Author:
Fairchild, Molly E

Title:
Organolithium-mediated assembly of five-membered rings bearing contiguous stereocentres

Organolithium-Mediated Assembly of Five-Membered Rings Bearing Contiguous Stereocentres

Molly E. Fairchild

Supervisor: Professor Varinder K. Aggarwal

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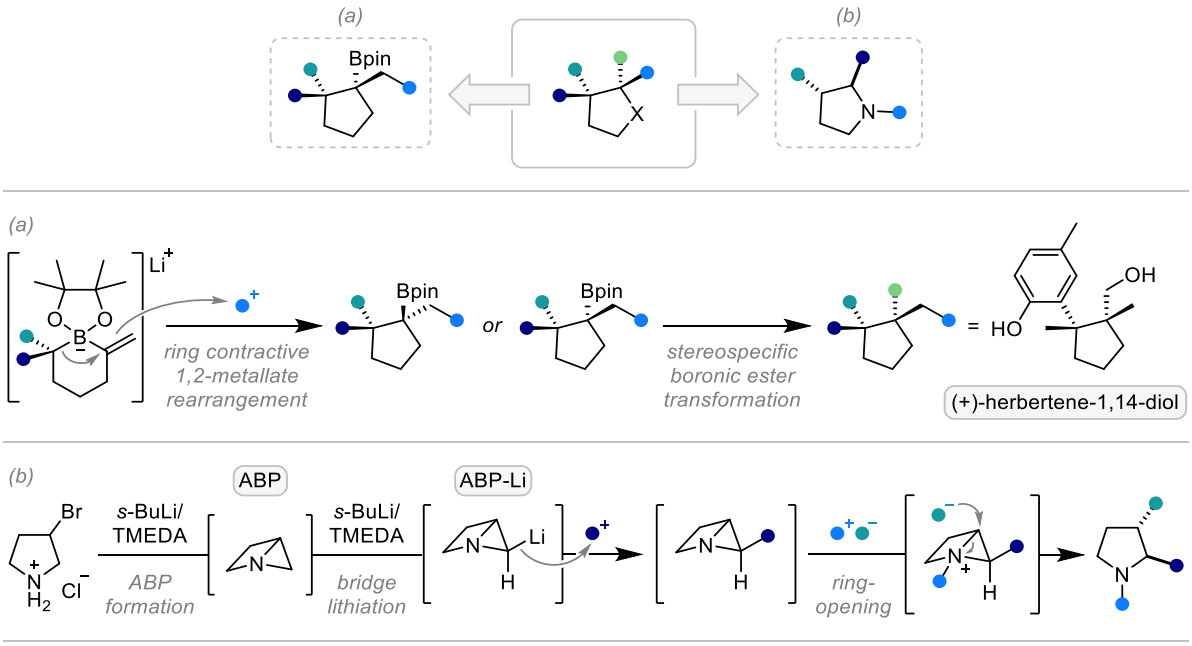
Abstract

Since the presence of contiguous stereocentres in a natural product or pharmaceutical target often presents an impediment to its synthesis, particularly if one or more of these stereocentres are quaternary, new methodologies for their stereoselective construction are of great importance to synthetic chemists. This thesis outlines the development of two novel and conceptually distinct methodologies for the organolithium-mediated assembly of 5-membered rings bearing contiguous stereocentres.

The diastereoselective synthesis of cyclopentyl boronic esters bearing two contiguous fully substituted stereocentres was achieved through the electrophile-induced ring contractive 1,2-metallate rearrangement of enantioenriched 6-membered cyclic alkenyl boronate complexes. A remarkable solvent-induced diastereodivergence was observed, allowing the synthesis of complementary diastereomeric pairs. Using this novel ring contractive methodology and through the subsequent stereospecific functionalisation of the boronic ester moiety, the asymmetric total synthesis of (+)-herbertene-1,14-diol was accomplished.

Additionally, the diastereoselective synthesis of 1,2,3-trifunctionalised pyrrolidines was realised through the formation, lithiation, functionalisation and ring-opening of novel strain-release reagent 1-azabicyclo[2.1.0]pentane (ABP). The lithiation/functionalisation of ABP proved highly regio- and diastereoselective and, upon electrophilic activation, ABP was shown to be more susceptible to nucleophilic attack than its lower and higher homologues.



Acknowledgements

Firstly, I would like to thank Varinder for his enduring guidance and encouragement. From the outset, Varinder trusted me to both run my own research project and supervise junior students in the lab. The latter proved to be simultaneously the most enriching and challenging part of my PhD, providing me with opportunities to connect with many members of the group and learn a lot both about chemistry and myself.

When the COVID-19 pandemic hit in early 2020, 6 months into my time in Bristol, I don't think I could have quite imagined the impact that it would have on my PhD studies. Despite the social restrictions of the time, I was able to forge valuable and long-lasting friendships during the shift work of my first year, building a support system from my 'bubble' (Charlotte, Vanessa and Jasper) that became critical to my four years in Bristol.

Charlotte showed me the ropes when I first arrived in the Aggarwal lab, equipping me with both the practical skills and pragmatic mentality necessary for a successful PhD. I am grateful to Vanessa for always bringing positive energy to the lab and to Jasper for encouraging me to always strive for a little bit more. I am certain that these friendships will live long beyond our shared time in N205.

I would also like to thank Sheenagh for being a constant source of support and conversation (mainly by the microwave… most of my lunches had to be heated up twice as they were cold by the time we had finished chatting). In the latter half of my PhD, Friday evenings at the pub also provided opportunities to connect with other PhD students in the group—Dawn, Jack, Chris, Kris, Malcolm, Dylan, Maryam, Tom, Hetty—and put the world to rights.

I feel very lucky to have had the opportunity to learn from so many talented post-docs during my time in the group. During my first few months, Durga, Adam E. and Kay quickly became role models in the lab, teaching me the skills I needed to independently run a research project. Whilst Daniele, Christian and Margherita ensured that I kept learning up until the final days of my PhD. The support from the group's research officer Adam has also been invaluable.

Finally, whilst a lot of my support came from within the SCB, most of it came from further afield. The unwavering support of my friends and family ensured that I never doubted my decision to pursue a PhD, and the infectious positivity and understanding of my partner Eddy made even the hardest days a little brighter. Whilst the sacrifice of living apart for 4 years felt like too much at times, there was never any doubt that it would be worth it in the end.

Author’s declaration

I declare that the work in this dissertation was carried out in accordance with the requirements 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 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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Contents

Acronyms and abbreviations

A	activator
ABB	azabicyclo[1.1.0]butane
ABH	1-azabicyclo[3.1.0]hexane
ABP	1-azabicyclo[2.1.0]pentane
Ac	acetyl
acac	acetylacetate
AIBN	azobisisobutyronitrile
aq.	aqueous
BCB	bicyclo[1.1.0]butane
Boc	*tert*-butyloxycarbonyl
Bn	benzyl
Bneo	neopentylglycol boronic ester
Bpin	pinacol boronic ester
bpy	2,2′-bipyridine
Bz	benzoyl
Cb	*N*,*N*-diisopropylcarbamoyl
Cbz	benzyloxycarbonyl
cod	cycloocta-1,5-diene
Cy	cyclohexyl
dba	bis(dibenzylideneacetate)
DCE	1,2-dichloroethane
DIBALH	diisobutylaluminium hydride
dippf	1,1′-bis(diisopropylphosphino)ferrocene
DMA	dimethylacetamide
DMAP	4-dimethylaminopyridine
DME	dimethoxyethane
dppf	1,1'-bis(diphenylphosphino)ferrocene
d.r.	diastereomeric ratio
E	electrophile
e.e.	enantiomeric excess
e.r.	enantiomeric ratio
e.s.	enantiospecificity
eq.	equivalent(s)
EWG	electron-withdrawing group
GCMS	gas chromatography mass spectrometry
h	hour(s)

HFIP	1,1,1,3,3,3-hexafluoroisopropanol
HMDS	hexamethyldisilazane
HMPA	hexamethylphosphoramide
HPLC	high performance liquid chromatography
LDA	lithium diisopropylamide
LG	leaving group
m-CPBA	*m*eta-chloroperoxybenzoic acid
Mes	mesityl
min	minute(s)
MOM	methoxymethyl
NBS	*N*-bromosuccinimide
n.d.	not determined
nOe	nuclear Overhauser effect
o/n	overnight
PIDA	phenyliodine(III) diacetate
PMP	4-methoxyphenyl
ppy	2-phenylpyridine
quant.	quantitative
rac	racemic
rsm	returned starting material
rt	room temperature
SFC	supercritical fluid chromatography
TBAB	tetra-*n*-butylammonium bromide
TBAF	tetra-*n*-butylammonium fluoride
TBS	*tert*-butyldimethylsilyl
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
TFE	2,2,2-trifluoroethanol
TIB	2,4,6-triisopropyl benzoate
TMEDA	tetramethylethylenediamine
TMP	tetramethylpiperidide
TMS	trimethylsilyl
Tol	tolyl
Troc	trichloroethoxycarbonyl
Ts	toluenesulfonyl

1. Introduction

1.1. Constructing contiguous stereocentres

A carbon stereocentre bears four different substituents at the four vertices of a tetrahedron. If two or more stereocentres are adjacent in a molecule, they are labelled 'contiguous'. The synthesis of molecules bearing two or more contiguous stereocentres is challenging, particularly if one or more of these stereocentres are quaternary (*i.e.* the four different substituents are all carbon-based).[1–4] This owes to the difficulty in constructing a sterically congested quaternary centre at an already highly hindered site, whilst simultaneously controlling stereochemistry.

Contiguous stereocentres represent an important structural feature existing in many complex natural product and pharmaceutical targets.[1–4] The presence of such motifs in low molecular weight compounds often presents the main impediment to their synthesis (Figure 1).[5–7]

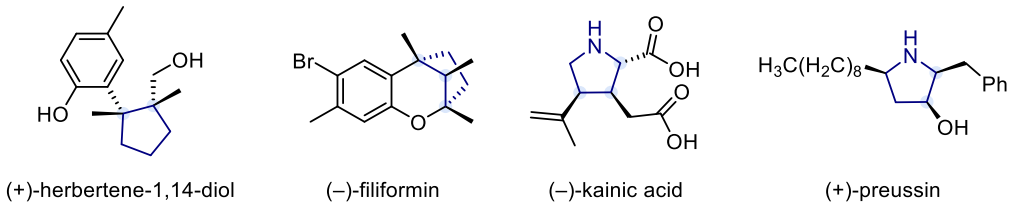


Figure 1. Natural products bearing two or more contiguous stereocentres.

In a chiral molecule bearing two contiguous stereocentres, four possible stereoisomers exist (Figure 2). Since the absolute and relative configurations of stereocentres in a chiral molecule can influence its properties *in vivo*, different enantiomers/diastereomers may exhibit different biological activities.[8] In this way, the continual development of new synthetic methodologies for the stereoselective construction of contiguous stereocentres is of paramount importance.

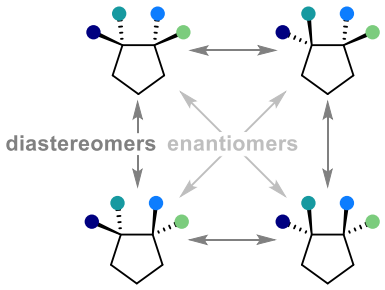


Figure 2. Four possible stereoisomers of a 1,1,2,2-tetrasubstituted cyclopentane.

1.2. Outline of projects

The following discussion outlines the development of two novel and conceptually distinct methodologies for the diastereoselective synthesis of 5-membered rings bearing contiguous stereocentres (Figure 3).

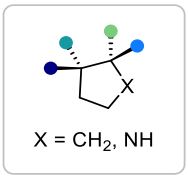
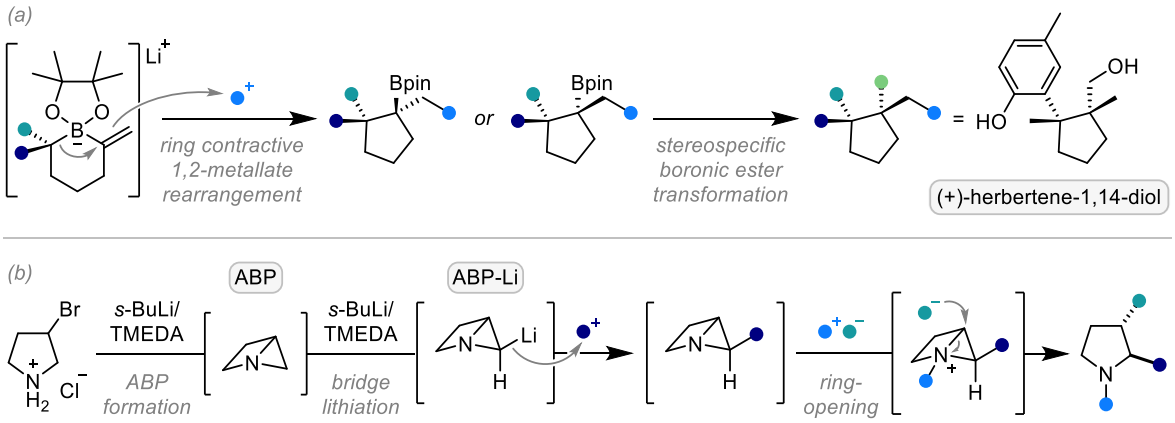


Figure 3. 5-Membered rings bearing contiguous stereocentres.

Chapter 2 discusses the development of a novel electrophile-induced ring contractive 1,2-metallate rearrangement of enantioenriched 6-membered cyclic alkenyl boronate complexes for the enantiospecific and diastereoselective synthesis of cyclopentyl boronic esters bearing two contiguous fully substituted stereocentres (Scheme 1a).

Chapter 3 extends this methodology to the asymmetric total synthesis of the natural product (+)-herbertene-1,14-diol, with a focus on the construction of the two contiguous quaternary stereocentres through the derivatisation of the boronic ester moiety.

Chapter 4 details investigations into the synthesis, lithiation, functionalisation and ring-opening of the novel strain-release reagent 1-azabicyclo[2.1.0]pentane (ABP), enabling the diastereoselective synthesis of pyrrolidines bearing two contiguous stereocentres (Scheme 1b). The rationale behind the unexpected selectivity of the lithiation is also discussed.



Scheme 1. Outline of projects for the organolithium-mediated assembly 5-membered rings bearing contiguous stereocentres.

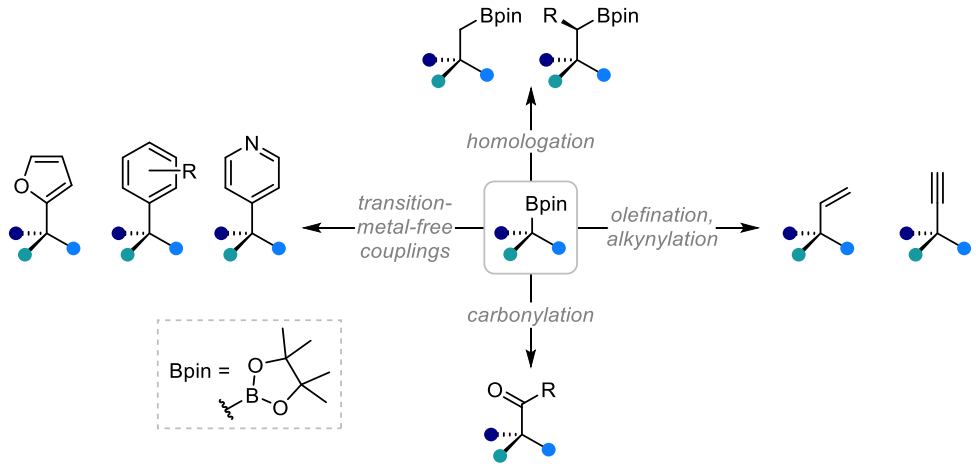
2. Diastereodivergent synthesis of cyclopentyl boronic esters bearing contiguous fully substituted stereocentres

2.1. Tertiary boronic esters as versatile synthetic handles

Enantioenriched tertiary boronic esters are highly useful synthetic intermediates in the synthesis of quaternary stereocentres, owing to their air and moisture stability and the ability of the C–B bond to be directly transformed into a C–C bond, yielding a quaternary stereocentre.[9]

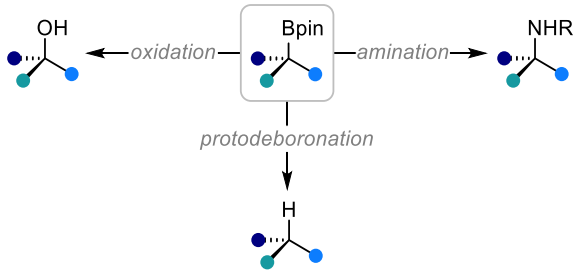
Whilst primary and secondary boronic esters are employed extensively in cross-coupling reactions, such as the Suzuki-Miyaura reaction,[10–13] couplings with tertiary boronic esters are not yet possible. However, a range of stereospecific transition-metal-free boronic ester functionalisation reactions have enabled the synthesis of quaternary stereocentres from enantioenriched tertiary boronic ester starting materials (Scheme 2).[9,14,15]

New C(sp^3)–C(sp^3) bonds can be constructed in homologation reactions, whilst new C(sp^3)–C(sp^2) bonds can be constructed in olefination, arylation and carbonylation reactions. Alkynylation reactions enable the construction of new C(sp^3)–C(sp) bonds.



Scheme 2. Stereospecific transformations of tertiary boronic esters to give quaternary stereocentres.

Enantioenriched tertiary alcohols and amines can also be accessed from enantioenriched boronic esters, as well as tertiary stereocentres, where the C–B bond is replaced by a C–H bond (Scheme 3).[9]



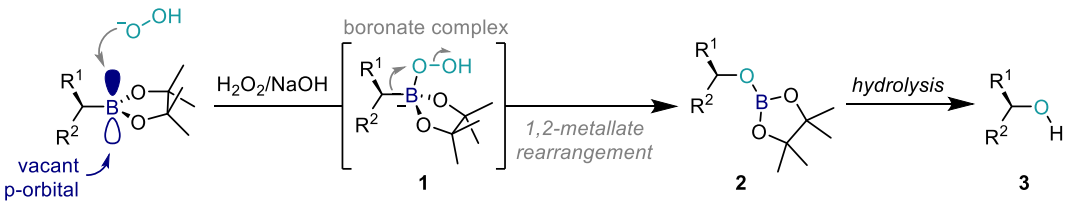
Scheme 3. Stereospecific transformations of tertiary boronic esters to give tertiary stereocentres.

2.2. 1,2-Metallate rearrangements of boronate complexes

2.2.1. Boronate complexes and their reactivity

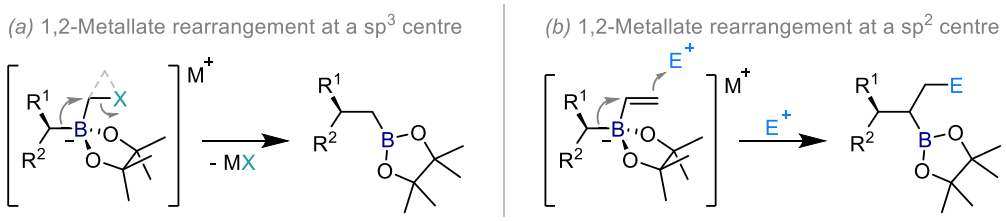
Boronic esters are Lewis acids with an empty *p*-orbital on boron. This empty *p*-orbital is able to accept a pair of electrons from a nucleophilic species to give a negatively charged boron-'ate' complex or boronate complex. This boronate complex can undergo a rearrangement whereby one substituent on boron migrates to an adjacent electrophilic site with complete stereospecificity: a 1,2-metallate rearrangement.

This reactivity is exemplified in the oxidation of boronic esters by basic hydrogen peroxide (Scheme 4).[9] In the oxidation of boronic esters, the 1,2-shift of the boronate complex (**1**) occurs with expulsion of a hydroxyl leaving group to give a borate ester (**2**), hydrolysed on work-up to give an alcohol product (**3**).



Scheme 4. Oxidation of boronic esters by basic hydrogen peroxide.

New C–C bonds can be forged upon 1,2-metallate rearrangement when there is an electrophilic carbon site adjacent to boron. A range of leaving groups on a sp^3 carbon adjacent to boron can induce the 1,2-metallate rearrangement (Scheme 5a); this can also occur concomitantly with the ring-opening of a strained (hetero)cyclic alkane. Alternatively, an adjacent alkenyl group can be activated by an electrophilic species, rendering the α-carbon to boron electrophilic and inducing the 1,2-metallate rearrangement (Scheme 5b).



Scheme 5. 1,2-Metallate rearrangements of boronate complexes.

2.2.2. 1,2-Metallate rearrangements at sp^3 centres

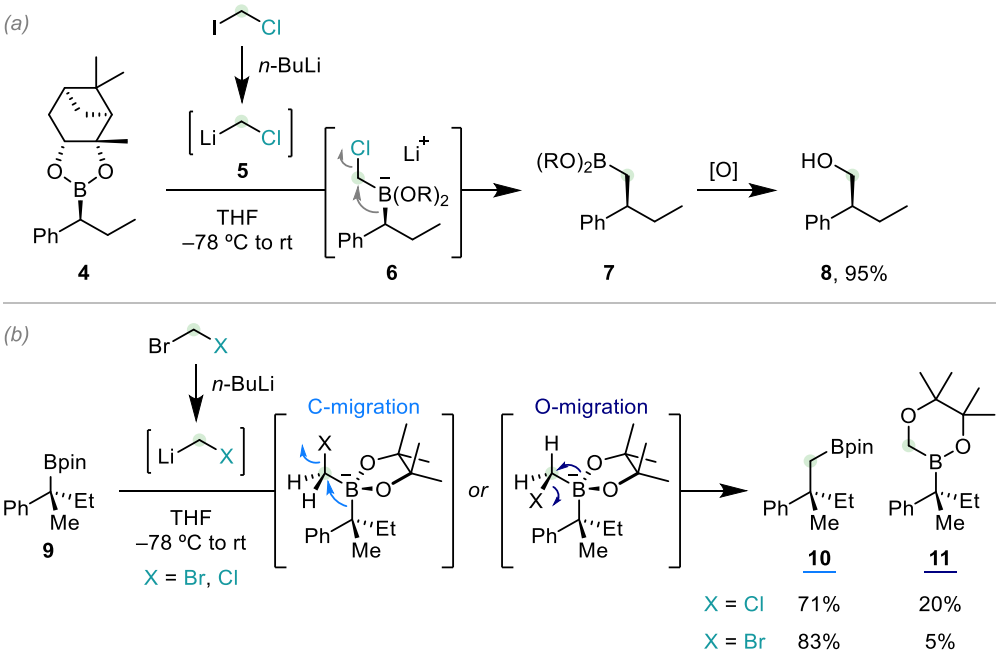
2.2.2.1. Leaving-group-driven 1,2-metallate rearrangements

A boronate complex may undergo a 1,2-metallate rearrangement if an adjacent sp^3 carbon bears a leaving group. This occurs with the displacement of this group.

The Matteson homologation is an archetypal leaving-group-driven 1,2-metallate rearrangement, introducing a methylene unit into a C–B bond (Scheme 6). This reaction was first reported by Matteson in 1985 (Scheme 6a).[16] Lithium-iodine exchange of chloroiodomethane affords lithium carbenoid **5** which, in the presence of boronic ester **4**, generates boronate complex **6**. Upon warming to room temperature, the 1,2-metallate rearrangement of boronate complex **6** occurs with displacement of a chloride ion to give homologated boronic ester **7**, isolated as alcohol **8** upon oxidation. The antiperiplanar relationship of the migrating C–B σ-bond with the C–Cl σ-bond is a prerequisite for this rearrangement, owing to the necessity for the donation of electron density from the C–B σ-bond into the C–Cl σ*-orbital. Stereodefined boronic esters thus undergo this homologation reaction with enantiospecificity.[9]

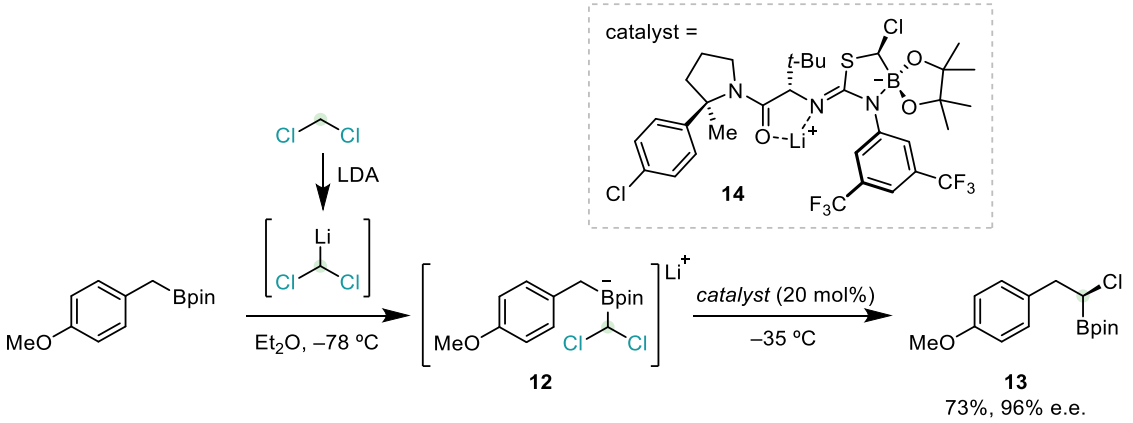
Since this initial discovery, a range of Matteson homologation protocols have been developed,[17–19] with typical conditions employing *n*-butyl lithium and bromochloromethane to generate the required lithium carbenoid.

Interestingly, when investigating the homologation of tertiary boronic esters, such as **9**, Aggarwal and co-workers identified competitive 1,2-migration processes (Scheme 6b).[15] Both *C*- and *O*-migration could be observed through ^{11}B NMR spectroscopic analysis, giving desired boronic ester **10** and undesired borinic ester **11**, respectively. However, *O*-migration could be limited through use of a more bulky and less polar bromide leaving group.



Scheme 6. Matteson homologation: 1,2-metallate rearrangement of α-halo boronate complexes.

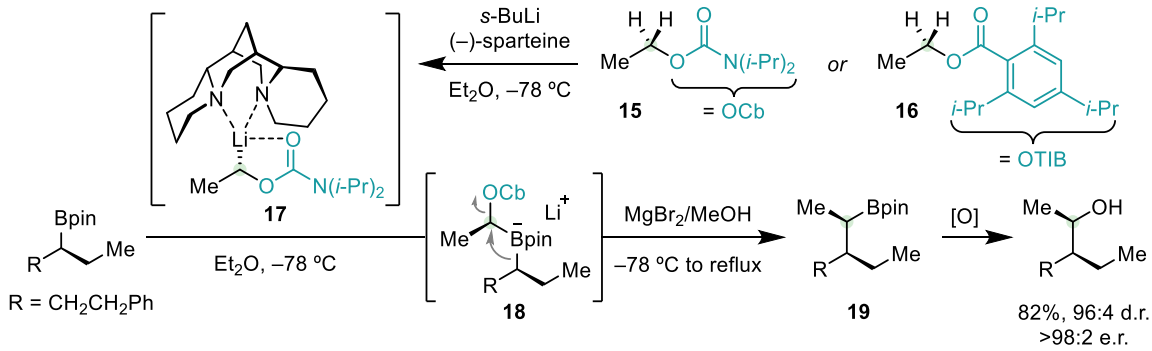
In 2021, Jacobsen and co-workers reported an enantioselective, catalytic Matteson homologation for the synthesis of highly enantioenriched α-chloro boronic esters (Scheme 7).[20] Upon addition of the active catalyst to prochiral dichloromethyl boronate complex **12**, an enantioselective 1,2-metallate rearrangement occurs, with enantioselective abstraction of chloride to give **13**. The identity of the catalytic species was confirmed to be lithium-isothiourea-boronate complex **14**.



Scheme 7. Jacobsen's enantioselective, catalytic Matteson homologation.

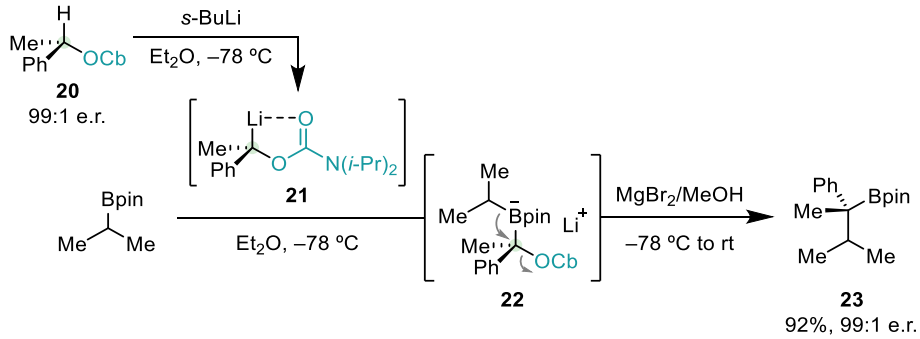
Methodology developed by Aggarwal and co-workers has extended the concept of leaving-group-driven 1,2-metallate rearrangements beyond that initially developed by Matteson, through use of carbamate[21,22] and benzoate[23] leaving groups (Scheme 8). The

advantage of these lies in the ability to generate chiral lithium carbenoids, such as **17**, in high enantiomeric excess through a reagent-controlled enantioselective deprotonation of a prochiral carbamate (**15**) or benzoate (**16**).[24] These dipole-stabilised[25] α-lithiated species have been demonstrated to be chemically and configurationally stable at –78 °C.[26] Boronate complex **18** undergoes a stereospecific 1,2-metallate rearrangement with inversion of configuration at elevated temperatures. Homologations with chiral boronic esters lead to products with contiguous stereocentres (**19**).[21] This methodology has been termed 'lithiation–borylation'.



Scheme 8. Aggarwal's lithiation–borylation homologation for the synthesis of secondary boronic esters.

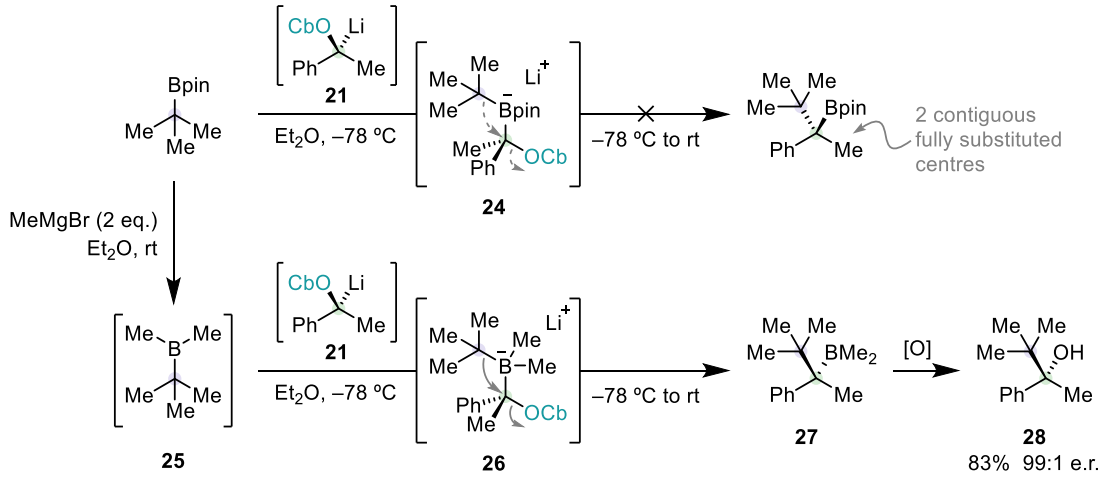
Building on this premise, Aggarwal and co-workers developed a methodology for the synthesis of tertiary boronic esters, employing chiral lithium carbenoid **21**, generated through the deprotonation of enantioenriched carbamate **20** (Scheme 9).[27,28] Boronate complex **22** again undergoes a stereospecific 1,2-metallate rearrangement with inversion of configuration at ambient temperature to give tertiary boronic ester **23** with complete enantiospecificity; there is perfect chirality transfer from **20** to **23**. The addition of $MgBr_2$/MeOH prior to warming ensured the excellent e.r. of the product by preventing the racemisation of **21** at elevated temperatures.[28]



Scheme 9. Aggarwal's lithiation–borylation homologation for the synthesis of tertiary boronic esters.

However, extension of this methodology for the assembly of contiguous fully substituted centres proved challenging (Scheme 10).[29] Boronate complex **24** did not undergo the desired

1,2-metallate rearrangement, with reversal back to lithiated carbamate **21** dominating. At ambient temperature, decomposition of **21** occurred. However, when the tertiary boronic ester was transformed to dimethyl borane **25** and then added to lithiated carbamate **21** to give tetraalkyl ate complex **26**, the desired 1,2-metallate rearrangement occurred to give borane **27**, which is tertiary and bears an adjacent quaternary centre.



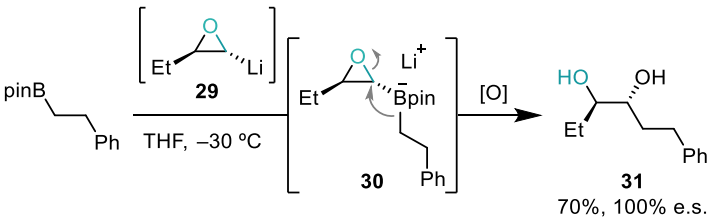
Scheme 10. Lithiation–borylation for the construction of contiguous fully substituted carbon centres.

It was hypothesised that the success of the transformation of borane **25** was due to its lesser steric hindrance and enhanced electrophilicity compared to the boronic ester. In addition, ate complexes derived from boranes have been observed to have a lower barrier to 1,2-migration.[29]

Borane **27** was directly oxidised to give alcohol **28**. The lower air and moisture stability of boranes compared to boronic esters limits the utility of this methodology, since the useful boron-containing functional handle cannot be retained in a bench-stable product.

2.2.2.2. Strain-release-driven 1,2-metallate rearrangements

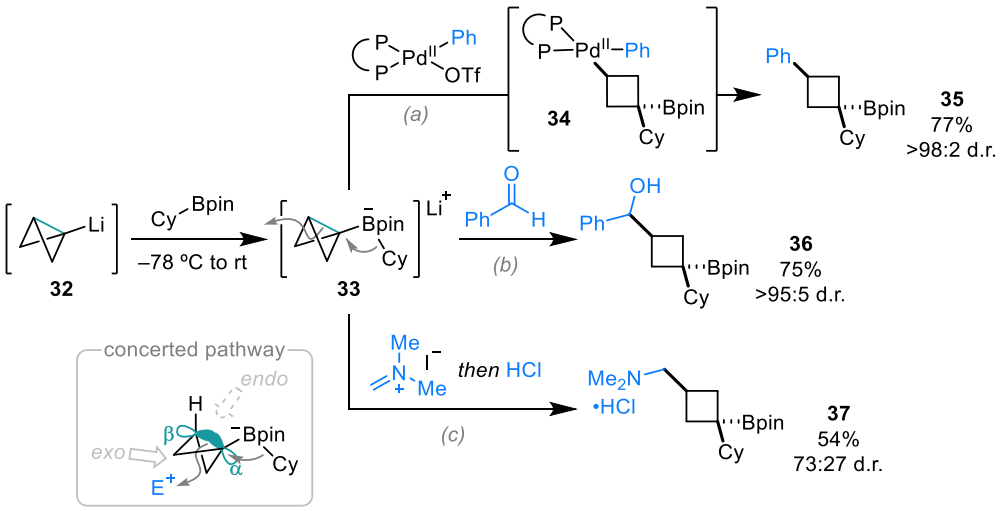
The release of strain from small cycles can also accompany 1,2-metallate rearrangements.[30] This includes the homologation of boronic esters with lithiated epoxides (Scheme 11).[31] Boronate complex **30**, formed by stereoretentive trapping of enantioenriched epoxide **29** by a boronic ester, undergoes a 1,2-metallate rearrangement. This occurs with relief of the ring strain present in the epoxide, giving extended chain **31** with complete diastereoselectivity and enantiospecificity. Methods for the homologation of boronic esters with lithiated aziridines[32] and lithiated azetidinium ions[33] have also been developed. This principle has since been extended to involve the cleavage of strained C–C bonds,[34] such as in the ring-opening of activated cyclopropanes.[35]



Scheme 11. 1,2-Metallate rearrangements driven by the cleavage of strained 3-membered rings.

Moreover, bicyclo[1.1.0]butyl (BCB) boronate complex **33**, formed through the addition of a boronic ester to bicyclo[1.1.0]butyl lithium **32**, was found to undergo electrophile-induced 1,2-metallate rearrangements, occurring with cleavage of the central, strained C–C σ-bond (Scheme 12). Electrophilic palladium complexes have been shown to induce this 1,2-migration with formation of a C–Pd bond at the β-carbon to give aryl-Pd(II) species **34** (Scheme 12a).[36] Subsequent reductive elimination yields cross-coupled product **35** in high yield and diastereoselectivity. The origin of this high diastereoselectivity has been attributed to the dominance of a concerted pathway, where reaction with the electrophile occurs at the exo face of the β-carbon, where greatest electron density resides.

The diastereoselective difunctionalisation of the C–C σ-bond in BCB-boronate complex **33** has been extended to include a range of classical electrophiles, including aldehydes to furnish cyclobutyl boronic ester **36** (Scheme 12b) and iminium salts for nitrogen atom incorporation in **37** (Scheme 12c).[37]



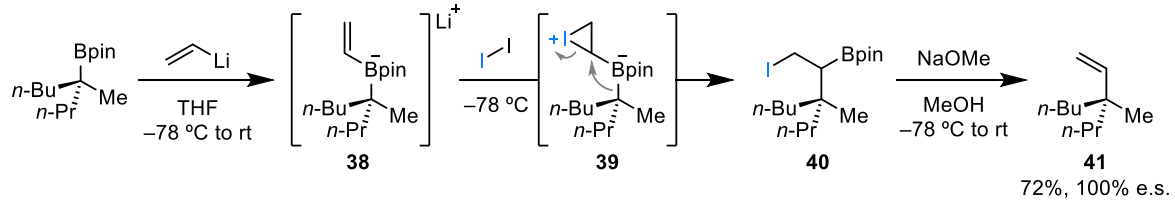
Scheme 12. Electrophile-induced 1,2-metallate rearrangements of bicyclo[1.1.0]butyl boronate complexes.

2.2.3. 1,2-Metallate rearrangements at sp^2 centres

2.2.3.1. Electrophile-induced 1,2-metallate rearrangements

A boronate complex may undergo a 1,2-metallate rearrangement if an adjacent alkenyl group is activated, leaving an electrophilic α-carbon in the boronate complex to which migration can occur. The activation of the alkenyl boronate complex may occur through interaction with a classical electrophile.[38]

Whilst first developed to stereospecifically convert vinyl boranes to alkenes using iodine and sodium hydroxide,[39] the Zweifel olefination reaction has since been extended to boronic ester starting materials (Scheme 13).[40,41] Alkenyl boronate complexes (such as **38**) are accessible through the treatment of alkyl boronic esters with vinyllithium.[42] Treatment of **38** with iodine gives zwitterionic intermediate **39**. A stereospecific 1,2-metallate rearrangement of **39** results, with ring-opening of the ring-strained three-membered iodonium heterocycle, affording β-iodo boronic ester **40**. Upon treatment with base, **40** eliminates to give alkene **41**.



Scheme 13. Zweifel olefination: 1,2-metallate rearrangement of an alkenyl boronate complex activated by iodine.

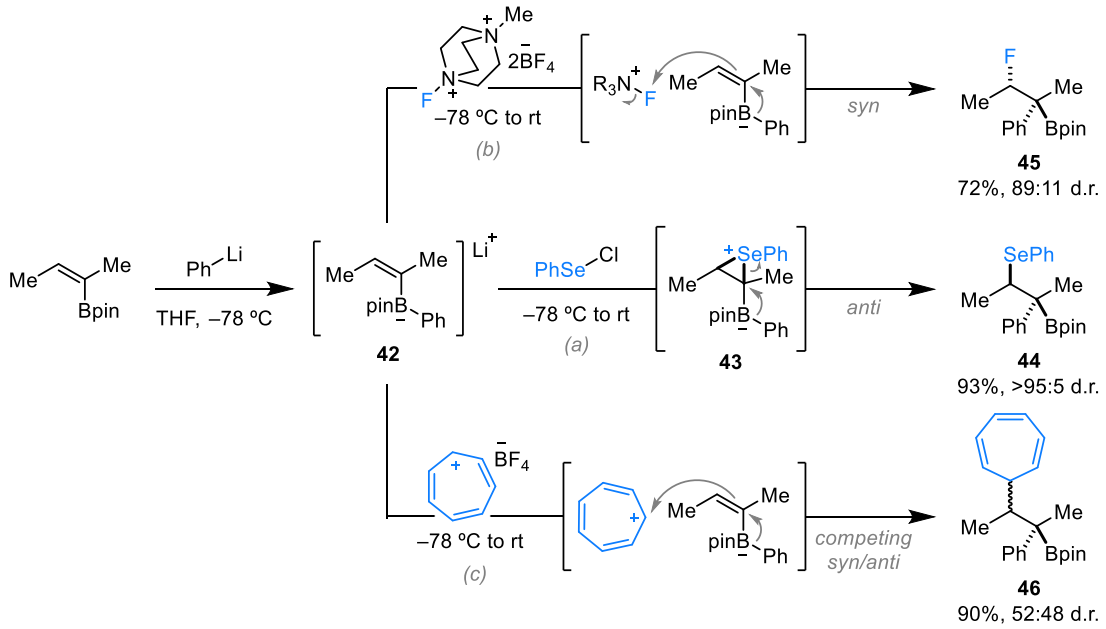
A range of heteroatom- and carbon-based electrophiles have also been explored in an analogous transformation which retains the boronic ester functional handle in the products (Scheme 14).[43,44] The diastereoselectivity of the transformation was found to depend upon the identity of the electrophile.

Addition of phenylselenyl chloride to boronate complex **42** first yields 3-membered selenium-containing hetereocycle (seleniranium cation) **43**, which is then ring-opened on 1,2-metallate rearrangement to give boronic ester **44** (Scheme 14a). This transformation occurs with high levels of anti diastereoselectivity, since the closed 3-membered heterocyclic ring is opened by a concerted *anti*-migration.

Activation of the same boronate complex by Selectfluor, however, yields β-fluoro boronic ester **45** with high syn diastereoselectivity (Scheme 14b). Such syn diastereoselectivity has been identified as typical for electrophiles reacting through concerted addition/migration

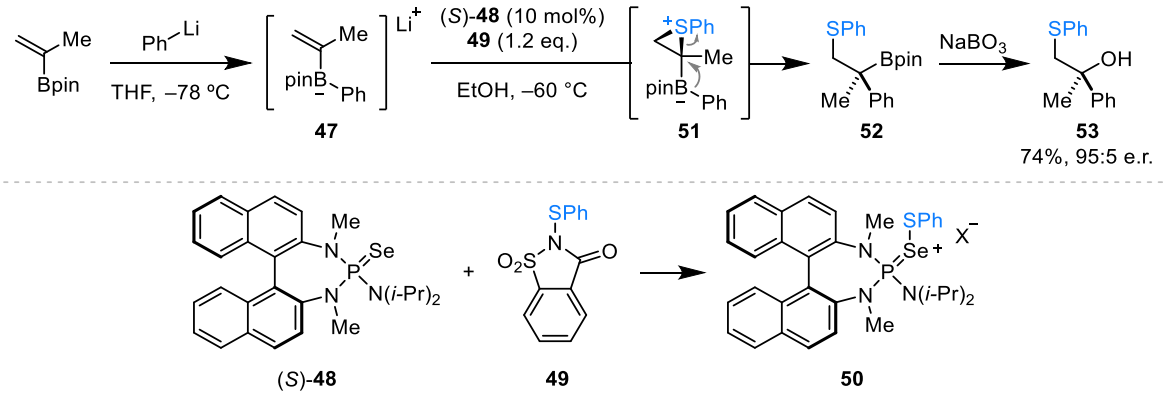
mechanisms, such as in the iridium-catalysed allylation of alkenyl boronate complexes (see Scheme 23)[45] and in the addition of activated *N*-heterocycles to alkenyl boronate complexes (see Scheme 16).[46]

Electrophilic carbon reagent tropylium tetrafluoroborate induces an unselective 1,2-migration, giving boronic ester **46** in poor diastereoselectivity, likely as a result of competing *syn*- and *anti*-migration (Scheme 14c). Such competing *syn*-/*anti*-migration could reflect the asynchronous nature of bond formation with more reactive, charged electrophiles.



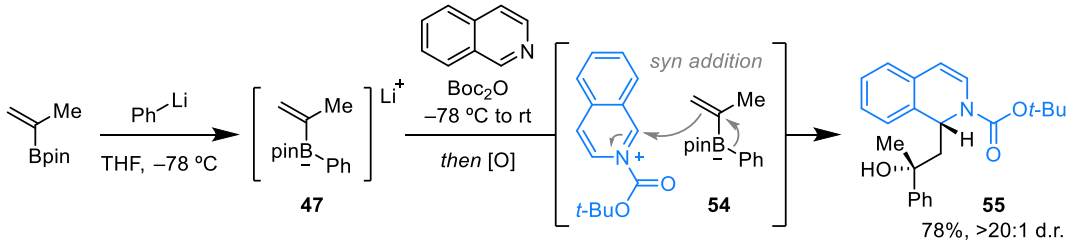
Scheme 14. 1,2-Metallate rearrangements of an alkenyl boronate complex activated by electrophiles.

This transformation has been rendered asymmetric by Denmark and co-workers through the use of a chiral sulfenylating reagent (Scheme 15).[47] The combination of chiral Lewis base catalyst (*S*)-**48** and the *N*-(phenylthio)saccharin **49** was shown to give the chiral highly-electrophilic **50**. The addition of **50** to boronate complex **47** yields thiianium ion **51** with high enantioselectivity. Intermediate **51** then undergoes a stereospecific 1,2-metallate rearrangement to give highly enantioenriched boronic ester **52**, isolated as its alcohol derivative **53**.



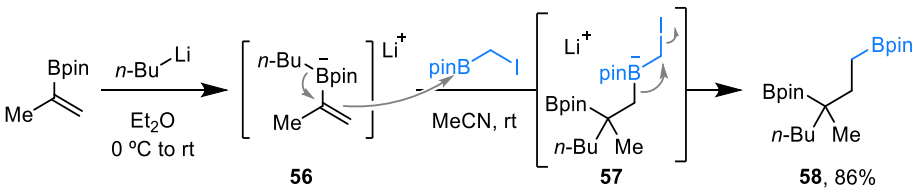
Scheme 15. Asymmetric 1,2-metallate rearrangement of an alkenyl boronate complex activated by a chiral sulfenylating reagent.

More recently, Ready and co-workers have demonstrated the addition of acylated isoquinolines to alkenyl boronate complexes, giving dearomatized products (**55**) in high yields and diastereoselectivities (Scheme 16).[46] It is postulated that in coulombic pair **54** the nitrogen cation is aligned with boronate complex **47** and a *syn*-migration occurs. Activated quinolines also proved excellent electrophiles in this sequence, however activated pyridines failed to engage in the desired reactivity.



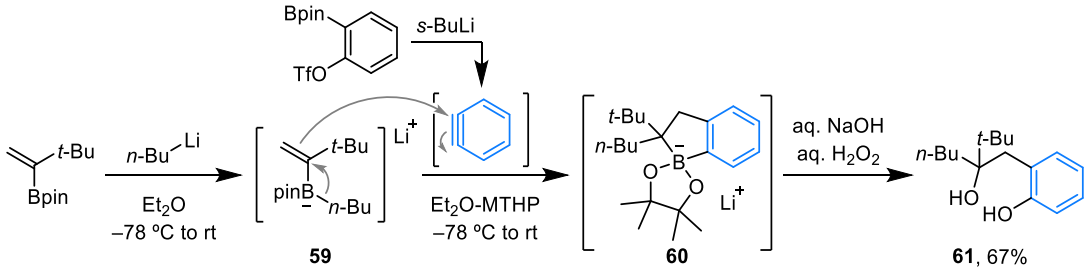
Scheme 16. 1,2-Metallate rearrangement of an alkenyl boronate complex activated by an activated isoquinoline.

The synthesis of 1,3-bis(boryl)alkanes has been achieved by Studer and co-workers, through the addition of ICH_2Bpin to alkenyl boronate complexes (Scheme 17).[48] It was proposed that a boronic ester-induced sequential bis-1,2-migration cascade is operational: concomitant 1,2-migration and electrophile addition to alkenyl boronate complex **56** provides boronate complex **57**, which then undergoes a second 1,2-migration with expulsion of the iodide leaving group to give **58**.



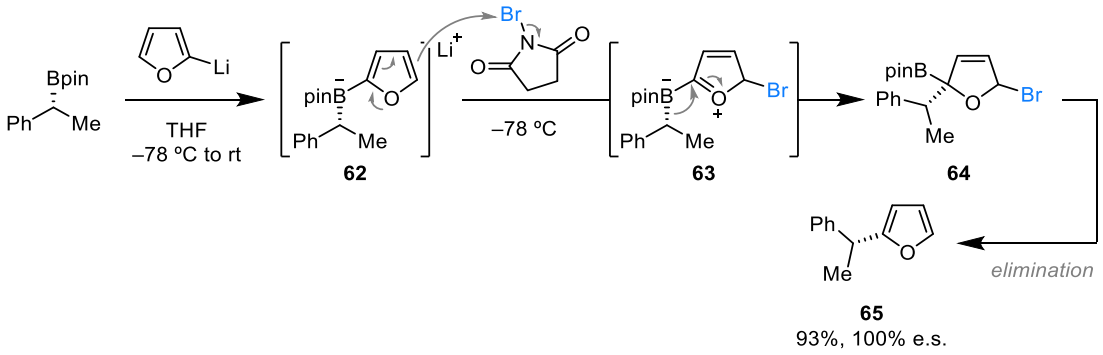
Scheme 17. Boronic ester-induced double 1,2-metallate rearrangement.

