (CH_3).

IR (neat) ν_{max}: 2935, 1715, 1646, 1398, 1371, 1168, 1043, 759 cm^{-1}.

HRMS (ESI) calculated for $C_5H_9NNaO_2$ $(M+Na)^+$: 138.0525, found: 138.0528.

(Phenylthio)methyl 2,4,6-triisopropylbenzoate (393)



Following a modified literature reported procedure,[224] to a solution of 2,4,6-triisopropylbenzoic acid (1.72 g, 6.90 mmol) and Cs_2CO_3 (2.3 g, 6.9 mmol) in DMF (11 mL) was added chloromethyl phenyl sulfide (1.0 g, 6.3 mmol) and the resulting reaction mixture was stirred at 85 °C for 16 h. After cooling to room temperature, the precipitate was filtered off and the filtrate was concentrated under reduced pressure. The residue was dissolved in $CHCl_3$ (20 mL) and washed with 20% aq. $NaHCO_3$ solution (3 × 20 mL). The organic phases were combined, dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. Purification by flash column chromatography on SiO_2 (hexane:EtOAc = 98:2) afforded the pure benzoate **393** (2.2 g, 94%) as a white solid.

R_f: 0.22 (hexane:Et_2O = 98:2).

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.48 (m, 2H, Ar-H), 7.35**–**7.16 (m, 3H, Ar-H), 6.99 (s, 2H, Ar-H), 5.68 (s, 2H, CH_2), 2.88 (m, 3H, C*H*(CH_3)$_2$ × 3), 1.24 (d, *J* = 6.9 Hz, 6H, CH_3 × 2), 1.19 (d, *J* = 6.8 Hz, 12H, CH_3 × 4).

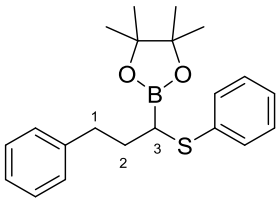
^{13}C NMR ($CDCl_3$, 101 MHz) δ: 170.2 (CO), 150.5 (Ar-C), 145.0 (2C, Ar-C × 2), 134.8 (Ar-C), 129.8 (2C, Ar-C × 2), 129.4 (Ar-C), 129.1 (2C, Ar-C × 2), 127.1 (Ar-C), 120.9 (2C, Ar-C × 2), 68.3 (CH_2), 34.4 (*C*H-(CH_3)$_2$), 31.3 (2C, *C*H-(CH_3)$_2$ × 2), 24.1 (4C, CH_3 × 4), 23.9 (2C, CH_3 × 2).

IR (neat) ν_{max}: 2966, 1735, 1234, 1060, 1046, 748 cm^{-1}.

HRMS (ESI) calculated for $C_{23}H_{30}NaO_2S$ $(M+Na)^+$: 393.1859, found: 393.1859.

M.P.: 47**–**49 ºC.

4,4,5,5-Tetramethyl-2-(3-phenyl-1-(phenylthiol)propyl)-1,3,2-dioxaborolane (392)



To a solution of diisopropylamine (55 µL, 0.40 mmol) in anhydrous THF (200 µL) was added *n*-BuLi (1.6 M in hexane, 0.25 mL, 0.40 mmol) at −78 °C. After stirring for 20 min at −78 °C and 10 min at room temperature, the solution was added dropwise to a mixture of benzoate **393** (148 mg, 0.400 mmol) and phenethyl pinacol boronic ester (46 mg, 0.20 mmol) in anhydrous THF (2 mL) at −78 °C. The resulting reaction mixture was stirred at −78 °C for 1 h, then it was allowed to warm to room temperature and stirred for additional 1 h. H_2O (10 mL) and Et_2O (10 mL) were sequentially added, the phases were separated and the aqueous phase was extracted with Et_2O (2 × 10 mL). The combined organic phases were dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. Purification by flash silica gel column chromatography (hexane:Et_2O = 95:5) afforded homologated boronic ester **392** (32 mg, 45%) as a colourless oil.

R_f: 0.53 (hexane:CH_2Cl_2 = 50:50).

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.35 (m, 2H, Ar-H), 7.29–7.11 (m, 8H, Ar-H), 2.88–2.61 (m, 3H, 1-H + 3-H), 2.03 (m, 2H, 2-H), 1.22 (d, *J* = 2.5 Hz, 12H, C-CH_3 × 4).

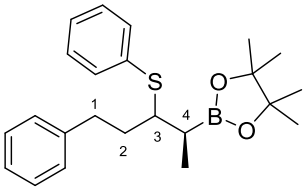
^{13}C NMR ($CDCl_3$, 101 MHz) δ: 141.7 (Ar-C), 136.3 (Ar-C), 130.0 (2C, Ar-C × 2), 128.6 (2C, Ar-C × 2), 128.5 (2C, Ar-C × 2), 128.3 (2C, Ar-C × 2), 126.0 (Ar-C), 125.8 (Ar-C), 84.0 (2C, B-O-C × 2), 34.7 (2-C), 32.8 (1-C), 24.7 (2C, C-*C*H_3 × 2), 24.6 (2C, C-*C*H_3 × 2); *carbon attached to boron not observed due to quadrupolar relaxation.*

^{11}B NMR ($CDCl_3$, 128 MHz) δ: 33.3.