New C–C bonds have also been forged through the coupling of aryne nucleophiles with alkenyl boronate complexes (Scheme 18).[49] The addition of boronate complex **59** to the aryne yields cyclic boronate complex **60**, where the intermediate aryl anion has attacked the electrophilic boron centre. Oxidation of this species yields diol **61**.



Scheme 18. 1,2-Metallate rearrangement of an alkenyl boronate complex activated by an aryne.

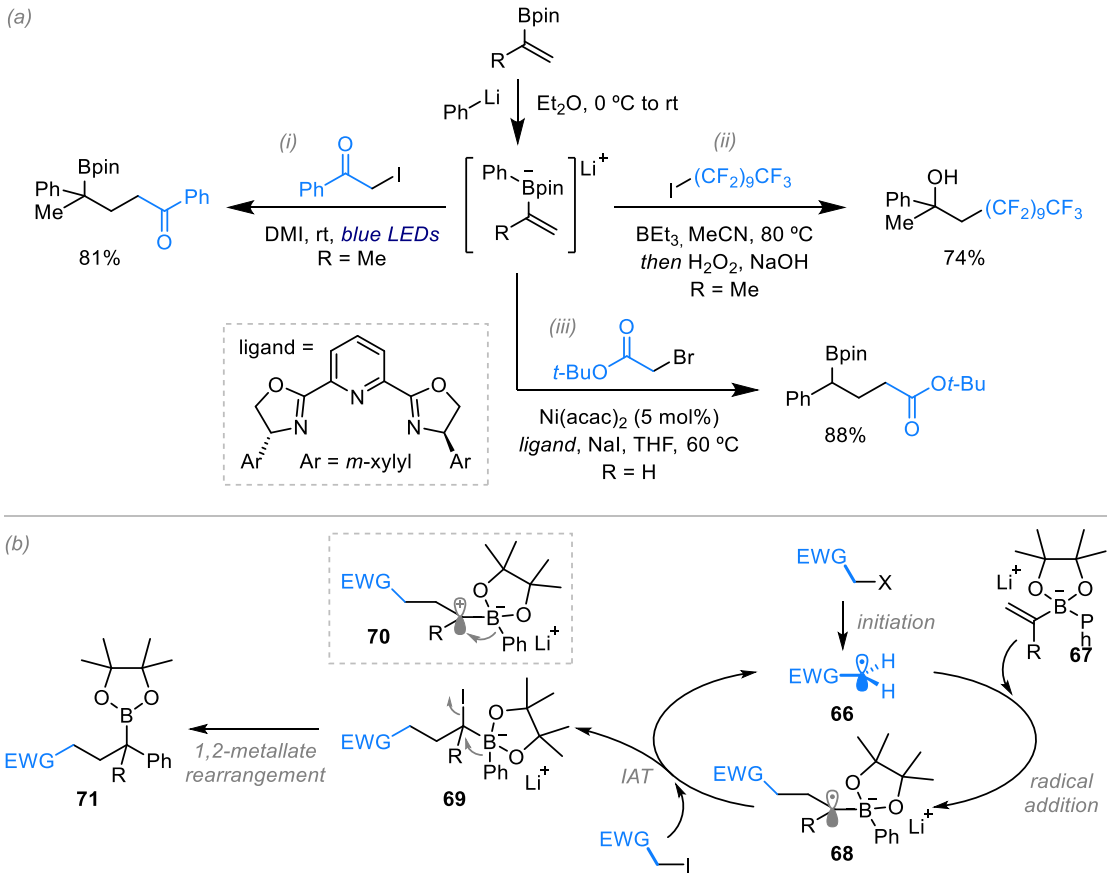
Aryl boronate complex **62** can be activated by the aromatic electrophilic substitution of the furan moiety by a brominating agent, leaving an electrophilic site at the α-carbon to boron in zwitterionic **63** (Scheme 19).[50] A 1,2-metallate rearrangement of **63** occurs, affording boronic ester **64** which subsequently eliminates to rearomatise and give furan **65** in high yield and complete stereospecificity. This constitutes a stereospecific transition-metal-free coupling of a lithiated aromatic species and an enantioenriched boronic ester.



Scheme 19. 1,2-Metallate rearrangement of an activated furyl boronate complex.

2.2.3.2. Radical-induced 1,2-metallate rearrangements

Methods of alkenyl boronate complex activation have been extended to encompass electron-deficient radical electrophiles (Scheme 20).



Scheme 20. 1,2-Metallate rearrangement of alkenyl boronate complexes activated by an electron-deficient radical.

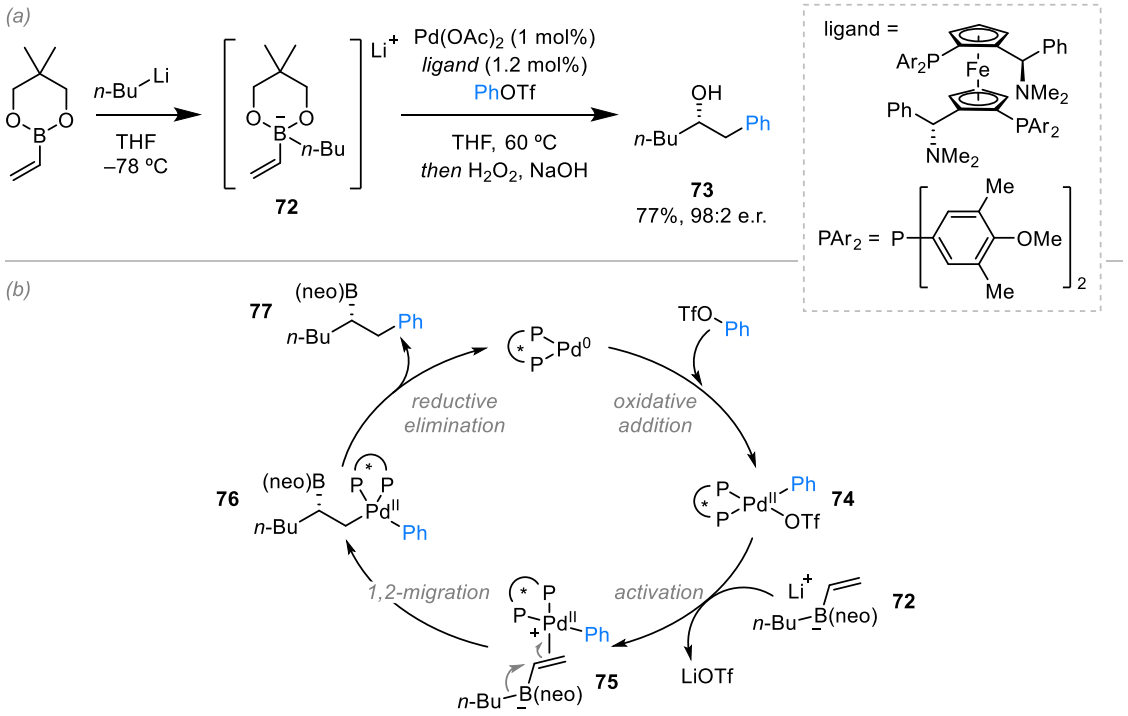
Mechanistically, it is proposed that electron-deficient radical **66** adds to the electron rich double bond of alkenyl boronate complex **67** to give α-boryl radical **68** (Scheme 20b). This species can then undergo an iodine atom transfer (IAT) event to give α-iodo boronate complex **69**.[51] Alternatively, a single electron transfer (SET) event has been proposed to occur, yielding zwitterionic **70**. A 1,2-metallate rearrangement, with expulsion of the iodide leaving group in the case of **69**, delivers product **71**.

The generation of electron-deficient radical **66** has been achieved through visible-light-mediated photocatalytic homolysis of a C–X bond in an alkyl halide (Scheme 20ai) (without the need for a photocatalyst in the case of alkyl iodide radical precursors),[52,53] using trialkyl boryl radical initiators (Scheme 20aii)[54–56] or through nickel catalysis (Scheme 20aiii).[57]

2.2.3.3. Metal-induced 1,2-metallate rearrangements

An alkenyl boronate complex can also react with an electrophilic metal species, with the resultant 1,2-metallate rearrangement occurring concomitantly with C–metal σ-bond formation.[38,58]

In 2016, Morken and co-workers demonstrated that an electrophilic vinyl/aryl-Pd(II) species can successfully induce the 1,2-metallate rearrangement of boronate complex **72** (Scheme 21).[59] The conjunctive cross-coupling cycle occurs with oxidative addition of the C(sp^2)–OTf bond to the Pd(0) species to give **74**, followed by a palladium-induced 1,2-metallate rearrangement of **75** to form a C–Pd σ-bond (**76**). Subsequent reductive elimination yields the cross-coupled product and regenerates the Pd(0) catalytic species. This boronic ester product (**77**) is then oxidised *in situ* to give alcohol **73**. A range of cross-coupling partners (vinyl/aryl triflates) were employed alongside various organolithium reagents. The use of a chiral ligand enabled the 1,2-metallate rearrangement to occur with high levels of enantioselectivity, giving chiral alcohol **73**.

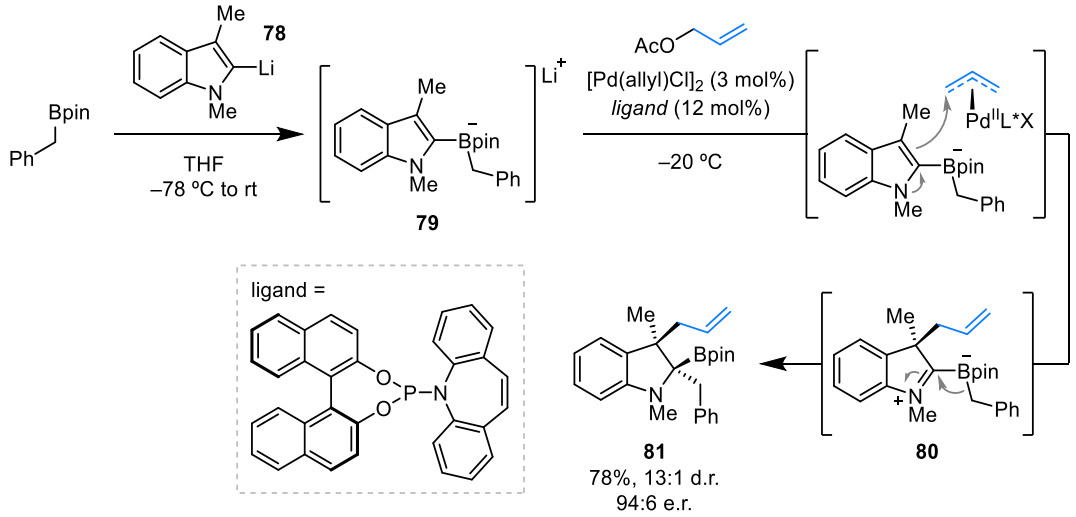


Scheme 21. Enantioselective palladium-catalysed cross-coupling of alkenyl boronic esters, organolithium reagents and vinyl/aryl halides.

Morken has since extended this protocol, with the addition of sodium triflate as both a halide scavenger and Grignard-activator, allowing the use of both Grignard reagents and vinyl/aryl halides as cross-coupling partners.[60] In the initial protocol, Morken had noted that the presence

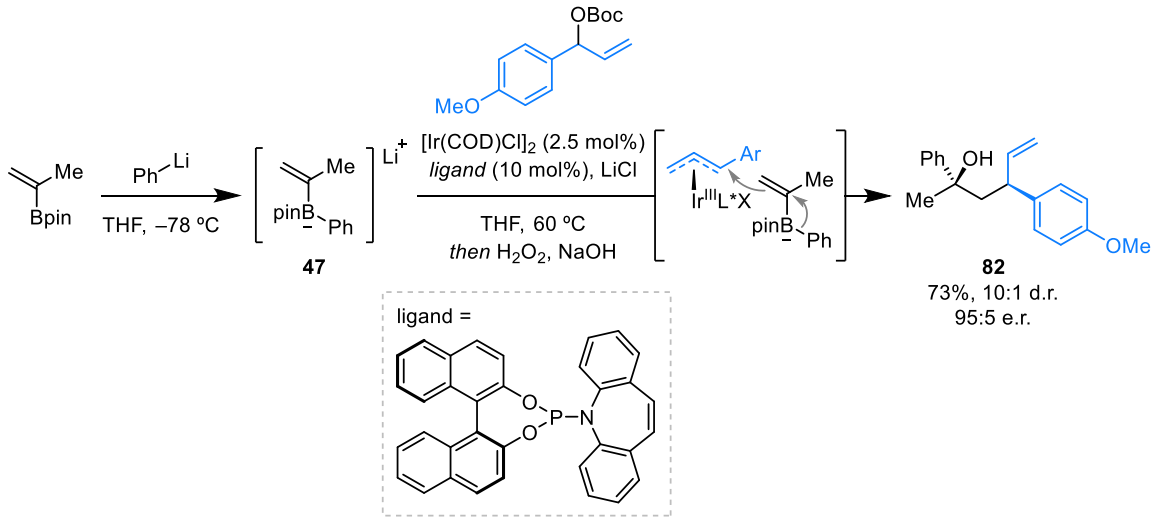
of trace halide ions (at mol% quantities) significantly reduced the efficiency of the reaction, necessitating the use of 'halide-free' alkenyl boronate complexes. It was hypothesised that the halide ions outcompete the alkenyl boronate complex for binding to the cationic palladium(II) complex, thus their removal from solution is desirable.[60]

Electrophilic palladium complexes have also been utilised to trigger a 1,2-metallate rearrangement in indolyl boronate complexes (Scheme 22).[61] Indolyl boronate complex **79** reacts with a Pd(π-allyl) complex to first yield allylated boronate complex **80**, which then undergoes a 1,2-metallate rearrangement to give 3-allyl boronic ester product **81**. Since **78** has a substituent at the 3-position of the indole, the product, enantioenriched boronic ester **81**, bears two contiguous fully substituted stereocentres.[62] It is proposed that the high anti diastereoselectivity arises from stepwise allylation and alkyl migration steps.



Scheme 22. Enantioselective palladium-catalysed three-component coupling of lithiated indoles, boronic esters and allylic acetates.

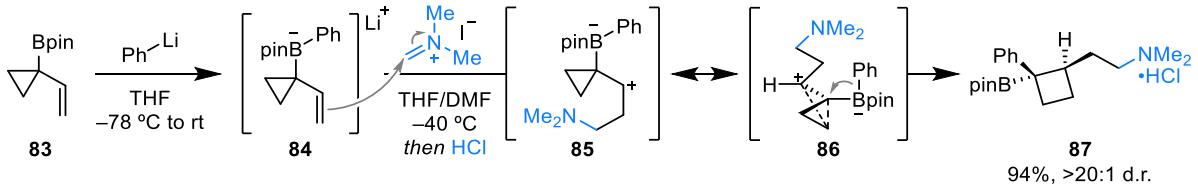
More recently, Ready and co-workers have demonstrated the ability of chiral Ir(π-allyl) complexes to trigger a 1,2-metallate rearrangement of alkenyl boronate complexes, enabling the synthesis of tertiary boronic esters bearing non-adjacent stereocentres with high levels of enantio- and diastereocontrol (Scheme 23).[45] Boronate complex **47** reacts with the Ir(π-allyl) species in a concerted *syn*-selective manner, indicated by DFT studies,[63] to yield **82**.



Scheme 23. Enantioselective iridium-catalysed three-component coupling of organolithium reagents, alkenyl boronic esters and secondary allylic aryl carbonates.

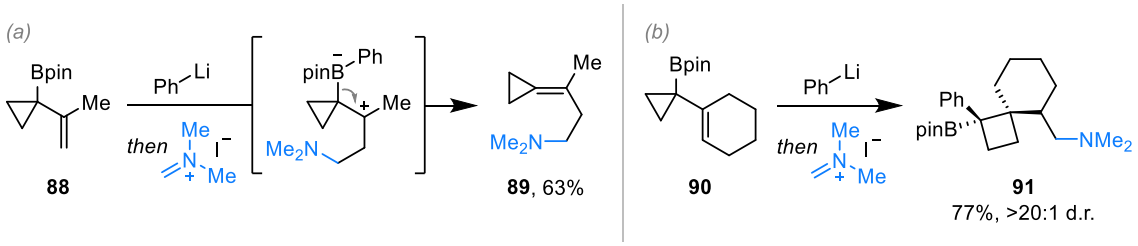
2.2.3.4. Ring-expansion-induced 1,2-metallate rearrangements

Recently, a new trigger for a 1,2-metallate rearrangement was developed: a ring expansion of vinylcyclopropyl boronate complexes (Scheme 24).[64] Treatment of vinylcyclopropyl boronic ester **83** with an organolithium affords boronate complex **84**. Reaction of **84** with an electrophile gives zwitterionic intermediate **85**, calculated to exist as non-classical carbocation **86**, which undergoes a ring expansion 1,2-metallate rearrangement to afford the cyclobutyl boronic ester product **87** with high diastereoselectivity.



Scheme 24. 1,2-Metallate rearrangement of vinylcyclopropyl boronate complexes activated by an electrophile.

However, this methodology does not provide a general route towards cyclobutyl boronic esters with quaternary stereocentres at the β-carbon. Boronic ester **88** gave only product **89**, formed through a competing allylation pathway (Scheme 25a). Only cyclohexyl-derived boronic ester **90** could undergo the desired rearrangement to afford spirocycle **91** with three contiguous stereocentres, two of which are fully substituted (Scheme 25b).



Scheme 25. Competing allylation of vinylcyclopropyl boronate complexes activated by an electrophile.

2.3. 1,2-Metallate rearrangements of cyclic boronate complexes

2.3.1. Ring contraction reactions: definition and examples

A ring contraction reaction is defined by Redmore and Gutsche as a reaction which leads to a product with a ring that is smaller than that in the substrate and an exocyclic atom that was previously part of the cycle (Figure 4).[65] There should be no isolable intermediate with fewer rings than the initial substrate. A ring expansion reaction is the reverse transformation.

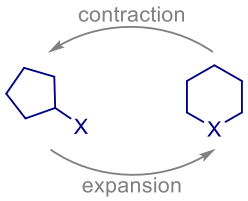
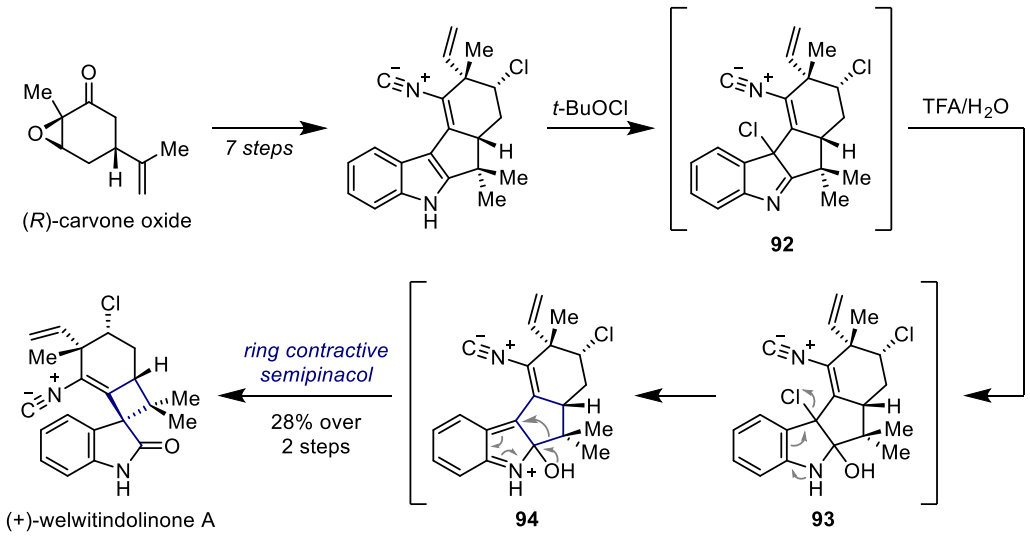


Figure 4. Ring contraction (and expansion) reactions.

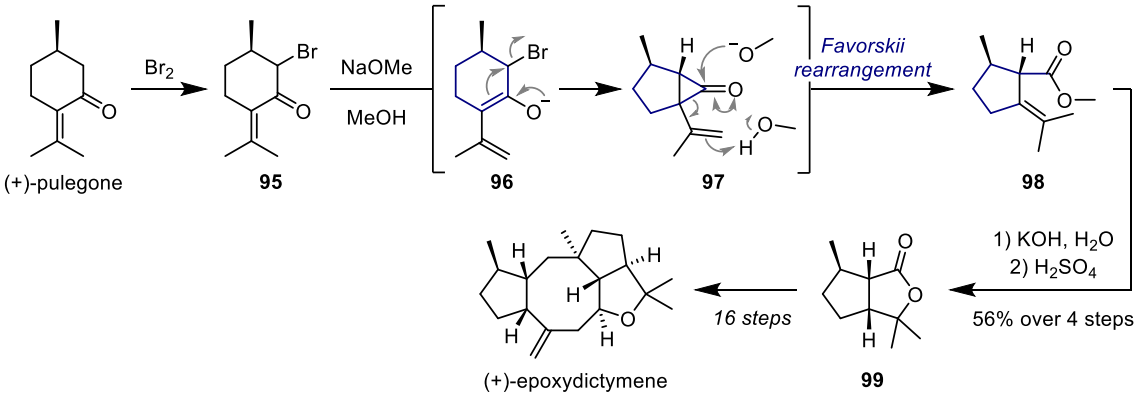
Ring contraction reactions have been employed as key steps in the synthesis of natural products, in particular in the synthesis of small carbocycles bearing contiguous stereocentres, including contiguous quaternary stereocentres.[66]

Baran and co-workers utilised a late-stage semipinacol 5–4 ring contraction in the final step of their synthesis of welwitindolinone A (Scheme 26).[67] Indoline **93**, formed from the hydrolysis of imine **92**, undergoes a dearomative displacement of chloride to yield **94**. The semipinacol rearrangement of intermediate **94**, with alkyl migration, occurs with rearomatisation to yield the natural product and assemble the second of two contiguous quaternary centres**.**



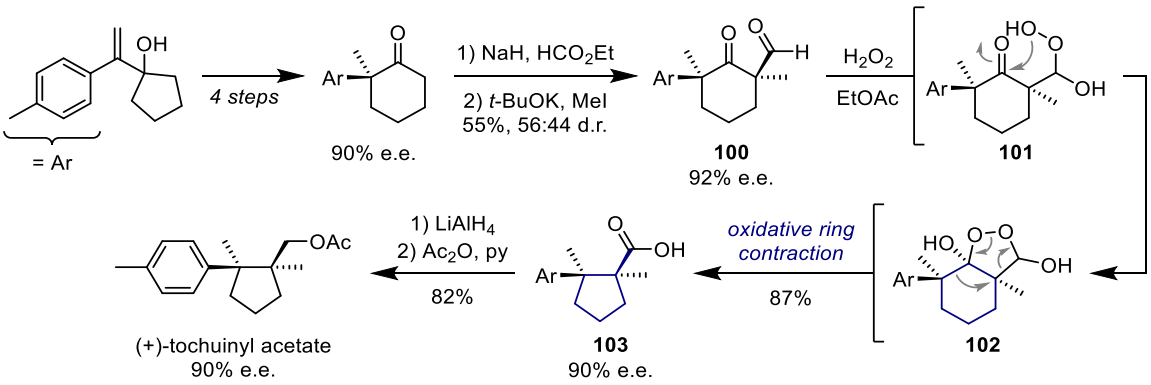
Scheme 26. Baran's synthesis of welwitindolinone A featuring a late-stage semipinacol ring contraction.

Schreiber and co-workers used a Favorskii 6–5 ring contraction to generate stereodefined cyclopentane **98** which was then subject to further transformations in the synthesis of (+)-epoxydictymene (Scheme 27).[68] Allylic deprotonation of **95** gives enolate **96**, primed for cyclisation to give cyclopropenone **97**. Addition of methoxide to **97** yields ring-opened **98**. Basic hydrolysis of the ester followed by acid-promoted cyclisation yields *cis*-fused **99**.



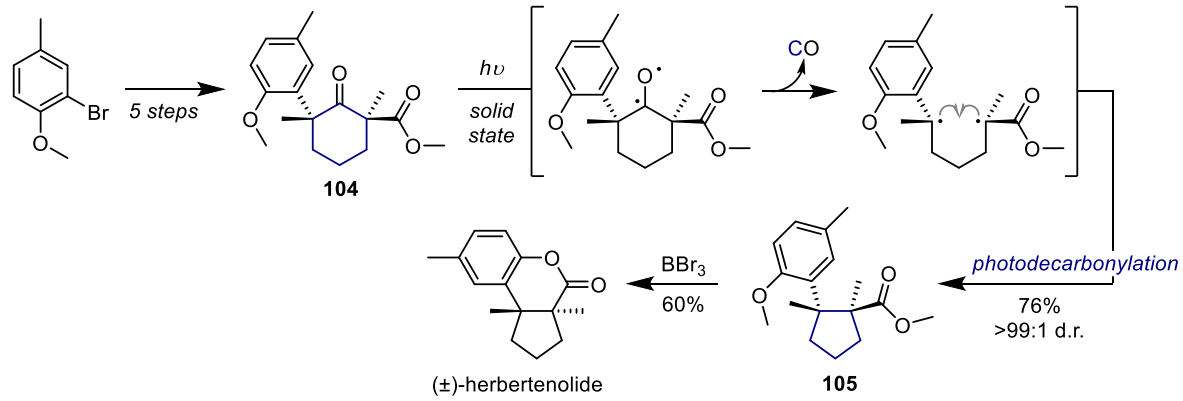
Scheme 27. Schreiber's synthesis of (+)-epoxydictymene featuring a Favorskii rearrangement.

In their total synthesis of (+)-tochuinyl acetate, Xie and co-workers employed an oxidative 6–5 ring contraction reaction to assemble two contiguous quaternary stereocentres on a cyclopentane core (Scheme 28).[69] Condensation of hydrogen peroxide into the aldehyde moiety of **100** followed by intramolecular cyclisation of **101** yields 1,2-dioxolane **102** which expels formic acid upon a ring contractive alkyl migration. This sequence is enantiospecific and thus the two contiguous quaternary stereocentres were assembled in **103** with high enantiomeric excess.



Scheme 28. Xie's synthesis of (+)-tochuinyl acetate featuring an oxidative ring contraction.

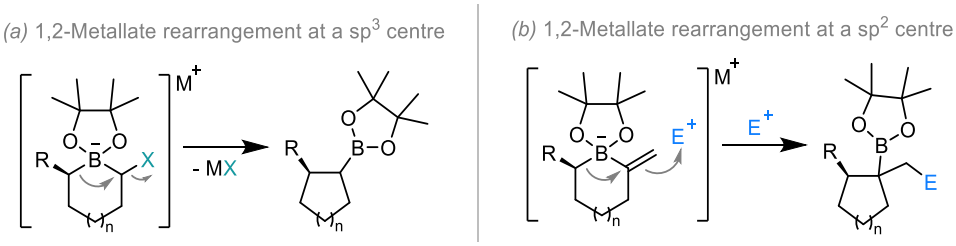
Garcia-Garibay and co-workers also used a ring contractive strategy in their synthesis of a related natural product, (±)-herbertenolide (Scheme 29).[70] In this case, a photodecarbonylation reaction extrudes carbon monoxide from cyclohexanone **104** to yield cyclopentane **105**. This transformation formally constitutes a 'deletion' reaction, since the exocyclic group has been removed from the ring contracted product.[71]



Scheme 29. Garcia-Garibay's synthesis of (±)-herbertenolide featuring a photodecarbonylative carbonyl deletion reaction.

2.3.2. Ring contraction reactions of cyclic boronate complexes

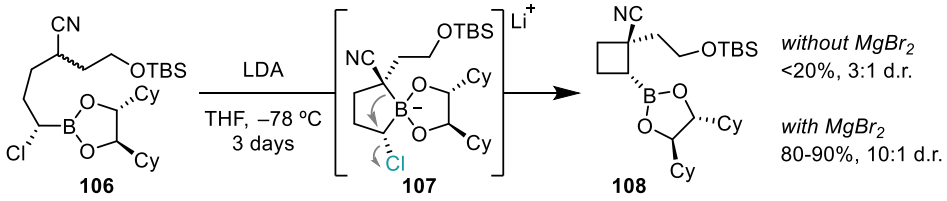
In a cyclic boronate complex, the two carbon substituents on boron are connected by an extended alkyl chain. If one of the substituents on boron migrates to an adjacent electrophilic site, this 1,2-metallate rearrangement constitutes a formal ring contraction; a cyclic boronate complex is contracted to a cycloalkyl boronic ester. In theory, the methodologies employed to trigger 1,2-metallate rearrangements in boronate complexes could be extended to cyclic boronate complexes (Scheme 30). However, ring contraction reactions of cyclic boronate complexes have been under-explored compared to those of acyclic boronate complexes.



Scheme 30. 1,2-Metallate rearrangements of cyclic boronate complexes.

2.3.2.1. At sp^3 carbon centres

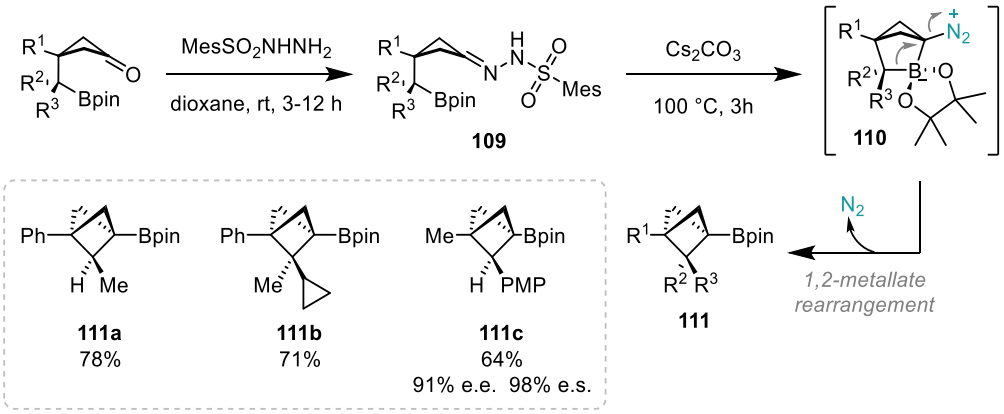
In 1999, Matteson and co-workers developed a methodology by which 5-membered cyclic boronate complex **107** undergoes a 1,2-metallate rearrangement with displacement of a chloride leaving group at a sp^3 centre, affording cyclobutyl boronic ester **108** (Scheme 31).[72] The 1,2-metallate rearrangement constitutes a 5–4 ring contraction. However, the limitations of this methodology include the necessity of the acidifying cyano group in **106** for the deprotonation step prior to cyclisation. The long reaction time and requirement for the Lewis acid $MgBr_2$ also indicate the reluctance of **107** to undergo the ring contractive 1,2-metallate rearrangement; the increase in ring strain is only energetically possible if the C–Cl σ-bond is sufficiently weakened by coordination of a Lewis acid.[72]



Scheme 31. Matteson's 1,2-metallate rearrangement of 5-membered cyclic boronate complexes with leaving group displacement at the α-carbon.

More recently, Qin and co-workers disclosed a ring-contractive approach to substituted bicyclo[1.1.1]pentanes bearing a bridgehead boronic ester substituent (Scheme 32).[73] Formation of high-energy bicyclic [2.1.1] zwitterionic intermediate **110** was achieved using an intramolecular coupling reaction between a sulfonyl hydrazone and a boronic ester, both tethered to a cyclobutyl ring in **109**. Expulsion of nitrogen furnished the product boronic esters **111** in good yield. Boronic esters with α,α-disubstitution were competent substrates, allowing the synthesis of highly substituted boronic esters, such as **111b**. Notably, enantiomerically enriched boronic ester **111c** underwent this sequence with minimal erosion of enantiomeric excess. The entropic favourability of the reaction, as a result of the expulsion of gaseous

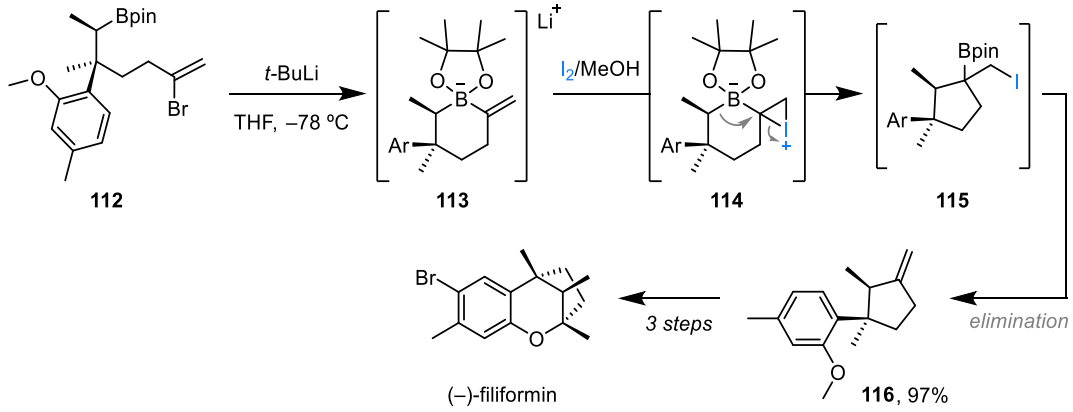
nitrogen, likely outweighs the increase in strain energy associated with the ring contractive 1,2-metallate rearrangement and thus provides its driving force.



Scheme 32. Qin's 1,2-metallate rearrangement of bicyclic boronate complexes with nitrogen extrusion.

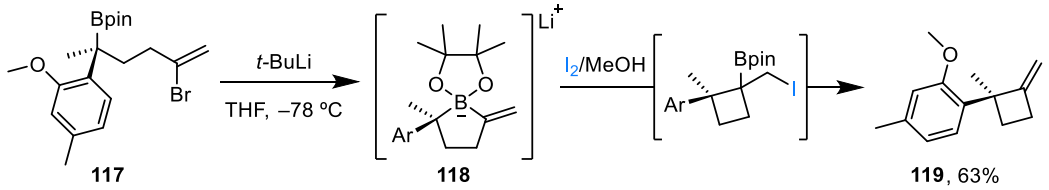
2.3.2.2. At sp^2 carbon centres

In 2014, Aggarwal and co-workers developed a novel intramolecular Zweifel-type olefination as a key step in the synthesis of (–)-filiformin (Scheme 33).[74] The generation of 6-membered cyclic alkenyl boronate complex **113** occurred through lithium-bromine exchange of **112** using *tert*-butyl lithium. Treatment of **113** with iodine and methanol, under Zweifel olefination-type conditions, gave zwitterionic **114** which underwent a ring contractive 1,2-metallate rearrangement to give β-iodo boronic ester **115**. Spontaneous elimination of **115** afforded methylene cyclopentane **116**.



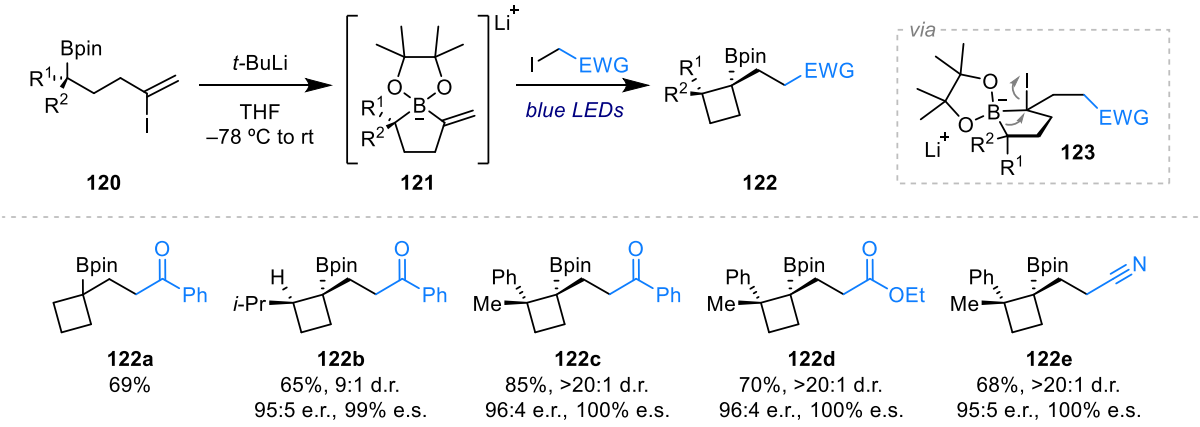
*Scheme 33. Aggarwal's Zweifel-type olefination of 6-membered cyclic alkenyl boronate complex **113**.*

In the same study, alkenyl bromide **117**, which differs from **112** by the absence of a $(H_3C)CH$ group, was subjected to the same reaction conditions to give 5-membered cyclic boronate complex **118** (Scheme 34).[74] The formation of methylene cyclobutane **119** upon addition of iodine indicates that this methodology can also be applied to the synthesis of cyclobutanes.



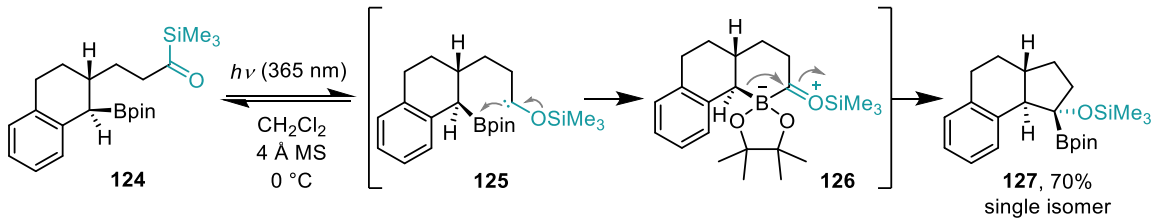
*Scheme 34. Aggarwal's intramolecular Zweifel-type olefination of 5-membered cyclic alkenyl boronate complex **118**.*

Building on this premise, further work by Aggarwal and co-workers probed the radical-induced 1,2-metallate rearrangement of 5-membered cyclic alkenyl boronate complexes (Scheme 35).[75] The *tert*-butyl lithium-induced lithium-iodine exchange of **120** gave 5-membered cyclic alkenyl boronate complex **121**. The proposed mechanism reflects that of acyclic alkenyl boronate complexes (see Section 2.2.3.2), with the 1,2-metallate rearrangement of **123** constituting a formal ring contraction, affording boronic ester **122**. Importantly, this methodology was extended to the synthesis of cyclobutyl boronic esters with two contiguous fully substituted stereocentres (**122c**, **122d**, **122e**) in excellent yield, diastereoselectivity and enantiospecificity.



Scheme 35. Aggarwal's visible light-induced ring contraction of 5-membered cyclic alkenyl boronate complexes.

More recently, Kusama and co-workers developed a photoinduced intramolecular coupling of an acylsilane (**124**), isomerised to a siloxycarbene (**125**) under photoirradiation, and a secondary boronic ester to give zwitterionic **126**, primed for a ring contractive 1,2-metallate rearrangement to give highly strained *trans*-fused bicyclo[4.3.0]nonane **127** (Scheme 36).[76]

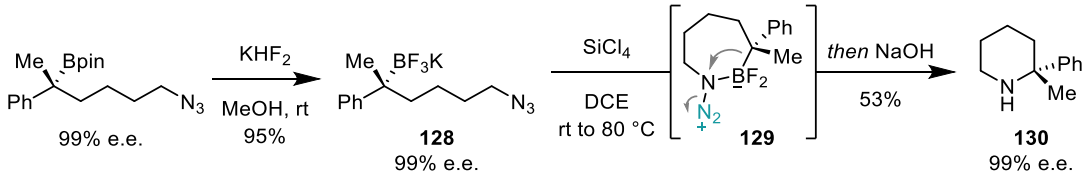


Scheme 36. Kusama's photoinduced intramolecular cyclisation of acylsilanes.

2.3.2.3. At heteroatoms with leaving group expulsion

By contrast to their all-carbon analogues, the construction of heterocycles using ring contractive reactions of cyclic α-heteroboronate complexes is well explored, typically with expulsion of a leaving group followed by deborylation of the heteroatom.

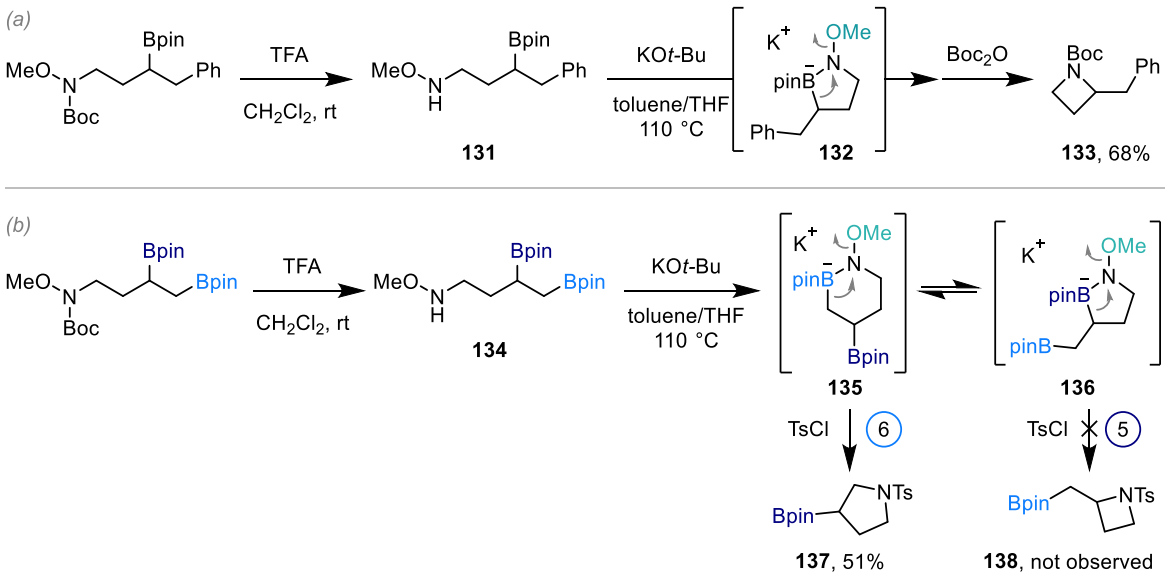
Early examples of such an approach to form azacycles came from Evans[77] and Matteson,[78] with Aggarwal establishing the use of this approach to form 2,2-disubstituted piperidine **130** with perfect enantiospecificity (Scheme 37).[79] The defluoridation of trifluoroborate salt **128** allowed the formation of aminoboronate complex **129** and nitrogen extrusion furnished the product.



*Scheme 37. Aggarwal's 2,2-disubstituted piperidine synthesis via ring contraction of boronate complex **129**.*

More recently, Morken and co-workers expanded on this concept for the synthesis of azetidines, pyrrolidines, and piperidines.[80] Addition of potassium *tert*-butoxide to methoxyamine **131** allows formation of aminoboronate complex **132** (Scheme 38a). The ring contractive 1,2-metallate rearrangement then expels the methoxy group to give the *N*-boryl azetidine, which is Boc-protected to give **133**.

Extension of this work focused on the site-selective amination of diboron compounds, such as **134**, which can either form pyrrolidine **137** from 6-membered cyclic aminoboronate complex **135**, or azetidine **138** from 5-membered **136** (Scheme 38b). The authors suggest that the formation of aminoboronate complexes **135** and **136** should be equally favourable since they have negligible differences in strain energy. However, the dominance of 1,2-metallate rearrangement of aminoboronate complex **135** suggests that this is the faster of the two rearrangements.

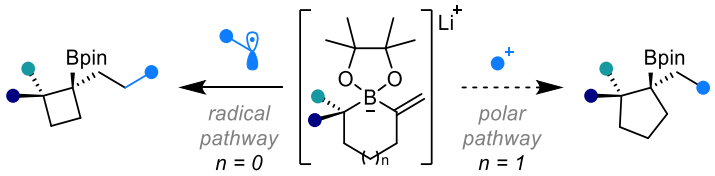


Scheme 38. Morken's intramolecular amination via 1,2-metallate rearrangement of an α-amino cyclic boronate complex.

2.4. Project proposal

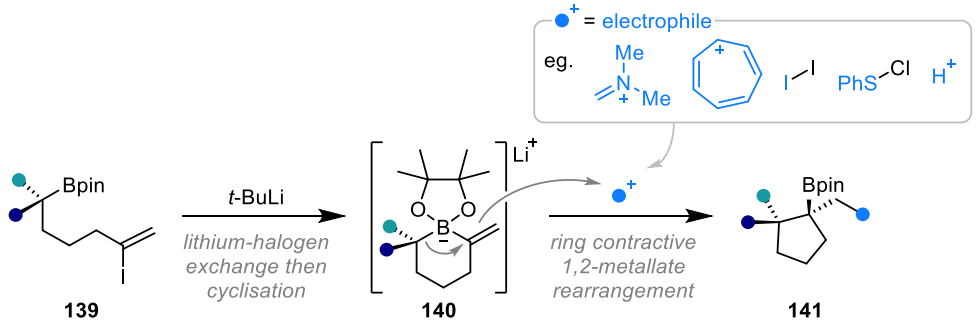
2.4.1. Project outline

This work sought to further develop ring contractive 1,2-metallate rearrangements of cyclic alkenyl boronate complexes, with focus on the stereoselective synthesis of highly substituted cyclopentyl boronic esters using electrophile-induced ring contractive 1,2-metallate rearrangements (Scheme 39).



Scheme 39. Further development of the ring contractive 1,2-metallate rearrangement.

Boronic ester **139** was proposed as a precursor to cyclic alkenyl boronate complex **140**, which could be accessed through the lithium-halogen exchange of **139** and cyclisation of the resultant alkenyl lithium (Scheme 40). The reactivity of the cyclic alkenyl boronate complex towards classical electrophiles could then be investigated, allowing the synthesis of substituted cyclopentyl boronic esters **141**.



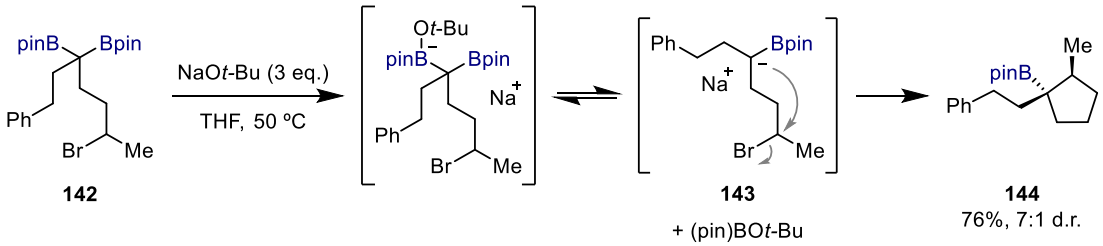
Scheme 40. Proposed electrophile-induced ring contractive 1,2-metallate rearrangements of 6-membered cyclic alkenyl boronate complexes.

The work summarised in Section 2.5 is also outlined in the following publication: M. E. Fairchild, A. Noble, V. K. Aggarwal, *Angew. Chem. Int. Ed.* **2022**, *61*, e202205816.[81]

2.4.2. Methods for the synthesis of substituted cyclopentyl boronic esters

Highly substituted cycloalkyl boronic esters are an attractive synthetic target, however few methods exist for their synthesis.

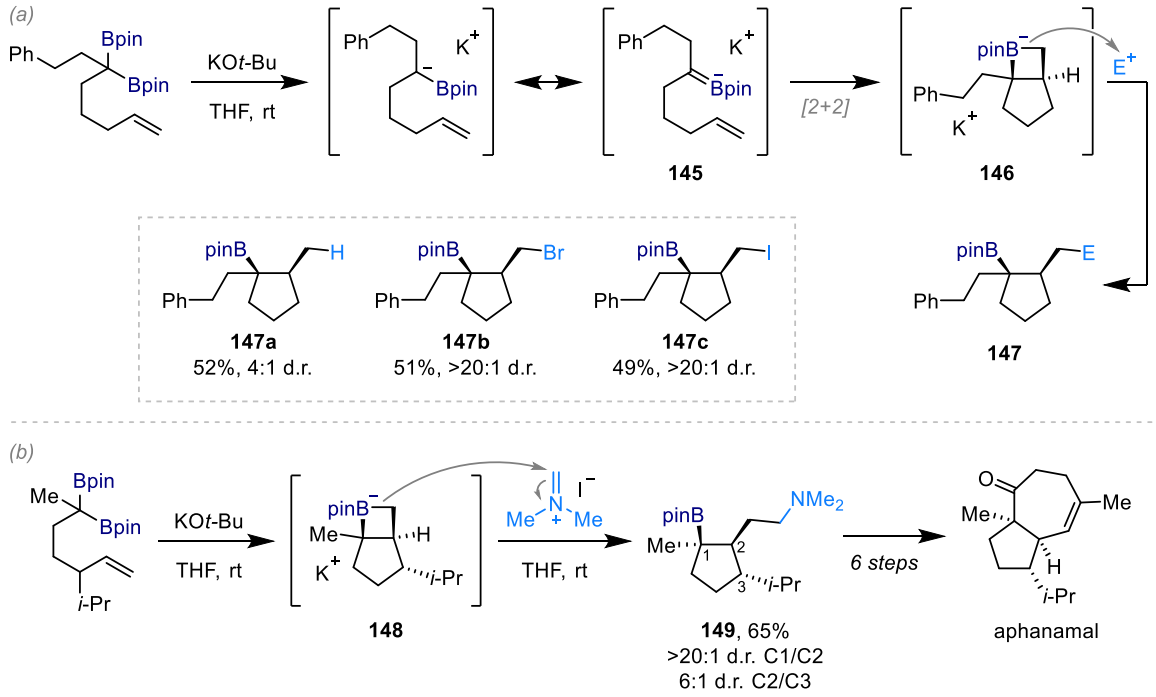
Morken and co-workers have developed an intramolecular deborylative alkylation for the construction of carbocyclic boronic esters, including one example of a cyclopentyl boronic ester (Scheme 41).[82] The metal alkoxide induced deborylation of bis(boronic ester) **142** results in the formation of α-boryl anion **143**. Since this anion is accompanied by an accessible leaving group, a substitution reaction results with expulsion of bromide, giving cyclopentyl boronic ester **144** in good yield and diastereoselectivity.