IR (neat) ν_{max}: 2976, 1455, 1367, 1330, 1141, 845, 739 cm^{-1}.

HRMS (ESI) calculated for $C_{21}H_{28}BO_2S$ $(M+H)^+$: 355.1901, found: 355.1915.

4,4,5,5-Tetramethyl-2-(1-phenyl-4-(phenylthio)pentan-3-yl)-1,3,2-dioxaborolane (395)



Following a literature reported procedure,[73] a solution of stannane (*R*)-**109** (158 mg, 0.360 mmol) in anhydrous Et_2O (2.0 mL) was cooled to −78 °C and *n*-BuLi (225 µL, 0.360 mmol) was added dropwise. The mixture was stirred at −78 °C for 1 h, then a solution of crude boronic ester **392** (0.3 mmol) in Et_2O (1.0 mL) was added dropwise at −78 °C. After stirring at −78 °C for 30 min, the mixture was warmed to room temperature and heated at 35 °C for 16 h. H_2O (10 mL) and Et_2O (10 mL) were added, the phases were separated and the aqueous phase was extracted with Et_2O (2 × 10 mL). The combined organic phases were dried over $MgSO_4$, filtered and the solvent was removed *in vacuo*. Purification by flash column chromatography on silica gel (hexane:Et_2O = 95:5) afforded boronic ester **395** (30 mg, 26%, 1:1 d.r.) as a colourless oil.

R_f: 0.42 (hexane:CH_2Cl_2 = 60:40).

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.48–7.43 (m, 4H, Ar-H), 7.31–7.08 (m, 16H, Ar-H), 3.33 (m, 2H, 3-H), 2.95–2.66 (m, 4H, 1-H), 2.05–1.78 (m, 4H, 2-H), 1.47 (m, 2H, 4-H), 1.25 (d, *J* = 1.9 Hz, 24H, C-CH_3 × 8), 1.14 (d, *J* = 7.4 Hz, 3H, CH-C*H*$_3$ diast. a), 1.07 (d, *J* = 7.4 Hz, 3H, CH-C*H*$_3$ diast. b).

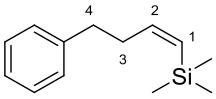
^{13}C NMR ($CDCl_3$, 101 MHz) δ: 142.2 (Ar-C, diast. a), 142.1 (Ar-C, diast b), 136.3 (Ar-C, diast. a), 136.2 (Ar-C, diast. b), 131.9 (2C, Ar-C × 2, diast. a), 131.9 (2C, Ar-C × 2, diast. b), 128.7 (2C, Ar-C × 2, diast. a), 128.7 (2C, Ar-C × 2, diast. b), 128.5 (2C, Ar-C × 2, diast. a), 128.4 (2C, Ar-C × 2, diast. b), 128.3 (2C, Ar-C × 2, diast. a), 128.2 (2C, Ar-C × 2, diast. b), 126.4 (Ar-C, diast. a), 126.4 (Ar-C, diast. b), 125.7 (Ar-C, diast. a), 125.7 (Ar-C, diast. b), 83.3 (2C, B-O-C × 2, diast. a), 83.3 (2C, B-O-C × 2, diast. b), 52.8 (3-C, diast. a), 51.9 (3-C, diast. b), 36.7 (2-C, diast. a), 34.9 (2-C, diast. b), 33.4 (1-C, diast. a), 33.3 (1-C, diast. b), 24.9 (2C, C-*C*H_3 × 2, diast. a), 24.9 (2C, C-*C*H_3 × 2, diast. a), 24.7 (2C, C-*C*H_3 × 2, diast. b), 24.7 (2C, C-*C*H_3 × 2, diast. b), 12.5 (CH-*C*H_3, diast. a), 11.8 (CH-*C*H_3, diast. b); *carbon attached to boron not observed due to quadrupolar relaxation.*

^{11}B NMR ($CDCl_3$, 128 MHz) δ: 33.6.

IR (neat) ν_{max}: 2976, 2930, 1454, 1379, 1318, 1141, 966, 856, 744 cm^{-1}.

HRMS (ESI) calculated for $C_{23}H_{31}BNaO_2S$ $(M+Na)^+$: 405.2034, found: 405.2062.