Scheme 41. Morken's intramolecular alkylation of an α-boryl carbanion.

However, when this α-boryl anion, drawn as alkylidene **145**, is accompanied by a tethered alkene, a net [2+2] cycloaddition was reported to occur, giving boracycle intermediate **146** (Scheme 42a).[83] The addition of electrophiles to the less hindered nucleophilic C–B bond in intermediate **146** gave cyclopentyl boronic esters **147** in moderate yields and good to excellent diastereoselectivities. The range of such electrophiles able to functionalise the β-carbon is limited. The α-substituent in the product is a feature of the original bis(boronic ester) and must

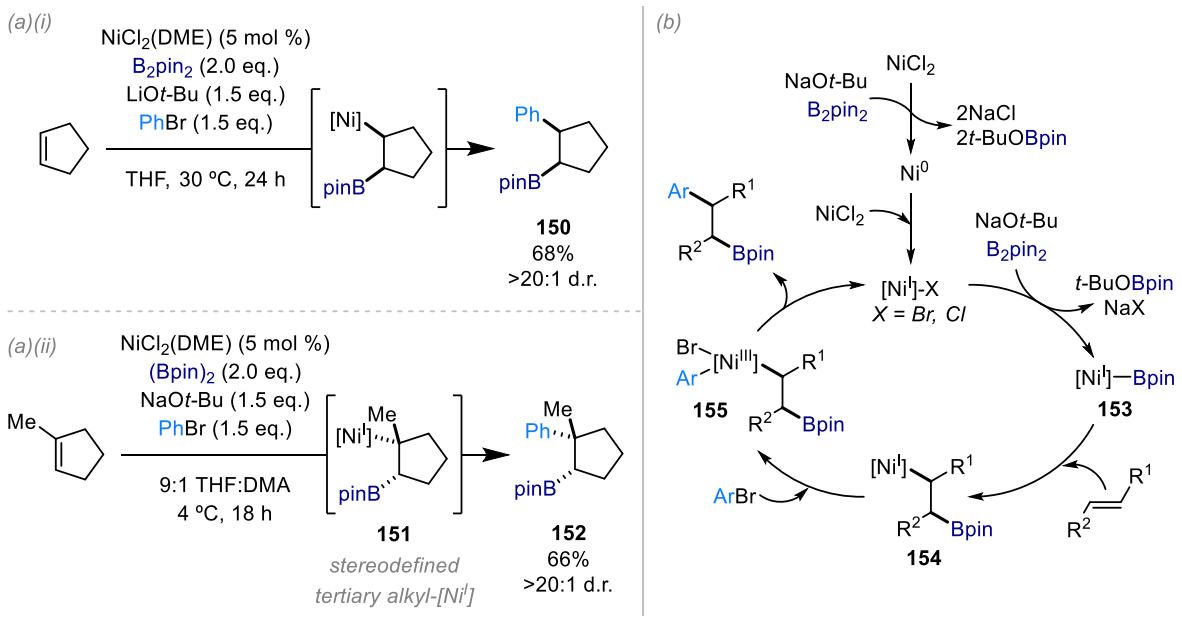
be pre-installed. This methodology was also utilised for the setting of the relative stereochemistry of the three contiguous stereocentres present on the cyclopentane ring in the natural product aphanamal, with successful addition of Eschenmoser's salt to boracycle **148** to give decorated cyclopentyl boronic ester **149** (Scheme 42b).



Scheme 42. Morken's boron alkylidene–alkene cycloaddition reaction with electrophile trapping and its application to the total synthesis of aphanamal.

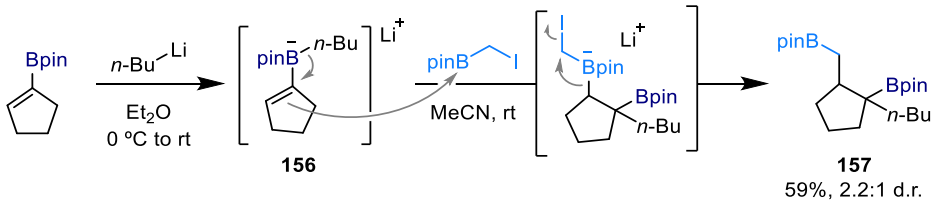
Brown and co-workers have developed a nickel-catalysed arylboration of alkenes, which can be applied to cyclopentene for the synthesis of cyclopentyl boronic ester **150** with very high diastereoselectivity (Scheme 43ai).[84] Slight modifications to the reaction conditions have since allowed the synthesis of the more highly substituted cyclopentyl boronic ester **152** (Scheme 43aii).[85]

Formation of Ni(I) complex **153** under the reaction conditions precedes its addition to the alkene to give Ni(I) complex **154** (Scheme 43b). Oxidative addition of the aryl bromide to complex **154** affords Ni(III) complex **155**. Reductive elimination furnishes the C–C bond with high stereoselectivity. In the case of trisubstituted alkenes, the formation of tertiary alkyl-Ni(I) intermediate **151** is both highly regio- and diastereoselective. The high regioselectivity owes to the minimisation of steric clash between the oxygen atoms of the pinacol boronic ester and the methyl substituent, placing the boronic ester distal from the methyl group. The dominance of *syn*-borylnickelation leads to the formation of the product with high diastereoselectivity.[85]



Scheme 43. Brown's nickel-catalysed arylboration of di- and tri-substituted alkenes.

Studer and co-workers have reported the synthesis of 1,3-bis(boronic ester) **157** through the boronic ester-induced double 1,2-metallate rearrangement of cyclopentenyl boronate complex **156** (Scheme 44).[48] In fact, the synthesis of such α,β-disubstituted cyclopentyl boronic esters should be possible through the reactivity of cyclopentenyl boronate complexes with a range of classical electrophiles, but the generality of this transformation is yet to be reported.



*Scheme 44. Studer's boronic ester-induced double 1,2-metallate rearrangement with cyclopentenyl boronate complex **156**.*

Access to highly substituted cyclopentyl boronic esters is at present limited to the synthesis of α,β-disubstituted cyclopentyl boronic esters (Figure 5a) and β,β-disubstituted cyclopentyl boronic esters (Figure 5b). The difficulties associated with establishing two contiguous fully substituted stereocentres on a cyclopentyl boronic ester are yet to be overcome (Figure 5c). Indeed, the synthesis of such motifs in an enantioenriched form is also yet to be achieved.

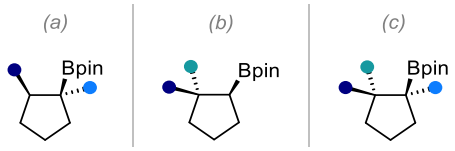


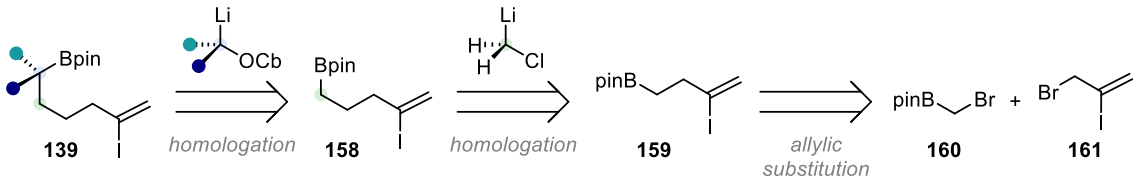
Figure 5. Highly substituted cyclopentyl boronic esters.

The limits on Morken's chemistry likely arise from the steric restraints of the [2+2] cycloaddition to give the required boronate complex (Scheme 42). Whereas Brown's nickel-catalysed arylboration it yet to be demonstrated on tetrasubstituted alkenes, presumably as a consequence of the difficult addition of the Ni(I)–Bpin complex across a sterically hindered alkene (Scheme 43). 1,2-Metallate rearrangements of highly substituted alkenyl boronate complexes are also yet to be reported, likely owing to the steric hindrance of the reacting alkene. Thus, seeking an alternative route towards cyclopentyl boronic esters could unlock new substitution pattens, and perhaps provide access to the elusive tetrasubstituted cyclopentyl boronic ester (Figure 5c).

2.5. Results and discussion

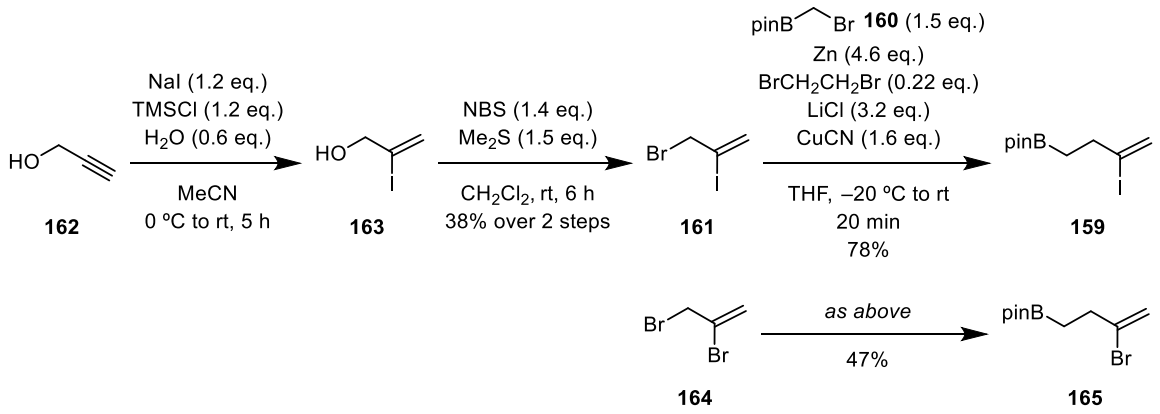
2.5.1. Divergent synthesis of boronic ester starting materials

Access to the required starting materials was straightforward, with routes to simple boronic ester **159** from alkenyl iodide building block **161** literature-known (Scheme 45).[74,75] The first homologation step to introduce a methylene unit (to give **158**) is also literature-known, and the second homologation (to give **139**) is a simple extension to literature procedures.[75]



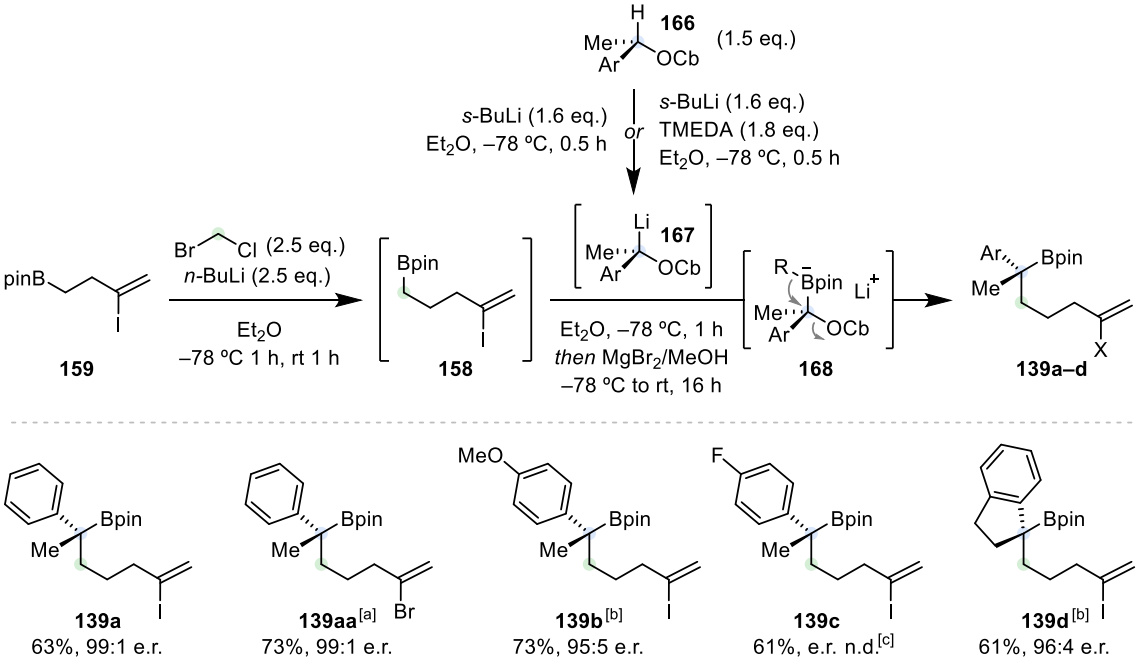
Scheme 45. Retrosynthetic analysis of the required starting materials.

Alkenyl iodide **161** was accessed in 2 steps through the allylic bromination of alcohol **163**, which was accessed from the addition of hydrogen iodide to propargyl alcohol (**162**) (Scheme 46). Nucleophilic attack on **161** by an *in situ* generated organozinc-copper organometallic derivative of **160** afforded boronic ester **159**. Commercially available alkenyl bromide **164** was subjected to the same conditions to afford boronic ester **165**.



*Scheme 46. Synthesis of boronic ester building blocks **159** and **165**.*

The introduction of a methylene unit was achieved using a Matteson homologation to give common intermediate **158**. A second homologation was then performed, to either give a tertiary, secondary or primary boronic ester. Pleasingly, the two homologation steps could be performed in one pot, without the need for isolation of the once-homologated intermediate. In order to generate benzylic, tertiary boronic esters, the final homologation step was performed using known lithiation–borylation chemistry (Scheme 47).[27]



Scheme 47. Synthesis of tertiary boronic ester starting materials.

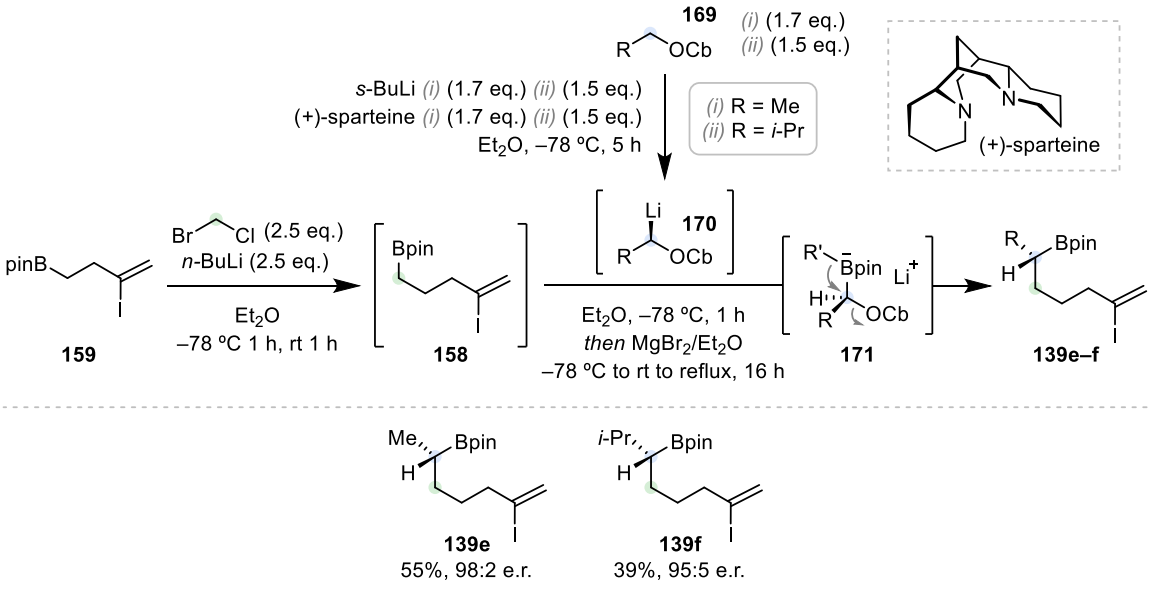
*Yields are of isolated products. Enantiomeric ratio (e.r.) was determined by chiral HPLC analysis of the oxidation products. [a] Using alkenyl bromide **165** instead of **159**. [b] With TMEDA. [c] The e.r. could not be determined (n.d. = not determined) by chiral HPLC, chiral SFC or using a chiral solvating agent.*

Chiral carbamate **166** was lithiated using *sec*-butyl lithium, ligated with TMEDA when this lithiation was slow. This lithiated species is configurationally stable at –78 °C. To **167** was

added the once homologated boronic ester (**158**) to give boronate complex **168**, primed for a 1,2-metallate rearrangement which occurred upon warming to room temperature with expulsion of the carbamate leaving group and inversion of stereochemistry at the reacting centre. In all cases this sequence proceeded smoothly, affording product boronic esters (**139a–d**) in good yields over 2 steps.

Determination of the enantiomeric ratio of these starting boronic esters was achieved through their stereospecific oxidation using basic hydrogen peroxide, yielding alcohol products for which enantiomeric separation by chiral HPLC was facile. Transformation of enantioenriched boronic esters to alcohols has been shown to improve the separation of enantiomers by chiral chromatography, owing to their increased polarity and thus increased retention times.

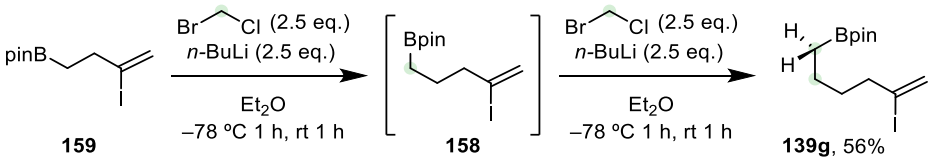
Secondary boronic esters were accessed in an analogous fashion (Scheme 48).[21,22] In this case, an asymmetric lithiation of carbamate **169** was performed through the ligation of *sec*-butyl lithium with chiral diamine ligand (+)-sparteine. Again, chiral lithium carbenoid **170** is configurationally stable at –78 °C, at which temperature the once homologated boronic ester (**158**) was added to give boronate complex **171**. The invertive 1,2-metallate rearrangement at elevated temperatures gave the product boronic esters (**139e–f**). This approach enabled the synthesis of α-methyl and α-isopropyl boronic esters (**139e** and **139f**, respectively). Again, the high enantiomeric ratio of the boronic esters was confirmed by their oxidation to the corresponding alcohols.



Scheme 48. Synthesis of secondary boronic ester starting materials.

Yields are of isolated products. Enantiomeric ratio (e.r.) was determined by chiral HPLC analysis of the oxidation products.

Parent boronic ester **139g**, with no substitution at the α-position, was accessed in 56% yield over 2 steps by performing two sequential Matteson homologation reactions (Scheme 49).

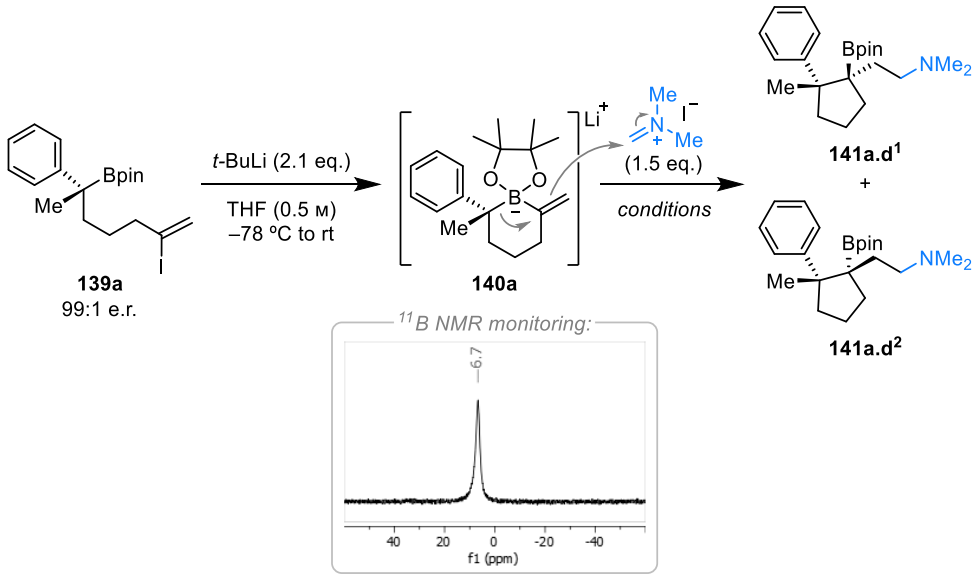


*Scheme 49. Synthesis of primary boronic ester starting material **139g**.*

2.5.2. Initial reactivity and optimisation

With a range of starting boronic esters in hand, initial probes into their reactivity were conducted. First, boronic ester **139a** was subjected to known lithium-halogen exchange conditions, employing 2.1 equivalents of *tert*-butyl lithium (Scheme 50).[75] Reaction monitoring by ^{11}B NMR spectroscopy confirmed the full formation of boronate complex **140a**, displaying a characteristic peak at 6.7 ppm.

Having confirmed formation of boronate complex **140a**, a screen of electrophile addition conditions was conducted. Eschenmoser's salt was used as the model electrophile and boronic ester **139a** the model substrate, since the product boronic ester **141a** possesses two contiguous fully substituted stereocentres and a tertiary amine functionality, and thus is a highly valuable target.



Scheme 50. Optimisation of reaction conditions for the electrophile addition step.

Pleasingly, when Eschenmoser's salt was added to the boronate complex, product ring contracted cyclopentyl boronic ester **141a** was formed in a very good initial yield (Table 1; Entry 1). The major diastereomer formed was **141a.d[1]**, with the boronic ester functionality cis to the methyl group.

The influence of the reaction solvent for the electrophile addition step was then investigated (Entries 2–6). Following the formation of boronate complex **140a** in THF, the solvent was removed *in vacuo* and replaced by an alternative reaction solvent. The addition of the neat electrophile occurred at either –78 °C or –40 °C, depending on the freezing point of the reaction solvent. No solvent outperformed THF (Entry 1) in terms of both yield and diastereoselectivity.

Since Eschenmoser's salt is sparingly soluble in THF at low temperatures, the influence of 1:1 THF/solvent mixtures was investigated. Following the formation of boronate complex **140a** in THF, a co-solvent was added to the reaction mixture (thus halving the reaction concentration). The addition of the neat electrophile then followed. Acetonitrile (Entry 7) and *N*,*N*-dimethylformamide (Entry 8) were investigated as potential co-solvents; this approach improved yields and diastereoselectivities with respect to the complete solvent swap (Entries 3 and 4, respectively) but did not improve upon the original result with THF (Entry 1).

Table 1. Optimisation of reaction conditions for the electrophile addition step: the influence of solvent.

entry	solvent (x M)	temperature (°C)	^{1}H NMR yield (%)	d^1/d^2
1	THF (0.5 M)	–78 °C 2 h, then rt	70	89:11
2	EtCN (0.5 M)	–78 °C 2 h, then rt	91	73:27
3	MeCN (0.5 M)	–40 °C 2 h, then rt	73	68:32
4	DMF (0.5 M)	–40 °C 2 h, then rt	39	80:20
5	CH_2Cl_2 (0.5 M)	–78 °C 2 h, then rt	50	75:25
6	Et_2O (0.5 M)	–78 °C 2 h, then rt	62	84:16
7	1:1 THF/MeCN (0.25 M)	–40 °C 2 h, then rt	78	81:19
8	1:1 THF/DMF (0.25 M)	–40 °C 2 h, then rt	56	86:14

All reactions conducted on a 0.10 mmol scale. Yields were determined by ^{1}H NMR (400 MHz, $CDCl_3$) spectroscopic analysis using CH_2Br_2 as the internal standard. Diastereomeric ratio (d^1/d^2) was also determined by ^{1}H NMR spectroscopic analysis.

An important breakthrough arose when the addition of hydrogen bond donating co-solvents was investigated (Table 2). A 1:1 ratio of THF and methanol as the solvent system for electrophile addition gave the product in a poorer yield but, remarkably, in inverted diastereoselectivity (Entry 9). The major diastereomer formed was **141a.d[2]**, with the boronic ester functionality trans to the methyl group. This effect proved most pronounced with

fluorinated alcohols, with 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) (Entry 10) and 2,2,2-trifluoroethanol (TFE) (Entry 12) co-solvents, enabling access to **141a** in high yield and diastereoselectivity. The high freezing point of *tert*-butanol (25 °C) limited its use at low temperatures; a 10% *tert*-butanol in THF solvent system did not give inverted diastereoselectivity. (Entry 11).

The optimal ratio of THF/TFE was then sought, investigating THF and then TFE as the major component (Entries 13 and 14, respectively). However, no improvement was observed. Employing pure TFE as the solvent gave a complex crude reaction mixture and ^{1}H NMR spectroscopic analysis was not possible (Entry 15).

Table 2. Optimisation of reaction conditions for the electrophile addition step: the influence of hydrogen bond donating solvent.

entry	solvent (x M)	temperature (°C)	^{1}H NMR yield (%)	d^1/d^2
1	THF (0.5 M)	–78 °C 2 h, then rt	70	89:11
9	1:1 THF/MeOH (0.25 M)	–78 °C 2 h, then rt	64	28:72
10	1:1 THF/HFIP (0.25 M)	–40 °C 2 h, then rt	83	10:90
11	10:1 THF/*t*-BuOH (0.25 M)	–78 °C 2 h, then rt	84	70:30
12	1:1 THF/TFE (0.25 M)	–78 °C 2 h, then rt	96	14:86
13	10:1 THF/TFE (0.25 M)	–78 °C 2 h, then rt	82	37:63
14	1:5 THF/TFE (0.25 M)	–60 °C 2 h, then rt	76	11:89
15	TFE (0.25 M)	–40 °C 2 h, then rt	-[a]	-

All reactions conducted on a 0.10 mmol scale. Yields were determined by ^{1}H NMR (400 MHz, $CDCl_3$) spectroscopic analysis using CH_2Br_2 as the internal standard. Diastereomeric ratio (d^1/d^2) was also determined by ^{1}H NMR spectroscopic analysis. [a] A complex mixture of unknown products was observed.

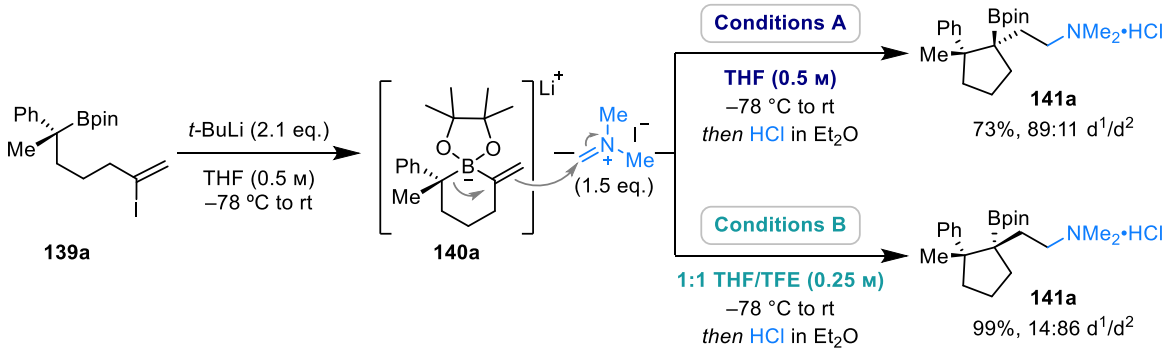
Finally, the influence of temperature was probed (Table 3). The addition of the electrophile to the boronate complex dissolved in THF at low temperatures without subsequent warming gave no product (Entries 16–17), likely as a result of poor electrophile solubility in THF at low temperatures. The addition of the electrophile at low temperatures followed by warming to room temperature was not necessary for good diastereoselectivity in this system (Entry 18). However, this variable temperature protocol was maintained to account for variations in electrophile solubility at low temperatures. By contrast, the slow warming sequence with a 1:1 THF/TFE solvent mixture is necessary for high yields but seems to have no effect on diastereoselectivity in this system (Entries 19–20).

Table 3. Optimisation of reaction conditions for the electrophile addition step: the influence of temperature.

entry	solvent (x M)	temperature (°C)	^{1}H NMR yield (%)	d^1/d^2
1	THF (0.5 M)	–78 °C 2 h, then rt	70	89:11
16	THF (0.5 M)	–78 °C	0	-
17	THF (0.5 M)	–40 °C	0	-
18	THF (0.5 M)	rt	72	86:14
12	1:1 THF/TFE (0.25 M)	–78 °C 2 h, then rt	96	14:86
19	1:1 THF/TFE (0.25 M)	–60 °C	17	13:87
20	1:1 THF/TFE (0.25 M)	–40 °C	32	12:88

All reactions conducted on a 0.10 mmol scale. Yields were determined by ^{1}H NMR (400 MHz, $CDCl_3$) spectroscopic analysis using CH_2Br_2 as the internal standard. Diastereomeric ratio (d^1/d^2) was also determined by ^{1}H NMR spectroscopic analysis.

Extensive optimisation studies have resulted in the development of two sets of conditions, each leading to a distinct diastereochemical outcome, termed ‘conditions A’ and ‘conditions B’ (Scheme 51). This diastereodivergence is remarkable, the substrate bias for one diastereomer over the other can be overcome simply through the addition of a co-solvent.



*Scheme 51. Solvent-dependent diastereodivergence in the ring contractive 1,2-metallate rearrangement of boronate complex **140a**.*

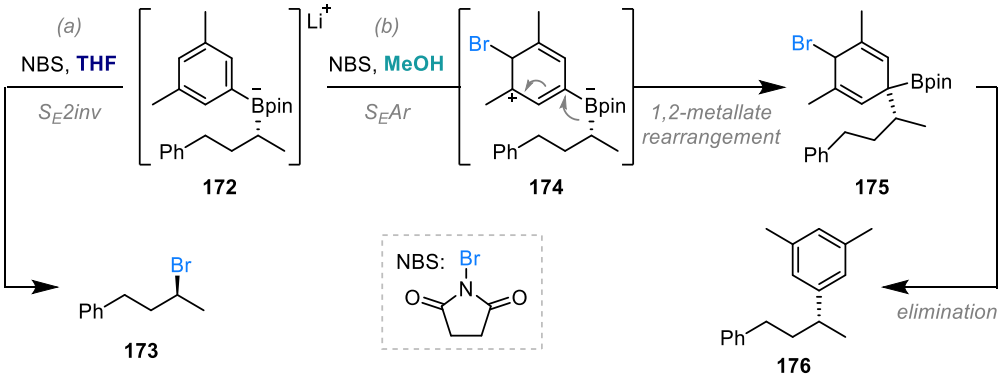
Yields are of isolated hydrochloride salts. Diastereomeric ratio (d^1/d^2) was determined by ^{1}H NMR (400 MHz, $CDCl_3$) spectroscopic analysis.

2.5.3. Origin of diastereodivergence

The origin of the solvent-induced diastereodivergence is not clear. However, there have been previous reports from the Aggarwal group detailing the influence of hydrogen bond donating solvents on the reactivity of boronate complexes with electrophiles. It is thought that, in the presence of such a hydrogen bond donating solvent, there is a hydrogen bond between the alcohol and the Lewis basic pinacol oxygens in the boronate complex, modulating the nucleophilicity of the C–B bonds. Since the reversal in diastereoselectivity occurs in the

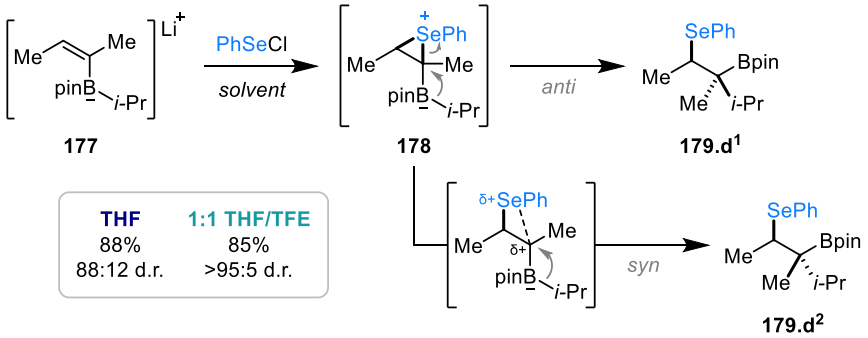
presence of various hydrogen bond donating solvents (see Table 2), the same hypothesis was considered to be reasonable in this system.

In 2014, Aggarwal and co-workers reported the solvent-induced divergent reactivity of aryl boronate complexes (**172**) upon addition of an electrophilic source of bromine (Scheme 52).[50] In THF an undesired, invertive S_E2 pathway dominated, giving bromoalkane **173** as the major product (99:1 **173**/**176**) (Scheme 52a). However, in methanol the desired reactivity was observed, with addition of bromine to the aryl group to give **174**, 1,2-metallate rearrangement to give **175** and then elimination affording sp^2-sp^3 coupled product **176** (99:1 **176**/**173**) (Scheme 52b). It was suggested that the electrophilic aromatic substitution reactions are more successful in more polar media, owing to the stabilisation of intermediate cationic **174**.



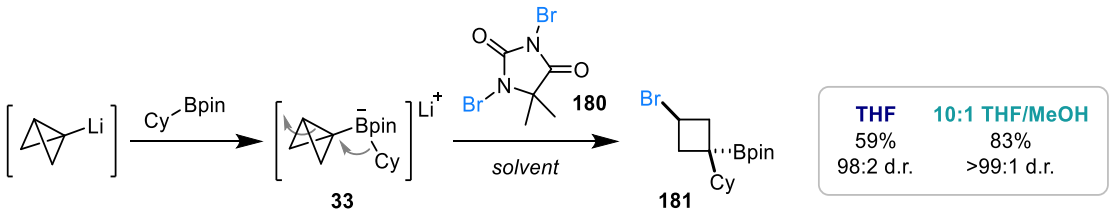
*Scheme 52. Solvent-induced divergent reactivity of boronate complex **172** with NBS.*

In another study, the reactivity of alkenyl boronate complex **177** with phenylselenyl chloride was influenced by a hydrogen bond donating solvent (Scheme 53).[43] Zwitterionic seleniranium intermediate **178** undergoes an *anti*-migration sequence, giving diastereomer **179.d^1**. However, partial opening of the 3-membered heterocycle, allowing the formation of a partial positive charge at the α-carbon, can result in some competing *syn*-migration affording diastereomer **179.d^2**, which erodes the overall diastereomeric ratio of the product. By contrast, electrophile addition to the boronate complex dissolved in a 1:1 mixture of THF/TFE sees no competing *syn*-migration and thus perfect diastereoselectivity. This can be attributed to the modulation of the reactivity of boronate complex **178** by the TFE co-solvent, limiting the partial seleniranium ring-opening.



Scheme 53. Influence of solvent on diastereoselectivity in the addition of PhSeCl to an alkenyl boronate complex.

Moreover, the yield and diastereoselectivity of the reaction of bicyclo[1.1.0]butyl boronate complex **33** with electrophilic brominating reagent **180** improved when a methanol co-solvent was added (Scheme 54).[37] The increased yield of **181** was partly attributed to the quenching of any excess organolithium, which could interfere with the electrophile.

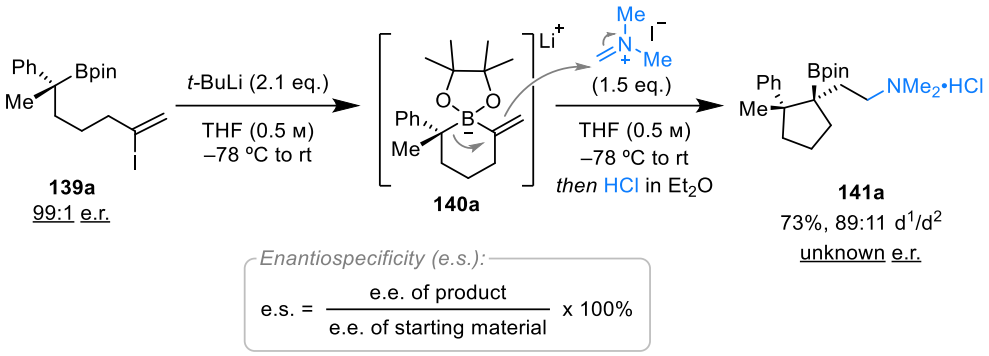


*Scheme 54. Influence of solvent on diastereoselectivity in the addition of **180** to a bicyclo[1.1.0]butyl boronate complex.*

2.5.4. Reaction enantiospecificity

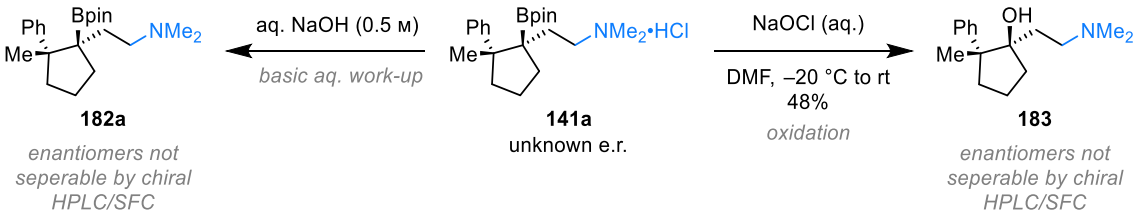
The enantiospecificity (e.s.) of the ring contractive 1,2-metallate rearrangement was then investigated (Scheme 55): is the stereochemical information installed in the synthesis of the starting boronic ester retained throughout the reaction? It was thus necessary to determine the enantiomeric ratio of the product boronic ester.

Typically, the enantiomeric ratio of a chiral compound is determined using analytical chiral chromatography (high-performance liquid chromatography (HPLC); supercritical fluid chromatography (SFC)), using chiral stationary phases to differentiate the enantiomeric components. Alternatively, NMR techniques can be employed to this end, such as using chiral solvating agents (CSAs) or chiral derivatising agents (CDAs) to determine enantiomeric excess and even absolute configuration.[86,87]



Scheme 55. Investigating the reaction enantiospecificity.

The enantiomers of free base **182a** proved inseparable by chiral HPLC and chiral SFC (Scheme 56). Stereospecific oxidation of **141a** to tertiary alcohol **183** was successful using atypical conditions (as discussed in Section 2.5.9.2),[88] however no enantiomeric separation was observed. As a result, the enantiomeric ratio of product **141a** could not be determined by chiral chromatographic means and an alternative method was sought.



*Scheme 56. Attempts to determine the enantiomeric ratio of **141a**.*

2.5.4.1. The use of chiral solvating agents for the determination of enantiomeric ratio

Enantiomerically pure chiral solvating agents (CSAs), such as those shown in Figure 6, can be used for the determination of the enantiomeric ratio of an enantioenriched analyte.[86] CSAs bind to the analyte through non-covalent, intermolecular forces to generate transient adducts between the CSA and each enantiomer of the analyte, which are distinguishable by NMR spectroscopic analysis. The discrimination of the enantiomers by NMR spectroscopic analysis is possible for two reasons. The first being that the associated complexes are diastereomers, and so the nuclei in each enantiomer are influenced by local magnetic anisotropic effects to different extents depending on their location in space with respect to the enantiomerically pure CSA. Secondly, the association constants of the enantiomer and CSA are different, giving different time-averaged solvation environments and thus different chemical shifts.

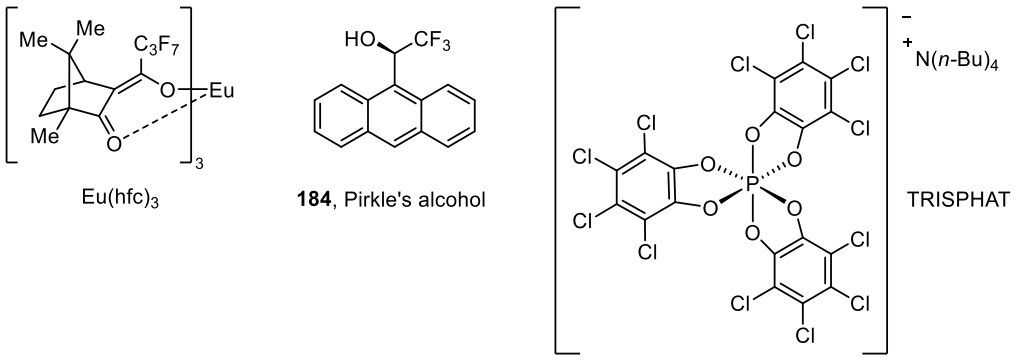


Figure 6. Chiral solvating agents.

Previous work in the Aggarwal group has shown that Pirkle's alcohol ((*R*)-(–)-1-(9-anthryl)-2,2,2-trifluoroethanol, **184**)[89] is able to form diastereomeric complexes with molecules containing boronic esters, and thus allow for the determination of their enantiomeric excess.[35]

In order to probe the utility of Pirkle's alcohol in this system, 30 μmol of enantiomerically pure **184** was added to an NMR tube containing 30 μmol of racemic amino boronic ester **(±)-141a** in 0.6 mL of $CDCl_3$ (0.05 M) (Figure 7). The resultant ^{1}H NMR spectrum is shown in Figure 9 and for reference the ^{1}H NMR spectrum of **141a** is shown in Figure 8 with key peaks of interest highlighted. Upon addition of **184**, the two singlets corresponding to the diastereotopic pinacol methyl protons (purple) are split into two further singlets, giving four signals. Each of these peaks is split perfectly in two, with a 50:50 ratio in their integrals, indicating a racemic mixture. Additionally, the apparent triplet of doublets corresponding to the proton β to the dimethylamine (teal) is shifted to lower chemical shift and split into two signals, with a 50:50 integral ratio.

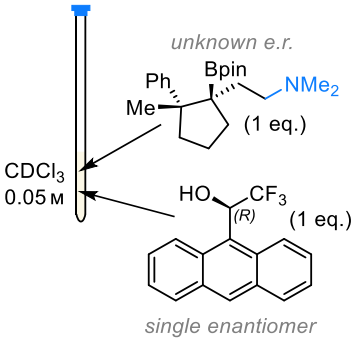


Figure 7. Experimental set-up for the use of a CSA for enantiomeric ratio determination.

The ^{1}H NMR spectrum of the mixture of enantiomerically enriched boronic ester **141a** and enantiomerically pure **184** (1:1 molar ratio) is shown in Figure 10. In the case of the triplet of

doublets (teal), there is complete depletion of one of the diastereomeric peaks. This means that there is a >98:2 diastereomeric ratio in the NMR tube, giving a >98:2 enantiomeric ratio of boronic ester **141a**. This same observation is seen with the diastereotopic pinacol methyl protons (purple), where the four signals were reduced to two signals. In this case, since the enantiomeric ratio is so high, it is not possible to integrate the minor peak.

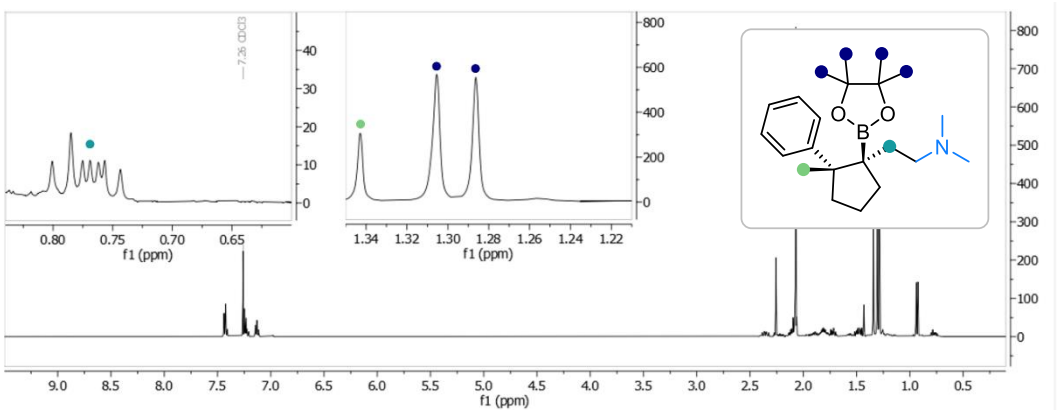


*Figure 8. ^{1}H NMR (500 MHz, $CDCl_3$) spectrum of **141a**.*

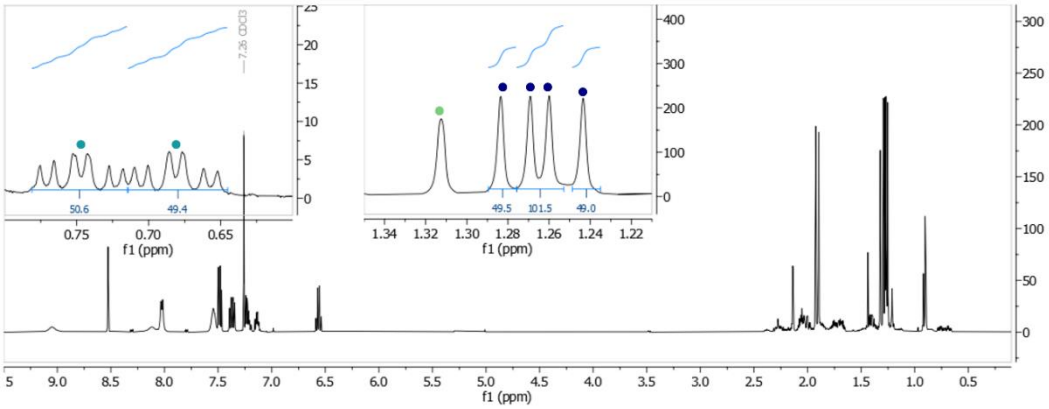


*Figure 9. ^{1}H NMR (500 MHz, $CDCl_3$) spectrum of **(±)-141a** and 1 equivalent of **(R)-184**.*

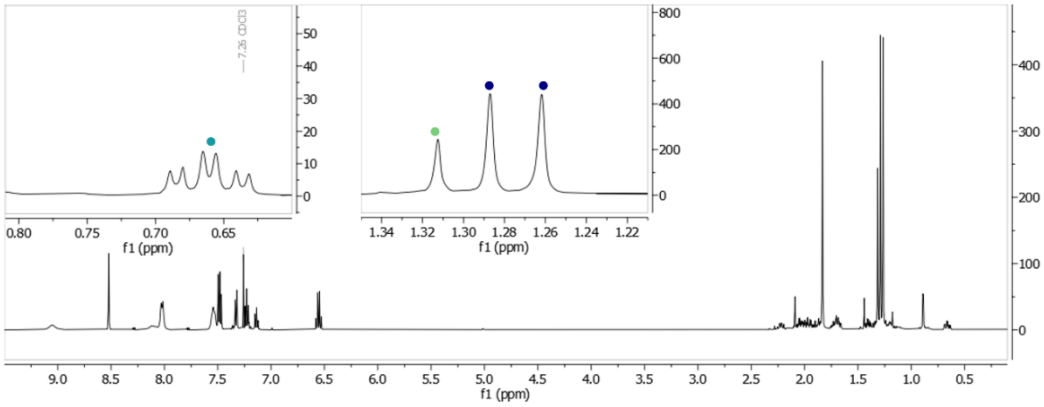


*Figure 10. ^{1}H NMR (500 MHz, $CDCl_3$) spectrum of **141a** and 1 equivalent of **(R)-184**.*

This method was extended throughout this project for the determination of the enantiomeric ratio of amino boronic esters. In each case, the pinacol methyl signals split into diastereomeric peaks. Perhaps this implies that the non-covalent, intermolecular forces at work in the diastereomeric complexes are hydrogen bonding interactions between the electron pairs on the pinacol oxygens and the alcohol functional group of **184** (Figure 11). Alternatively, there could be coordination of the Lewis basic oxygen of **184** to the Lewis acidic boron of the boronic ester.

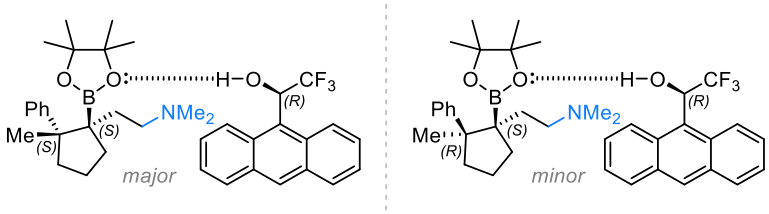
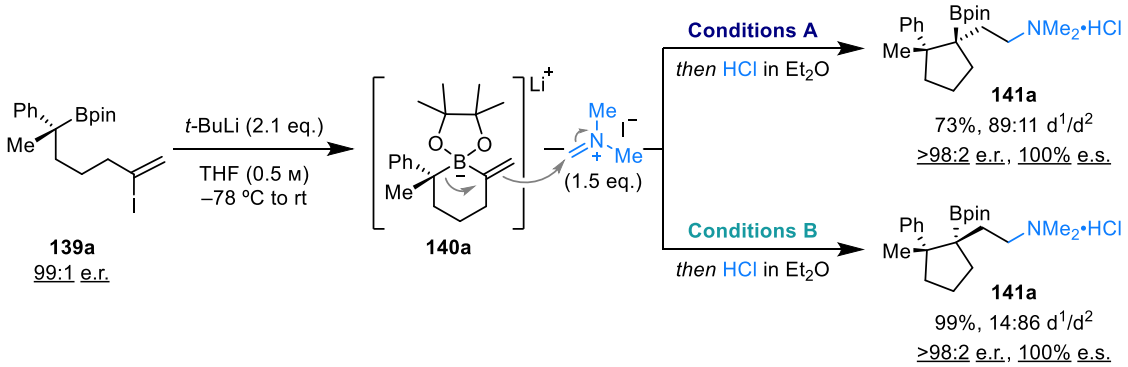


*Figure 11. Postulated diastereomeric complexes formed between **141a** and **184**.*

With a method for the determination of the enantiomeric ratio of the γ-amino boronic esters in hand, it was possible to confirm the enantiospecificity of the transformation under both conditions A and B; the chiral information installed in **139a** was completely transferred into product **141a** (Scheme 57).