(*Z*)-Trimethyl(4-phenylbut-1-en-1-yl)silane ((*Z*)-400)



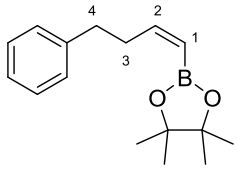
To a solution of (2-bromovinyl)trimethylsilane (approx. 90% *trans*, 108 mg, 0.600 mmol) in anhydrous Et_2O (2.0 mL) was added *t*-BuLi (1.7 M in pentane, 710 µL, 1.20 mmol) dropwise at −78 °C. The reaction mixture was stirred at −78 °C for 45 min, then a solution of phenethyl pinacol boronic ester **43** (70 mg, 0.30 mmol) in Et_2O (0.50 mL) was added dropwise. The mixture for stirred at −78 °C for 30 min, warmed to 0 °C and stirred for additional 30 min. A solution of I_2 (168 mg, 0.660 mmol) in anhydrous MeOH (2.0 mL) was added dropwise at 0° C, the reaction mixture was stirred for 30 min at this temperature and then warmed to room temperature for 1 h. Sat. aq. $Na_2S_2O_3$ (10 mL) and Et_2O (10 mL) were sequentially added, the phases were separated and the aqueous phase was extracted with Et_2O (2 × 10 mL). The combined organic phases were dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. Purification by flash column chromatography on silica gel (hexane) afforded desired alkene (*Z*)-**400** (38 mg, 62%, >95:5 *Z*:*E*) as a colourless oil.

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.33–7.27 (m, 2H, Ar-H), 7.23–7.16 (m, 3H, Ar-H), 6.35 (dt, J_1 = 14.3 Hz, J_2 = 7.3 Hz, 1H, 2-H), 5.54 (dt, J_1 = 14.0 Hz, J_2 = 1.3 Hz, 1H, 1-H), 2.70 (t, J = 8.4 Hz, 2H, 4-H), 2.45 (q, J = 7.3 Hz, 2H, 3-H), 0.09 (s, 9H, Si-CH_3 × 3).

^{13}C NMR ($CDCl_3$, 101 MHz) δ: 147.8 (2-C), 141.8 (Ar-C), 129.8 (Ar-C), 128.4 (2C, Ar-C × 2), 128.3 (2C, Ar-C × 2), 125.8 (1-C), 36.1 (4-C), 35.5 (3-C), 0.2 (3C, CH_3 × 3).

All analytical data matched that previously reported in the literature.[225]

(*Z*)-4,4,5,5-Tetramethyl-2-(4-phenylbut-1-en-1-yl)-1,3,2-dioxaborolane ((*Z*)-401)



Following a literature reported procedure,[192] to a solution of (*Z*)-**400** (0.02 g, 0.05 mmol) in anhydrous CH_2Cl_2 (2.0 mL) at −30 °C was added BCl_3 (1.0 M in CH_2Cl_2, 400 µL, 0.400 mmol) dropwise. The reaction mixture was stirred at −30 °C for 5 h, then a solution of pinacol (35 mg, 0.30 mmol) and Et_3N (85 µL, 0.60 mmol) in CH_2Cl_2 (2.0 mL) was added and the resulting mixture was stirred at room temperature for 16 h. Sat. aq. Na_2CO_3 was added (10 mL), followed by Et_2O (10 mL). The phases were separated and the aqueous phase was extracted with Et_2O (2 × 10 mL). The combined organic phases were dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. Purification by flash column chromatography on silica gel (hexane:Et_2O = 98:2) afforded alkene (*Z*)-**401** (16 mg, 62%, >95:5 *Z*:*E*) as a colourless oil.

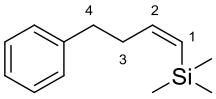
^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.31–7.15 (m, 5H, Ar-H), 6.47 (m, 1H, 2-H), 5.37 (d, *J* = 13.4 Hz, 1H, 1-H), 2.77–2.68 (m, 4H, 4-H + 3-H), 1.26 (s, 12H, CH_3 × 4).

^{13}C NMR ($CDCl_3$, 101 MHz) δ: 153.9 (2-C), 142.9 (Ar-C), 128.6 (2C, Ar-C × 2), 128.3 (2C, Ar-C × 2), 125. 8 (Ar-C), 82.9 (2C, B-O-C × 2), 36.1 (4-C), 34.0 (3-C), 24.9 (4C, CH_3 × 4); *carbon attached to boron not observed due to quadrupolar relaxation.*

^{11}B NMR ($CDCl_3$, 128 MHz) δ: 28.8.

All analytical data matched that previously reported in the literature.[226]

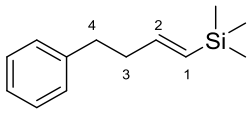
(*Z*)-Trimethyl(4-phenylbut-1-en-1-yl)silane ((*Z*)-400)



Following a literature reported procedure,[98] to a solution of (2-bromovinyl)trimethylsilane (approx. 90% *trans*, 108 mg, 0.600 mmol) in anhydrous THF (2.0 mL) was added *t*-BuLi (1.7 M in pentane, 710 µL, 1.20 mmol) dropwise at −78 °C. The reaction mixture was stirred at −78 °C for 45 min, then a solution of phenethyl pinacol boronic ester **40** (70 mg, 0.30 mmol) in THF (0.50 mL) was added dropwise. The mixture for stirred at −78 °C for 30 min, warmed to 0 °C and stirred for additional 30 min. A solution of PhSeCl (69 mg, 0.36 mmol) in anhydrous THF (0.50 mL) was added dropwise at −78° C. The reaction mixture was stirred for 30 min at this temperature, warmed to room temperature for 15 min and then cooled to 0 °C. A suspension of NaOMe (81 mg, 1.5 mmol) in MeOH (3.0 mL) was added dropwise and the mixture was stirred at 0 °C for 2 h. Sat. aq. $Na_2S_2O_3$ (10 mL) and Et_2O (10 mL) were sequentially added, the phases were separated and the aqueous phase was extracted with Et_2O (2 × 10 mL). The combined organic phases were dried over $MgSO_4$ and the solvent was removed under reduced pressure. Purification by chromatography on silica gel (hexane) afforded alkene (*Z*)-**400** (25 mg, 41%, >95:5 *Z*:*E*) as a colourless oil.

Spectral data matched that previously described in this report.

(*E*)-Trimethyl(4-phenylbut-1-en-1-yl)silane ((*E*)-400)



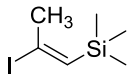
Following a literature reported procedure,[98] to a solution of (2-bromovinyl)trimethylsilane (approx. 90% *trans*, 108 mg, 0.600 mmol) in anhydrous THF (2.0 mL) was added *t*-BuLi (1.7 M in pentane, 710 µL, 1.20 mmol) dropwise at −78 °C. The reaction mixture was stirred at −78 °C for 45 min, and a solution of phenethyl pinacol boronic ester **43** (70 mg, 0.30 mmol) in THF (0.50 mL) was added dropwise. The mixture for stirred at −78 °C for 30 min, warmed to 0 °C and stirred for additional 30 min. A solution of PhSeCl (69 mg, 0.36 mmol) in anhydrous THF (0.50 mL) was added dropwise at −78° C. The reaction mixture was stirred for 30 min at −78° C, warmed to room temperature for 15 min and then filtered through a short plug of SiO_2 washing with Et_2O. The filtrate was concentrated under reduced pressure and the residue was dissolved in THF (0.50 mL). A solution of *m*-CPBA (104 mg, 0.60 mmol) in THF (3.0 mL) was added dropwise at −78 °C and the resulting solution was warmed to −45 °C and stirred for 30 min. Dimethylsulfide (0.44 mL, 6.0 mmol) was added at −45 °C and the mixture was allowed to warm to room temperature and subsequently filtered through a short plug of SiO_2 washing with Et_2O. The filtrate was concentrated under reduced pressure and the residue was purified by chromatography on SiO_2 (hexane) to afford desired alkene (*E*)-**400** (22 mg, 36%, >95:5 *E*:*Z*) as a colourless oil.

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.32–7.22 (m, 2H, Ar-H), 7.22–7.13 (m, 3H, Ar-H), 6.08 (dt, J_1 = 18.5 Hz, J_2 = 6.1 Hz, 1H, 2-H), 5.54 (dt, J_1 = 18.6 Hz, J_2 = 1.5 Hz, 1H, 1-H), 2.71 (t, J = 7.5 Hz, 2H, 4-H), 2.41 (m, 2H, 3-H), 0.04 (s, 9H, Si-CH_3 × 3).

^{13}C NMR ($CDCl_3$, 101 MHz) δ: 146.1 (2-C), 142.0 (Ar-C), 130.4 (Ar-C), 128.5 (2C, Ar-C × 2), 128.2 (2C, Ar-C × 2), 125.7 (1-C), 38.5 (4-C), 35.2 (3-C), −1.0 (3C, CH_3 × 3).

All analytical data matched that previously reported in the literature.[225]

(*E*)-(2-Iodoprop-1-en-1-yl)trimethylsilane (403)



Following a literature reported procedure,[193] to a solution of molybdenum catalyst $Mo(CO)_2(allyl)Br(MeCN)_2$* (151 mg, 0.425 mmol) in THF (8.5 mL) at room temperature, was added 1-(trimethylsilyl)-1-propyne (983 mg, 8.76 mmol). Bu_3SnH (2.3 mL, 8.5 mmol) was added dropwise over 2 min and the resulting dark reaction mixture was stirred for 1 h, then the solvent was removed under reduced pressure. The residue was taken up in hexane and filtered through a short plug of silica gel washing with hexane. The solvent was removed *in vacuo* to afford a mixture of the desired hydrostannylated product and Bu_3SnH that was used directly in the next step without further purification.