Scheme 57. Investigating the reaction enantiospecificity under conditions A and B.

Yields are of isolated products. Diastereomeric ratio (d^1/d^2) was determined by ^{1}H NMR (400 MHz, $CDCl_3$) spectroscopic analysis. Enantiomeric ratio (e.r.) was determined by ^{1}H NMR (500 MHz, $CDCl_3$) spectroscopic analysis using Pirkle's chiral solvating agent.

2.5.5. Substrate scope

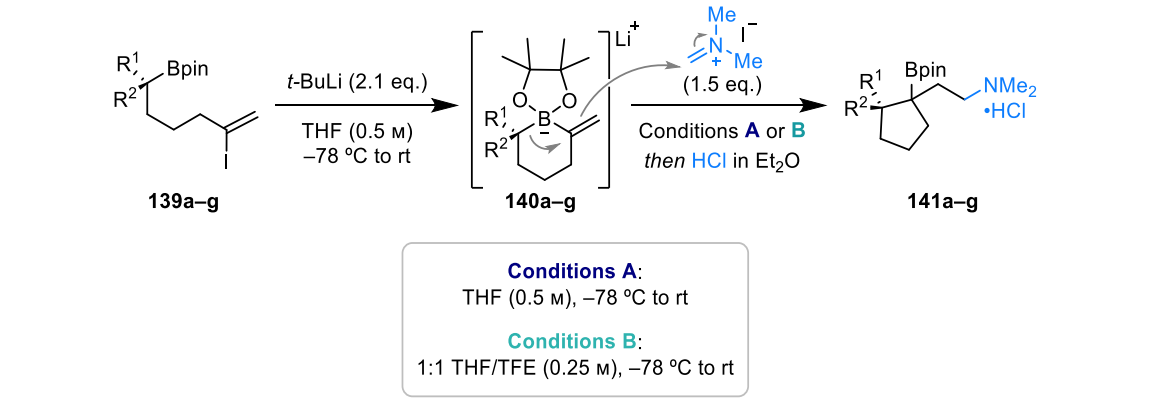
Having established two sets of conditions which gave divergent outcomes in the model system, the generality of the transformation was explored in a substrate scope study, synthesising a range of γ-amino boronic esters through the addition of Eschenmoser's salt to a range of boronate complexes (**140a–g**) (Scheme 58). In all cases, the product tertiary amines could be isolated without the need for chromatographic purification, simply by precipitating out the HCl salt and washing the resultant off-white foam with cold Et_2O.

Investigations into the substrate scope first focused on the reactivity of benzylic tertiary boronic esters, accessed in their enantioenriched form using lithiation–borylation chemistry (see Section 2.5.1) and then subjected to conditions for lithium-halogen exchange and cyclisation to give the required cyclic alkenyl boronate complexes. Pleasingly, the addition of Eschenmoser's salt to these boronate complexes enabled the efficient and enantiospecific synthesis of α,β,β-trisubstituted cyclopentyl boronic esters **141a**, **141b** and **141c**, constructing two contiguous fully-substituted stereocentres with high levels of diastereocontrol and perfect enantiofidelity under both conditions A and B. Gratifyingly, in all three cases solvent-induced diastereodivergency was observed, enabling access to the complementary diastereomeric partner through the simple addition of a TFE co-solvent (conditions B).

A structurally complex spirocyclic cyclopentyl boronic ester (**141d**) could also be accessed in high yield and as a single diastereomer, installing a challenging, all-carbon quaternary spirocentre in the ring contractive transformation.[90] In this case, no solvent-induced diastereodivergency was observed, conditions A no longer led to the opposite diastereochemical outcome to conditions B and instead delivered the product in similar yields and diastereoselectivity. This effect likely owes to the already overriding diastereochemical bias present in the system.

The reactivity of secondary boronic esters was then investigated. Substrates bearing α-methyl and α-isopropyl substituents performed well, giving highly enantioenriched products (**141e** and **141f**, respectively) in excellent yields and as essentially single diastereomers under conditions B. Again, conditions A did not reverse the diastereoselectivity in the system.

The parent cyclic alkenyl boronate complex, with no substituents at the α-carbon, successfully underwent the ring contractive transformation to give **141g**.



Scheme 58. Cyclic alkenyl boronate complex scope for the ring contractive 1,2-metallate rearrangement with Eschenmoser's salt.

*All reactions conducted on a 0.20 mmol scale. Yields are of isolated products. Diastereomeric ratio (d.r., d^1/d^2) was determined by ^{1}H NMR (400 MHz, $CDCl_3$) spectroscopic analysis. Enantiomeric ratio (e.r.) was determined by ^{1}H NMR (500 MHz, $CDCl_3$) spectroscopic analysis using Pirkle's chiral solvating agent. [a] The e.r. could not be determined (n.d. = not determined) by chiral HPLC, chiral SFC or using a chiral solvating agent. [b] Using racemic **139** (0.10 mmol) and so product e.r. was not determined (n.d.).*

2.5.6. Electrophile scope

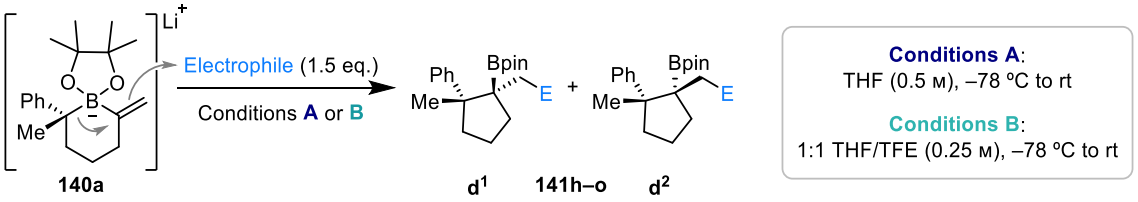
Exploration of the scope of electrophiles able to induce the ring contractive 1,2-metallate rearrangement of cyclic alkenyl boronate complex **140a** was then investigated, forging a range of new C–C and C–heteroatom bonds in product boronic esters bearing two contiguous fully substituted stereocentres (Scheme 59).

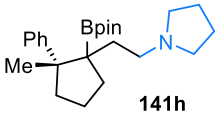
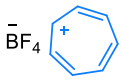
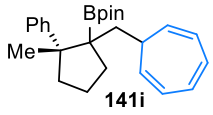
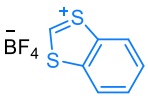
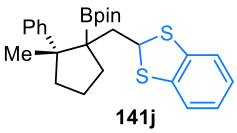
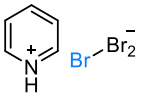
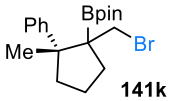
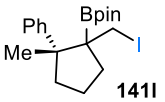
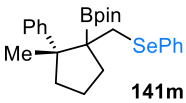
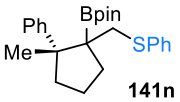
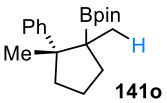
Adding 1-methylenepyrrolidin-1-ium iodide, another iminium salt, to boronate complex **140a** induced the desired enantiospecific ring contraction, introducing a valuable pyrrolidine functionality into enantioenriched boronic ester **141h** with good diastereoselectivity. Conditions A and B gave diastereodivergent outcomes, however the yield of **141h** was limited under conditions A by poor electrophile solubility in THF.

Next other cationic, carbon-based electrophiles were explored. The tropylium functionality was successfully introduced using tropylium tetrafluoroborate, furnishing a new C–C bond in boronic ester **141i**.

Interestingly, under conditions A (slightly modified for enhanced electrophile solubility), two products derived from the reaction of boronate complex **140a** with the electrophile were observed (Scheme 60). Desired product **141i** was observed in 44% yield and 94:6 diastereomeric ratio, alongside 21% of **185**. It is believed that **185** originates from reaction of the electrophile with the nucleophilic C(sp^3)–B bond. Under conditions B, where the nucleophilicity of the C(sp^3)–B bond is modulated by the presence of hydrogen bond donor TFE, no **185** is observed. Instead, an increased yield of **141i** is seen, favouring the opposite diastereomer.

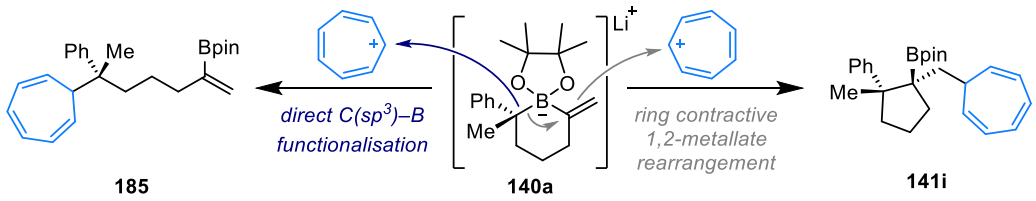
The formation of boronic ester **185** is not enantiospecific. It is believed that this reaction occurs with predominant inversion of configuration, with electrophile approach occurring from the opposite side to boron.[91] This is an observation consistent with previous work into the reactivity of boronate complexes as nucleophiles, where the reaction with an electrophile occurs through two competing pathways: i) polar pathway (2 electron) giving products with inversion at the reacting centre, ii) SET pathway (1 electron) with racemisation.[91]



Electrophile	Product	Conditions A	Conditions B
	 **141h**	27% 82:18 d^1/d^2 >98:2 e.r. 100% e.s.	60% 18:82 d^1/d^2 >98:2 e.r. 100% e.s.
	 **141i**	44%[a] 94:6 d^1/d^2 99:1 e.r. 100% e.s.	69% 17:83 d^1/d^2 99:1 e.r. 100% e.s.
	 **141j**	26% 84:16 d^1/d^2 99:1 e.r. 100% e.s.	44%[b] 54:46 d^1/d^2 e.r. n.d.
	 **141k**	30%[b][c] 7:93 d^1/d^2 e.r. n.d.	57%[c] 5:95< d^1/d^2 99:1 e.r. 100% e.s.
	 **141l**	66%[b] 7:93 d^1/d^2 e.r. n.d.	68% 5:95< d^1/d^2 99:1 e.r. 100% e.s.
	 **141m**	20%[b] 44:56 d^1/d^2 e.r. n.d.	38% 15:85 d^1/d^2 99:1 e.r. 100% e.s.
	 **141n**	44%[b][c] 18:82 d^1/d^2 e.r. n.d.	76%[c] 17:83 d^1/d^2 99:1 e.r. 100% e.s.
	 **141o**	53%[a] 14:86 d^1/d^2 99:1 e.r. 100% e.s.	29%[b] 27:73 d^1/d^2 e.r. n.d.

*Scheme 59. Electrophile scope for the ring contractive 1,2-metallate rearrangement of cyclic alkenyl boronate complex **140a**.*

*All reactions conducted on a 0.20 mmol scale. Yields are of isolated products. Diastereomeric ratio (d.r., d^1/d^2) was determined by ^{1}H NMR (400 MHz, $CDCl_3$) spectroscopic analysis. Enantiomeric ratio (e.r.) was determined by either chiral HPLC analysis, chiral SFC analysis or ^{1}H NMR (500 MHz, $CDCl_3$) spectroscopic analysis using Pirkle's chiral solvating agent. [a] Modified conditions A: 1:1 THF/MeCN (0.25 M). [b] Using racemic **139a** (0.10 mmol) and so product e.r. was not determined (n.d.). [c] Boronate complex **140a** derived from alkenyl bromide **139aa** (0.20 mmol, 99:1 e.r.).*



21% 93:7 e.r., 88% e.s.	**Conditions A**[a]	44%, 94:6 d^1/d^2 99:1 e.r., 100% e.s.
0%	**Conditions B**	69%, 17:83 d^1/d^2 99:1 e.r., 100% e.s.

*Scheme 60. Tropylium tetrafluoroborate in the ring contractive 1,2-metallate rearrangement of cyclic alkenyl boronate complex **140a**.*

Yields are of isolated products. Diastereomeric ratio (d.r., d^1/d^2) was determined by ^1H NMR (400 MHz, $CDCl_3$) spectroscopic analysis. Enantiomeric ratio (e.r.) was determined by chiral HPLC or chiral SFC analysis. [a] Modified conditions A: 1:1 THF/MeCN (0.25 M).

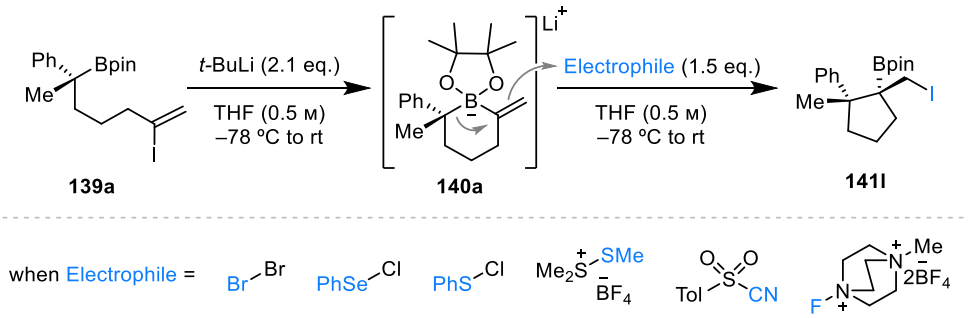
The benzodithiole functional group was also incorporated into enantioenriched cyclopentyl boronic ester **141j** using 1,3-benzodithiolylium tetrafluoroborate as the electrophile. Under conditions A, a low yield of product **141j** was observed with good diastereoselectivity. Unfortunately, under conditions B the diastereomeric ratio was altered but not reversed.

New C–heteroatom bonds could also be formed using this methodology. Highly enantioenriched β-bromo and β-iodo boronic esters (**141k** and **141l**, respectively) were synthesised in good yields and as single diastereomers under conditions B, with negligible competing elimination. This methodology also enabled the diastereoselective and enantiospecific formation of β-selenyl and β-sufenyl boronic esters (**141m** and **141n**, respectively) in good yields. In all cases, conditions B gave the β-halo product in the highest yields and diastereoselectivities and conditions A led to no reversal in diastereoselectivity.

Pleasingly, a proton could act as the electrophilic activating agent, giving boronic ester **141o**. Under modified conditions A, the product was obtained in 53% yield and 86:14 diastereomeric ratio, favouring the diastereomer with two cis methyl groups. Under conditions B, the reaction became less efficient, perhaps as a result of the acidic protons of the TFE co-solvent interfering with desired reactivity.

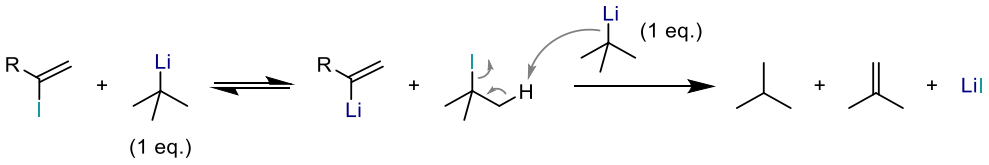
2.5.6.1. Limitations: influence of lithium iodide

Whilst the electrophile scope was wide, some of the electrophiles tested gave little or no desired product. Instead, the electrophiles were interacting with the lithium iodide in the reaction mixture to generate an electrophilic iodine species, iodinating the alkenyl boronate complex to give β-iodo boronic ester **141l** (Scheme 61).



*Scheme 61. Undesired formation of β-iodo boronic ester **141l**.*

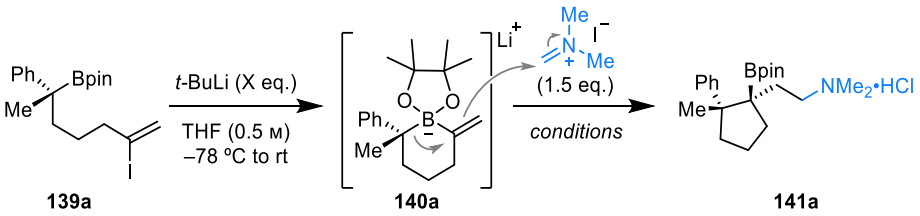
An equivalent of lithium iodide is generated in the lithium-halogen exchange process to generate boronate complex **140a**. Whilst 1 equivalent of *tert*-butyl lithium is sufficient for lithium-halogen exchange, another equivalent is added to enable the favourable elimination of *tert*-butyl iodide (Scheme 62).



Scheme 62. Lithium-halogen exchange using tert-butyl lithium.

The importance of 2.1 equivalents of *tert*-butyl lithium was demonstrated by comparing the yields of ring contracted boronic ester **141a** using 2.1 and 1.0 equivalents of *tert*-butyl lithium in the lithium-halogen exchange (Table 4). The approximate halving in yield of **141a** when using 1.0 equivalents can be attributed to the competitive elimination of *tert*-butyl iodide.

*Table 4. Changing the number of equivalents of tert-butyl lithium in the lithium-halogen exchange of **139a**.*

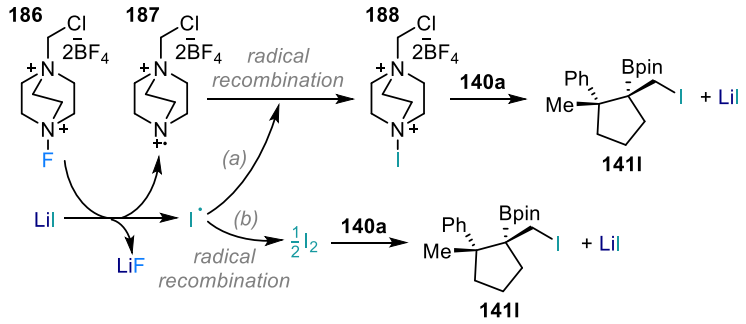


entry	X eq.	^{1}H NMR yield
1	2.1	70%
2	1.0	45% (25% rsm)

All reactions conducted on a 0.10 mmol scale. Yields were determined by ^{1}H NMR (400 MHz, $CDCl_3$) spectroscopic analysis using CH_2Br_2 as the internal standard. rsm = returned starting material.

The exact identity of the electrophilic iodine species is unknown. It has been proposed that lithium bromide, in the presence of Selectfluor (**186**), can undergo a single electron transfer sequence to liberate lithium fluoride, a bromine radical and a radical cation **187**.[92] This could be extended to lithium iodide, which would give instead an iodine radical (Scheme 63). The radical can recombine with radical cation **187** to give **188**, the iodine analogue of Selectfluor, which can react with boronate complex **140a** to give β-iodo boronic ester **141l** (Scheme 63a). Alternatively, two iodine radicals can combine to give elemental iodine which can react with **140a** as previously described (Scheme 63b).

Indeed the brown colour of the reaction mixture following overnight stirring supports this second hypothesis, alongside literature precedent.[93] This colour was lost on a saturated aqueous sodium thiosulfate quench, indicating the presence of elemental iodine.



*Scheme 63. Proposed generation of an electrophilic iodine species for the formation of β-iodo boronic ester **141l**.*

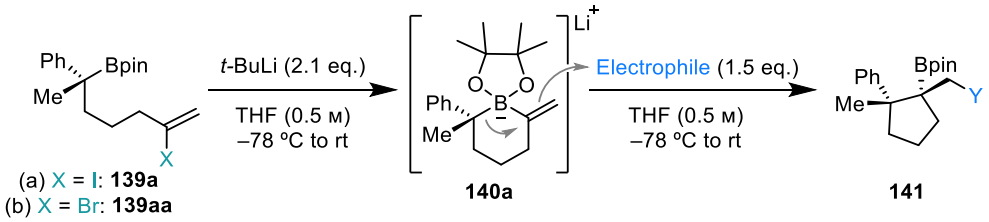
It was proposed that this problem could be circumvented by using alkenyl bromide **139aa** as the precursor to boronate complex **140a** instead of alkenyl iodide **139a** (Table 5). It was anticipated that the bromide anion would be less readily oxidised to the bromine radical than the iodide anion to the iodine radical.[94] Performing a lithium-bromine exchange instead of a lithium-iodide exchange was successful; reaction monitoring by ^{11}B NMR spectroscopic analysis confirmed the full formation of boronate complex **140a** from alkenyl bromide **139aa**. A range of electrophiles were then investigated under these modified reaction conditions.

First, phenylselenyl and phenylsulfenyl chloride were investigated (Entries 1 and 2, respectively). Whilst phenylselenyl chloride had previously proved a competent electrophile, giving product **141m** in 55% NMR yield and 84:16 diastereomeric ratio, β-iodo boronic ester **141l** was also observed in 18% NMR yield (Entry 1a). When using alkenyl bromide **139aa**, the competing addition of an electrophilic halogen species was limited and thus the yield of desired **141m** was increased to 96% NMR yield (Entry 1b). However, the diastereomeric ratio of the

product surprisingly fell to 66:34. By comparison, phenylsulfenyl chloride did not yield any desired **141n** when employing alkenyl iodide **139a**, with β-iodo boronic ester **141l** observed as the only product (Entry 2a). However, when using alkenyl bromide **139aa** a 75% NMR yield of **141n** was observed (Entry 2b).

Initial attempts to synthesise β-bromo boronic ester **141k** sought to use elemental bromine as the electrophile (Entry 3). Whilst a mixture of desired β-bromo boronic ester **141k** and β-iodo boronic ester **141l** was observed when using alkenyl iodide **139a** (Entry 3a), only **141k** was formed when using alkenyl bromide **139aa** as the starting material, in 56% NMR yield and 94:6 diastereomeric ratio (Entry 3b).

*Table 5. Expansion of the electrophile scope: alkenyl iodide **139a** vs alkenyl bromide **139aa**.*



entry		electrophile	Y = E	^{1}H NMR yield (%) for Y = E	Y = I	Y = Br
1a	I	PhSeCl [a]	**141m**	55 (84:16 d.r.)	18	-
1b	Br			96 (66:34 d.r.)	-	0
2a	I	PhSCl [a]	**141n**	0	50	-
2b	Br			75 (83:17 d.r.)	-	0
3a	I	Br–Br	**141k**	16	36	
3b	Br			56 (94:6 d.r.)	-	
4a	I	Me_2S^+–SMe BF_4^-	**141p**	0	40	-
4b	Br			13	-	0
5a	I	Tol–S(=O)(=O)–CN	**141q**	0	18[b]	-
5b	Br			9	-	0
6a	I	F–N$^+$ (bicyclic) N$^+$–Me $2BF_4^-$	**141r**	0	63	-
6b	Br			*not attempted*	-	-

All reactions conducted on a 0.10 mmol scale. Yields were determined by ^{1}H NMR (400 MHz, $CDCl_3$) spectroscopic analysis using CH_2Br_2 as the internal standard. Diastereomeric ratio (d.r.) was also determined by ^{1}H NMR spectroscopic analysis. [a] Under conditions B: 1:1 THF/TFE (0.25 M). [b] Isolated yield.

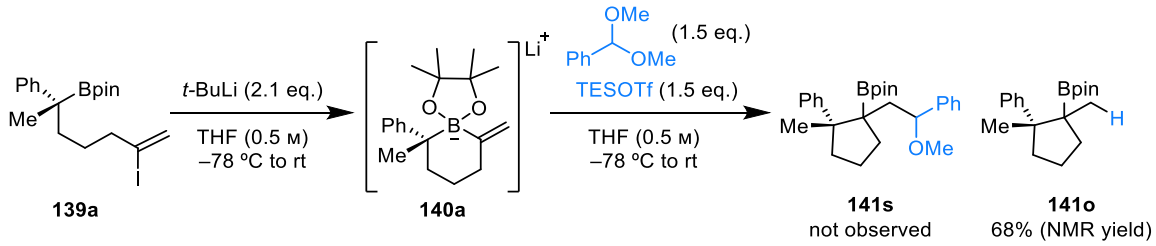
Unfortunately, the desired product was not formed under these modified conditions for all electrophiles. Less electrophilic species, such as dimethyl(methylthio)sulfonium tetrafluoroborate (Entry 4) and *p*-toluenesulfonyl cyanide (Entry 5), were slow to react and the

remaining boronate complex decomposed on work-up. However, the electrophile scope was deemed sufficiently broad at this stage so further investigations into these electrophiles were not undertaken.

2.5.6.2. Limitations: other unsuccessful electrophiles

A range of other electrophiles were not successful in the ring contractive 1,2-metallate rearrangement.

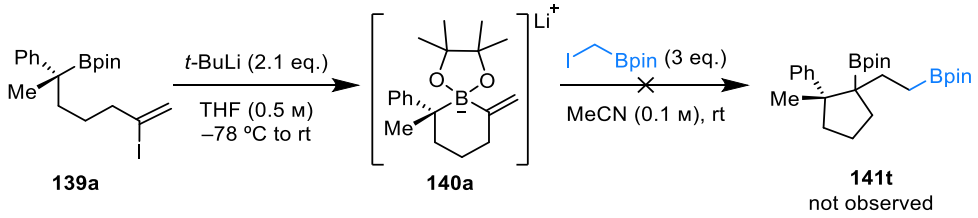
The introduction of oxygen functionality was attempted using an *in situ* generated oxonium cation (Scheme 64). Unfortunately, no desired boronic ester **141s** was observed. Instead, protonated **141o** dominated, likely because of a triflic acid impurity in the TESOTf.



Scheme 64. Unsuccessful electrophiles: oxonium cation.

Yield was determined by ^{1}H NMR (400 MHz, $CDCl_3$) spectroscopic analysis using CH_2Br_2 as the internal standard.

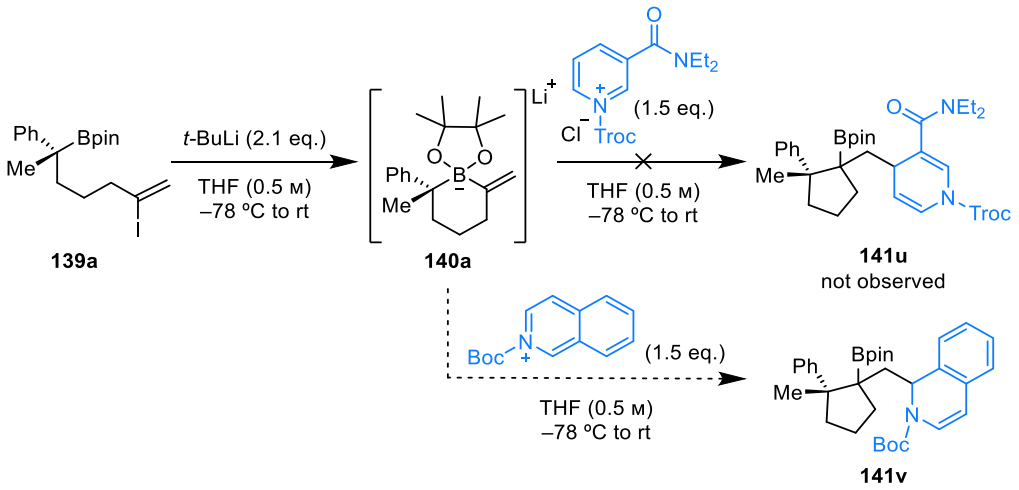
An attempt to extend Studer and co-worker's boronic ester-induced double 1,2-metallate rearrangement also proved fruitless, with no CH_2Bpin incorporated **141t** observed (Scheme 65).[48]



Scheme 65. Unsuccessful electrophiles: (iodomethyl)boronic acid pinacol ester.

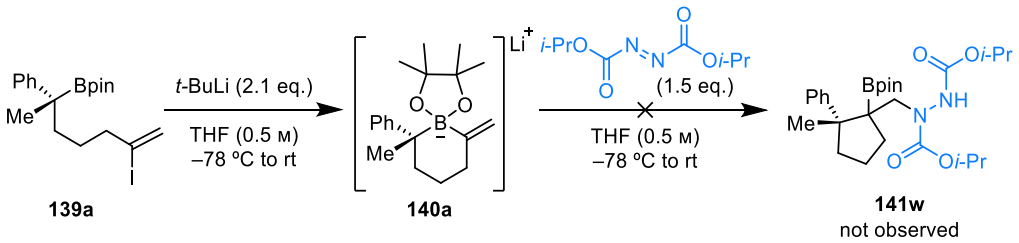
Addition to an activated pyridine was also unsuccessful, failing to yield any **141u**, and full decomposition of boronate complex **140a** was observed in the ^{1}H NMR spectrum of the crude reaction mixture, alongside the unreacted pyridine (Scheme 66). This result is in line with Ready's recent investigations into the addition of activated (iso)quinolines and pyridines to alkenyl boronate complexes (see Scheme 16).[46] Whilst quinolines and isoquinolines proved excellent electrophiles, pyridines did not engage efficiently in the transformation. It would be

interesting to extend Ready's reactivity to couple cyclic alkenyl boronate complexes and activated (iso)quinolines, potentially yielding alkylated, dearomatized heterocycle **141v**.



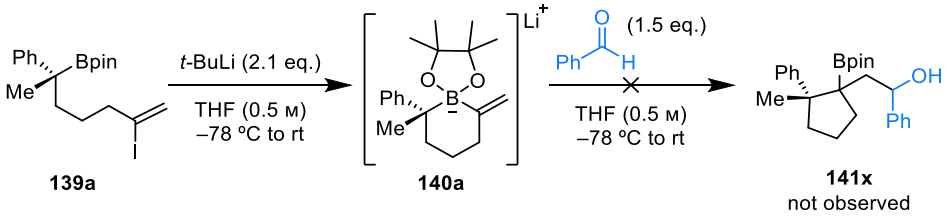
Scheme 66. Unsuccessful electrophiles: activated pyridines.

It was not possible to directly forge a new C–N bond through the addition of diisopropyl azodicarboxylate (DIAD) to boronate complex **140a** (Scheme 67). Again, only decomposition of **140a** was observed with no formation of **141w**.



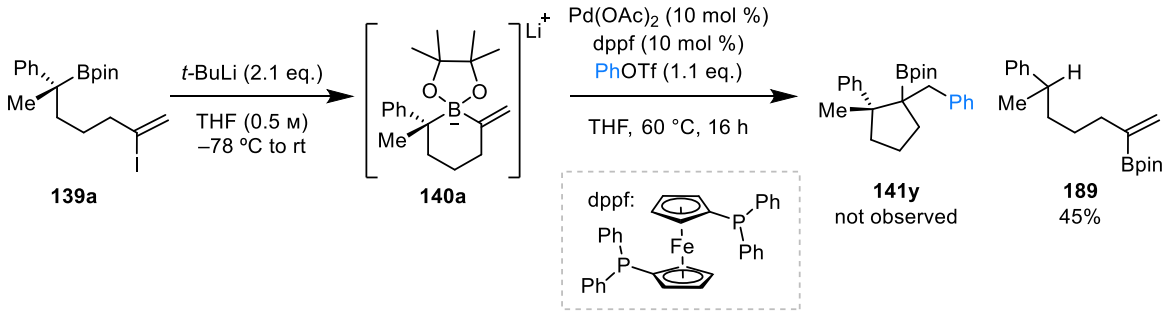
Scheme 67. Unsuccessful electrophiles: azodicarboxylate.

Boronate complex **140a** was insufficiently nucleophilic for addition to benzaldehyde to give **141x** (Scheme 68). There are no reports of alkenyl boronate complexes adding to aldehydes or ketones, only bicyclo[1.1.0]butyl boronate complexes have been reported to do so.[37]



Scheme 68. Unsuccessful electrophiles: benzaldehyde.

A Morken-type palladium-catalysed conjunctive cross coupling of cyclic alkenyl boronate complex **140a** and phenyl triflate was attempted (Scheme 69).[59] Instead of yielding cross coupled product **141y**, alkenyl boronic ester **189** was isolated, indicating no interaction between the aryl palladium(II) complex and **140a** had occurred. It is likely that the generation of lithium iodide in the formation of **140a** from **139a** inhibits the catalytic process, outcompeting the alkenyl boronate complex for coordination to the palladium.[60] The addition of halide scavengers, such as NaOTf, could limit this inhibition.



Scheme 69. Unsuccessful electrophiles: aryl palladium(II) complex.

Yield is of isolated product.

2.5.7. Relative configuration of the boronic ester products

2.5.7.1. Ring currents and their influences on the NMR chemical shifts of adjacent nuclei

An aromatic ring current is an electronic phenomenon observed in aromatic molecules (Figure 12). If an external magnetic field, B_0, is applied perpendicular to the plane of the aromatic system, a ring current is induced in the π-system. This ring current creates its own magnetic field, B_{ind}. For nuclei in the same plane as the aromatic ring, for example protons on a phenyl ring, the external and induced magnetic fields are additive, giving a higher local magnetic field. Thus, a higher frequency or lower external magnetic field is required to achieve resonance. However, for nuclei above or below the plane of the aromatic ring the reverse is true since the local magnetic field is lower. The deshielding influence on aromatic protons is ubiquitous. The shielding influence of aromatic groups on adjacent groups is a phenomenon observed in a variety of contexts but is perhaps less well recognised.

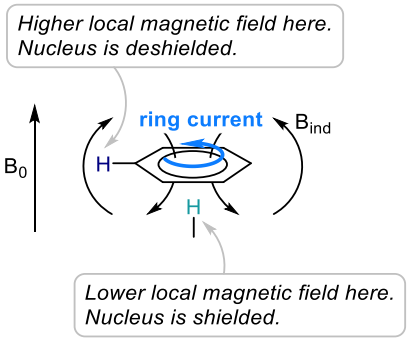
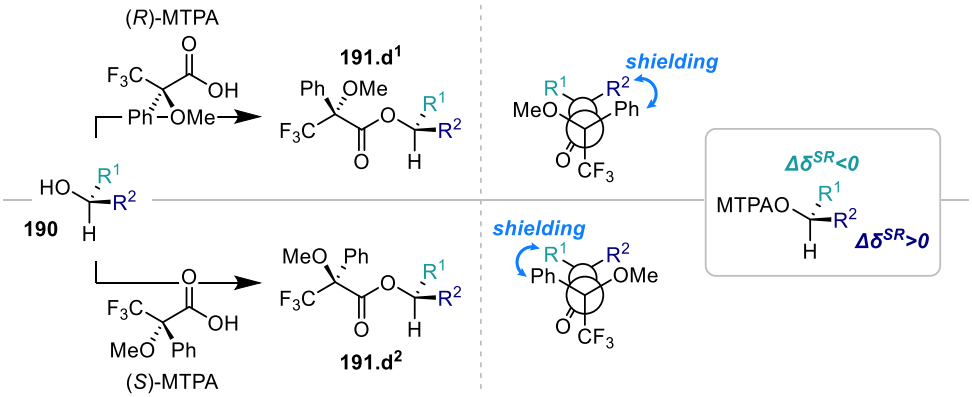


Figure 12. Ring currents and their influence on proton chemical shifts.

A common strategy, second to chiral chromatographic analysis, for the determination of the enantiomeric excess of a compound is the use of chiral derivatising agents (CDAs) and chiral solvating agents (CSAs; discussed in Section 2.5.4.1).[86] CDAs differ from CSAs by forming covalent bonds to the analyte in question, giving diastereomeric compounds which are first isolable and then differentiable by NMR spectroscopic analysis. The most widely used CSA is Mosher's reagent, α-methoxy-α-trifluoromethylphenylacetic acid (MTPA) (Scheme 70). Discrimination of the diastereomeric compounds **191.d^1** and **191.d^2** by ^{1}H NMR spectroscopic analysis is possible due to two key functionalities of MTPA. The first is the presence of an aromatic ring. Protons situated adjacent to the aromatic ring will be influenced by its ring current. If sat above the ring, the ring current will shield these protons, resulting in a lower chemical shift. The second feature is an electron-withdrawing group, CF_3, meaning that one conformer of the product dominates, with the CF_3 group and the carbonyl eclipsed. This means that the phenyl group is preferentially oriented towards either R^1 or R^2.[95] The absolute configuration of alcohol **190** can be assigned using this technique.[95]



Scheme 70. Mosher's reagent for enantiomeric ratio determination and the origins of diastereomeric discrimination.

Ring current effects of aromatic rings on adjacent protons are often very pronounced in highly substituted 5-membered rings (Figure 13), where the aromatic group is forced to take a face-on conformation with vicinal substituents due to adjacent steric bulk.[96] In diastereomer **192.d²**, where the phenyl group is face on to the adjacent methyl group, the chemical shift of this methyl group is significantly reduced compared to the methyl resonance in diastereomer **192.d¹**, where it experiences no ring current influence.

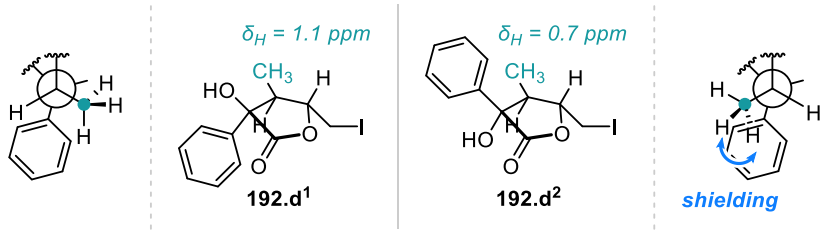


Figure 13. Influence of ring currents on ^{1}H NMR (60 MHz, $CDCl_3$) chemical shifts in a 5-membered lactone.

Silyl diether compounds **193** adopt a predominant conformation with a stabilising intramolecular hydrogen bond, giving a 5-membered chelate-like structure (Figure 14).[97] Whichever group is on the same face as the shielding phenyl group displays a lower chemical shift compared to when it is distal to the phenyl group.

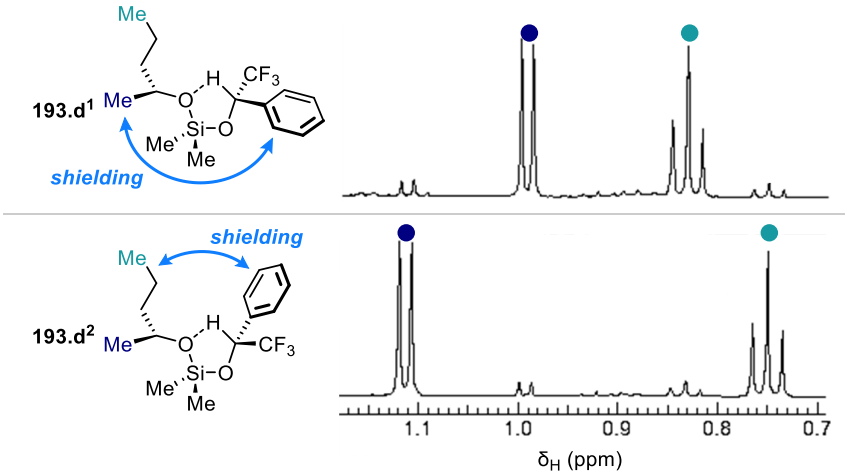


Figure 14. Influence of ring currents on ^{1}H NMR chemical shifts in a silyl diether compounds with a 5-membered chelate-like structure. ^{1}H NMR ($CDCl_3$) spectra reproduced from ref. 97.

2.5.7.2. Use of ring current effects for the determination of relative configuration

Such shielding influences are a characteristic feature of the ^{1}H NMR spectra of herbertane- and cuparane-type sesquiterpene natural products, such as in diastereomeric herbertene-1,14-diol and herbertene-1,15-diol (Figure 15).[5]

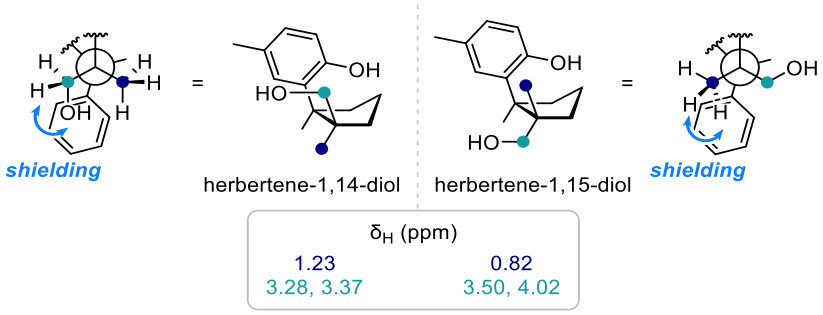


Figure 15. Influence of ring currents on the ^{1}H NMR (600 MHz, $CDCl_3$) chemical shifts of herbertene-1,14-diol and herbertene-1,15-diol.

The ^{1}H NMR chemical shifts of the methyl protons (teal) and the methylene protons (purple) vary significantly in each diastereomer ($\Delta\delta \approx 0.4$ ppm). Whichever functionality is in close proximity (cis relationship) to the aromatic group has a lower chemical shift than when it is further away (trans relationship).

During the course of this work, it was noted that the ^{1}H NMR chemical shifts of the alcohol proton (green) and methyl protons (teal) in cyclopentyl alcohol **141o'** varied significantly between each diastereomer (Figure 16). Indeed, in a previous synthesis of **141o'** this variation was again attributed to the influence of the ring currents of the phenyl group.[98]

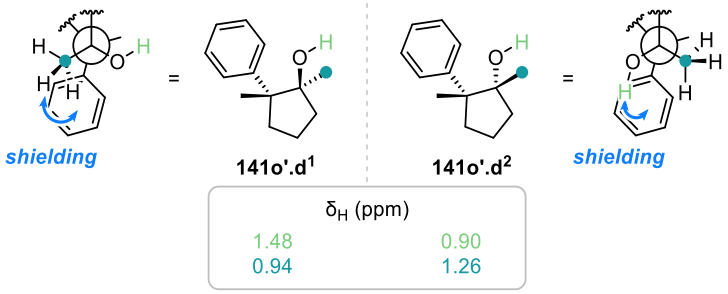


*Figure 16. Influence of ring currents on the ^{1}H NMR (400 MHz, $CDCl_3$) chemical shifts of the two diastereomers of alcohol **141o'**.*

Interestingly, the same phenomenon could be identified in the two diastereomers of related cyclopentyl boronic ester **141o**, with significant variation observed in the ^{1}H NMR chemical shifts of the pinacol methyl protons (purple) and methyl protons (teal) (Figure 17).

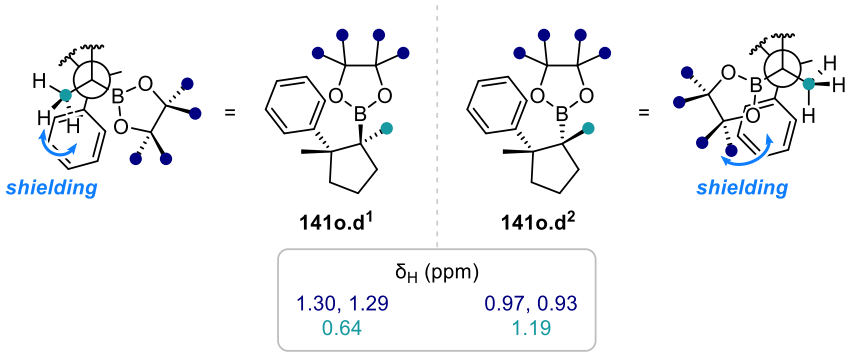


*Figure 17. Influence of ring currents on the ^{1}H NMR (400 MHz, $CDCl_3$) chemical shifts of the two diastereomers of boronic ester **141o**.*

This variation between diastereomers was found to be typical for all cyclopentyl boronic esters bearing an aromatic group synthesised in this study. The ^{1}H NMR chemical shifts of the pinacol methyl protons (purple and pink) and methylene protons (teal and green) adjacent to the electrophile of all the product cyclopentyl boronic esters in the boronic ester scope (Figure 18) and the electrophile scope (Figure 19) are presented.

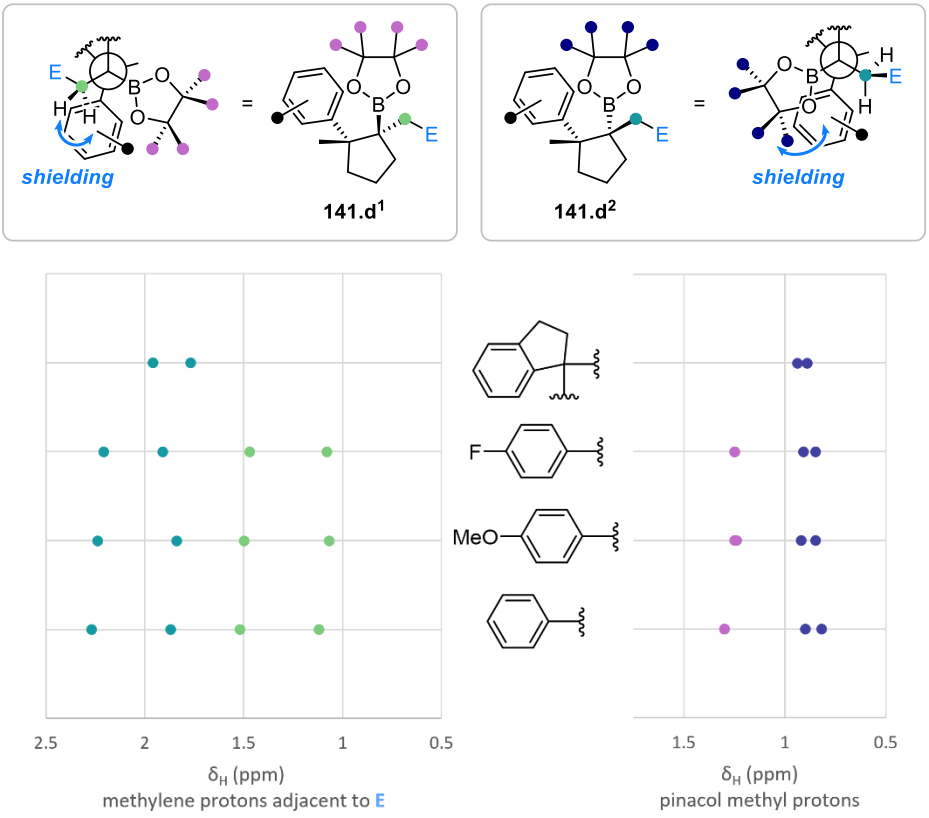


Figure 18. Substrate scope: comparison between the ^{1}H NMR (400 MHz, $CDCl_3$) chemical shifts of the pinacol and methylene protons in cyclopentyl boronic esters.

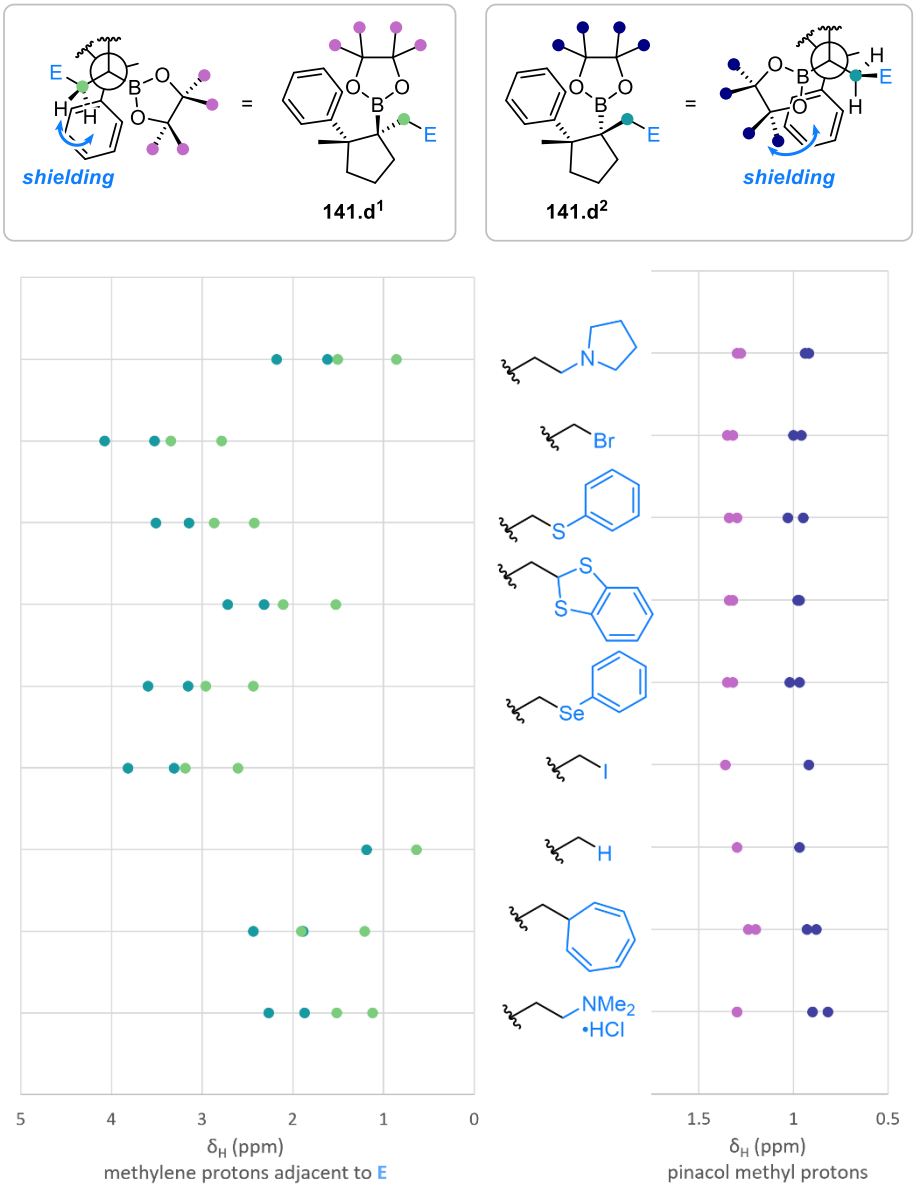


Figure 19. Electrophile scope: comparison between the ^{1}H NMR (400 MHz, $CDCl_3$) chemical shifts of the pinacol and methylene protons in cyclopentyl boronic esters.

Following these patterns, it is easy to assign the relative configuration of the major diastereomer formed. The clearest trend is observed in the pinacol methyl proton shifts (*n.b.* the *gem*-dimethyl groups are diastereotopic and thus give two singlets or, in some cases, two coincident singlets which are seen as one peak). The trend is still evident when looking at the diastereotopic methylene protons, however the identity of the electrophile can result in large variations in chemical shift between compounds.