To a solution of the hydrostannylated product in CH_2Cl_2 (25 mL) at 0 °C was added a solution of I_2 (2.2 g, 8.5 mmol) in CH_2Cl_2 (85 mL) dropwise *via* cannula until a dark purple colour persisted. The mixture was immediately quenched with sat. aq. $Na_2S_2O_3$ (40 mL) and allowed to warm to room temperature. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 40 mL). The combined organic phases were dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. Purification by flash column chromatography on SiO_2 afforded alkene **403** (620 mg, 31%) as a colourless oil.

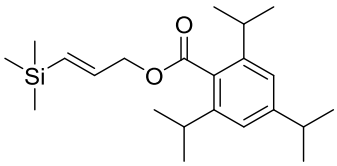
^{1}H NMR ($CDCl_3$, 400 MHz) δ: 6.29 (q, *J* = 1.0 Hz, 1H, CH), 2.54 (d, *J* = 1.0 Hz, 3H, C-CH_3), 0.14 (s, 9H, Si-CH_3 × 3).

^{13}C NMR ($CDCl_3$, 101 MHz) δ: 144.2 (Si-CH), 110.0 (C_q), 34.7 (C-CH_3), −0.2 (3C, Si-CH_3 × 3).

All analytical data matched that previously reported in the literature.[193]

* $Mo(CO)_2(allyl)Br(MeCN)_2$ was prepared as follows:[227] $Mo(CO)_6$ (1.3 g, 5.0 mmol) was dissolved in a mixture of anhydrous benzene and CH_3CN (1/1 *v*/*v*, 20 mL in total) and allyl bromide (0.65 mL, 7.5 mmol) was added. The resulting white suspension was heated at 80 °C for 4 h to give a yellow/orange solution. The reaction mixture was allowed to cool to room temperature and the resulting yellow precipitate was filtered and washed with benzene. IR spectrum recorded on the solid after drying *in vacuo* was found to be in agreement with the values reported in the literature.[227]

(*E*)-3-(Trimethylsilyl)allyl 2,4,6-triisopropylbenzoate (426)



A solution of TIBOH (857 mg, 3.45 mmol), (*E*)-3-(trimethylsilyl)prop-2-en-1-ol (500 mg, 3.84 mmol), and PPh_3 (997 mg, 3.80 mmol) in anhydrous THF (14.0 mL) was cooled to −5 °C and DIAD (750 µL, 3.80 mmol) was added dropwise. The resulting mixture was stirred at −5 °C for 30 min, then it was warmed to room temperature and stirred overnight. Sat. aq. $NaHCO_3$ (10 mL) and H_2O (10 mL) were added, the phases were separated and the aqueous phase was extracted with Et_2O (2 × 20 mL). The combined organic phases were dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The crude residue was dissolved in the minimum amount of hot CH_2Cl_2 and the resulting solution was poured into stirred cold pentane. The formed precipitate was filtered off and the solvent was removed *in vacuo*. Purification of the crude residue by flash column chromatography on silica gel (hexane:Et_2O = 98:2) afforded benzoate **426** (1.05 g, 85%) as a colourless oil.

R_f: 0.30 (hexane:CH_2Cl_2 = 90:10).

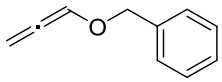
^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.01 (s, 2H, Ar-H), 7.16 (dt, J_1 = 18.7 Hz, J_2 = 5.1 Hz, 1H, Si-CH), 6.06 (dt, J_1 = 18.7 Hz, J_2 = 1.2 Hz, 1H, CH_2-C*H*), 4.82 (dd, J_1 = 5.1 Hz, J_2 = 1.2 Hz, 2H, CH_2), 2.88 (hept, J = 6.8 Hz, 3H, C*H*$(CH_3)_2$ × 3), 1.24 (d, J = 6.9 Hz, 18H, CH_3 × 6), 0.08 (s, 9H, Si-$(CH_3)_3$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ: 170.4 (CO), 150.2 (Ar-C), 144.8 (2C, Ar-C × 2), 138.9 (CH_2-*C*H), 134.8 (Si-*C*H), 130.3 (Ar-C), 120.9 (2C, Ar-C × 2), 67.2 (CH_2), 34.4 (*C*H-$(CH_3)_2$), 31.4 (2C, *C*H-$(CH_3)_2$ × 2), 24.1 (4C, CH_3 × 4), 24.0 (2C, CH_3 × 2), −1.5 (3C, Si-$(CH_3)_3$).

IR (neat) ν_{max}: 2959, 1728, 1247, 1069, 862, 837 cm^{-1}.

HRMS (ESI) calculated for $C_{22}H_{37}O_2Si$ $(M+H)^+$: 361.2557, found: 361.2567.