The relative configurations of the product cyclopentyl boronic esters which do not bear an aromatic group, and thus do not exhibit these ^{1}H NMR chemical shift differences between diastereomers, were assigned using one dimensional ^{1}H nOe experiments (see Section 6.2.6).

2.5.8. Stereochemical model for diastereoselectivity

Having identified the major diastereomer formed in the transformation, the origin of the substrate-dependent diastereodivergent reactivity was probed (see Scheme 58 and Scheme 59).

It was proposed that the 6-membered cyclic alkenyl boronate complex could be drawn in two possible chair conformations, related by a ring flip (Figure 20).

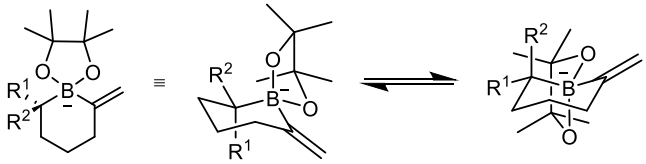
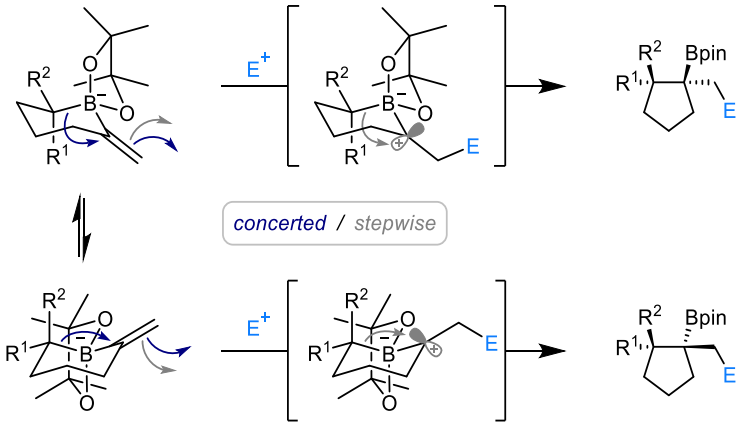


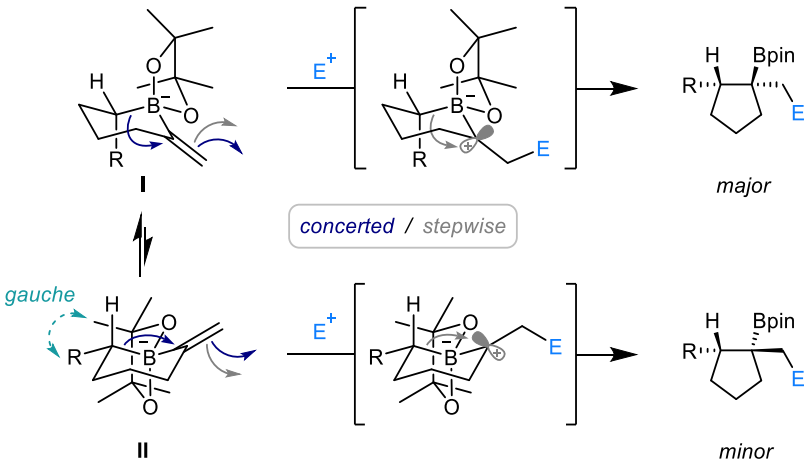
Figure 20. Proposed chair conformations of the 6-membered cyclic alkenyl boronate complex.

It was suggested that the reactivity of each conformer of the boronate complex with an electrophile would give a distinct diastereochemical outcome as a result of the required orbital overlap. This would proceed *via* either a concerted (purple curly arrows) or stepwise (grey curly arrows) mechanism (Scheme 71).



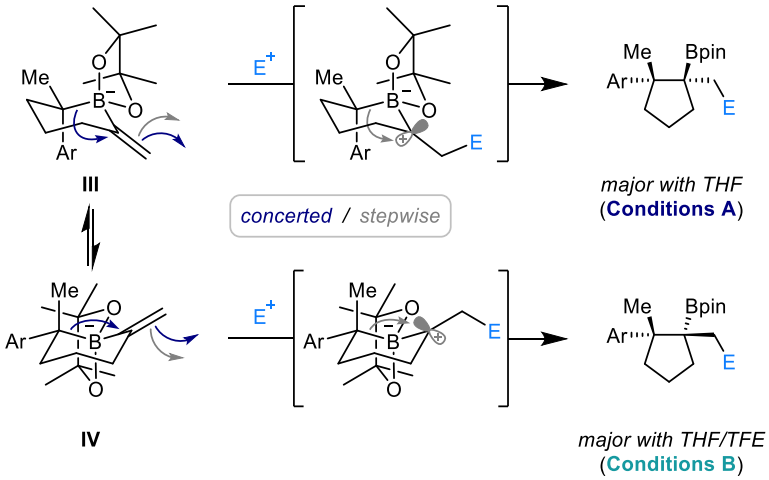
Scheme 71. Proposed stereochemical model for the addition of electrophiles to boronate complexes.

In the addition of electrophiles to boronate complexes derived from secondary boronic esters, it was proposed that the diastereoselectivity observed is dictated by the preferred conformation of the boronate complex (Scheme 72). A destabilising gauche-like interaction between the pinacol and the alkyl substituent disfavours reacting conformation **II**. In the preferred reacting conformation (**I**) the large R group is placed axial to minimise this destabilising interaction. Under both reaction conditions A and B, the same major diastereomer was generated.



Scheme 72. Proposed stereochemical model for the addition of electrophiles to boronate complexes derived from secondary boronic esters.

In the addition of electrophiles to boronate complexes derived from tertiary boronic esters, it was proposed that the difference in energy between conformations **III** and **IV** is very small (Scheme 73).



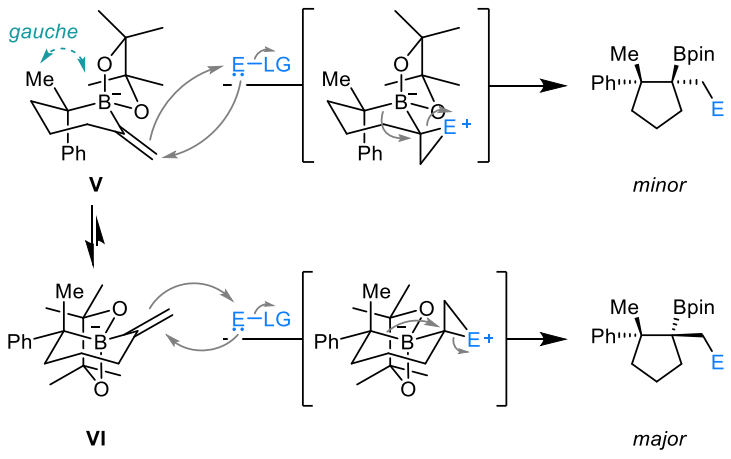
Scheme 73. Proposed stereochemical model for the addition of electrophiles to boronate complexes derived from tertiary boronic esters.

Upon addition of the co-solvent, under conditions B, the switch in selectivity could result from changes in the steric environment around the boronate complex compared to the system without the co-solvent (conditions A). Since the presence of hydrogen bond interactions between the TFE co-solvent and the Lewis basic pinacol oxygens in the boronate complex have been postulated (see Section 2.5.3), such steric differences were considered reasonable to propose. Additionally, the electronics of the migrating C–B bond may be altered upon the addition of the co-solvent. Indeed, modulation of the nucleophilicity of the C–B bonds was proposed as

the rationale behind the differing reactivity of boronate complex **140a** with tropylium tetrafluoroborate (see Scheme 60). The direct reactivity of the C(sp^3)–B bond with the electrophile was eliminated in the presence of a TFE co-solvent, likely as a result of its reduced nucleophilicity.

A computational study to elucidate the origins of the diastereodivergency was considered. However, in a previously reported computational study of cyclic alkenyl boronate complexes, this proved highly challenging.[75] In one case, the energy difference between the reactive conformers in the stereodetermining step was calculated to be small, yet experimentally the diastereoselectivity was observed to be high. This suggested that other effects, not able to be accounted for in the calculations, may play a role in the preference for one conformer over another. These could include fluxional effects in the lithium coordination sphere, such as interactions between the lithium counterion and solvent molecules, the pinacol oxygen atoms, or aryl substituents. Therefore, it is anticipated that it would be very difficult to draw conclusions from computational studies looking at the solvent-dependent diastereoselectivity of this system.

In the addition of heteroatom-based electrophiles to boronate complexes derived from tertiary boronic esters, it was proposed that the diastereoselectivity observed is dictated by the preferred conformation of the boronate complex in the formation of the heterocyclic onium ion (Scheme 74).



Scheme 74. Proposed stereochemical model for the addition of heteroatom-based electrophiles to boronate complexes derived from tertiary boronic esters.

A destabilising gauche-like interaction between the pinacol and the methyl substituent disfavours reacting conformation **V**, whereas in conformation **VI** the planarity of the phenyl

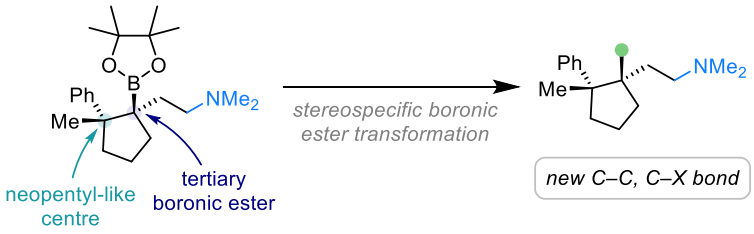
group mitigates against this destabilising interaction and thus this is the favoured reacting conformation. Under both reaction conditions A and B, the same major diastereomer was generated.

2.5.9. Product transformation

2.5.9.1. Transformation of hindered boronic esters

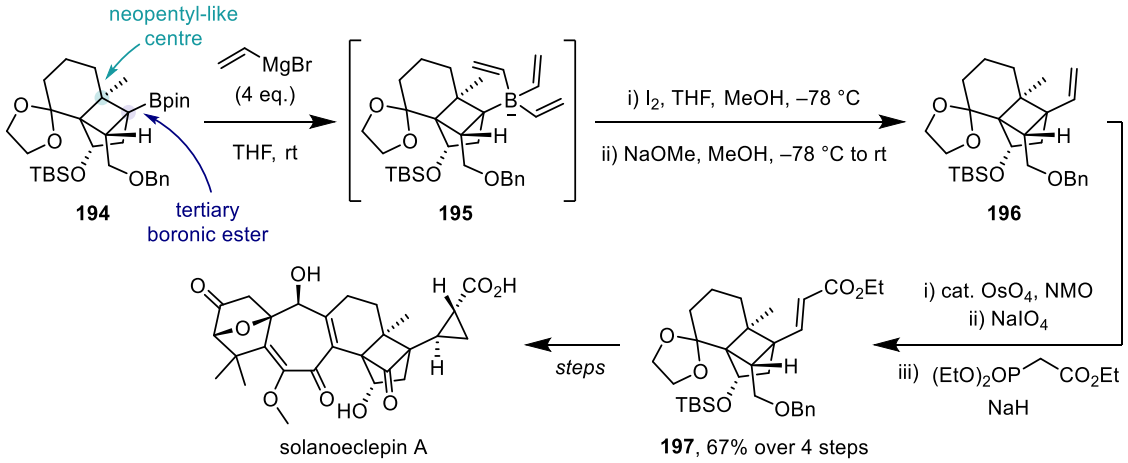
In order to demonstrate the synthetic utility of this methodology in the construction of cyclopentanes bearing two contiguous fully substituted stereocentres, methods were sought to directly and stereospecifically transform the C–B bond into a new C–C or C–heteroatom bond (Scheme 75). Of particular interest were transformations that enabled access to molecules with two contiguous quaternary stereocentres, forging a new C–C bond.

Whilst methods for the stereospecific transformation of tertiary boronic esters are well established,[14,15] it was anticipated that critical to success in the functionalisation of the cyclopentyl boronic esters would be the influence of the adjacent neopentyl-like centre.



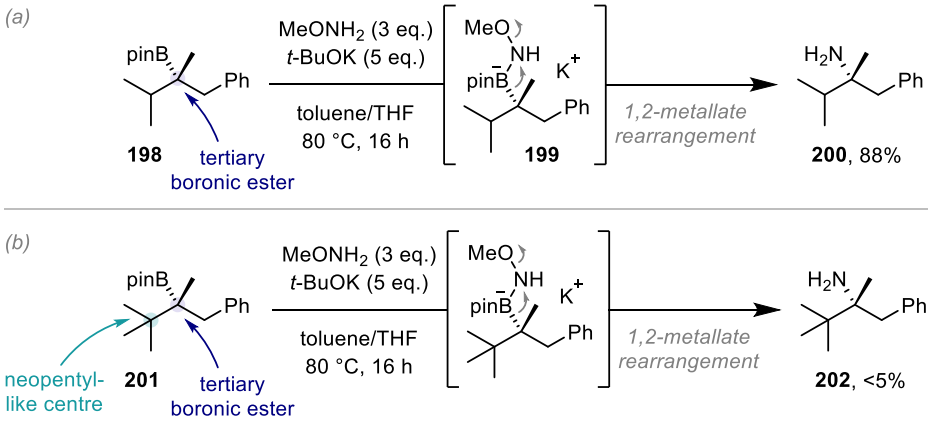
Scheme 75. Stereospecific transformation of sterically hindered cyclopentyl boronic ester.

There are few reports of the functionalisation of tertiary boronic esters bearing adjacent neopentyl-like quaternary centres. In 2016, Hiemstra and co-workers reported the Zweifel olefination of boronic ester **194** as a key step in their formal total synthesis of solanoeclepin A (Scheme 76).[99] Trivinyl boronate complex **195** was formed from boronic ester **194** upon addition of excess vinylmagnesium bromide. Addition of iodine followed by sodium methoxide delivered the vinylated product (**196**), used in subsequent steps without purification. Oxidative cleavage of the alkene and Horner–Wadsworth–Emmons olefination gave **197** in 67% yield over 4 steps.



Scheme 76. Application of a sterically demanding Zweifel olefination in Hiemstra's formal synthesis of solanoeclepin A.

The challenges associated with the derivatisation of such sterically hindered tertiary boronic esters were demonstrated by Morken and co-workers in their development of an amination protocol (Scheme 77).[100] Deprotonation of methoxyamine with potassium *tert*-butoxide followed by boronic ester (**198**) addition was shown to yield boronate complex **199** which, upon heating to 80 °C, undergoes a 1,2-metallate rearrangement to forge the new C–N bond in **200**. This methodology was successful with tertiary boronic ester **198** (Scheme 77a), however failed when applied to **201**, which is tertiary and bears an adjacent quaternary centre, with only traces of **202** observed (Scheme 77b).

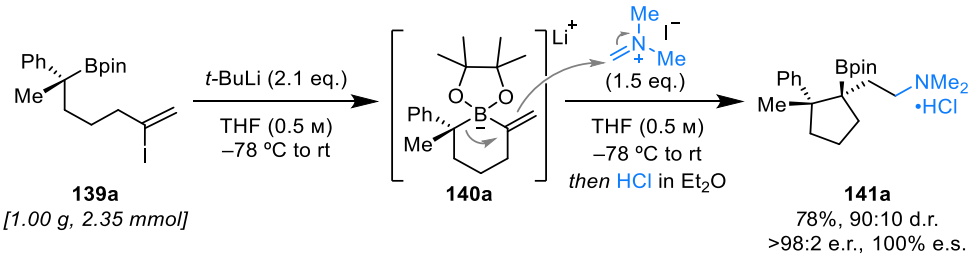


Scheme 77. Morken's amination of (a) tertiary boronic esters and (b) hindered tertiary boronic esters.

2.5.9.2. Transformation of hindered cyclopentyl boronic esters

To investigate the transformation of the cyclopentyl boronic ester products, the ring contractive 1,2-metallate rearrangement of **140a** with Eschenmoser's salt was conducted on gram-scale (1.00 g of **139a**), giving γ-amino boronic ester **141a** in comparable yield and

diastereoselectivity to that achieved on a tenth of the scale (0.20 mmol) (Scheme 78). Boronic ester **141a** could then be used as the model substrate for functionalisation studies.



139a
[1.00 g, 2.35 mmol]

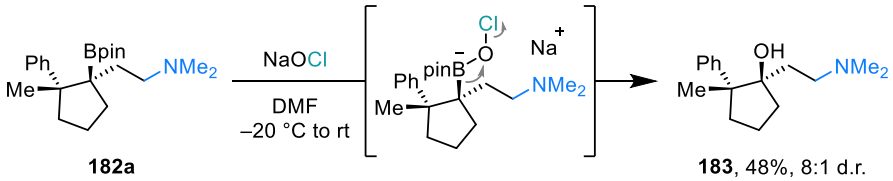
140a

141a
78%, 90:10 d.r.
>98:2 e.r., 100% e.s.

*Scheme 78. Gram-scale ring contractive 1,2-metallate rearrangement of **140a** with Eschenmoser's salt.*

Yield is of isolated product. Diastereomeric ratio (d.r.) was determined by ^{1}H NMR (400 MHz, $CDCl_3$) spectroscopic analysis. Enantiomeric ratio (e.r.) was determined by ^{1}H NMR (500 MHz, $CDCl_3$) spectroscopic analysis using Pirkle's chiral solvating agent.

First, the oxidation of γ-amino boronic ester **182a**, generated from **141a** by washing with aqueous sodium hydroxide followed by organic extraction, to γ-amino alcohol **183** was investigated (Scheme 79). Since typical oxidation conditions, a combination of NaOH and H_2O_2, failed to yield any product, even with prolonged reaction times and elevated temperatures, alternative oxidation protocols were investigated. Pleasingly, aqueous sodium hypochlorite proved a sufficiently strong oxidant to give alcohol **183** in moderate yield.[88]



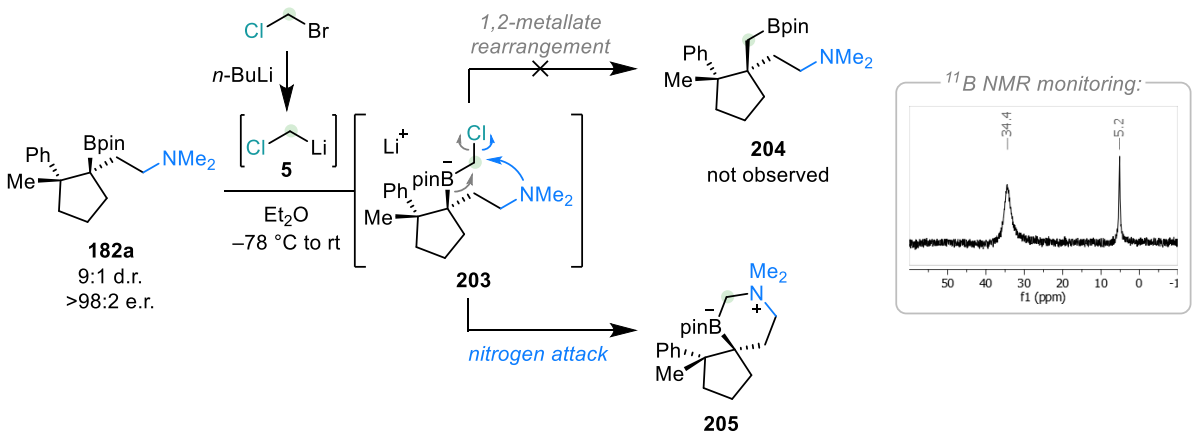
182a
9:1 d.r.
>98:2 e.r.

183, 48%, 8:1 d.r.
>98:2 e.r., 100% e.s.

*Scheme 79. Oxidation of γ-amino boronic ester **182a**.*

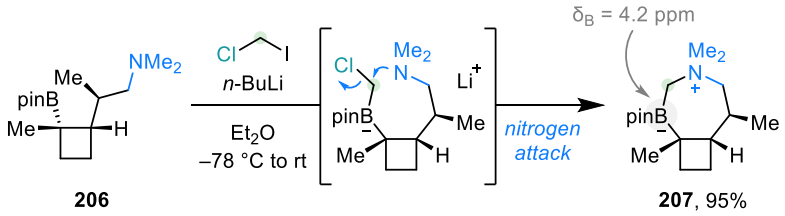
Yield is of isolated product. Enantiomeric ratio (e.r.) was determined by ^{1}H NMR (500 MHz, $CDCl_3$) spectroscopic analysis using Pirkle's chiral solvating agent.

Initial attempts to generate a new C–C bond employed Matteson homologation conditions (Scheme 81).[15] It was expected that the addition of lithium carbenoid **5** to boronic ester **182a** would give boronate complex **203** which can undergo a 1,2-metallate rearrangement with expulsion of chloride to yield homologated boronic ester **204**. Unfortunately, homologated **204** was not observed, and instead **182a** was returned in diminished amounts. This result was disappointing, since the homologation of tertiary boronic esters is known.[15] It is evident that boronic ester **182a**, which is both tertiary and bears an adjacent quaternary centre, is exceptionally hindered, limiting boronate complex formation and subsequent 1,2-migration.



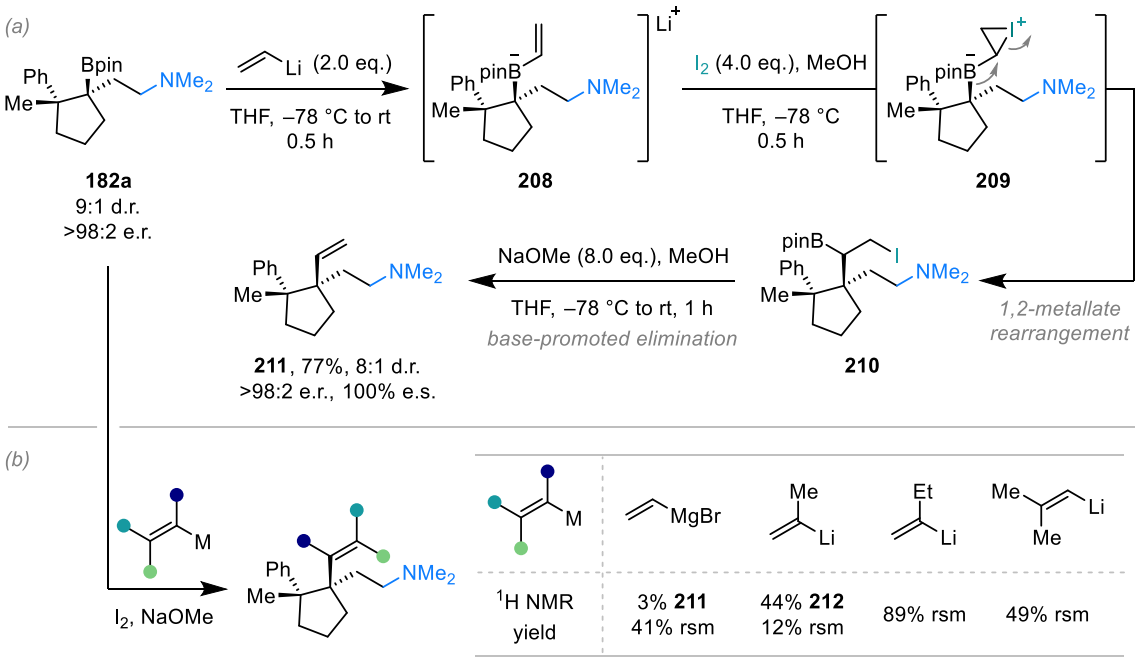
*Scheme 80. Attempted homologation of γ-amino boronic ester **182a**.*

Interestingly, the ^{11}B NMR spectrum of the crude reaction mixture showed not only the peak corresponding to boronic ester **182a** (δ_B = 34.4 ppm) but another peak at 5.2 ppm, indicative of the presence of a boronate complex. It is unlikely that this peak corresponds to boronate complex **203**, since its formation is reversible at room temperature and lithium carbenoid **5** is likely unstable at room temperature.[101] Instead, it is hypothesised that this peak (δ_B = 5.2 ppm) corresponds to **205**, formed through the intramolecular attack of the dimethylamine functionality. This has been previously reported in the attempted Matteson homologation of δ-amino boronic ester **206** to form 7-membered zwitterionic **207** (Scheme 81).[64] However, in this case, **205** was not isolable or able to be characterised.



*Scheme 81. Previous observations in the attempted homologation of δ-amino boronic ester **206**.*

Next, the Zweifel olefination of boronic ester **182a** was explored (Scheme 82a), employing vinyllithium in the formation of boronate complex **208**.[15,41] Addition of iodine to **208** to give iodonium **209** precedes the 1,2-metallate rearrangement, yielding β-iodo boronic ester **210** which is prone to elimination to give **211**. Pleasingly, the desired product was formed in 77% isolated yield and in an enantiospecific manner, successfully forging two contiguous, all-carbon quaternary stereocentres.

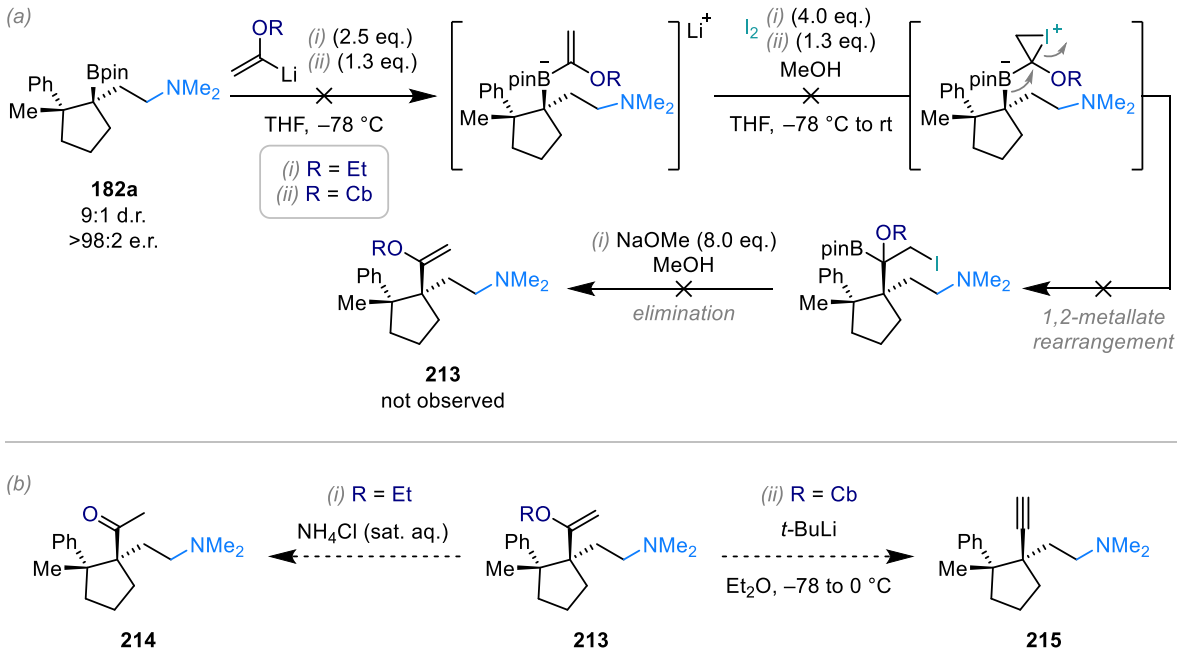


*Scheme 82. Olefination of γ-amino boronic ester **182a**.*

(a) *Yield is of isolated product. Enantiomeric ratio (e.r.) was determined by ^{1}H NMR (500 MHz, $CDCl_3$) spectroscopic analysis using Pirkle's chiral solvating agent. (b) All reactions conducted on a 0.10 mmol scale. Yields were determined by ^{1}H NMR (400 MHz, $CDCl_3$) spectroscopic analysis using CH_2Br_2 as the internal standard. rsm = returned starting material **182a**.*

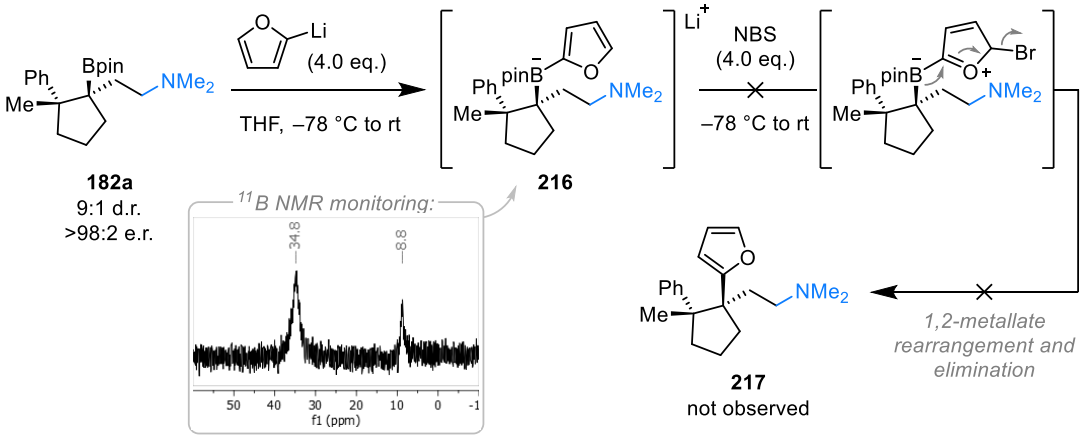
Olefination with 2-lithiopropene was less successful, giving alkene **212** in 44% NMR yield. However, extending this to 2-lithio-1-butene or 1-lithio-2-methyl propene proved unsuccessful (Scheme 82b). It is clear that the size of the coupling partner is critical to the success of the olefination reaction; increasing the size of the organolithium coupling partner makes the required boronate complex formation/1,2-metallate rearrangement more challenging. Indeed, vinylmagnesium bromide was a poor alternative to vinyllithium.

Encouraged by the success of the Zweifel olefination, other sp^2-hybridised coupling partners were then explored (Scheme 83). First, ethoxy vinyllithium was used in attempts to yield enol ether **213** in a manner analogous to the Zweifel olefination (Scheme 83a). Enol ether **213** can be subjected to acid hydrolysis conditions to yield methyl ketone **214** (Scheme 83bi).[15] Unfortunately, **213** was not observed and monitoring by ^{11}B NMR spectroscopic analysis indicated no formation of the required boronate complex. The same outcome occurred with 1,1-*O*-carbamoyl vinyllithium, where intermediate **213** can be converted to alkyne **215** (Scheme 83bii).[102]



*Scheme 83. Attempted olefination of γ-amino boronic ester **182**.*

The next attempt to forge a new C(sp^3)–C(sp^2) bond employed 2-lithio furan, added to boronic ester **182a** in attempts to form boronate complex **216** which can be activated to 1,2-metallate rearrangement through the addition of NBS (Scheme 84).[50] Monitoring by ^{11}B NMR spectroscopy confirmed that some boronate complex was being formed (δ_B = 8.8 ppm), however significant boronic ester remained (δ_B = 34.8 ppm). Upon addition of NBS no desired product (**217**) was observed, even at elevated temperatures and stoichiometry. Presumably the steric hindrance of boronic ester **182a** limits both boronate complex formation and subsequent electrophilic activation/1,2-metallate rearrangement.

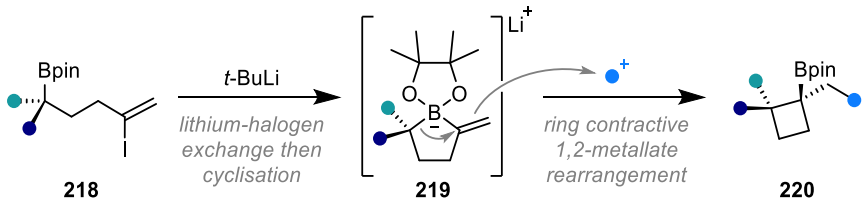


*Scheme 84. Attempted arylation of γ-amino boronic ester **182**.*

Whilst an array of methods for the functionalisation of tertiary boronic esters exist,[14,15] many of these methods fail when applied to the tertiary boronic esters bearing an adjacent quaternary stereocentre generated in this work. The neopentyl-like character of the quaternary centre adjacent to the boronic ester functional handle likely prevents the required boronate complex formation and 1,2-migration steps. The successful C–C bond forming reactions described above employ small, sp^2-hybridised organolithium reagents for the introduction of olefin functional handles.

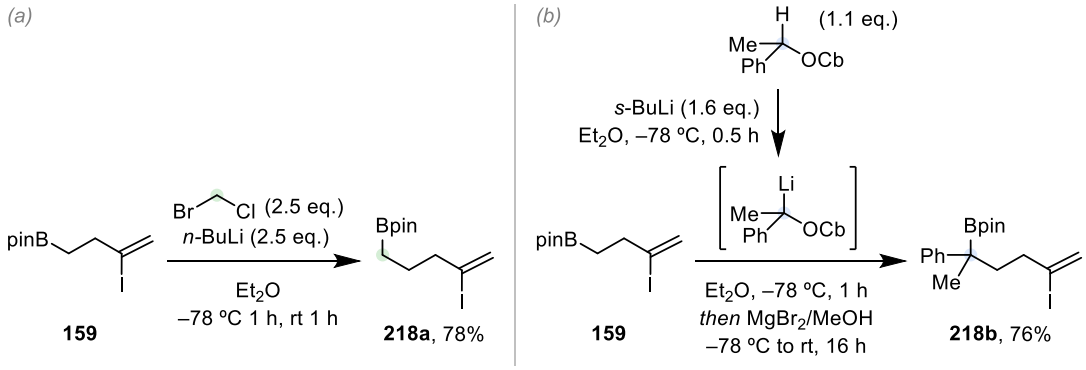
2.5.10. Extension to other ring sizes

It was hypothesised that the synthesis of cyclobutyl boronic esters could be achieved using the electrophile-induced 1,2-metallate rearrangement of 5-membered cyclic alkenyl boronate complex **219** (Scheme 85). However, a significant increase in strain energy would occur.



Scheme 85. Extension to the synthesis of cyclobutyl boronic esters.

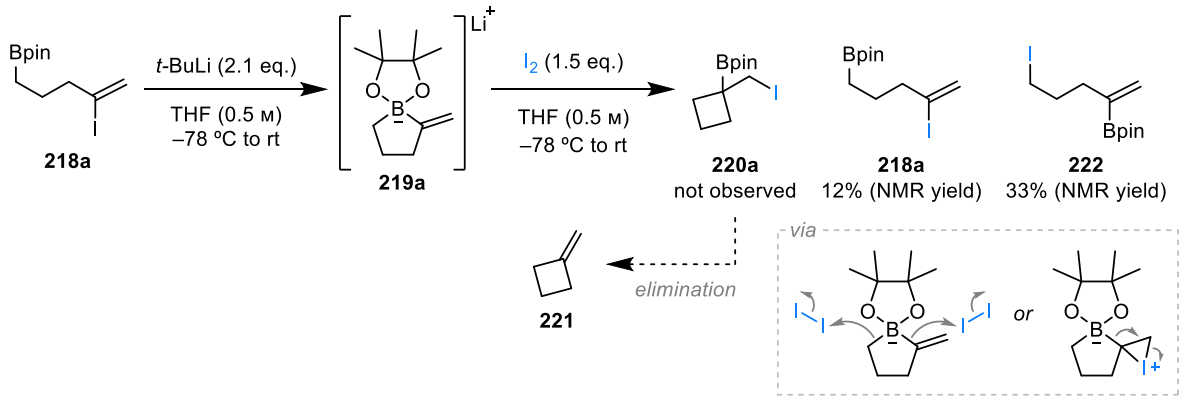
The required starting materials could be synthesised according to literature procedures from boronic ester **159**, employing either (a) a Matteson homologation reaction or (b) a lithiation–borylation reaction to install the carbon next to boron (Scheme 86).[75]



*Scheme 86. Divergent synthesis of starting materials through the homologation of boronic ester **159**.*

With the desired starting materials in hand, their reactivity was probed. The optimised conditions for the ring contractive 1,2-metallate of 6-membered cyclic alkenyl boronate complexes were used. Boronate complex formation was achieved quantitatively in each case using literature conditions.[75]

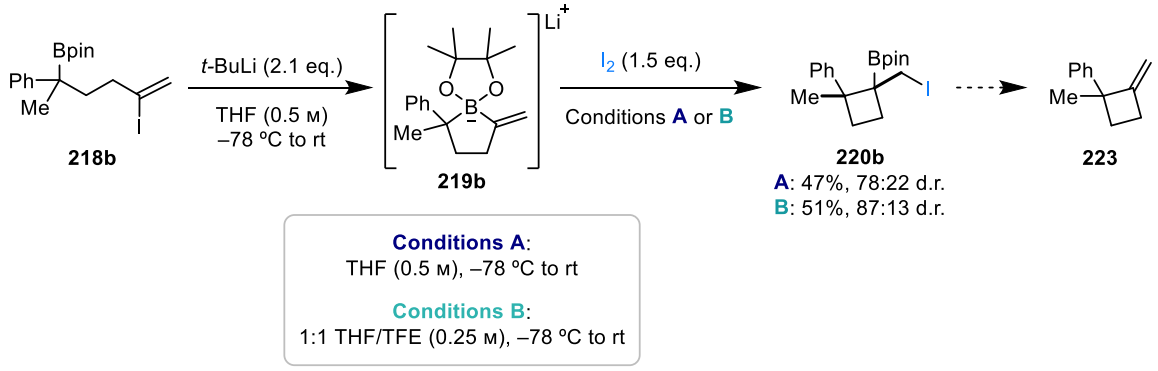
Initially, parent boronic ester **218a** was investigated (Scheme 87). Upon addition of iodine to boronate complex **219a**, no desired product **220a** was observed. Instead, compounds **218a** and **222** were observed in low yields. Their origins are likely the undesired reactivity of the nucleophilic C–B bonds in boronate complex **219a** with iodine. It is possible that the desired ring-contracted product **220a** was formed but swiftly eliminated to give highly volatile methylene cyclobutane **221**, which would not be observed.



*Scheme 87. Reactivity of boronate complex **219a** with iodine.*

Yields were determined by ^{1}H NMR (400 MHz, $CDCl_3$) spectroscopic analysis using CH_2Br_2 as the internal standard.

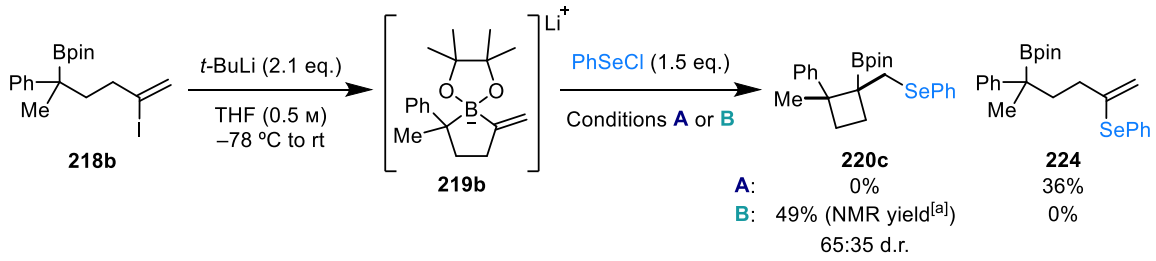
Boronic ester **218b** was thus investigated, since the additional substitution was hoped to circumvent the problems associated with side-product volatility (Scheme 88). Addition of iodine was performed in two solvent systems: THF and 1:1 THF/TFE. In each case, the desired product (**220b**) was observed. As with the previous synthesis of cyclopentanes, the addition of a TFE co-solvent improved the diastereomeric ratio of **220b**. However, in both cases the ^{11}B NMR spectrum of the reaction mixture prior to work-up alluded to the formation of eliminated methylene cyclobutane **223**, which could not be isolated (likely due to its volatility).



*Scheme 88. Reactivity of boronate complex **219b** with iodine.*

Yields are of isolated products. Diastereomeric ratio (d.r.) was determined by ^{1}H NMR (400 MHz, $CDCl_3$) spectroscopic analysis.

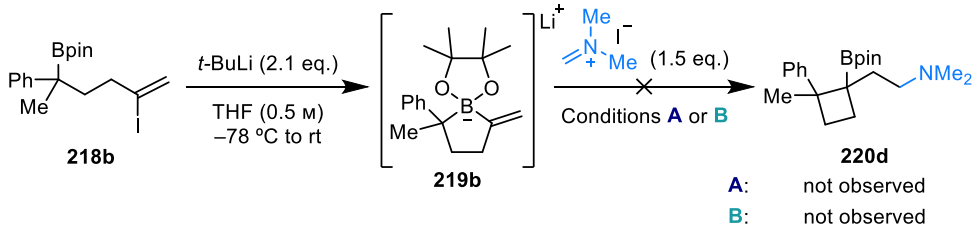
Interestingly, when employing phenylselenyl chloride as the electrophile, previously shown to be highly competent in the ring contraction of a 6-membered alkenyl boronate complex, the reactivity observed differed depending on the solvent system (Scheme 89). The reaction with THF as the solvent gave solely **224**, likely formed in an analogous way to the side products observed with iodine. By contrast, the addition of a TFE co-solvent encouraged the sole formation of cyclobutyl boronic ester **220c** in reasonable yield, albeit in poor diastereoselectivity.



*Scheme 89. Reactivity of boronate complex **219b** with phenylselenyl chloride.*

Yields are of isolated products. Diastereomeric ratio (d.r.) was determined by ^{1}H NMR (400 MHz, $CDCl_3$) spectroscopic analysis. [a] Yield was determined by ^{1}H NMR (400 MHz, $CDCl_3$) spectroscopic analysis using CH_2Br_2 as the internal standard.

Finally, Eschenmoser's salt was explored as an electrophile (Scheme 90), since it provided a range of ring contracted cyclopentyl boronic esters in excellent to quantitative yields in the analogous 6–5 ring contractive 1,2-metallate rearrangement (see Scheme 58). Under both sets of conditions, no desired product (**220d**) was observed by crude GCMS or crude ^{1}H NMR spectroscopic analysis.



*Scheme 90. Reactivity of boronate complex **219b** with Eschenmoser's salt.*

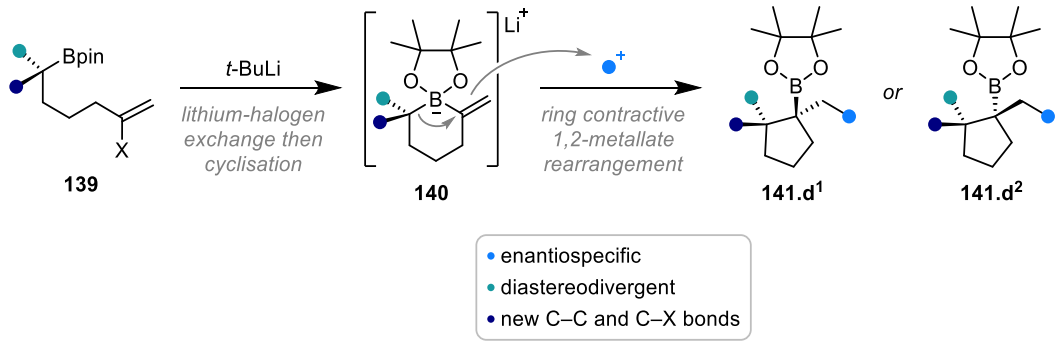
The synthesis of cyclobutyl boronic esters through an electrophile-induced ring contractive 1,2-metallate rearrangement of 5-membered cyclic alkenyl boronate complexes proved more challenging than that of the 6-membered analogues employed for the synthesis of cyclopentyl boronic esters. Only heteroatom-based electrophiles were able to induce the desired 1,2-metallate rearrangement and it occurred with poor to moderate diastereoselectivity.

2.6. Conclusions and future work

2.6.1. Conclusions

A method for the synthesis of highly substituted and highly enantioenriched cyclopentyl boronic esters has been developed (Scheme 91). Enantioenriched boronic esters **139** smoothly undergo lithium-halogen exchange to give 6-membered cyclic alkenyl boronate complexes **140**, which are configurationally stable at room temperature. Following addition of carbon-based electrophiles, an enantiospecific ring contractive 1,2-metallate rearrangement ensues, the diastereoselectivity of which is dictated by the solvent system employed. Heteroatom-based electrophiles can also enable the desired ring contraction, affording the product boronic ester in excellent diastereoselectivity and perfect enantiospecificity.

The breadth in functionalisation of the cyclopentyl boronic ester products, however, was limited by the significant steric bulk around the boronic ester moiety. Only olefination reactions, employing small sp^2-hybridised organolithium reagents, were successful. Regardless, such transformations have provided evidence that this methodology can enable access to cyclopentanes bearing contiguous quaternary stereocentres.



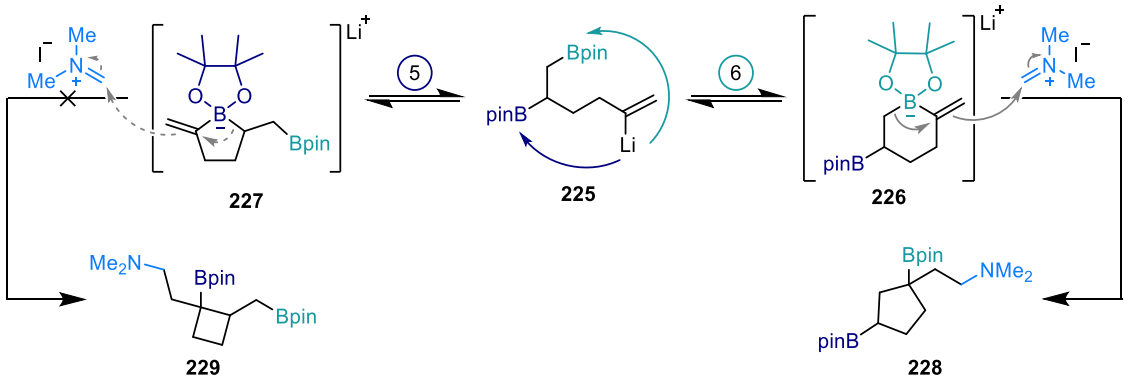
Scheme 91. Electrophile-induced ring contractive 1,2-metallate rearrangement of 6-membered cyclic alkenyl boronate complexes.

The electrophile-induced ring contractive 1,2-metallate rearrangement of 5-membered cyclic alkenyl boronate complexes had limited success, likely owing to the significant increase in strain energy in the transformation.

2.6.2. Future work

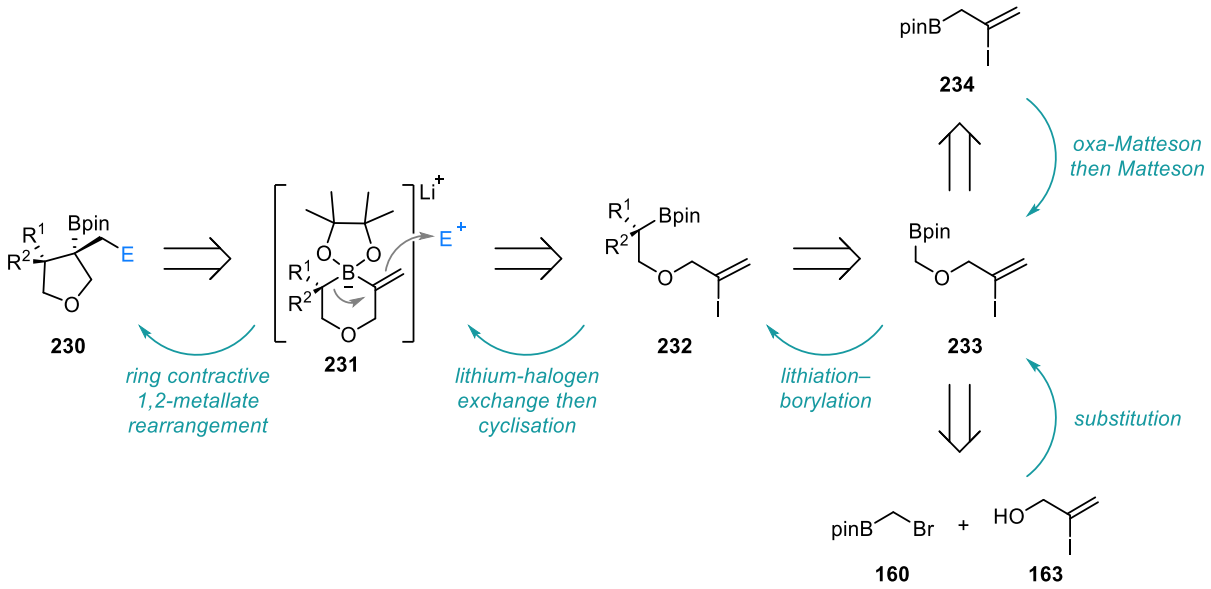
The favourability of the ring contractive 1,2-metallate rearrangement of a 6-membered alkenyl boronate complex compared to that of a 5-membered alkenyl boronate complex could be exploited (Scheme 92). Alkenyl lithium **225** could form two cyclic alkenyl boronate complexes

(**226** and **227**), which are able to interconvert. Formation of these boronate complexes is likely to be equally favourable due to the small differences in strain energy between the 6- and 5-membered ring systems.[80] However, it is likely that only the 6–5 ring contraction would occur upon addition of Eschenmoser's salt, selectively affording bis(boronic ester) **228** over bis(boronic ester) **229**. It is possible that stepwise functionalisation of the two boronic ester moieties could then be achieved, first at the less hindered secondary boronic ester and then at the tertiary site.



*Scheme 92. Proposed competition experiment with bis(boronic) alkenyl lithium **225**.*

It would be interesting to probe whether this methodology could enable the synthesis of highly substituted saturated heterocycles, such as THF rings (**230**) (Scheme 93). β-Oxy cyclic alkenyl boronate complex **231** could be accessible from extended chain boronic ester **232** through lithium-halogen exchange and cyclisation. Installation of the stereocentre adjacent to boron could be achieved using lithiation–borylation chemistry. Boronic ester **233** could be formed either through sequential oxa-Matteson[103] and Matteson homologation reactions, or through simple substitution of **160** by allylic alcohol **163**.