((Propa-1,2-dien-1-yloxy)methyl)benzene (318a)



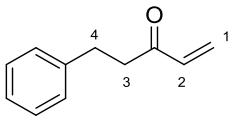
Following a literature reported procedure,[200] to a solution of benzyl propargyl ether (5.0 g, 34 mmol) in anhydrous THF (20 mL) at room temperature was added *t*-BuOK (1.14 g, 10.2 mmol). The resulting suspension was stirred at room temperature for 3 h and then filtered through a pad of celite washing with Et_2O. The solvent was removed under reduced pressure and the crude residue was purified by chromatography on silica gel (hexane:Et_2O = 98:2 with 0.5% Et_3N, silica gel was washed with 1% Et_3N before running the column) to afford allene **318a** (4.47 g, 89%) as a yellowish liquid.

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.40−7.27 (m, 5H, Ar-H), 6.84 (t, *J* = 5.9 Hz, 1H, CH), 5.48 (d, *J* = 5.9 Hz, 2H, C-CH_2), 4.62 (s, 2H, Ph-CH_2).

^{13}C NMR ($CDCl_3$, 101 MHz) δ: 201.3 (C_q), 137.3 (Ar-C), 128.4 (2C, Ar-C × 2), 127.8 (Ar-C), 127.8 (2C, Ar-C × 2), 121.6 (CH), 91.1 (C-*C*H_2), 70.6 (Ph-CH_2).

All analytical data matched that previously reported in the literature.[200]

5-Phenylpent-1-en-3-one (443)



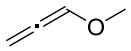
To a solution of allene **318a** (53 mg, 0.36 mmol) in anhydrous Et_2O (2.0 mL) at −42 °C was added *n*-BuLi (1.6 M in hexane, 225 µL, 0.360 mmol) dropwise. The reaction mixture was stirred at −42 °C for 30 min, warmed to 0 °C and stirred for additional 10 min. The mixture was cooled to −78 °C and a solution of phenethyl pinacol boronic ester **43** (70 mg, 0.30 mmol) in Et_2O (0.50 mL) was added dropwise. The reaction was stirred at −78 °C for 30 min and at 0 °C for further 30 min, then a suspension of NaOMe (49 mg, 0.90 mmol) in MeOH (0.50 mL) was added dropwise at −78 °C, immediately followed by the addition of a solution of I_2 (91 mg, 0.36 mmol) in MeOH (1.5 mL). The mixture was stirred at −78 °C for 1 h and at 0 °C for 10 min. Sat. aq. $Na_2S_2O_3$ (10 mL) and Et_2O (10 mL) were added, the phases were separated and the aqueous phase was extracted with Et_2O (2 × 10 mL). The combined organic phases were sequentially washed with sat. aq. $NaHCO_3$ (20 mL), 1.0 M HCl (20 mL) and sat. aq. $NaHCO_3$ (20 mL), dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. Purification of the crude reaction mixture by flash column chromatography on silica gel (hexane:Et_2O = 95:5) afforded enone **443** (21 mg, 44%) as a colourless oil.

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.37−7.08 (m, 5H, Ar-H), 6.36 (dd, J_1 = 17.7 Hz, J_2 = 10.5 Hz, 1H, 2-H), 6.21 (dd, J_1 = 17.7 Hz, J_2 = 1.0 Hz, 1H, 1-H$_{trans}$), 5.83 (dd, J_1 = 10.5 Hz, J_2 = 1.0 Hz, 1H, 1-H$_{cis}$), 3.04–2.84 (m, 4H, 3-H + 4-H).

^{13}C NMR ($CDCl_3$, 101 MHz) δ: 199.7 (CO), 141.0 (Ar-C), 136.5 (2-C), 128.5 (2C, Ar-C × 2), 128.3 (2C, Ar-C × 2), 128.2 (1-C), 126.1 (Ar-C), 41.2 (3-C), 29.8 (4-C).

All analytical data matched that previously reported in the literature.[228]

1-Methoxypropa-1,2-diene (318b)



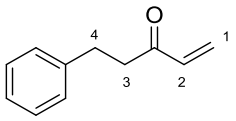
Following a modified literature reported procedure,[229] to neat methyl propargyl ether (5.7 g, 80 mmol) at room temperature was added *t*-BuOK (0.90 g, 8.0 mmol). The resulting suspension was heated at 65 °C for 3 h and then allowed to cool to room temperature. The condenser was removed and the reaction flask was connected to a receiving vessel cooled to −78 °C. Distillation under vacuum without heating afforded allene **318b** (3.2 g, 56%) as a colourless liquid.

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 6.77 (t, *J* = 5.9 Hz, 1H, CH), 5.48 (d, *J* = 5.9 Hz, 2H, C-CH_2), 3.41 (s, 3H, Ph-CH_2).

^{13}C NMR ($CDCl_3$, 101 MHz) δ: 201.1 (C_q), 122.9 (CH), 91.3 (C-*C*H_2), 55.9 (CH_3).