Scheme 93. Proposed extension to the synthesis of highly substituted THF rings.

3. Asymmetric total synthesis of (+)-herbertene-1,14-diol

3.1. Sesquiterpene natural products bearing contiguous quaternary stereocentres

Sesquiterpenes are a class of natural products containing a C_{15} backbone, made up of three isoprene units. Of particular synthetic interest are the herbertane- and laurane-type sesquiterpenes depicted in Figure 21,[5,104–106] since they bear two contiguous quaternary stereocentres at the perimeter of a cyclopentane core (see Section 1.1).

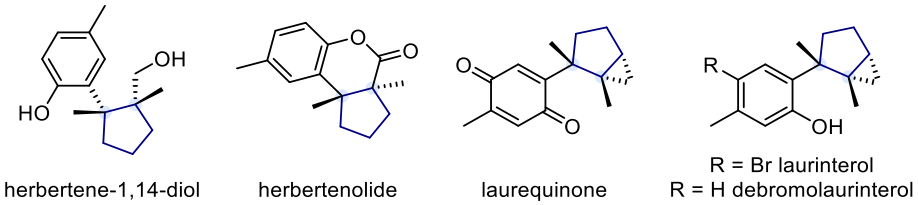


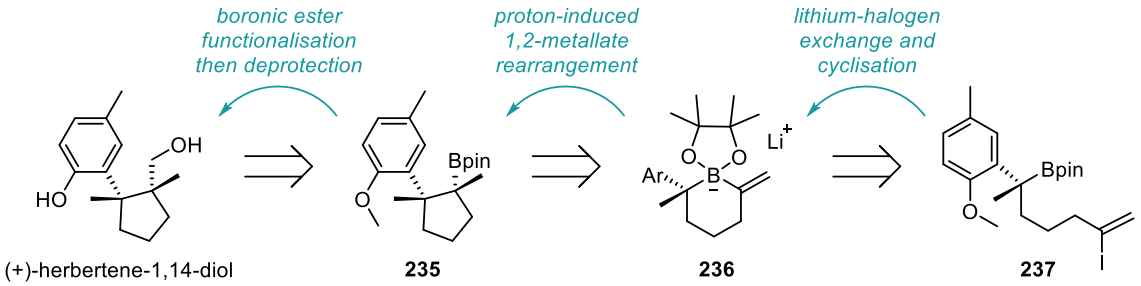
Figure 21. Selected sesquiterpene natural products bearing contiguous quaternary stereocentres on a cyclopentane core.

3.2. Project proposal

3.2.1. Project outline and proposed synthetic route

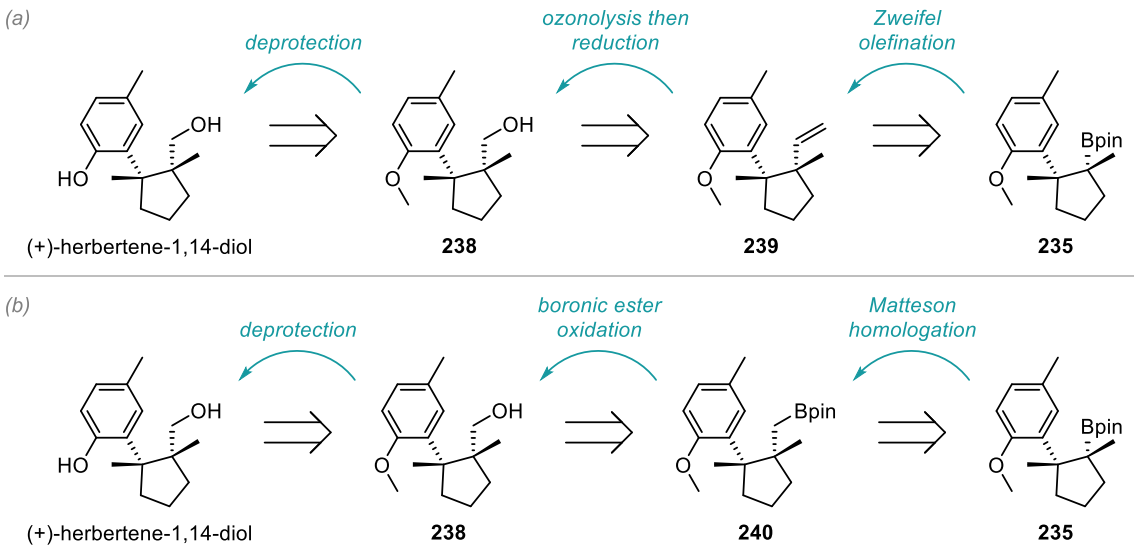
The ring contractive 1,2-metallate rearrangement of enantioenriched 6-membered cyclic alkenyl boronate complexes has been demonstrated to be an efficient method for the assembly of highly enantioenriched cyclopentyl boronic esters bearing two contiguous, fully substituted stereocentres. It was proposed that, through judicious choice of the electrophilic activator and subsequent manipulation of the boronic ester functional handle, this methodology could be applied to the asymmetric synthesis of sesquiterpene natural products bearing contiguous quaternary stereocentres on a cyclopentane core.

(+)-Herbertene-1,14-diol was identified as a suitable target (Scheme 94). It was anticipated that the Brønsted acid-induced 1,2-metallate rearrangement of enantioenriched boronate complex **236**, formed from boronic ester **237**, could provide access to cyclopentyl boronic ester **235** with high levels of enantio- and diastereocontrol. Stereospecific functionalisation of the boronic ester moiety could then assemble the second quaternary stereocentre, followed by removal of protecting groups.



Scheme 94. Proposed synthetic route to (+)-herbertene-1,14-diol.

Two possible functionalisation reactions of boronic ester **235** were envisaged (Scheme 95). The first involved the transformation of the boronic ester moiety to a vinyl group in a Zweifel olefination reaction (Scheme 95a). Ozonolysis of alkene **239** followed by reduction would deliver alcohol **238**, which could be transformed to the natural product through demethylation. Alternatively, a methylene group could be inserted into the C–B bond of **235** in a Matteson homologation reaction to give homologated **240** (Scheme 95b). The resultant primary boronic ester could then be oxidised to access common intermediate **238**.



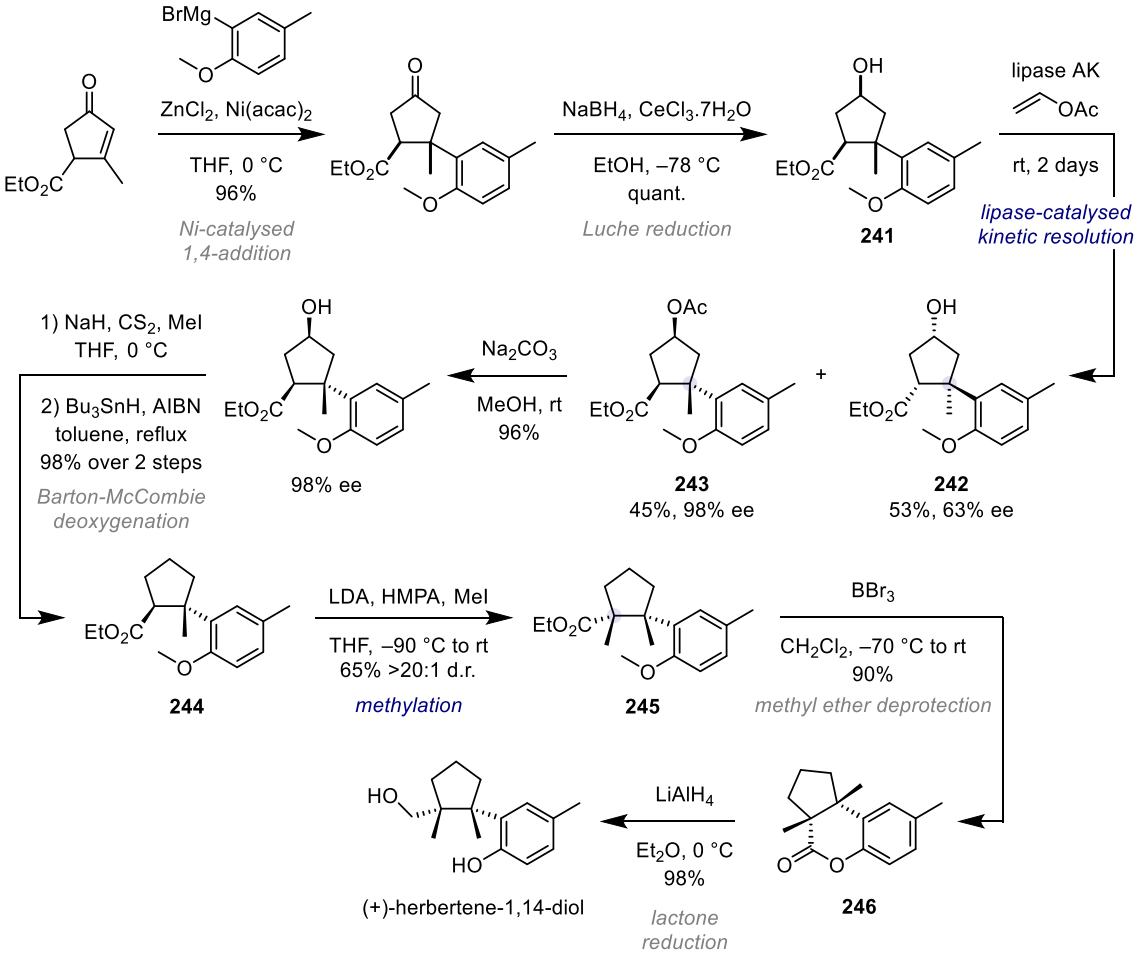
Scheme 95. Proposed transformation of the boronic ester moiety: (a) Zweifel olefination, (b) Matteson homologation.

The work summarised in Section 3.3 is also outlined in the following publication: M. E. Fairchild, A. Noble, V. K. Aggarwal, *Angew. Chem. Int. Ed.* **2022**, *61*, e202205816.[81]

3.2.2. Previous syntheses of (+)-herbertene-1,14-diol

Numerous reports of the synthesis of (±)-herbertene-1,14-diol were disclosed in the early 2000s.[107–111] However, prior to this work, only one asymmetric total synthesis of (+)-herbertene-1,14-diol had been reported.

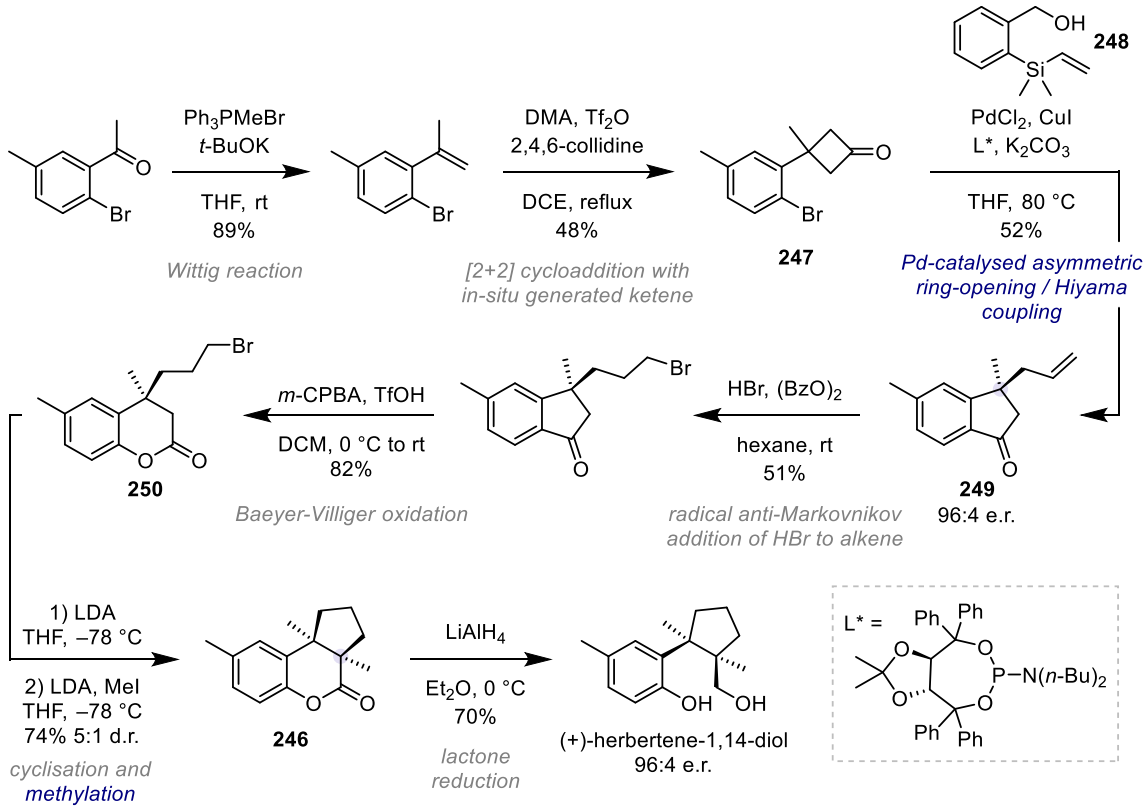
In 2004, Monti and co-workers described an enzymatic route towards the natural product (Scheme 96).[112] A lipase-catalysed kinetic resolution of racemic alcohol **241** yielded acetylated product **243** in 45% yield, assembling the first quaternary stereocentre (highlighted in purple) in near perfect enantioselectivity. By consequence of the kinetic resolution, there is an inherent loss of half of **241** as moderately enantioenriched alcohol **242**. Deacetylation and deoxygenation yielded 1,1,2-trisubstituted cyclopentane **244**. The second quaternary stereocentre (highlighted in purple) was installed in a substrate-controlled methylation reaction to give **245**, placing the two methyl groups cis to each other with high levels of diastereocontrol. Addition of boron tribromide enabled aryl methyl ether deprotection and concomitant lactonisation gave **246**. Reduction of the lactone with lithium aluminium hydride then yielded the natural product.



Scheme 96. Monti's asymmetric total synthesis of (+)-herbertene-1,14-diol featuring a lipase-catalysed kinetic resolution.

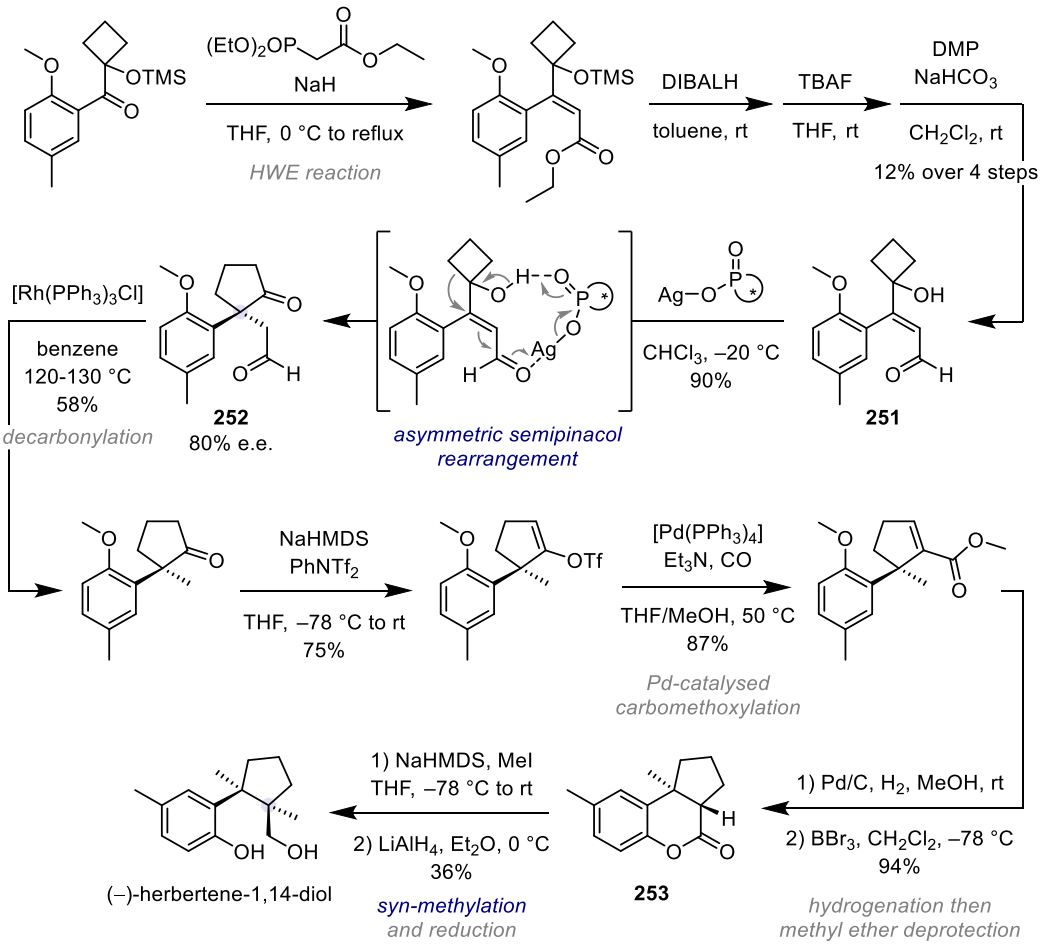
In late 2022, after the completion of the total synthesis described in this chapter, a third route towards (+)-herbertene-1,14-diol was reported by Cao and Xu (Scheme 97).[113] Their route

employed a novel palladium-catalysed asymmetric ring-opening and Hiyama coupling sequence to install the first quaternary stereocentre (highlighted in purple) in **249** from ketone **247** and silane **248**. Installation of a bromide leaving group and Baeyer-Villiger oxidation yielded **250** which, upon treatment with base, underwent an intramolecular cyclisation to give the cyclopentane core. A second equivalent of base, followed by addition of methyl iodide, forged the secondary quaternary stereocentre (highlighted in purple) with moderate diastereoselectivity. A final reduction of lactone **246** yielded the natural product.



Scheme 97. Cao and Xu's asymmetric total synthesis of (+)-herbertene-1,14-diol featuring a palladium-catalysed ring-opening/Hiyama coupling sequence.

There has been one total synthesis of (–)-herbertene-1,14-diol, reported in 2015 by Wang and co-workers (Scheme 98).[114] Key to their synthesis was the construction of α-benzylic quaternary cyclopentanone **252** (quaternary stereocentre highlighted in purple) in 80% e.e. using a novel chiral silver(I) phosphate-catalysed semipinacol rearrangement of **251**. Further elaboration to lactone intermediate **253** was achieved in 5 steps, followed by *syn*-methylation to install the second quaternary stereocentre (highlighted in purple) and a final reduction to yield the natural product.

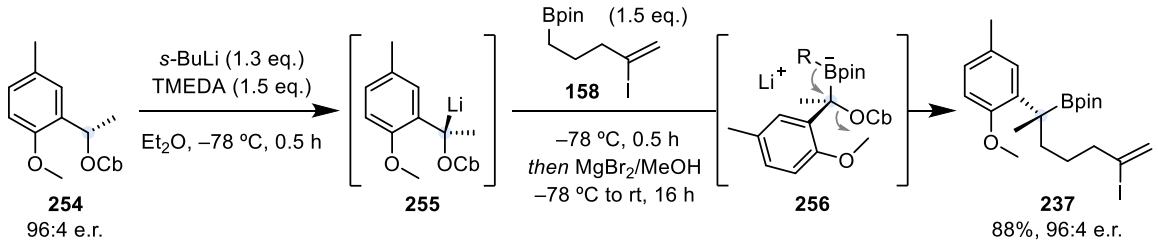


Scheme 98. Wang's asymmetric total synthesis of (–)-herbertene-1,14-diol featuring a chiral silver(I) phosphate-catalysed asymmetric semipinacol rearrangement.

3.3. Results and discussion

3.3.1. Synthesis of the boronic ester starting material

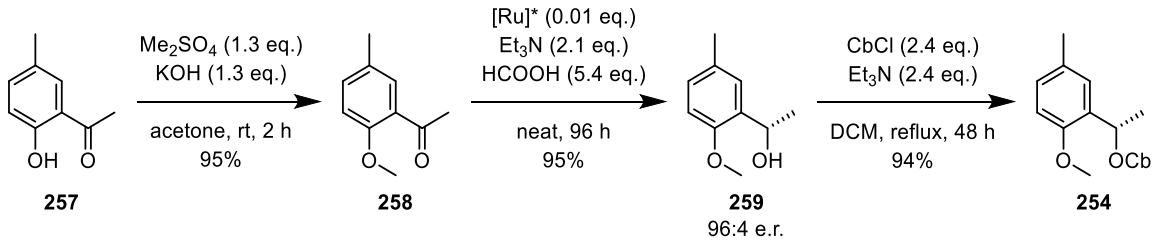
To investigate the key ring contractive step, a route towards boronic ester **237** was sought. By analogy to previous work (see Section 2.5.1), the stereocentre next to boron was introduced using a lithiation–borylation homologation of **158** (Scheme 99). Enantioenriched carbamate **254** was lithiated by TMEDA-ligated *sec*-butyl lithium to give **255**. Boronic ester **158** was then added to **255** to yield boronate complex **256**, primed for a stereoinvertive 1,2-metallate rearrangement with expulsion of the carbamate leaving group. Homologated boronic ester **237** was obtained in 88% yield and 96:4 enantiomeric ratio.



*Scheme 99. Synthesis of boronic ester **237**.*

Enantiomeric ratio (e.r.) was determined by chiral HPLC analysis of the oxidation product.

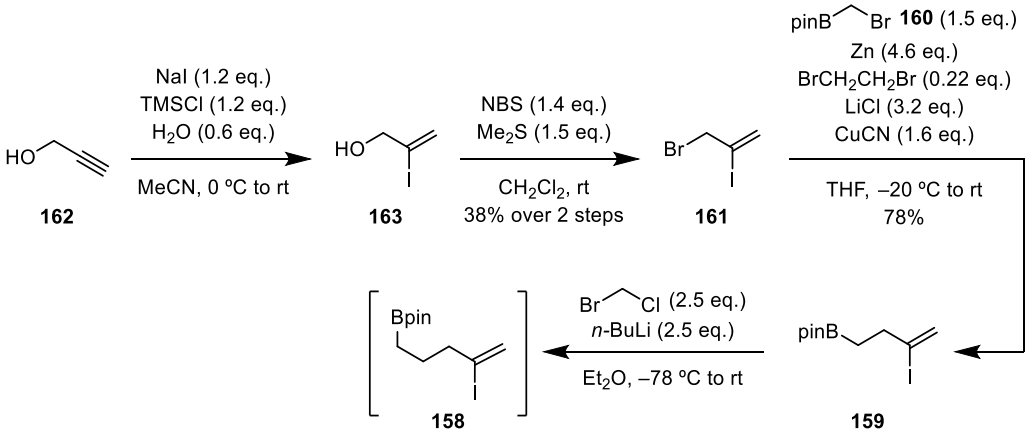
Enantioenriched carbamate **254** was synthesised in three high-yielding steps from ketone **257**, according to modified literature procedures (Scheme 100).[115] Protection of the phenol as the methyl ether was followed by Noyori asymmetric reduction[116,117] of ketone **258** to give enantioenriched alcohol **259** (96:4 e.r.). Carbamoylation of **259** yielded the required carbamate in 85% yield over 3 steps.



*Scheme 100. Synthesis of carbamate **254**.*

*Enantiomeric ratio (e.r.) of **259** was determined by chiral HPLC analysis. [Ru]*=RuCl(p-cymene)[(S,S)-Ts-DPEN]*

Boronic ester **158** was synthesised as previously described (Scheme 101) (see Section 2.5.1).

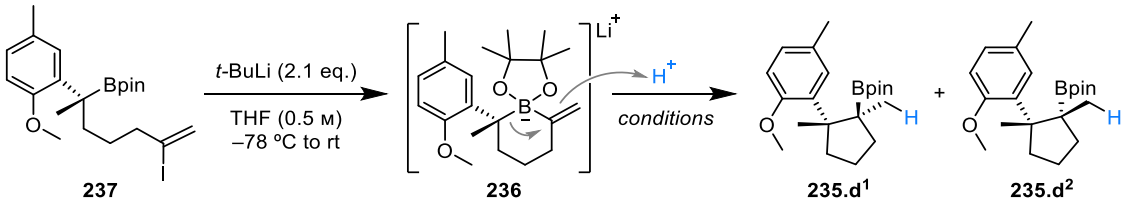


*Scheme 101. Synthesis of boronic ester **158**.*

3.3.2. Brønsted acid-induced ring contractive 1,2-metallate rearrangement

With the required boronic ester in hand, the ring contractive 1,2-metallate rearrangement was investigated (Table 6). Boronate complex **236** was accessed from **237**, using *tert*-butyl lithium to enact a lithium-halogen exchange and cyclisation sequence. Its formation was confirmed by ^{11}B NMR spectroscopic analysis, showing a characteristic peak at 6.6 ppm.

Table 6. Optimisation of reaction conditions for the ring contractive 1,2-metallate rearrangement.



237 236 235.d^1 235.d^2

entry	H^+ source	conditions	^{1}H NMR yield (%)	d.r.
1	$HBF_4.Et_2O$ (1.5 eq.)	THF (0.5 M), –78 °C 2 h, then rt	trace	-
2	$HBF_4.Et_2O$ (1.5 eq.)	1:1 THF/MeCN (0.25 M), –40 °C 2 h, then rt	7	3:1
3	$HBF_4.Et_2O$ (1.5 eq.)	MeCN (0.5 M), –40 °C 2 h, then rt	14	4:1
4	$HBF_4.Et_2O$ (1.5 eq.)	Et_2O (0.5 M), –78 °C 2 h, then rt	9	6:1
5	$HBF_4.Et_2O$ (1.5 eq.)	$CHCl_3$ (0.5 M), –60 °C 2 h, then rt	8	7:1
6	$HBF_4.Et_2O$ (1.5 eq.)	CH_2Cl_2 (0.5 M), –78 °C 2 h, then rt	29	5:1
7	$HBF_4.Et_2O$ (3 eq.)	CH_2Cl_2 (0.5 M), –78 °C 2 h, then rt	38	6:1
8	$HBF_4.Et_2O$ (5 eq.)	CH_2Cl_2 (0.5 M), –78 °C 2 h, then rt	21	4:1
9	HCl in Et_2O (3 eq.)	CH_2Cl_2 (0.5 M), –78 °C 2 h, then rt	24	4:1

All reactions conducted on a 0.10 mmol scale. Yields were determined by ^{1}H NMR (400 MHz, $CDCl_3$) spectroscopic analysis using CH_2Br_2 as the internal standard. Diastereomeric ratio (d.r.) was also determined by ^{1}H NMR spectroscopic analysis.

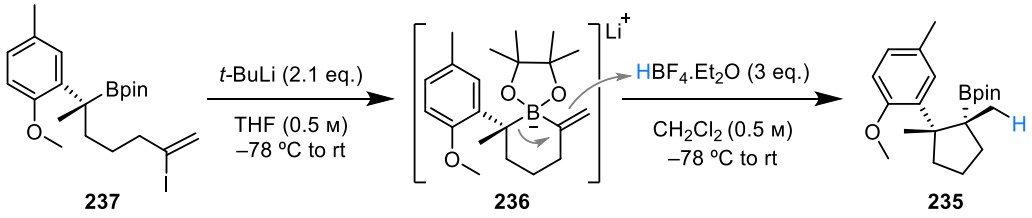
First, tetrafluoroboric acid diethyl ether complex (HBF_4•Et_2O) was trialled as the proton source, added neat to boronate complex **236** dissolved in THF at –78 °C (Entry 1). Following an overnight warming sequence and aqueous work-up, the desired product (**235**) was observed in trace amounts in the ^{1}H NMR spectrum of the crude reaction mixture. Pleasingly, adding an acetonitrile co-solvent to the boronate complex **236** prior to acid addition allowed appreciable amounts of **235** to be observed (Entry 2). The major diastereomer formed was **235.d^2**, as required, placing the two methyl groups cis to each other.

A range of solvents for the ring contractive step were then investigated (Entries 3–6). The solvent exchange was conducted after boronate complex formation. Dichloromethane proved a superior solvent for the ring contractive step (Entry 6), enabling the synthesis of cyclopentyl boronic ester **235** in 29% ^{1}H NMR yield and as a 5:1 mixture of diastereomers, still favouring

235.d². Increasing the number of equivalents of the proton source from 1.5 to 3 improved the yield further (Entry 7). However, a large excess (5 equivalents) resulted in a diminished yield (Entry 8). Whilst HCl•Et_2O could induce the 1,2-metallate rearrangement (Entry 9), HBF_4•Et_2O enabled the synthesis of **235** in enhanced yield.

As the transformation was scaled up from the 0.1 mmol test-scale reactions, a further increase in yield was obtained (Table 7). When performing the reaction on a 0.9 mmol scale, **235** could be accessed in a 47% ^{1}H NMR yield as an 85:15 mixture of diastereomers (Entry 3).

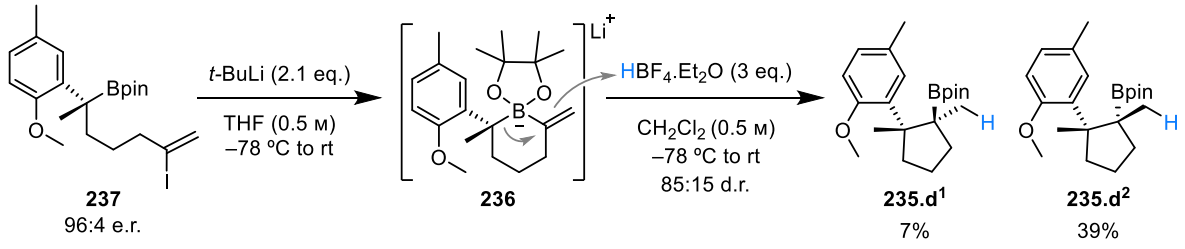
*Table 7. Influence of reaction scale on the yield of **235**.*



entry	reaction scale (mmol)	^{1}H NMR yield (%)
1	0.1	38
2	0.3	43
3	0.9	47 (46)

Yields were determined by ^{1}H NMR (400 MHz, $CDCl_3$) spectroscopic analysis using CH_2Br_2 as the internal standard. Isolated yield in parentheses.

The diastereomers of **235** proved separable through careful column chromatography (46% combined isolated yield), allowing diastereomerically pure **235.d²** to be used in the subsequent steps (Scheme 102).



*Scheme 102. Brønsted acid-induced ring contractive 1,2-metallate rearrangement of boronate complex **236**.*

The identity of the major diastereomer was confirmed according to the variation in ^{1}H NMR chemical shifts of the methyl group (teal) and pinacol methyl protons (purple) in each diastereomer (Figure 22) (see Section 2.5.7.2). In the minor diastereomer (**235.d¹**) the methyl group sits cis to the aromatic ring and is thus influenced by its shielding effects, giving it a

lower chemical shift than in the major diastereomer (**235.d^2**) where the methyl group sits trans to the aromatic ring. The same trend is observed with the pinacol methyl protons, which have a lower chemical shift in **235.d^2** than in **235.d^1**.

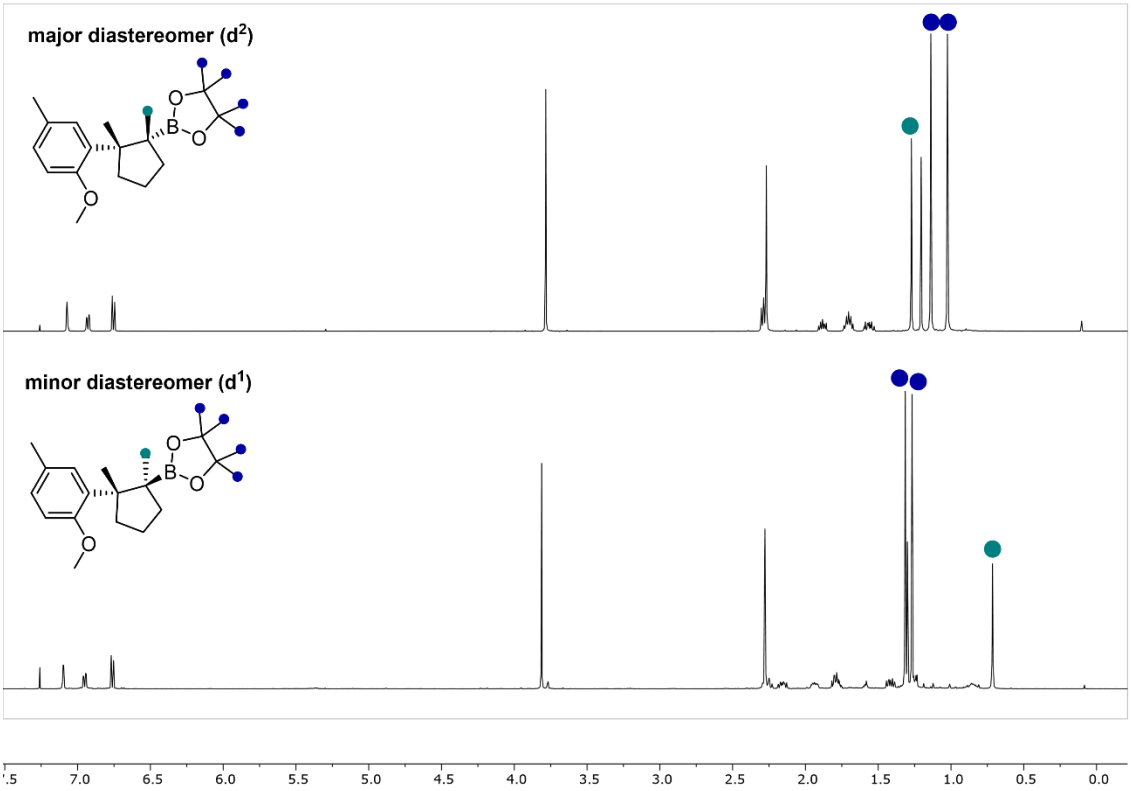


*Figure 22. Comparison between the ^{1}H NMR (400 MHz, $CDCl_3$) chemical shifts of the pinacol and methyl protons in the two diastereomers of boronic ester **235**.*

Whilst the optimised yield of the transformation was moderate, it was comparable to that previously observed in the model system using tetrafluoroboric acid as the electrophilic activator (see Section 2.5.6) and the reaction could be successfully scaled up to generate sufficient enantioenriched and diastereomerically pure **235** for further investigations.

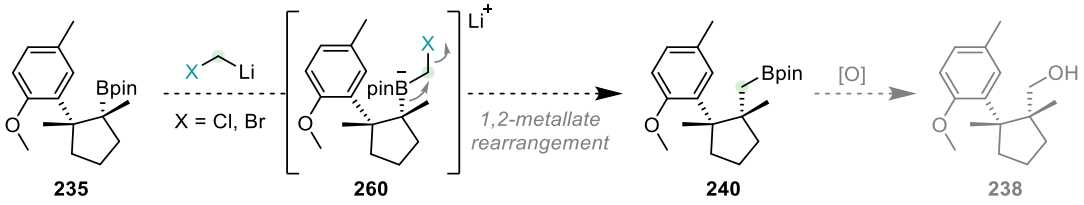
3.3.3. Boronic ester functionalisation

Two boronic ester functionalisation reactions were then investigated to stereospecifically introduce the second all-carbon quaternary stereocentre present in (+)-herbertene-1,14-diol.

The first, a Matteson homologation to yield **240**, proved challenging (Table 8). Chloromethyl lithium, generated from *n*-butyl lithium and bromochloromethane, was first explored as the lithium carbenoid (Entries 1–2). Unfortunately, only starting material (**235**) was returned, even when a large excess of chloromethyl lithium was employed with prolonged reaction times (Entry 2). A third protocol was then investigated, developed within the Aggarwal group for the

homologation of tertiary boronic esters,[15] with bromomethyl lithium as the lithium carbenoid. Again, no desired homologation was observed; 90% of **235** was returned.

*Table 8. Investigations into the Matteson homologation of boronic ester **235**.*

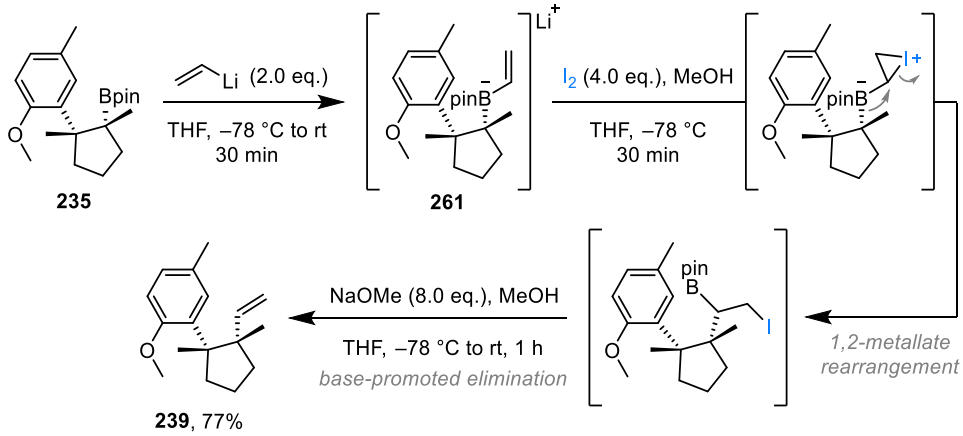


entry	X–Li	conditions	outcome
1	Cl–Li	CH_2BrCl (2.5 eq.), *n*-BuLi (2.5 eq.) THF, –78 °C 10 min, then rt o/n	85% rsm
2	Cl–Li	CH_2BrCl (5 eq.), *n*-BuLi (5 eq.) THF, –78 °C 3 h, then rt o/n	85% rsm
3	Br–Li	CH_2Br_2 (2.5 eq.), *n*-BuLi (2.2 eq.) THF, –78 °C 10 min, then rt 2 h	90% rsm

All reactions conducted on a 0.10 mmol scale. Yields were determined by ^1H NMR (400 MHz, $CDCl_3$) spectroscopic analysis using CH_2Br_2 as the internal standard. rsm = returned starting material.

It was hypothesised that the sp^3-hybridised halomethyl lithium species are too large to form the required boronate complex (**260**) for this transformation, owing to the high steric encumbrance of tertiary boronic ester **235**, and therefore decomposition of the carbenoid[101] likely outcompeted boronate complex formation.

Fortunately, it was found that boronic ester **235** could undergo Zweifel olefination to yield alkene **239** in 77% yield (Scheme 103).[15]

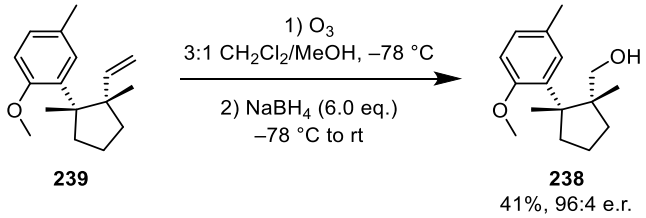


*Scheme 103. Zweifel olefination of boronic ester **235**.*

This transformation enabled the successful introduction of the second all-carbon quaternary stereocentre. The success of this transformation has been attributed to the small size of the sp^2-hybridised vinyllithium, enabling efficient boronate complex (**261**) formation.

3.3.4. Endgame: ozonolysis and demethylation

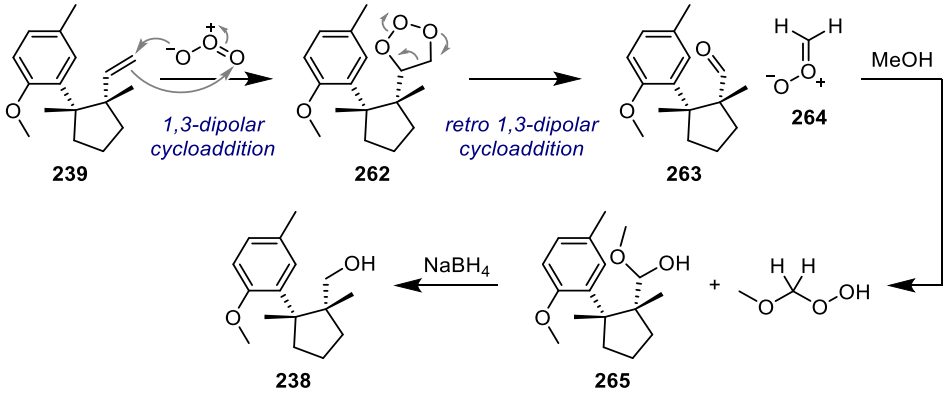
In order to introduce the carbinol moiety, ozonolysis of alkene **239** followed by reduction with sodium borohydride was attempted.[118] Gratifyingly, alcohol **238** was isolated in 41% yield and in 96:4 enantiomeric ratio, demonstrating that the ring contraction and Zweifel olefination steps had been enantiospecific (Scheme 104).



*Scheme 104. Ozonolysis and reduction of alkene **239**.*

Enantiomeric ratio (e.r.) was determined by chiral HPLC analysis.

The mechanism for this transformation is illustrated in Scheme 105. The 1,3-dipolar cycloaddition of ozone and alkene **239**, followed by a retro 1,3-dipolar cycloaddition of molozonide **262**, yields aldehyde **263** and Criegee intermediate **264**. Species **263** and **264** are trapped by the methanol solvent, with the reduction of **265** yielding alcohol **238**.

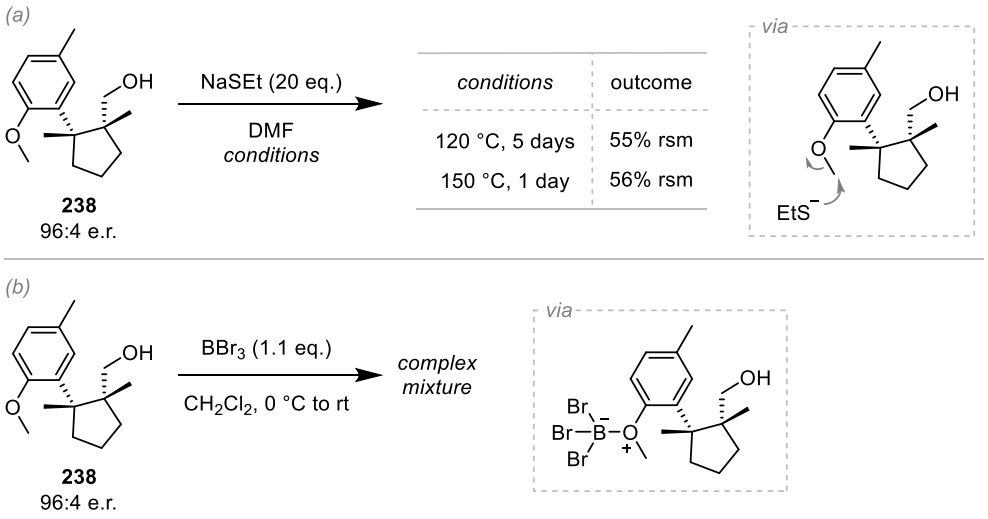


*Scheme 105. Mechanism for the ozonolysis and reduction of alkene **239**.*

The low yield of this transformation can be attributed to the poor stability of intermediate aldehyde **263** in oxygen. Indeed, lower yields of **238** were observed when the excess ozone in the reaction mixture was purged with oxygen instead of nitrogen. Since the bench-top generator

delivers the ozone in a stream of oxygen, likely decomposing a portion of intermediate aldehyde **263**, it was anticipated that improving the yield beyond 41% would be challenging.

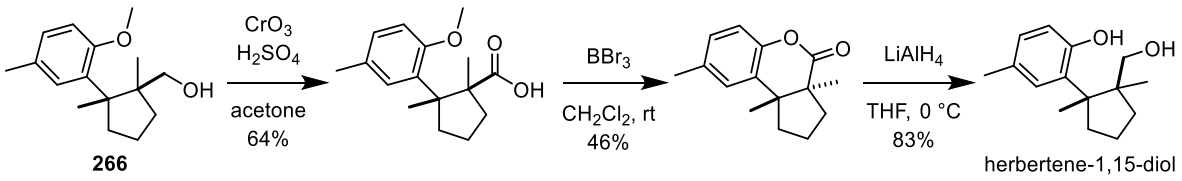
With alcohol **238** in hand, the final demethylation step was probed using standard conditions (Scheme 106). First sodium ethanethiolate was investigated, with demethylation expected to occur through S_N2 displacement (Scheme 106a).[74] Unfortunately, even at elevated temperatures and with prolonged reaction times, no conversion of starting material to the desired product was observed. When employing boron tribromide to enact the deprotection (Scheme 106b), a complex mixture of products was obtained, with no returned starting material and no methoxy groups remaining.



*Scheme 106. Attempts at the demethylation of **238** using (a) NaSEt and (b) BBr_3.*

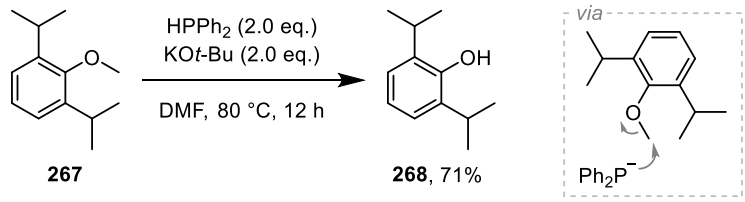
Yields were determined by ^1H NMR (400 MHz, $CDCl_3$) spectroscopic analysis using CH_2Br_2 as the internal standard. rsm = returned starting material.

The difficulty experienced in enacting this demethylation wasn't surprising, since in a previous synthesis of herbertene-1,15-diol a three-step sequence was employed for the transformation of **266** to the natural product (Scheme 107).[119]



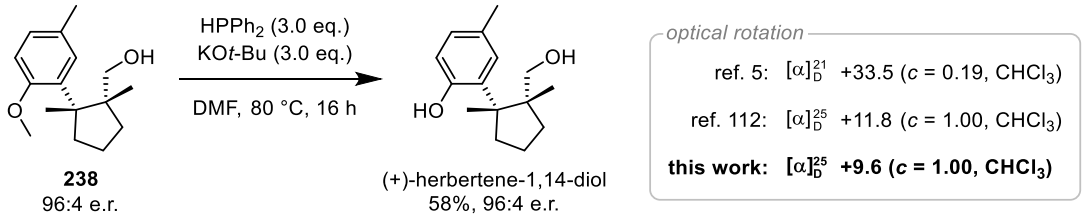
*Scheme 107. Synthesis of herbertene-1,15-diol from intermediate **266**.*

Upon examination of less common literature methods for the deprotection of aryl methyl ethers, a protocol using diphenylphosphine and potassium *tert*-butoxide was identified. This method showed tolerance of significant steric hindrance in the starting aryl methyl ether; sterically hindered aryl methyl ether **267** was transformed into phenol **268** in high yield (Scheme 108).



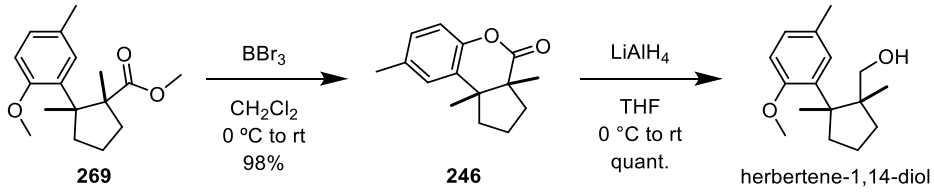
Scheme 108. Mild deprotection of aryl methyl ethers using $HPPh_2$/KOt-Bu.

Pleasingly, using slightly modified conditions to account for the presence of the free alcohol, aryl methyl ether **238** was transformed to (+)-herbertene-1,14-diol in 58% yield (Scheme 109), which had identical characterisation data to a previous report (Table 9).[112]



*Scheme 109. Demethylation of **238** using $HPPh_2$/KOt-Bu.*

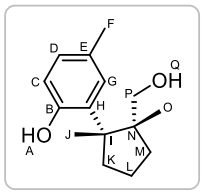
Whilst investigating the direct demethylation of **238**, the interception of a known late-stage intermediate methyl ester (**269**) was also attempted, since its transformation to herbertene-1,14-diol in two high yielding steps *via* lactone **246** is known (Scheme 110).[108]



*Scheme 110. Srikrishna's synthesis of herbertene-1,14-diol from methyl ester **269**.*

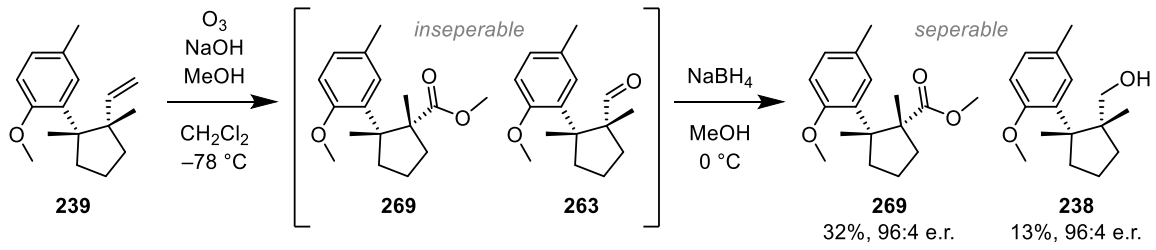
Alkene **239** was successfully transformed to methyl ether **269** in an ozonolysis reaction in the presence of sodium hydroxide and methanol.[120] To ease chromatographic separation, sodium borohydride was added to the crude reaction mixture to selectively reduce aldehyde **263** to alcohol **238**. It was at this point that the instability of aldehyde **263** in air was noted.

Table 9. Synthetic vs reported ^{1}H NMR and ^{13}C NMR data for (+)-herbertene-1,14-diol.