All analytical data matched that previously reported in the literature.[229]

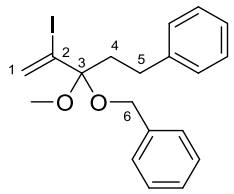
5-Phenylpent-1-en-3-one (443)



To a solution of allene **318b** (34 mg, 0.48 mmol) in anhydrous Et_2O (2.5 mL) at −42 °C was added *n*-BuLi (1.6 M in hexane, 300 µL, 0.480 mmol) dropwise. The reaction mixture was stirred at −42 °C for 30 min, warmed to 0 °C and stirred for additional 10 min. The mixture was cooled to −78 °C and a solution of phenethyl pinacol boronic ester **43** (93 mg, 0.40 mmol) in Et_2O (0.50 mL) was added dropwise. The reaction was stirred at −78 °C for 30 min and at 0 °C for further 30 min, then MeOH (3.0 mL) was added dropwise at 0 °C. The mixture was stirred at 0 °C for 30 min and at room temperature for 2 h before being quenched by addition of H_2O (10 mL). Et_2O (10 mL) was added, the phases were separated and the aqueous phase was extracted with Et_2O (2 × 10 mL). The combined organic phases were dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The crude reaction mixture was dissolved in a mixture of THF:H_2O (1:1 *v*/*v*, 10 mL) and $NaBO_3{\cdot}4H_2O$ (370 mg, 2.40 mmol) was added. The mixture was stirred at room temperature for 3 h, then H_2O (5 mL) and Et_2O (10 mL) were added. The phases were separated and the aqueous phase was extracted with Et_2O (2 × 10 mL). The combined organic phases were dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. Purification of the crude reaction mixture by flash column chromatography on silica gel (hexane:Et_2O = 95:5) afforded enone **443** (37 mg, 58%) as a colourless oil.

Spectral data matched that previously described in this report.

(3-(Benzyloxy)-4-iodo-3-methoxypent-4-en-1-yl)benzene (442a)



To a solution of allene **318a** (53 mg, 0.36 mmol) in anhydrous Et_2O (2.0 mL) at −42 °C was added *n*-BuLi (1.6 M in hexane, 225 µL, 0.360 mmol) dropwise. The reaction mixture was stirred at −42 °C for 30 min, warmed to 0 °C and stirred for additional 10 min. The mixture was cooled to −78 °C and a solution of phenethyl pinacol boronic ester **43** (70 mg, 0.30 mmol) in Et_2O (0.50 mL) was added dropwise. The reaction was stirred at −78 °C for 30 min and at 0 °C for further 30 min. A suspension of NaOMe (49 mg, 0.90 mmol) in MeOH (0.50 mL) was added dropwise at 0 °C, immediately followed by the addition of a solution of I_2 (228 mg, 0.90 mmol) in MeOH (1.5 mL). The mixture was stirred at 0 °C for 30 min and at room temperature for 2 h. Sat. aq. $Na_2S_2O_3$ (10 mL) and Et_2O (10 mL) were added, the phases were separated and the aqueous phase was extracted with Et_2O (2 × 10 mL). The combined organic phases were dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. Purification of the crude reaction mixture by flash column chromatography on silica gel (hexane:Et_2O = 98:2) afforded vinyl iodide **442a** (78 mg, 64%) as a colourless oil.

R_f: 0.50 (hexane:Et_2O = 95:5).

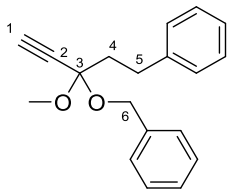
^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.44−7.33 (m, 5H, Ar-H), 7.32−7.27 (m, 2H, Ar-H), 7.22−7.15 (m, 3H, Ar-H), 6.87 (d, *J* = 1.3 Hz, 1H, 1-H), 6.25 (d, *J* = 1.2 Hz, 1H, 1-H), 4.53 (d, *J* = 11.5 Hz, 1H, 6-H), 4.45 (d, *J* = 11.5 Hz, 1H, 6-H), 3.30 (s, 3H, CH_3), 2.55−2.42 (m, 2H, 5-H), 2.31−2.16 (m, 2H, 4-H).

^{13}C NMR ($CDCl_3$, 101 MHz) δ: 141.3 (Ar-C), 138.0 (Ar-C), 131.5 (1-C), 128.4 (4C, Ar-C × 4), 128.2 (2C, Ar-C × 2), 127.5 (2C, Ar-C × 2), 127.5 (Ar-C), 125.9 (Ar-C), 111.1 (3-C), 102.7 (2-C), 63.9 (6-C), 49.7 (CH_3), 35.4 (4-C), 29.5 (5-C).

IR (neat) ν_{max}: 2960, 1609, 1497, 1453, 1147, 1070, 1040, 919, 732 cm^{-1}.

HRMS (ESI) calculated for $C_{19}H_{21}NaO_2$ $(M+Na)^+$: 431.0478, found: 431.0472.

(3-(Benzyloxy)-3-methoxypent-4-yn-1-yl)benzene (447a)



Following a literature reported procedure,[99] to a solution of vinyl iodide **442a** (37 mg, 0.091 mmol) in anhydrous DMF (1.2 mL) was added TBAF·$3H_2O$ (145 mg, 0.455 mmol) at room temperature. The resulting reaction mixture was heated at 60 °C for 1 h, then cooled to room temperature. H_2O (10 mL) was added, followed by Et_2O (10 mL), the phases were separated and the aqueous phase was extracted with Et_2O (2 × 10 mL). The combined organic phases were dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. Purification of the crude reaction mixture by flash column chromatography on silica gel (hexane:Et_2O = 97:3) afforded alkyne **447a** (24 mg, 93%) as a colourless oil.

R_f: 0.21 (hexane:Et_2O = 98:2).

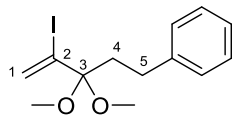
^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.41−7.33 (m, 4H, Ar-H), 7.33**–**7.26 (m, 3H, Ar-H), 7.25−7.17 (m, 3H, Ar-H), 4.76 (d, *J* = 11.5 Hz, 1H, 6-H), 4.63 (d, *J* = 11.4 Hz, 1H, 6-H), 3.41 (s, 3H, CH_3), 2.91**–**2.87 (m, 2H, 5-H), 2.67 (s, 1H, 1-H), 2.29−2.14 (m, 2H, 4-H).

^{13}C NMR ($CDCl_3$, 101 MHz) δ: 141.5 (Ar-C), 137.9 (Ar-C), 128.4 (2C, Ar-C × 2), 128.4 (4C, Ar-C × 4), 127.7 (Ar-C), 127.5 (Ar-C), 125.9 (2C, Ar-C × 2), 98.9 (3-C), 80.3 (2-C), 74.2 (1-C), 65.2 (6-C), 50.2 (CH_3), 39.4 (4-C), 30.5 (5-C).

IR (neat) ν_{max}: 3282, 2117, 1454, 1146, 1101, 1038, 1026, 731 cm^{-1}.

HRMS (ESI) calculated for $C_{19}H_{20}NaO_2$ $(M+Na)^+$: 303.1356, found: 303.1357.

(4-Iodo-3,3-dimethoxypent-4-en-1-yl)benzene (442b)



To a solution of allene **318b** (34 mg, 0.480 mmol) in anhydrous Et_2O (2.5 mL) at −42 °C was added *n*-BuLi (1.6 M in hexane, 300 µL, 0.48 mmol) dropwise. The reaction mixture was stirred at −42 °C for 30 min, then warmed to 0 °C and stirred for additional 10 min. The mixture was cooled to −78 °C and a solution of phenethyl pinacol boronic ester **43** (93 mg, 0.40 mmol) in Et_2O (0.50 mL) was added dropwise. The reaction was stirred at −78 °C for 30 min and at 0 °C for further 30 min. A suspension of NaOMe (65 mg, 1.2 mmol) in MeOH (0.50 mL) was added dropwise at 0 °C, immediately followed by the addition of a solution of I_2 (305 mg, 1.20 mmol) in MeOH (2.0 mL). The mixture was stirred at 0 °C for 30 min and at room temperature for 2 h. Sat. aq. $Na_2S_2O_3$ (10 mL) and Et_2O (10 mL) were added, the phases were separated and the aqueous phase was extracted with Et_2O (2 × 10 mL). The combined organic phases were dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. Purification of the crude reaction mixture by flash column chromatography on silica gel (hexane:Et_2O = 98:2) afforded vinyl iodide **442b** (81 mg, 61%) as a colourless oil.

R_f: 0.50 (hexane:Et_2O = 95:5).

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.33−7.23 (m, 2H, Ar-H), 7.23**–**7.14 (m, 3H, Ar-H), 6.75 (d, *J* = 1.1 Hz, 1H, 1-H), 6.20 (d, *J* = 1.2 Hz, 1H, 1-H), 3.24 (s, 6H, CH_3 × 2), 2.52−2.38 (m, 2H, 5-H), 2.17−2.07 (m, 2H, 4-H).

^{13}C NMR ($CDCl_3$, 101 MHz) δ: 141.4 (Ar-C), 131.3 (1-C), 128.4 (2C, Ar-C × 2), 128.2 (2C, Ar-C × 2), 125.9 (Ar-C), 111.1 (3-C), 102.5 (2-C), 49.4 (2C, CH_3 × 2), 34.8 (4-C), 29.5 (5-C).

IR (neat) ν_{max}: 2960, 1609, 1454, 1138, 1084, 1043, 918, 739 cm^{-1}.

HRMS (ESI) calculated for $C_{13}H_{17}INaO_2$ $(M+Na)^+$: 355.0165, found: 355.0176.

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