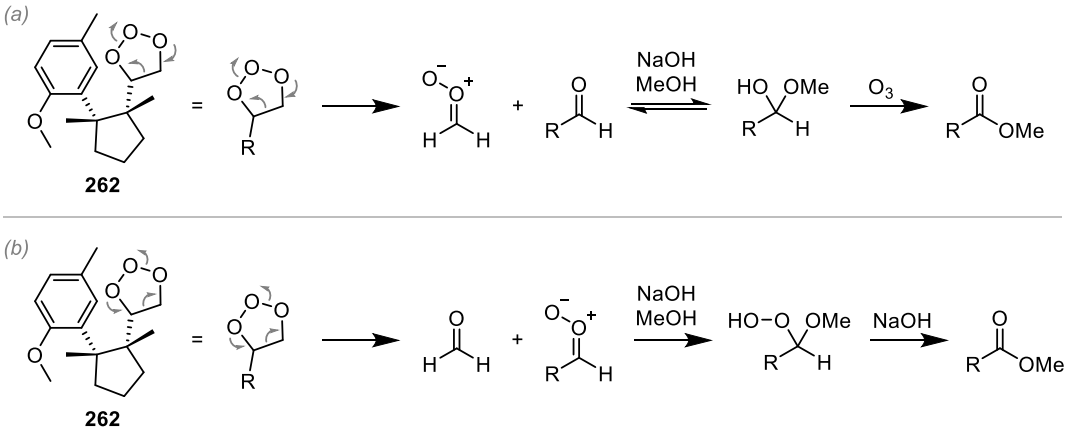
	^{1}H NMR data			^{13}C NMR data			
position	*synthetic* δ_H (ppm)	*reported* δ_H (ppm)	$\Delta\delta_H$ (ppm)	position	*synthetic* δ_C (ppm)	*reported* δ_C (ppm)	$\Delta\delta_C$ (ppm)
A	-	-	-	A	-	-	-
B	-	-	-	B	153.2	153.1	0.1
C	6.73	6.72	0.01	C	118.2	117.8	0.4
D	6.91	6.90	0.01	D	128.1	128.0	0.1
E	-	-	-	E	129.3	129.2	0.1
F	2.27	2.26	0.01	F	21.0	21.0	0.0
G	6.96	6.96	0.00	G	129.8	129.8	0.0
H	-	-	-	H	132.9	132.9	0.0
I	-	-	-	I	50.9	50.9	0.0
J	1.56	1.55	0.01	J	24.0	24.0	0.0
K	2.52–2.38 1.98–1.77	2.50–2.35 2.00–1.73	0.03 0.01	K	42.4	42.3	0.1
L	1.98–1.77	2.00–1.73	0.01	L	21.2	21.2	0.0
M	1.50–1.41 1.32–1.25	1.45–1.34 1.31–1.24	0.06 0.01	M	36.0	36.0	0.0
N	-	-	-	N	48.9	48.9	0.0
O	1.23	1.22	0.01	O	20.4	20.5	0.1
P	3.36 3.28	3.33 3.26	0.03 0.02	P	70.8	70.7	0.1
Q	-	-	-	Q	-	-	-

Synthetic ^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (125 MHz, $CDCl_3$) data generated in this study. Reported ^{1}H NMR (300 MHz, $CDCl_3$) and ^{13}C NMR (75 MHz, $CDCl_3$) data from ref. 112.



*Scheme 111. Interception of known late-stage intermediate **269** using an ozonolysis/basic methanolysis protocol.*
Enantiomeric ratio (e.r.) was determined by chiral HPLC analysis.

It is proposed that intermediate ozonide **262** can rearrange in two ways.[120] In the first, a substrate-derived aldehyde is obtained, to which methanol can add to give the hemiacetal (Scheme 112a). Base-assisted hydride abstraction by ozone affords the product. Alternatively, methanol can add to the substrate-derived carbonyl oxide to give a hydroperoxide which can dehydrate to give the product (Scheme 112b).



Scheme 112. Proposed mechanism for the ozonolysis/basic methanolysis.

Whilst this approach proved somewhat successful, the instability of the intermediate aldehyde to oxygen likely limited the yield of the transformation. This strategy was attempted concurrently with the investigations into the demethylation of **238**, and thus was not further investigated when the latter was successful.

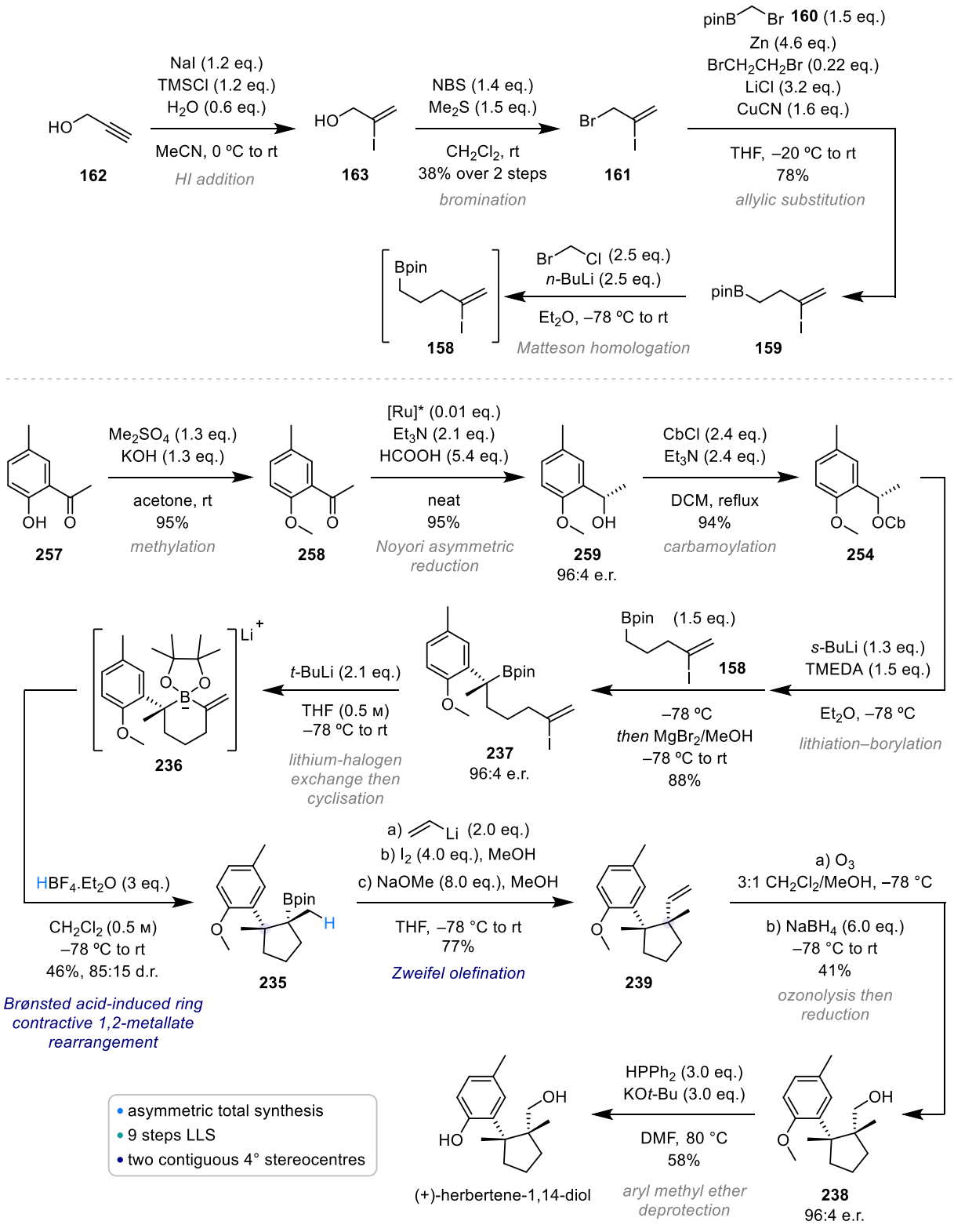
3.4. Conclusions and future work

3.4.1. Conclusions

The total synthesis of (+)-herbertene-1,14-diol was completed in 12 total steps, with 9 steps in the longest linear sequence (Scheme 113).

The two all-carbon quaternary stereocentres were installed through the manipulation and derivatisation of a boronic ester functional handle. The first all-carbon quaternary stereocentre was installed through the Brønsted acid-induced ring contractive 1,2-metallate rearrangement of boronate complex **236**. The forging of the contiguous stereocentres (one of which is quaternary) formed in this step occurred with complete retention of enantioenrichment and high diastereoselectivity. The second all-carbon quaternary stereocentre was assembled in the Zweifel olefination of highly sterically encumbered boronic ester **235**, stereospecifically transforming the C–B bond into a C–C bond. This represents the first asymmetric total synthesis of (+)-herbertene-1,14-diol where a methyl-bearing quaternary stereocentre is not installed through a substrate-controlled methylation reaction.

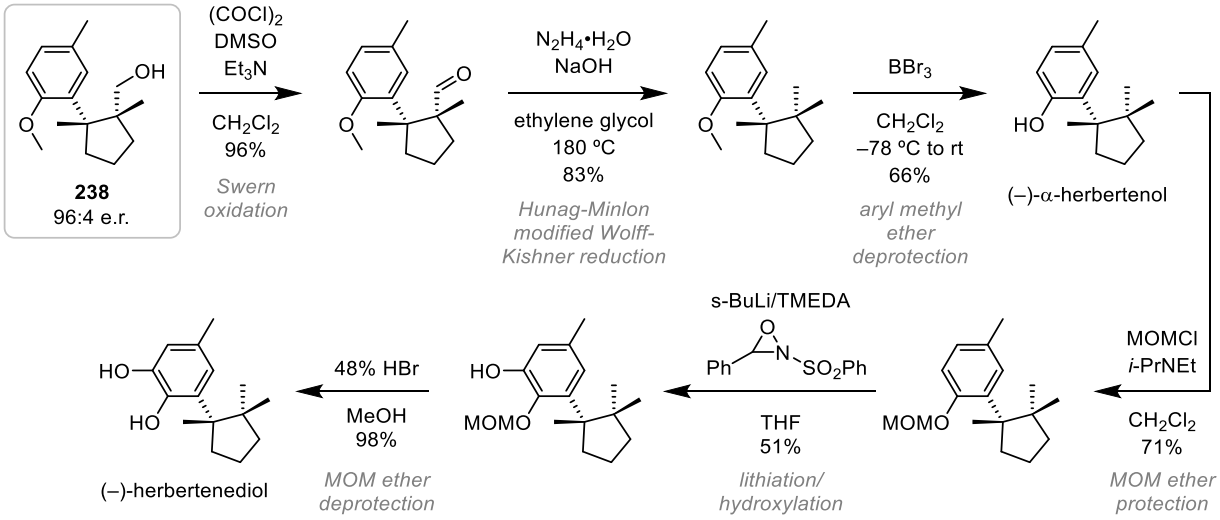
The challenges associated with the endgame steps of the synthesis likely reflect the highly hindered nature of the sites of reactivity in the late-stage intermediates, requiring the application of non-typical methods to overcome limitations in reactivity.



Scheme 113. Aggarwal's asymmetric total synthesis of (+)-herbertene-1,14-diol featuring a Brønsted acid-induced ring contractive 1,2-metallate rearrangement and a Zweifel olefination – this work.

3.4.2. Future work

Through the development of the synthetic route to (+)-herbertene-1,14-diol, a novel route towards enantioenriched intermediate **238** has been uncovered. This intermediate has been previously further elaborated in the total synthesis of herbertane-type sesquiterpenes (–)-α-herbertenol and (–)-herbertenediol (Scheme 114).[110] In this way, this novel methodology for the construction of **238** could provide access to a range of herbertane-type sesquiterpenes.



*Scheme 114. Intermediate **238** in the asymmetric total synthesis of other herbertane-type sesquiterpenes.*

4. 1-Azabicyclo[2.1.0]pentane (ABP): a novel reagent for the diastereoselective synthesis of highly substituted pyrrolidines

4.1. Strain-release-driven reactivity in synthesis

4.1.1. Strain in organic molecules

In 1885, Baeyer first introduced the concept of 'ring-strain', which he proposed is present as a result of bond angle distortions in any saturated carbocycle which deviates from tetrahedral ideality.[121] This picture of ring-strain was later shown to be incomplete, since additional factors such as bond length distortion, torsional strain and non-bonded (transannular) interactions also contribute to the destabilisation of cyclic molecules (Figure 23).[122]

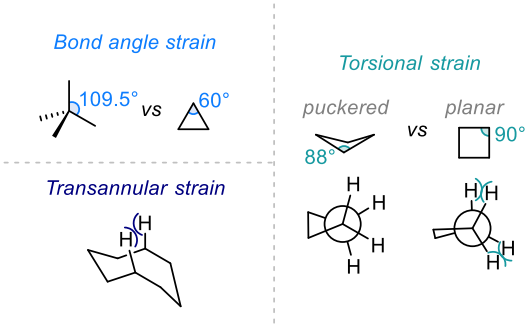


Figure 23. Elements of strain in organic molecules.

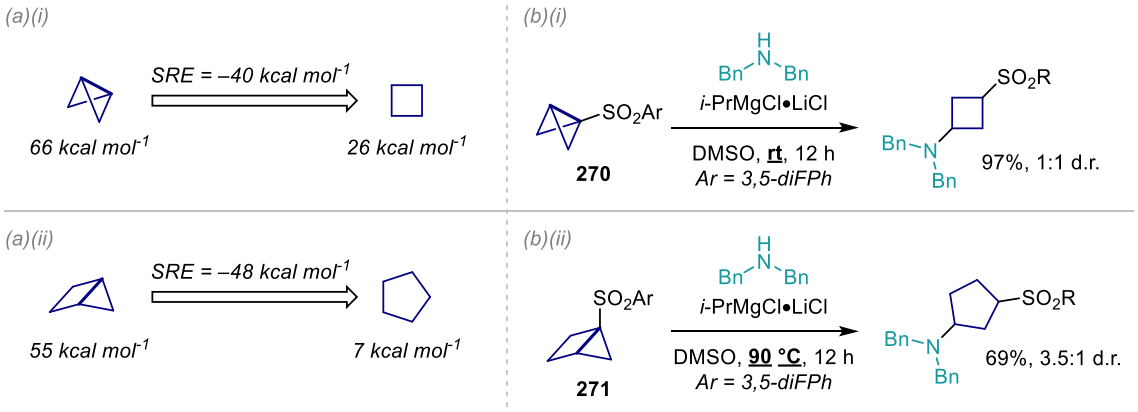
The strain energy of a cyclic molecule is defined as the difference between the experimental enthalpy of formation of the cyclic molecule (ΔH_f) and the sum of the theoretical enthalpies of formation of the individual strain-free fragments ($\Sigma\Delta H_f$) (Figure 24).[122]

Figure 24. Strain energy (SE) calculation for cyclopropane.

4.1.2. Strain-release energy

Strain-release energy is the difference in strain energy between products and reactants. The release of strain energy is often cited as the thermodynamic driving force for the ring-opening of the bridging bond in small, fused bi- and tri-cyclic molecules, since the product molecules are often significantly less strained than their destabilised precursors (Scheme 115a).[123]

However, strain-release energy alone cannot account for the kinetic barriers to such ring-opening reactions. In 2017, Baran and co-workers observed significant differences in the ring-opening reactivity of bicyclo[1.1.0]butyl sulfone **270** and bicyclo[2.1.0]pentyl sulfone **271** with an *in situ* generated 'turbo amide' (Scheme 115b).[124] Whilst the desired ring-opening of **270** occurred at room temperature, significantly elevated temperatures were required for the ring-opening of **271**. This is despite the strain-release energy of bicyclo[2.1.0]pentane being larger than that of bicyclo[1.1.0]butane (Scheme 115a).



Scheme 115. (a) Strain-release energy (SRE) for the ring-opening of bicyclo[1.1.0]butane vs bicyclo[2.1.0]pentane (data from ref. 128), and (b) their disparate reactivity in anionic ring-opening (from ref. 124).

There have been an array of theoretical justifications for such observations,[125–127] with a recent publication by Anderson and Duarte suggesting that a combination of strain-release energy and extent of 'bond delocalisation' contribute to the 'spring-loaded' reactivity of polycyclic fragments.[128] Since bond delocalisation is significant in three-membered rings, the more three-membered rings a particular bond forms part of (n_3), the more susceptible it is to cleavage. The authors go on to estimate the difference in activation barrier ($\Delta\Delta H^{\ddagger}$) for the ring-opening of two strained molecules through a combination of differential strain-release energy (ΔSRE) and degree of delocalisation (Δn_3) effects (Figure 25). This hypothesis corroborates experimental findings; the activation barrier for the anionic ring-opening of bicyclo[1.1.0]butane is 6 kcal mol^{-1} lower than that for bicyclo[2.1.0]pentane.

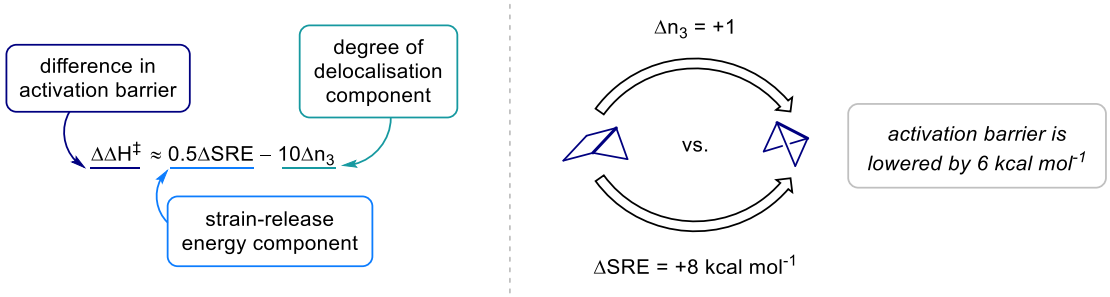


Figure 25. Anderson and Duarte's 'rule of thumb' equation for the determination of the difference in kinetic barrier to ring-opening between two strained systems (data from ref. 128).

4.2. Strain-release-driven reactivity of aza-bicycles

Nitrogen-containing heterocycles represent a key structural component of many pharmaceuticals. Indeed, a study from Njardarson and co-workers conducted in 2014 determined that 59% of U.S. FDA-approved drugs feature a nitrogen heterocycle.[129] Amongst the most highly represented nitrogen heterocycles are piperidine and pyrrolidine, with relatively few azetidine-containing pharmaceuticals approved to this day.

An attractive method for the synthesis of these saturated nitrogen-containing heterocycles exploits the strain-release-driven reactivity of small nitrogen-containing bicycles (Figure 26), in particular their ring-opening reactivity with nucleophiles and electrophiles.[123,130]

The strain-release-driven reactivity of azabicyclo[1.1.0]butane (ABB), 1-azabicyclo[2.1.0]pentane (ABP) and 1-azabicyclo[3.1.0]hexane (ABH) will be discussed herein. These compounds are named according to the convention for naming bicyclic compounds (Figure 27).

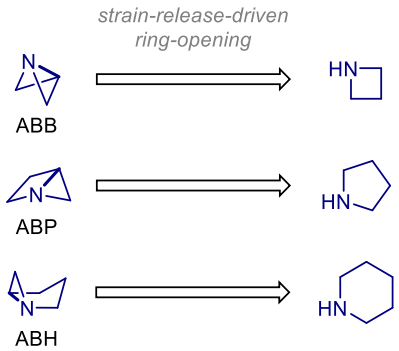


Figure 26. Strain-release-driven reactivity of aza-bicycles.

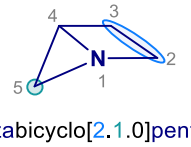


Figure 27. Naming convention for bicyclic compounds.

The difference in reactivity of two of these aza-bicycles has been calculated using Anderson and Duarte's combined strain-release/delocalisation framework (Figure 28).[128] It is suggested that, in anionic ring-opening reactivity, azabicyclo[1.1.0]butane (ABB) will be more reactive than its homologue 1-azabicyclo[2.1.0]pentane (ABP).

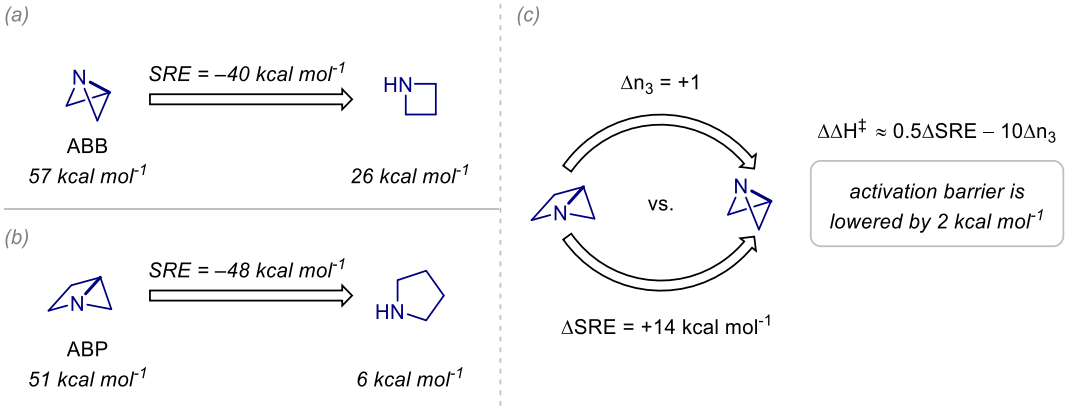


Figure 28. Anderson and Duarte's calculated reactivity differences of aza-bicycles in anionic ring-opening reactivity (data from ref. 128).

4.2.1. Azabicyclo[1.1.0]butane (ABB)

The azabicyclo[1.1.0]butane (ABB) ring system consists of two fused 3-membered rings and a bridgehead nitrogen (Figure 29). X-ray crystallographic analysis of ABB-containing compound **272** has confirmed a dihedral (inter-wing) angle of 119° and central C–N bond length of 1.52 Å.[131] These values resemble those for the all-carbon analogue bicyclo[1.1.0]butane.[132]

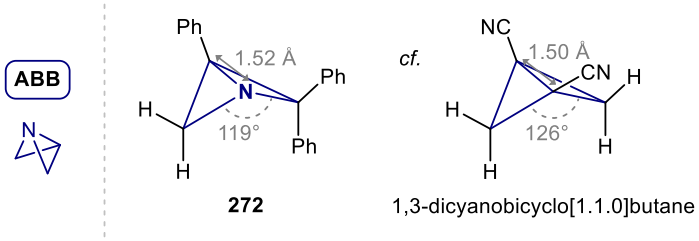
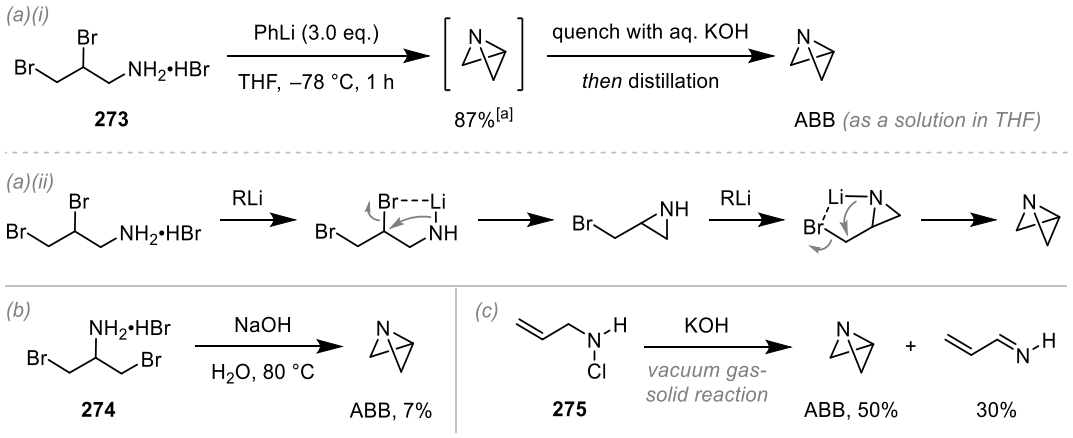


Figure 29. Azabicyclo[1.1.0]butane (ABB).

The synthesis and reactivity of ABB-containing molecules have been well explored, reported and reviewed.[130,133,134] A handful of methods for the synthesis of the parent ABB compound have been developed (Scheme 116). In 1999, Nagao and co-workers reported the synthesis of ABB in 87% yield from 2,3-dibromopropylamine hydrobromide **273**, through treatment with 3 equivalents of phenyl lithium (Scheme 116ai).[135] A solution of ABB in THF could be obtained, following a basic extraction and distillation. The same authors proposed that the mechanism consisted of two sequential aziridine cyclisation reactions, instead of azetidine formation followed by a transannular cyclisation (Scheme 116aii).[136] This procedure significantly improved upon the prior art. In 1969, Funke reported the synthesis of ABB from related dibromoamine **274** (Scheme 116b).[137] In 1988, Denis and co-workers disclosed the synthesis of ABB in 50% yield from *N*-chloroallylamine (**275**) using potassium hydroxide under vacuum gas-solid reaction conditions (Scheme 116c).[138]

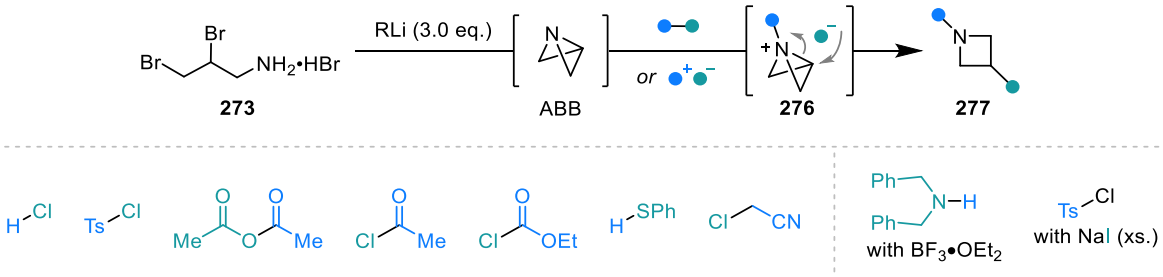


Scheme 116. Methods for the synthesis of ABB.

[a] HPLC yield.

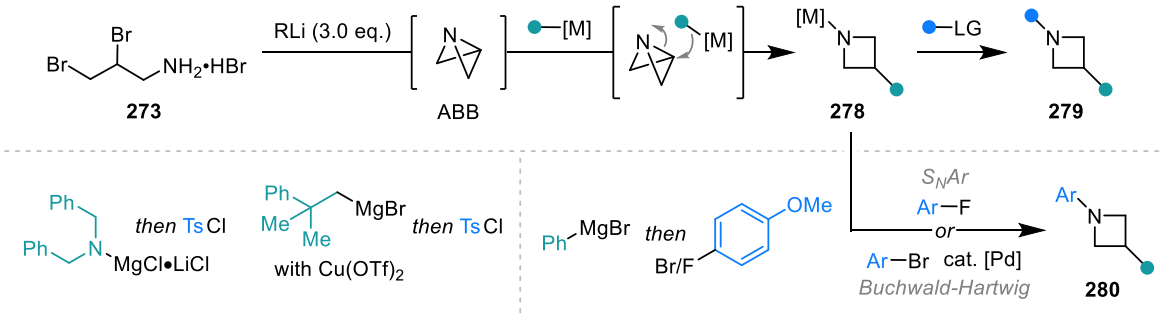
The reported reactivity of ABB is dominated by the electrophile-promoted addition of nucleophiles to the bridgehead position, with ring-opening and cleavage of the strained, central bond to yield azetidine products (**277**) (Scheme 117). Here, ABB is generated *in situ* from the treatment of dibromoamine **273** with 3 equivalents of organolithium base. It is believed that addition of the electrophile to the Lewis basic ABB nitrogen (to give **276**) precedes nucleophilic attack. Typically, the 'leaving group' of the electrophile goes on to act as the nucleophile, as in the addition of haloacids,[137,139] sulfonyl halides,[135,137] anhydrides,[137,139] acyl chlorides,[137] chloroformates,[139] thiols[137,140] and alkyl halides.[139] However, there have been reports of external amine nucleophiles being employed, under Lewis acid nitrogen activation,[137] for example. In addition to this, Lopchuck and co-workers were able to isolate a

3-iodo azetidine through the combination of tosyl chloride and a significant excess of sodium iodide.[141]



Scheme 117. Ring-opening reactivity of ABB: electrophile-promoted nucleophile addition.

The direct addition of harder nucleophiles to ABB, without need for formal activation of the nitrogen, has been the focus of recent efforts (Scheme 118). Intermediate nitrogen-metallated azetidine **278** can be functionalised in the same pot through the addition of an electrophile to give **279**. The addition of amido-Grignard reagents to ABB was first achieved by Baran and co-workers in 2016.[124,142] Direct alkylation of ABB was achieved by Gianatassio and co-workers, through the addition of organo-magnesium and organo-zinc reagents alongside sub-stoichiometric amounts of copper(II) triflate.[143] The intermediate nitrogen-metallated ABB species (**278**) has also been shown to undergo S_NAr reactions, as well as Buchwald-Hartwig cross-coupling reactions to give **280**.[144]



Scheme 118. Ring-opening reactivity of ABB: direct nucleophile addition.

4.2.2. 1-Azabicyclo[3.1.0]hexane (ABH)

The 1-azabicyclo[3.1.0]hexane (ABH) ring system consists of fused 5- and 3-membered rings and a bridgehead nitrogen, and typically sits in a boat conformation (Figure 30).[145] Natural product ficellomycin (**281**) contains this unusual fragment and it remains a desirable but highly challenging synthetic target.[146,147]

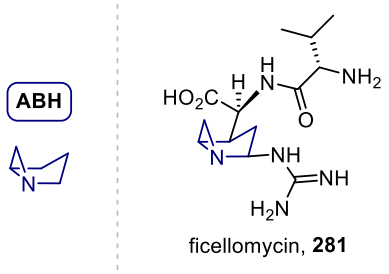
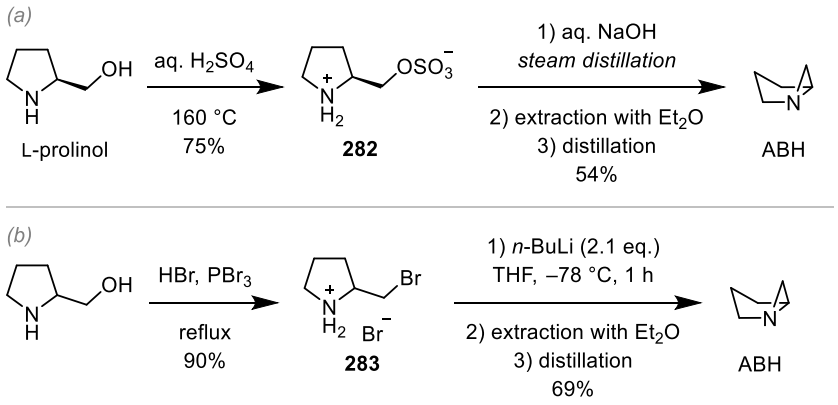


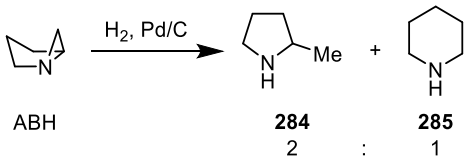
Figure 30. 1-Azabicyclo[3.1.0]hexane (ABH).

Whilst the synthesis of ABH-containing compounds is well explored,[148] few robust methods exist for the synthesis of the parent ABH compound. In 1967, Fentiman and co-workers reported the synthesis of 1-azabicyclo[3.1.0]hexane (ABH) from L-prolinol, proceeding through intermediate sulfuric acid ester **282** (Scheme 119).[149] Treatment of **282** with aqueous base, followed by steam distillation, extraction and a second distillation gave pure ABH in 54% yield. In 2009, Nagao and co-workers reported an analogous synthesis, proceeding instead through intermediate alkyl bromide **283**.[150] Again, treatment with base, extraction and distillation yielded pure ABH in an improved 69% yield.



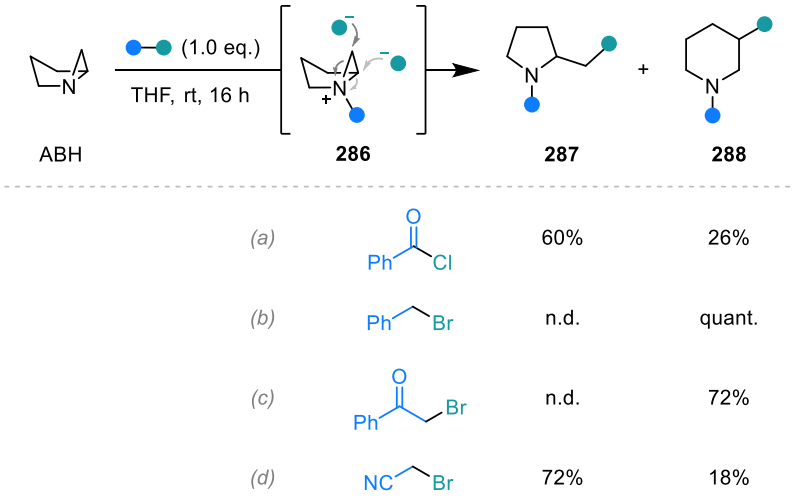
Scheme 119. Methods for the synthesis of ABH.

Fentiman and co-workers also reported the hydrogenation of ABH, yielding 2-methyl pyrrolidine (**284**) and piperidine (**285**) in a 2:1 ratio (Scheme 120).[149]



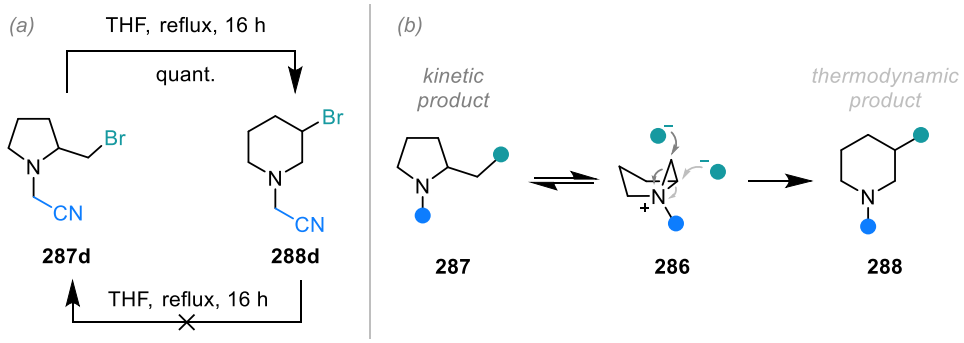
Scheme 120. Hydrogenation of ABH.

Significant understanding of the reactivity of ABH was gained by Nagao and co-workers in their exploration of the addition of acyl/alkyl halides to ABH (Scheme 121).[150] Strain-release-driven aziridine ring-opening was observed, likely proceeding *via* *N*-functionalised **286**. Upon addition of benzoyl chloride to ABH (Scheme 121a), a mixture of pyrrolidine **287** and piperidine **288** products was observed, originating from the addition of the nucleophile to either the aziridine bridge or the bridgehead of the bicycle. Interestingly, only piperidine product **288** was observed with alkyl halides (Scheme 121b) and α-haloalkylketones (Scheme 121c).



Scheme 121. Ring-opening reactivity of ABH with acyl/alkyl halides.

2-Bromoacetonitrile, however, yielded a mixture of products (Scheme 121d). When pyrrolidine **287d** was heated to reflux in THF, quantitative conversion to piperidine **288d** was observed (Scheme 122a). Whereas piperidine **288d** could not be transformed to pyrrolidine **287d** under the same conditions.



Scheme 122. Proposed equilibrium in the ring-opening reactivity of ABH with alkyl halides.

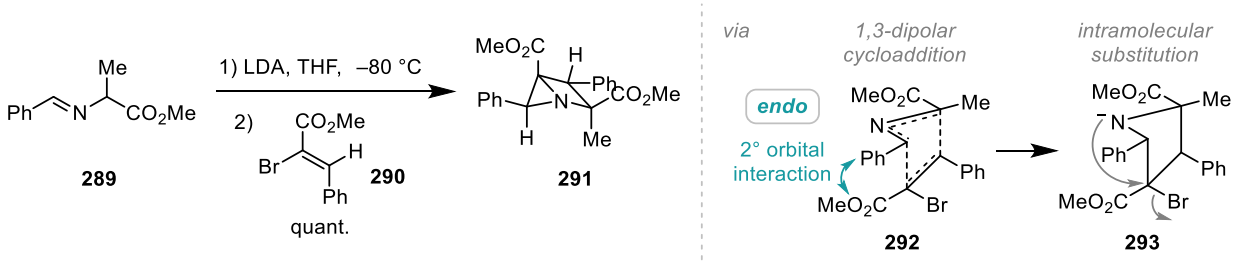
This observation provides evidence for the existence of an equilibrium between the activated ABH (**286**), the kinetic pyrrolidine product (**287**) and the thermodynamic piperidine product (**288**) (Scheme 122b). When the nitrogen atom is sufficiently nucleophilic (*i.e.* has alkyl substitution) the reverse reaction becomes feasible and thus the equilibrium enables complete funnelling of the product distribution to give the thermodynamic piperidine product.

4.2.3. 1-Azabicyclo[2.1.0]pentane (ABP)

The 1-azabicyclo[2.1.0]pentane (ABP) ring system consists of fused 4- and 3-membered rings and a bridgehead nitrogen (Figure 31).

Figure 31. 1- Azabicyclo[2.1.0]pentane (ABP).

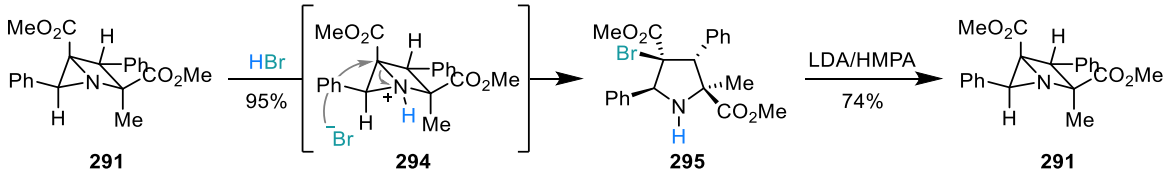
There have been no reports of the synthesis of the parent ABP compound. However there has been one report of the synthesis of a highly substituted ABP-containing compound.[151] Joucla and co-workers synthesised ABP-containing **291** in a quantitative yield from deprotonated imine **289** and bromoalkene **290** (Scheme 123). They suggest that a 1,3-dipolar cycloaddition occurs, with an endo approach favoured, owing to a postulated favourable secondary orbital interaction between the ester and phenyl groups (**292**). Indeed, if the ester group is replaced by a cyano group, a mixture of endo and exo products results. The resultant 3-bromo pyrrolidine anion **293** undergoes an intramolecular substitution reaction to deliver ABP-containing **291** as a single diastereomer.



*Scheme 123. Joucla's synthesis of ABP-containing **291** via a 1,3-dipolar cycloaddition followed by intramolecular substitution.*

The addition of hydrogen bromide to **291** was then trialled (Scheme 124).[151] 3-Bromo pyrrolidine **295** was obtained in a 95% yield, presumably through the addition of bromide to the bridgehead position of activated ABP **294**. Interestingly, ABP **291** could be regenerated

from **295** through treatment with LDA and intramolecular displacement of the bromide leaving group.



*Scheme 124. Joucla's synthesis and ring-opening of ABP-containing **291** via 3-bromo pyrrolidine **295**.*

Analysis of ABP-containing **296**, synthesised according to the methodology described above, by X-ray crystallographic methods enabled some structural parameters to be determined (Figure 32).[152] The dihedral (inter-wing) angle was calculated to be 121°, very similar to that of ABB (see Figure 29). Interestingly, the azetidine ring was found to be planar.

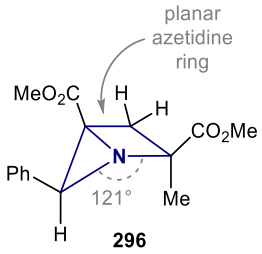


*Figure 32. Structural features of ABP **296**.*

4.2.4. 1-Azoniabicyclo[2.1.0]pentane

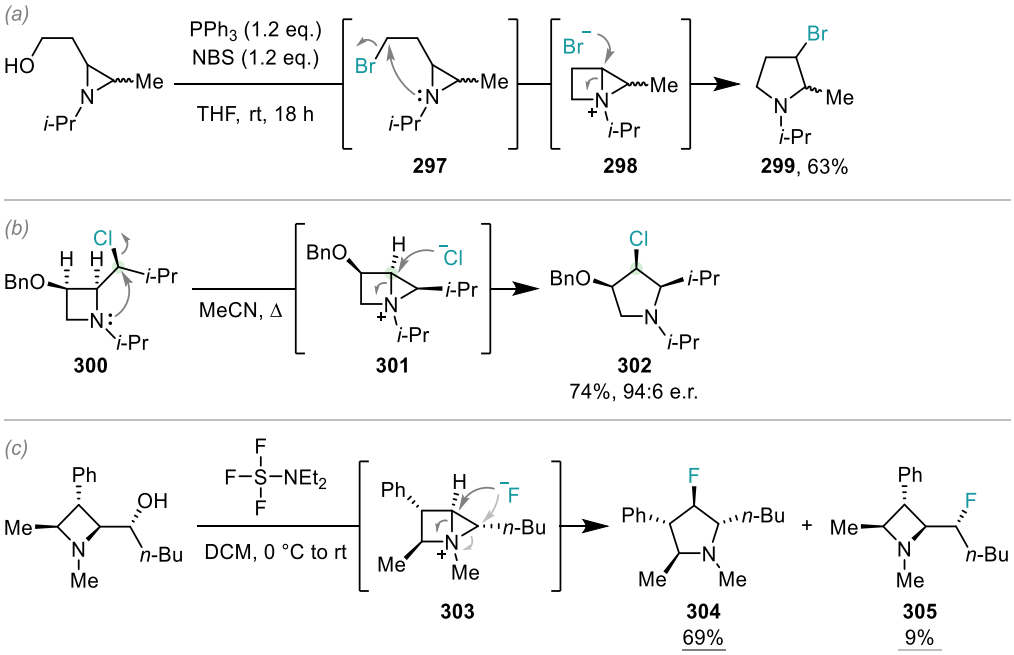
The 1-azoniabicyclo[2.1.0]pentane, a bicyclic aziridinium ion which is structurally related to 1-azabicyclo[2.1.0]pentane, has been invoked as a transient intermediate in the synthesis of pyrrolidines from smaller nitrogen-containing saturated heterocycles bearing a suitably located leaving group.[153,154]

N-Alkyl aziridines bearing a leaving group at the δ-position, such as **297**, can undergo an intramolecular cyclisation with displacement of this leaving group to give intermediate bicyclic aziridinium ion **298** (Scheme 125a).[155] The ejected bromide leaving group can then add at the bridgehead of the bicycle with ring-opening to give pyrrolidine **299**.

The stereochemical outcome of the heat-promoted structural isomerisation of β-chloro azetidine **300** to 3-chloro pyrrolidine **302** provides evidence of the intermediacy of the bicyclic aziridinium ion (**301**) (Scheme 125b).[156]

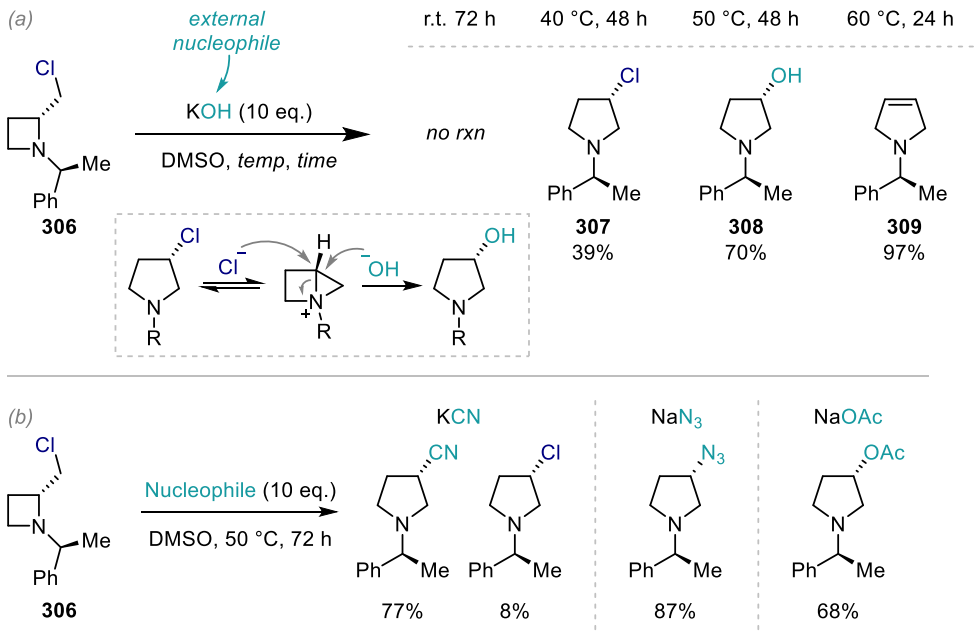
Whilst addition of the nucleophile to the bridgehead position of the 1-azoniabicyclo[2.1.0]pentane typically dominates, there has been one example of addition to

the aziridine bridge (**303**) (Scheme 125c).[157] Small amounts of azetidine product **305** were observed, in addition to pyrrolidine **304**.



Scheme 125. 1-Azoniabicyclo[2.1.0]pentane in the synthesis of pyrrolidines.

In 2008, Couty and co-workers disclosed the difficulties associated with the addition of external nucleophiles to intercept these bicyclic aziridinium ion intermediates (Scheme 126a).[158] The expelled chloride leaving group from **306** was found to act as a competitive nucleophile, re-adding to the bridgehead of the bicycle. Only at elevated temperatures (50 °C) could desired **308** be observed, since at this temperature the product distribution is driven towards its irreversible formation. At higher temperatures elimination occurred to give **309** and at lower temperatures 3-chloro pyrrolidine **307** was the major product. Under these optimised conditions, a range of nucleophiles could be added to intercept the bicycle (Scheme 126b). Critically, these nucleophiles had to be added in a large excess.

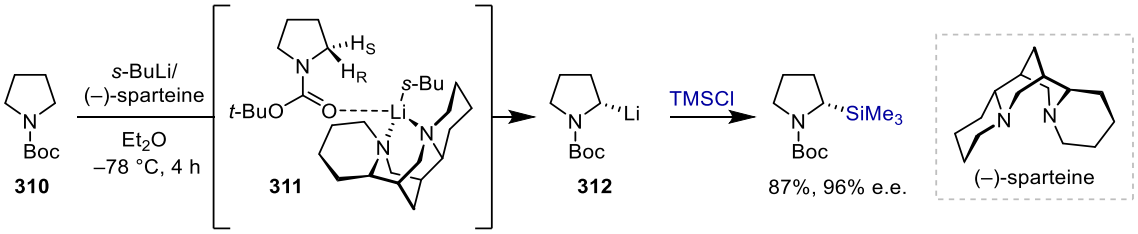


Scheme 126. Addition of external nucleophiles to a 1-azoniabicyclo[2.1.0]pentane.

4.3. Deprotonation of aza-cycles

4.3.1. Deprotonation of *N*-Boc pyrrolidines

In 1994, Beak and co-workers demonstrated the asymmetric deprotonation of *N*-Boc pyrrolidine (**310**) using (–)-sparteine-ligated *sec*-butyl lithium to give enantioenriched **312** (Scheme 127).[159] The formation of pre-lithiation complex **311**, with coordination between the diamine-ligated organolithium and the carbamate group, was postulated.[160] This lithiation is only possible in the presence of such a directing group on nitrogen.



*Scheme 127. Asymmetric deprotonation of N-Boc pyrrolidine **310** at the 2-position.*

4.3.2. Deprotonation of *N*-alkyl aziridines

The distortions from tetrahedral ideality in the structure of *N*-alkyl aziridines have implications on the molecular orbital contributions to their bonding (Figure 33).[161] The geometric constraints of the trigonal ring (*i.e.* the required 60 degree internal bond angles) result in a larger *p*-orbital contribution to the bonding in the core C–C and C–N bonds. As a result, the

remaining hybrid orbitals have enhanced *s*-orbital character. This means that the C–H aziridine bonds are more acidic. By consequence, the lone pair on nitrogen in aziridine (R = H) is less basic than that in dialkyl amines.[161] Moreover, the structural rigidity of the system means that the barrier to nitrogen inversion is higher than in acyclic analogues and thus nitrogen 'invertomers' exist.[161]

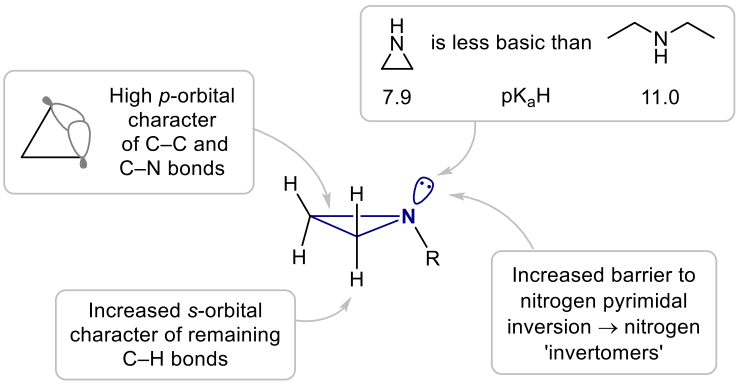
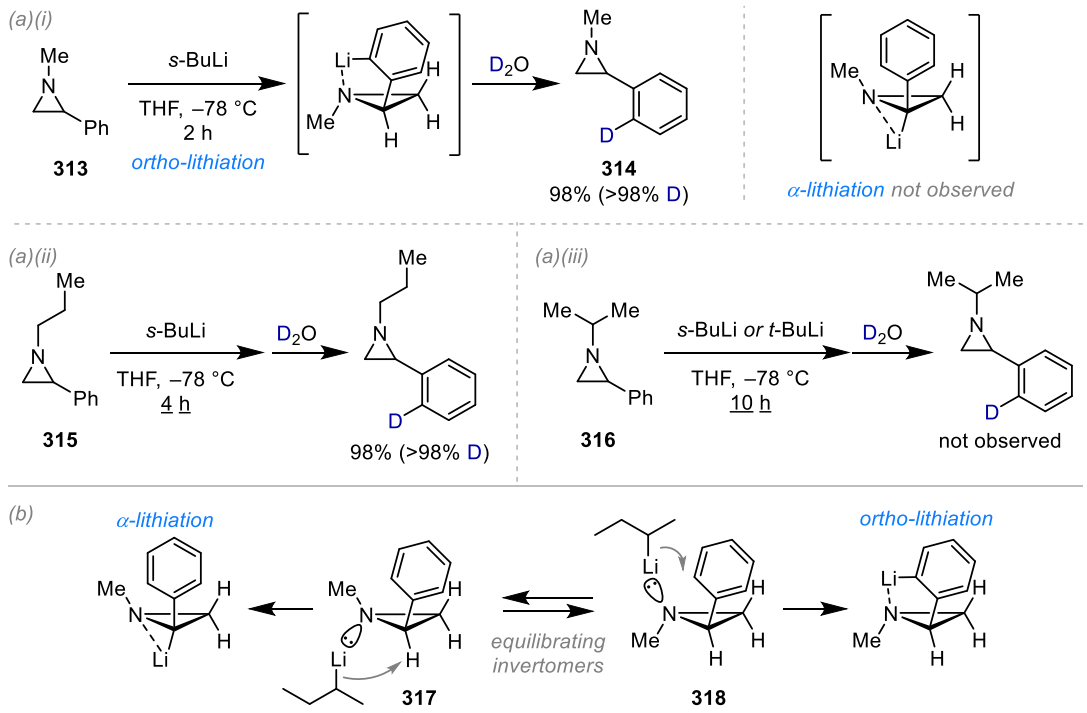


Figure 33. Structural features of N-alkyl aziridines contributing to the acidity of the C–H bonds.

The generation and reactivity of aziridinyl anions has been extensively explored.[162] The direct deprotonation of unsubstituted *N*-alkyl aziridines is unknown, however the presence of acidifying groups on the aziridine can enable deprotonation.

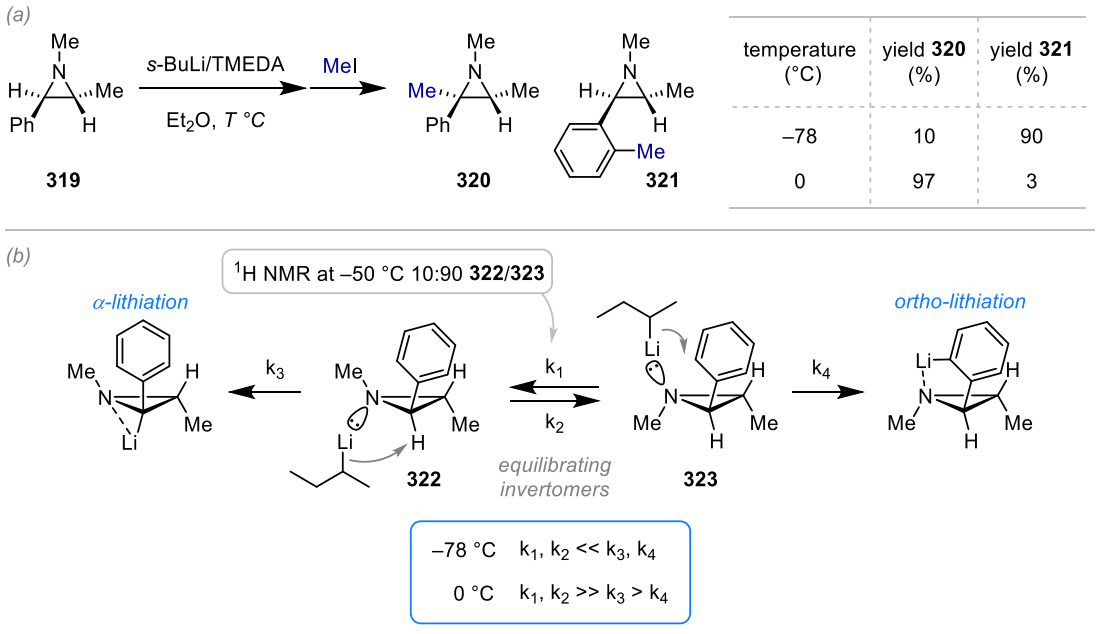
In 2005, Florio and co-workers found that *N*-methyl-2-phenyl aziridine **313**, when treated with *sec*-butyl lithium at –78 °C, did not undergo *α*-lithiation (Scheme 128ai).[163] Instead, **313** underwent an unusual *ortho*-lithiation, with deuterium incorporation occurring on the phenyl ring (**314**). When the steric bulk at nitrogen was increased (**315**) (Scheme 128aii), longer reaction times were necessary for complete lithiation. *N*-Isopropyl aziridine **316**, however, did not undergo any lithiation (Scheme 128aiii). It was suggested that these results imply a necessary pre-complexation of the organolithium with the nitrogen lone pair prior to deprotonation. This interaction is hindered when the steric bulk at nitrogen is significant.

The origin of selective *ortho*-lithiation has been attributed to the position of the equilibrium between two possible reactive invertomers (**317** *vs* **318**) of the aziridine (Scheme 128b). The coordination of the incoming organolithium to the Lewis basic nitrogen leads to lithiation being directed to the proximal acidic site. In each invertomer this leads to a distinct outcome. It is suggested that invertomer **318**, placing the *N*-methyl and phenyl groups trans to each other, is the dominant species on steric grounds, and thus *ortho*-lithiation dominates.



*Scheme 128. Deprotonation of N-alkyl aziridine **313** at the ortho position.*

Interestingly, the position of this equilibrium showed temperature dependence in the case of disubstituted aziridine **319** (Scheme 129).[164]

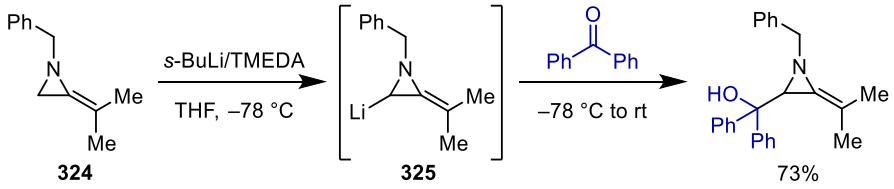


temperature (°C)	yield **320** (%)	yield **321** (%)
–78	10	90
0	97	3

*Scheme 129. Temperature-dependent deprotonation of N-alkyl aziridine **319**.*

Low temperature ^{1}H NMR and NOESY experiments concluded that invertomers **323** and **322** exist in a 90:10 ratio. At –78 °C *ortho*-lithiation dominates, reflecting the experimentally measured invertomer distribution at low temperature. Whereas at 0 °C α-lithiation dominates, likely as a consequence of fast invertomer interconversion relative to the rates of deprotonation. This is a Curtin-Hammett scenario; the product distribution does not reflect the reactant distribution, owing to the fast interconversion of reactants. This work in particular highlights the interplay between reaction conditions, nitrogen stereodynamics and complexation in the selectivity of deprotonation reactions of aziridines.

The deprotonation of *N*-alkyl methylene aziridines (**324**) at the unsubstituted aziridinyl position has also been demonstrated,[165–169] with the resultant organolithium (**325**) trapped with a range of electrophiles, such as ketones (Scheme 130).[165]



324 **325**

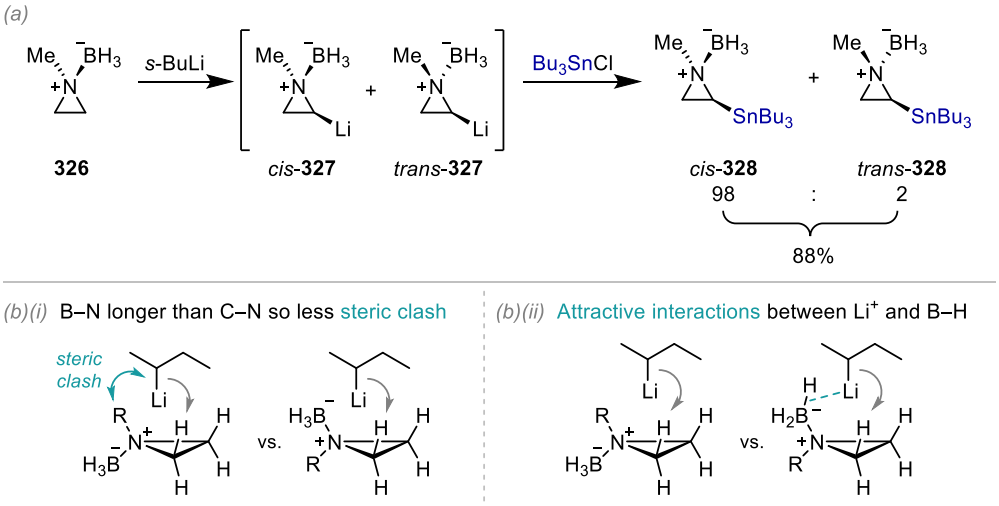
*Scheme 130. Deprotonation of N-alkyl methylene aziridine **324**.*

Whilst direct deprotonation of unsubstituted *N*-alkyl aziridines remains unknown, there has been significant progress in the deprotonation of *N*-alkyl aziridines activated by borane Lewis acids.[170–174] Amino borane **326** was deprotonated by *sec*-butyl lithium and the resultant organolithium trapped with tributyltin chloride, giving stannane **328** in 88% yield (Scheme 131a).[170] Interestingly, the cis product dominated, placing the stannane and borane groups on the same side of the aziridine.

It was confirmed that the intermediate organolithium compounds (*cis*-**327** and *trans*-**327**) were configurationally stable by subjecting a mixture of *cis*-**328** and *trans*-**328** to lithium-tin exchange conditions followed by stannylation, with the product stannane returned in a comparable cis/trans ratio to that of the starting materials.[170]

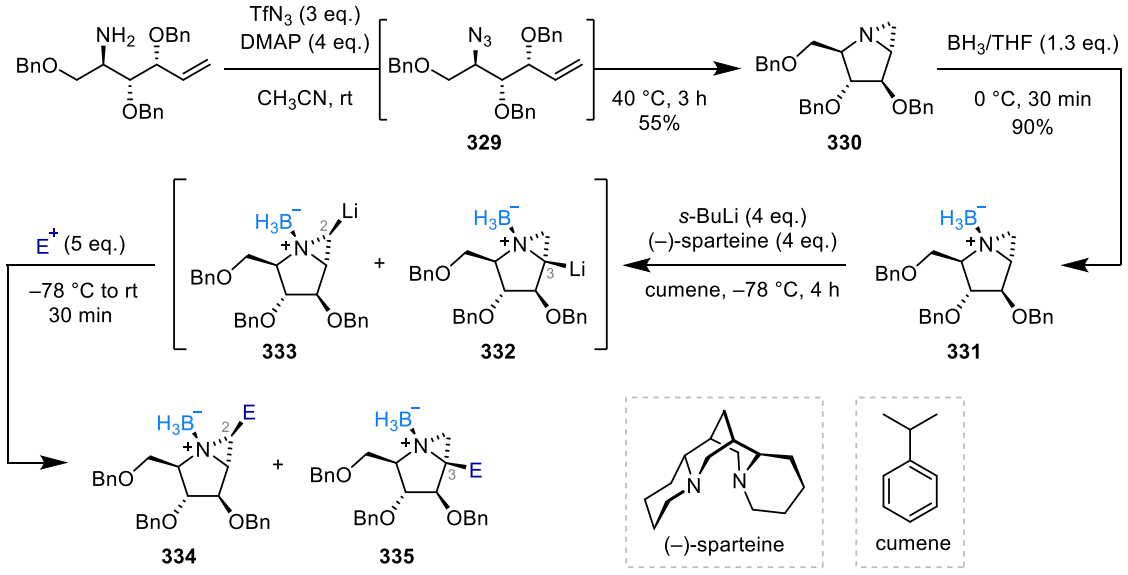
Thus, the origin of dominant *cis*-functionalisation was attributed to *syn*-lithiation. It is proposed that *syn*-lithiation occurs to reduce the steric clash between the incoming organolithium and the *N*-alkyl group, since the N–B bond is longer than the exocyclic N–C bond (Scheme 131bi).[171] Moreover, a favourable electrostatic interaction between the electron rich B–H bond

and the positive end of the C–Li dipole has been postulated (Scheme 131bii). This interaction positions the organolithium in prime position to deprotonate the *syn*-proton.



*Scheme 131. Deprotonation of N-alkyl aziridine borane adduct **326**.*

Interestingly, bicyclic aziridines have been shown to form aziridine borane complexes. Bicyclic sugar-derived aziridine **330** was accessed through the heating of azide **329** and, upon addition of BH_3/THF, borane adduct **331** was isolated (Scheme 132).[175]



*Scheme 132. Deprotonation of sugar-derived 1-azabicyclo[3.1.0]hexane borane adduct **331**.*

(–)-Sparteine-ligated *sec*-butyl lithium enacted the borane-directed deprotonation and the resultant organolithium was quenched with a range of electrophiles (Table 10). Upon addition of D_2O, a 1:1 mixture of 2- and 3-functionalised azetidine (**334** and **335**, respectively) was obtained, indicating that the deprotonation showed poor regioselectivity (Entry 1). An increase

in the steric bulk of the electrophile (Entries 2–4) improved the regioselectivity of the transformation but at the expense of the reaction yield; it is likely that the larger electrophiles react preferentially with the less hindered organolithium **333** over **332**.

*Table 10. Functionalisation of aziridine borane **331** by electrophiles.*

entry	E^+	**A**:**B**	yield (%)
1	D_2O	1:1	80
2	Bu_3SnCl	5:1	50
3	$P(O)(OEt)_2Cl$	1:0	15
4	$P(OEt)_2Cl$	1:0	20

4.3.3. Deprotonation of azabicyclo[1.1.0]butane (ABB)

The significant distortions from tetrahedral ideality in the structure of azabicyclo[1.1.0]butane have implications on the molecular orbital contributions to its bonding. Whilst there have been no investigations into hybridisation models of the molecular orbitals, it is often suggested that the central C3–N bond has significantly enhanced *p*-orbital contribution.[130] Indeed for the all-carbon analogue, bicyclo[1.1.0]butane, the central bond has been calculated to consist of 96% *p*-orbital character,[176] with a predominant σ interaction between these two essentially unhybridised *p*-orbitals.[177]

The non-classical hybridisation of the bonding at the bridgehead (C3) site is predicted to increase the acidity of the C3–H bond, owing to its likely increased *s*-orbital character (Figure 34). Whilst the pK_a of this proton has not been measured, the bridgehead proton of bicyclo[1.1.0]butane has been reported to have a pK_a of 37.9.[178] This value is considerably lower than that of a typical unstrained C(sp^3)–H bond.

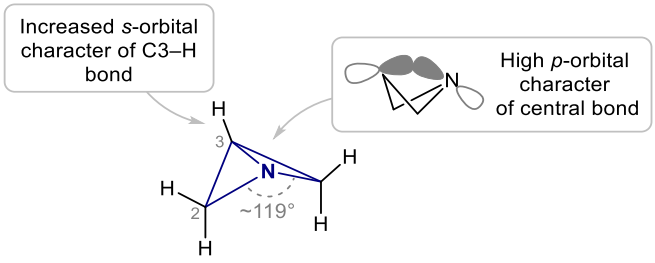
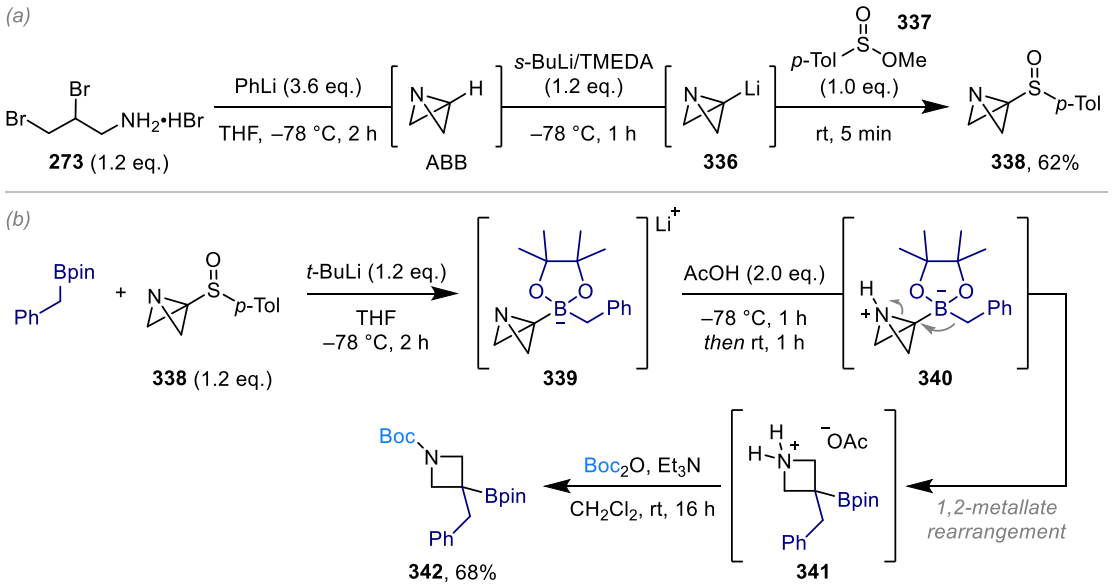


Figure 34. Structural features of ABB contributing to the acidity of the bridgehead bond.

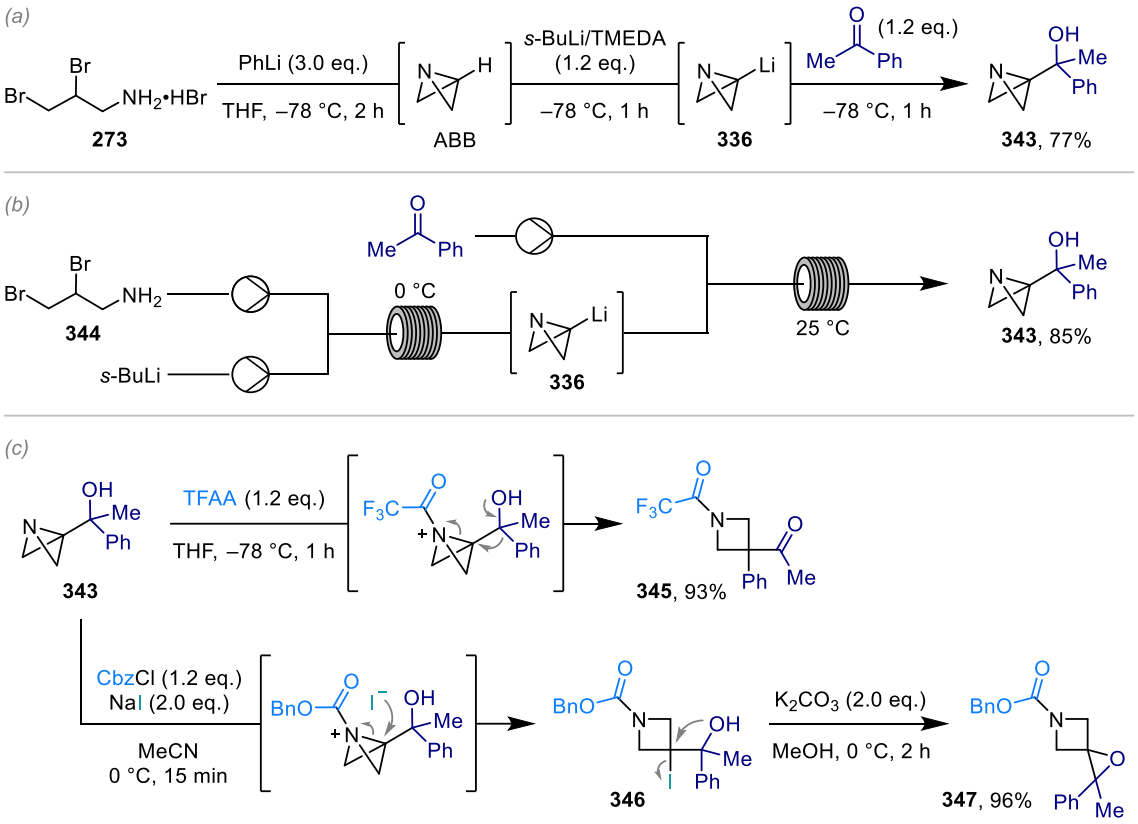
The deprotonation of ABB was first demonstrated by Aggarwal and co-workers in 2019 (Scheme 133a).[179] ABB, synthesised according to Nagao's protocol,[135] could be deprotonated at the bridgehead carbon using TMEDA-ligated *sec*-butyl lithium. Azabicyclo[1.1.0]butyl

lithium (ABB-Li, **336**) could then be trapped by sulfinate **337**, yielding bench stable sulfoxide **338**. Lithium-sulfoxide exchange using *tert*-butyl lithium enabled regeneration of ABB-Li in the presence of a boronic ester, yielding boronate complex **339** (Scheme 133b). Upon activation of the nitrogen by acetic acid, boronate complex **340** could undergo a strain-release-driven 1,2-metallate rearrangement, cleaving the central C–N bond to deliver azetidine salt **341**. Salt **341** could then be further functionalised through treatment with base and reaction with an electrophile to give **342**.



*Scheme 133. (a) First report of ABB-Li. (b) Synthesis of ABB boronate **339** from ABB-Li and its strain-release-driven 1,2-metallate rearrangement.*

The addition of ABB-Li (**336**) to ketones and aldehydes was reported simultaneously by Aggarwal[180] (Scheme 134a) and Luisi[181] (Scheme 134b). Whilst Aggarwal and co-workers demonstrated this reactivity in batch, Luisi and co-workers achieved the first synthesis of ABB-Li in continuous flow, adding ketone and aldehyde electrophiles to ABB-Li for the synthesis of ABB carbinols.[181] Interestingly, this continuous flow protocol removed the need for cryogenic temperatures and rendered the handling of the organolithium reagent safer and more scalable. Moreover, use of amine **344**, accessed from bench stable **273** through its extraction in the presence of aqueous base, meant that the protocol only required the use of a single organolithium reagent for the direct synthesis of ABB-Li.



Scheme 134. Synthesis of ABB carbinols from ABB-Li in (a) batch and (b) flow. (c) Divergent strain-release-driven reactivity of ABB carbinols.

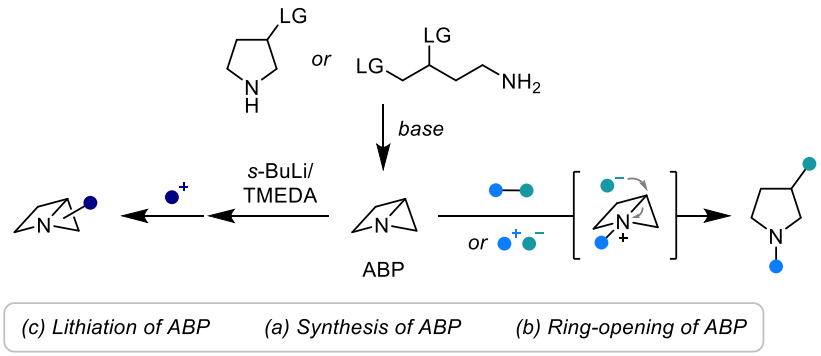
Aggarwal and co-workers demonstrated the ability of ABB carbinols, such as **343** derived from acetophenone, to undergo a strain-release-driven semipinacol rearrangement upon activation by trifluoroacetic anhydride (TFAA), yielding keto-azetidine **345** (Scheme 134c).[180] If the same ABB carbinol, however, was treated with benzyl chloroformate (CbzCl) in the presence of sodium iodide, a ring-opening reaction occurred, giving iodo-hydrin **346**. Upon treatment with base, this species underwent ring-closure with expulsion of iodide to yield spiroepoxy azetidine **347**.

The reactivity of ABB-Li with a range of electrophiles has since been reported, including Weinreb amides,[182] α-, β-, and γ-haloalkylketones,[183] alkyl halides,[184] and acyl silanes.[185] The resultant bench stable ABB-containing compounds have also been shown to undergo unique transformations.[186]

4.4. Project proposal

4.4.1. Project outline

This work sought to establish the first synthetic route towards the elusive parent 1-azabicyclo[2.1.0]pentane (ABP), identifying a bench stable precursor and robust conditions for its cyclisation to the bicycle (Scheme 135). With a route towards ABP in hand, its reactivity in strain-release-driven ring-opening reactions could then be explored, as well as the regioselectivity and extent of its lithiation and trapping with electrophiles. In this way, a library of highly functionalised pyrrolidines could be accessed from a novel, bicyclic starting material.

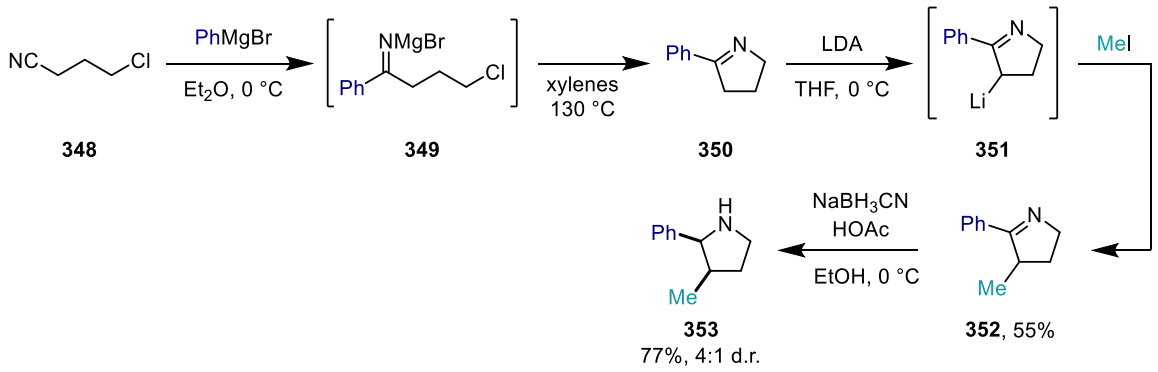


Scheme 135. Proposed investigations into the synthesis, ring-opening and lithiation of 1-azabicyclo[2.1.0]pentane (ABP).

4.4.2. Methods for the synthesis of 2,3-disubstituted pyrrolidines

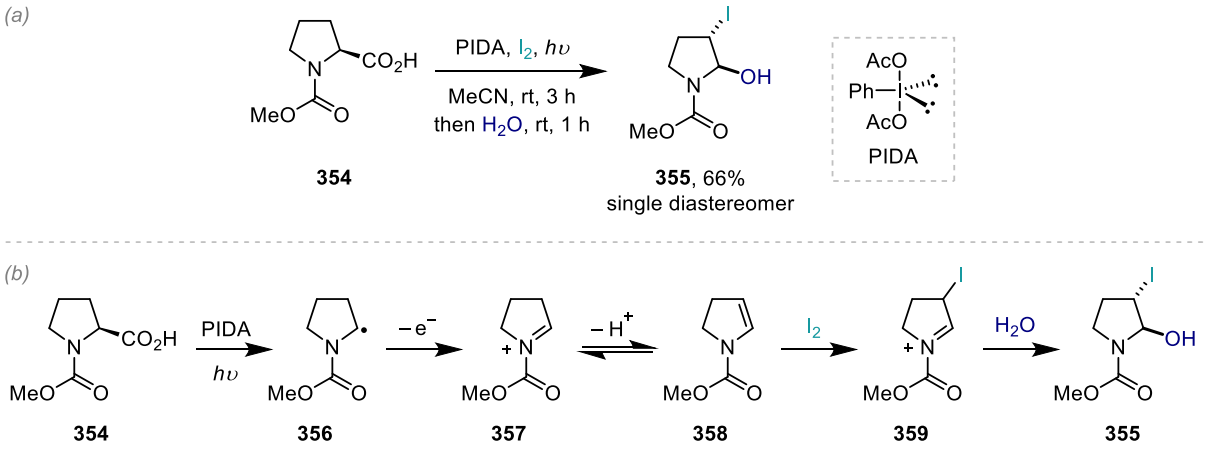
A plethora of methods for the synthesis of 2,3-disubstituted pyrrolidines have been developed. Most relevant to this work are methods which directly introduce functionality to an existing pyrrolidine ring; a selection of such methods are discussed herein.

The lithiation of 2-phenyl-1-pyrroline **350**, formed through the addition of phenylmagnesium bromide to **348** and cyclisation of the resultant amido Grignard (**349**), was demonstrated by Pal and co-workers (Scheme 136).[187] Organolithium **351** can then be treated with alkyl electrophiles and the resultant pyrroline (**352**) reduced to yield pyrrolidine **353** as a 4:1 mixture of diastereomers.



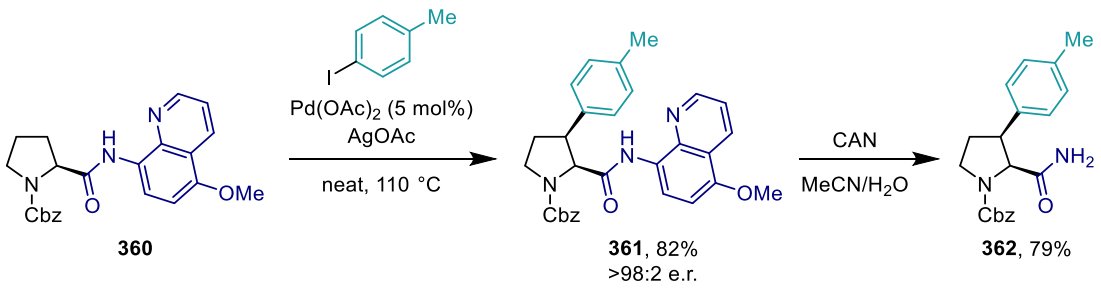
*Scheme 136. Lithiation, functionalisation and reduction of 2-phenyl-1-pyrroline **350**.*

The diastereoselective synthesis of 2-hydroxy-3-iodo pyrrolidines from L-proline derivatives has been achieved through a one-pot oxidative decarboxylation-iodination protocol (Scheme 137).[188] Decarboxylation of **354** yields α-amino radical **356**, which is oxidised to give *N*-acyliminium ion **357** (Scheme 137b). Formation of enecarbamate **358** is then proposed, with addition to iodine to give *N*-acyliminium ion **359** which, upon addition of water as a nucleophile from the opposite face to that of the iodine substituent, yields the product (**355**) as the trans diastereomer. Alkylation at the 2-position was also demonstrated, through the addition of *O*-protected enols.



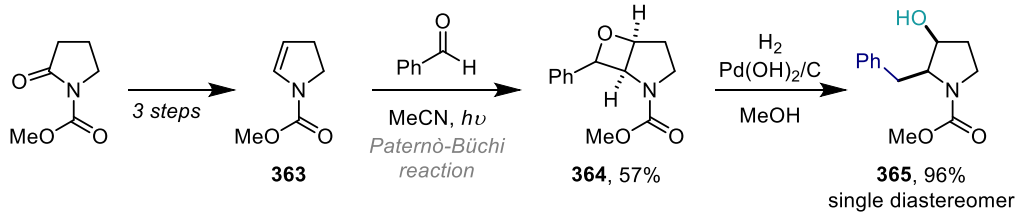
Scheme 137. Oxidative decarboxylation/iodination of L-proline derivatives.

Selective functionalisation of the 3-position in 2-substituted pyrrolidines was achieved by Bull and co-workers in 2014 (Scheme 138).[189] A Pd-catalysed C(sp^3)–H functionalisation of L-proline derivative **360** was developed, enabling the stereoselective installation of an aryl group at the 3-position of **361** by use of a methoxyaminoquinoline directing group. This directing group was easily cleaved to give primary amide **362**.



*Scheme 138. Pd-catalysed C−H functionalisation of **360** for the synthesis of 2-amido-3-aryl pyrrolidines. CAN = cerium(IV) ammonium nitrate.*

The synthesis of diastereomerically pure *cis*-2-benzyl-3-pyrrolidinols has been achieved through a Paternò-Büchi/hydrogenolysis sequence (Scheme 139).[190] The reaction of dihydropyrrole **363** with photoexcited benzaldehyde resulted in a [2+2] photocycloaddition, yielding oxetane **364**. The favoured *syn*-addition results in the thermodynamically stable cis products. Subsequent hydrogenolysis gave 2,3-disubstituted pyrrolidine **365** as a single diastereomer.

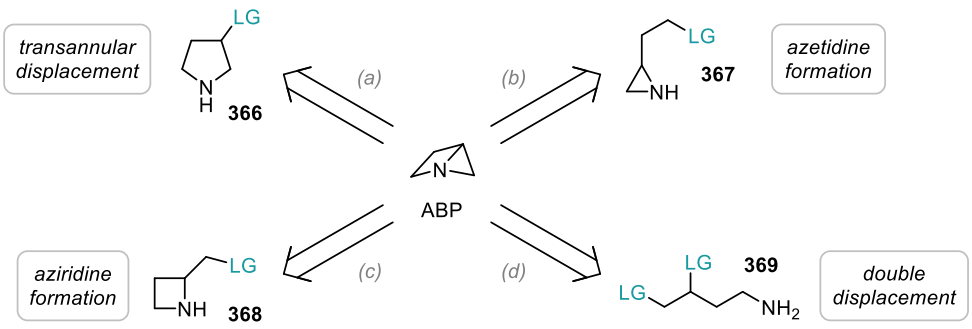


Scheme 139. Synthesis of 2-benzyl-3-pyrrolidinols by a Paternò-Büchi/hydrogenolysis sequence.

4.5. Results and discussion

4.5.1. Synthesis of 1-azabicyclo[2.1.0]pentane (ABP)

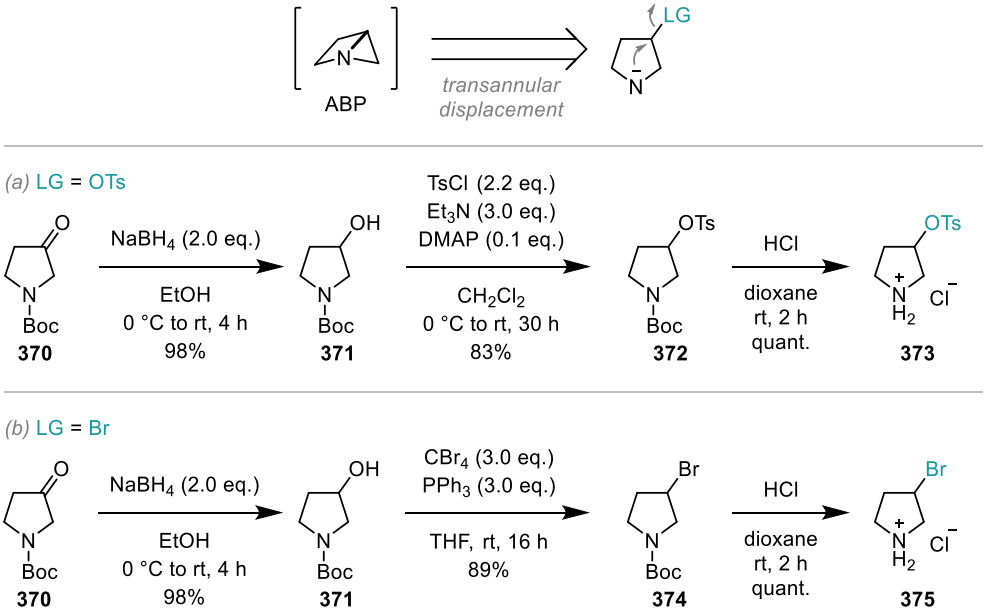
Four distinct strategies for the synthesis of parent 1-azabicyclo[2.1.0]pentane (ABP) were envisaged (Scheme 140). First, the central bridging bond could be constructed through the transannular cyclisation of a pyrrolidine ring bearing a leaving group in the 3-position (**366**) (Scheme 140a). Alternatively, with the aziridine ring pre-formed, an intramolecular displacement reaction of **367** could form the azetidine ring of the bicycle (Scheme 140b). Conversely, the aziridine ring could be formed through the cyclisation of azetidine **368** (Scheme 140c). Finally, by analogy to Nagao's synthesis of ABB,[135] a double displacement strategy could construct the two nitrogen-containing rings from extended chain **369** (Scheme 140d).



Scheme 140. Possible synthetic routes towards ABP.

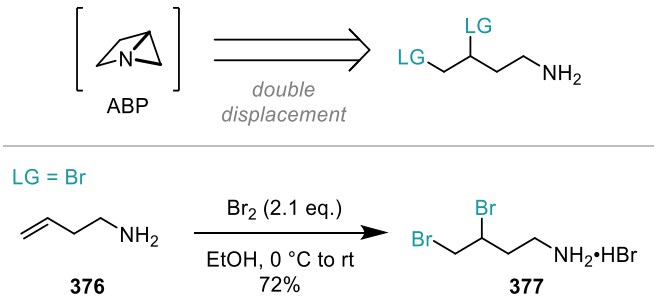
The first attempt sought to construct the bridging bond through a transannular nucleophilic substitution reaction in a 3-substituted pyrrolidine (Scheme 141). It was hypothesised that hydrochloride salts **373** and **375**, bearing tosylate and bromide leaving groups respectively, could be ideal bench-stable precursors to ABP and thus methods for their synthesis were sought.

N-Boc-3-pyrrolidinone (**370**) was reduced to alcohol **371** and then tosyl functionalised to give **372** (Scheme 141a). Subsequent Boc deprotection yielded hydrochloride salt **373**. To access 3-bromo pyrrolidine **374**, alcohol **371** was instead subjected to Appel-type conditions to install the 3-bromo functionality, followed by Boc deprotection to give **375** (Scheme 141b).



Scheme 141. Possible synthetic routes towards ABP: transannular displacement.

A double displacement strategy was also considered, forming the two C–N bonds in sequential cyclisation reactions (Scheme 142). The extension of Nagao's existing protocol to amine **376** enabled the efficient synthesis of dibromoamine hydrobromide salt **377** in good yield.[135]



Scheme 142. Possible synthetic routes towards ABP: double displacement.

4.5.2. Initial ring-opening reactivity and optimisation

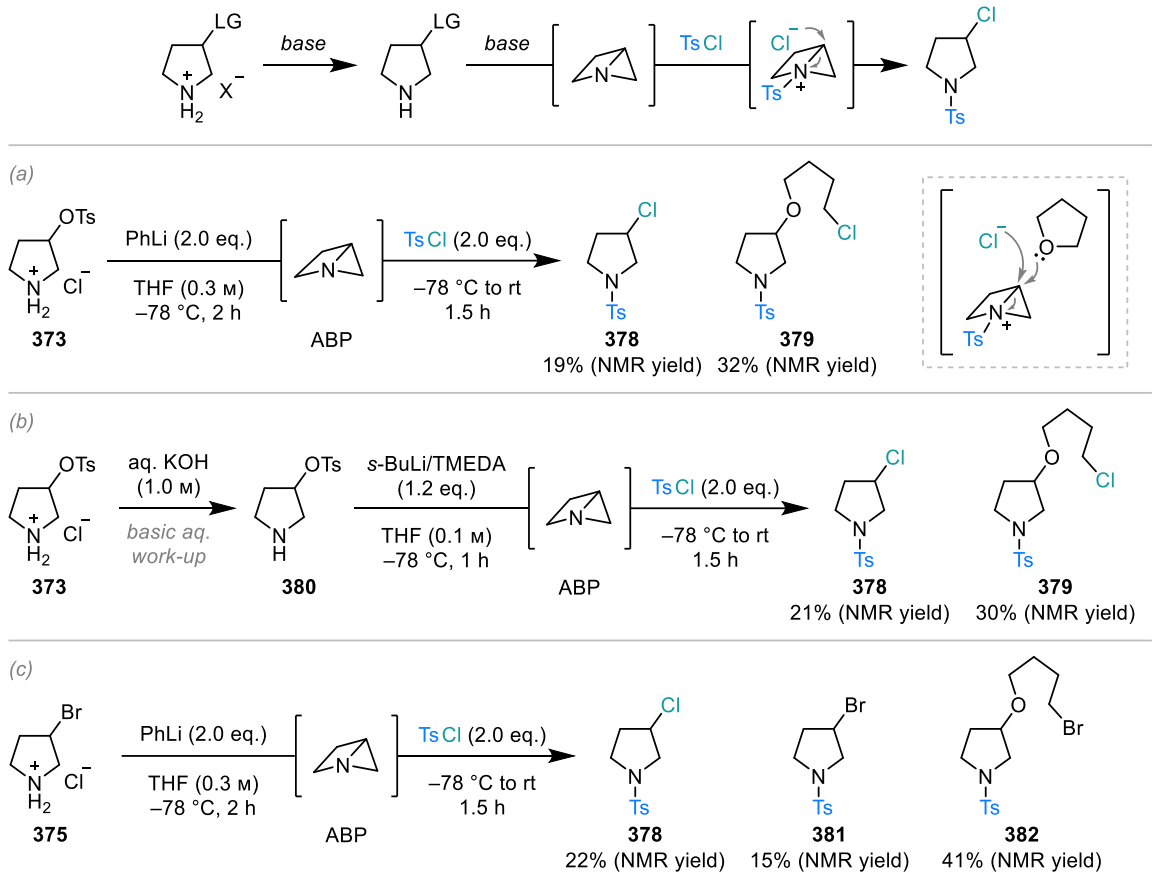
With three potential precursors to ABP in hand, a model system with which to probe their reactivity was sought. However, it was anticipated that it would be challenging to directly observe ABP formation, since ABP is likely volatile and highly reactive. Instead, observation of the ring-opening behaviour typical of strained aza-bicycles was sought (see Scheme 117 and Scheme 121).

Initial investigations focused on the pyrrolidine-based ABP precursors, first treating them with base to yield the free amine, followed by a further equivalent of base to induce ring-closure and formation of ABP (Scheme 143). Subsequent addition of tosyl chloride, according to Nagao's procedure for the ring-opening of ABB,[135] was predicted to generate ring-opened products that could confirm the generation of the targeted bicycle.

Pyrrolidine **373** was treated with 2 equivalents of phenyl lithium at –78 °C for 2 hours, followed by addition of tosyl chloride (Scheme 143a). Pleasingly, the formation of desired product **378** was observed in 19% NMR yield. Interestingly, pyrrolidine **379** was formed in 32% NMR yield. Its formation can be attributed to the addition of the THF reaction solvent to the 3-position of activated ABP, followed by the ring-opening of the THF ring by a chloride nucleophile.

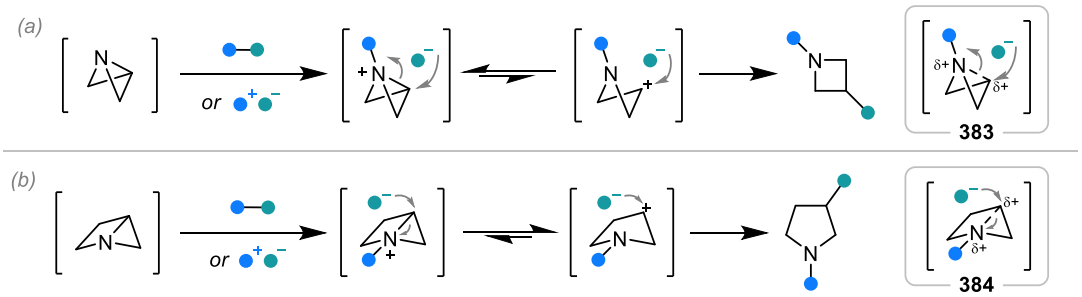
This reactivity is surprising, since the competitive addition of nucleophilic solvent has not been reported in analogous ring-opening reactions of ABB (or ABH). It is possible that in ABB and ABP there is a differing extent of central bond cleavage upon electrophilic activation of the nitrogen (**383** *vs* **384**) (Scheme 144). In ABP, a greater extent of carbocation-like character is likely present at the bridgehead carbon, and thus adventitious THF can add to this position.

Since both the chloride- and THF-opened products (**378** and **379**, respectively) likely derive from the intermediate bicycle, this early result was promising, since their formation provides evidence for the formation of the previously unknown unsubstituted ABP.



Scheme 143. Initial reactivity probes: formation and ring-opening of ABP.

Yields were determined by ^{1}H NMR (400 MHz, $CDCl_3$) spectroscopic analysis using CH_2Br_2 as the internal standard.



Scheme 144. Comparison between the ring-opening of ABB and ABP.

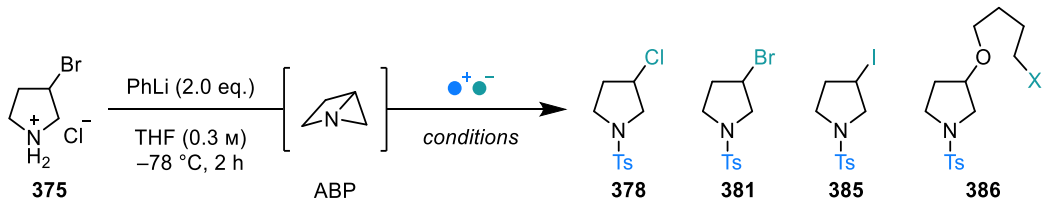
A similar result was obtained when hydrochloride salt **373** was subjected to a basic aqueous work-up (to give **380**) followed by addition of 1 equivalent of TMEDA-ligated *sec*-butyl lithium (Scheme 143b), according to conditions developed by Luisi and co-workers for the formation of ABB.[181]

Interestingly, three products were identified in the reaction of pyrrolidine **375** with phenyl lithium and tosyl chloride: desired 3-chloro pyrrolidine **378**, 3-bromo pyrrolidine **381** and THF adduct **382** (Scheme 143c). It is likely that all three products are derived from intermediate

ABP, and their ratio simply reflects the combined relative nucleophilicity and abundance of three competitive nucleophiles (chloride, bromide and THF) in the reaction mixture. The competitive re-addition of expelled leaving groups is known in the reactivity of 1-azoniabicyclo[2.1.0]pentanes (see Scheme 126). Regardless, the high combined mass balance of ABP-derived products (78%) encouraged further investigation of this system.

In order to generate a simpler product distribution, necessary for downstream investigations into the reactivity of ABP, a range of external nucleophile additives, added prior to addition of the electrophilic activator, was explored (Table 11).[141]

Table 11. Optimisation of reaction conditions for the ring-opening of ABP.



375 ABP **378** **381** **385** **386**

entry	and conditions	^{1}H NMR yield (%) 378	381	385	386
1	TsCl (2.0 eq.), –78 °C to rt, 1.5 h	22	15	-	41
2	NaI (10 eq.), –78 °C, 5 min; *then* TsCl (2.0 eq.), –78 °C to rt, 1.5 h	24	13	8	38
3	LiBr (10 eq.), –78 °C, 5 min; *then* TsCl (2.0 eq.), –78 °C to rt, 1.5 h	10	45	-	29
4	LiBr (10 eq.), 0 °C, 5 min; *then* TsCl (2.0 eq.), 0 °C to rt, 1 h	13	73	-	9
5	LiBr (10 eq.), 0 °C, 5 min; *then* Ts_2O (2.0 eq.), 0 °C to rt, 1 h	0	61	-	<4
6	LiBr (10 eq.), –20 °C, 5 min; *then* Ts_2O (2.0 eq.), –20 °C to rt, 1.5 h	0	68	-	<4

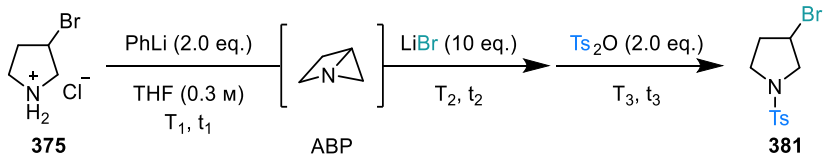
All reactions conducted on a 0.20 mmol scale. Yields were determined by ^{1}H NMR (400 MHz, $CDCl_3$) spectroscopic analysis using CH_2Br_2 as the internal standard.

Unfortunately, the addition of excess sodium iodide, according to Lopchuck's protocol,[141] led to a more complex product distribution (Entry 2). Whilst iodide is the superior nucleophile, its poor solubility in THF at –78 °C limited its availability for the ring-opening reaction. Adding excess lithium bromide improved the yield of **381** and reduced ring-opening by chloride, however significant competitive THF addition remained (Entry 3). As the solubility limit of lithium bromide in THF at –78 °C had been reached, its addition at 0 °C was investigated, since at this temperature complete dissolution of the excess reagent was observed (Entry 4). Pleasingly, this significantly reduced competitive THF addition and 3-bromo pyrrolidine **381** was observed in 73% NMR yield. Exchanging tosyl chloride for tosyl anhydride eliminated the formation of 3-chloro pyrrolidine **378** and, since the tosylate counterion is considered

non-nucleophilic, further simplified the product distribution (Entry 5). Addition of lithium bromide and tosyl anhydride at –20 °C further improved the yield of **381**. In this way, a set of ring-opening conditions which gave a single product in good yield had been developed.

Pleasingly, the protocol for the formation and ring-opening of ABP could be further streamlined (Table 12). When the deprotonation was performed over 15 minutes, followed by ring-opening, a comparable yield of **381** was observed and thus the formation of ABP was deemed to be completed after 15 minutes (Entry 2). The ring-opening was also identified to be complete within 15 minutes, since **381** was formed in similar amounts to when this step was conducted over 90 minutes (Entry 4). A final optimisation simplified the protocol further, with lithium bromide addition taking place at –78 °C and then the reaction warmed to ambient temperature to enable its full dissolution (Entry 6). The final addition of tosyl anhydride at room temperature did not impact the yield of the reaction. In this way, the initial protocol, which was performed over 3.5 hours and required 3 different temperatures (Entry 1), now only required 15 minutes at –78 °C and 15 minutes at room temperature (Entry 6).

Table 12. Streamlining of reaction conditions for the formation and ring-opening of ABP.

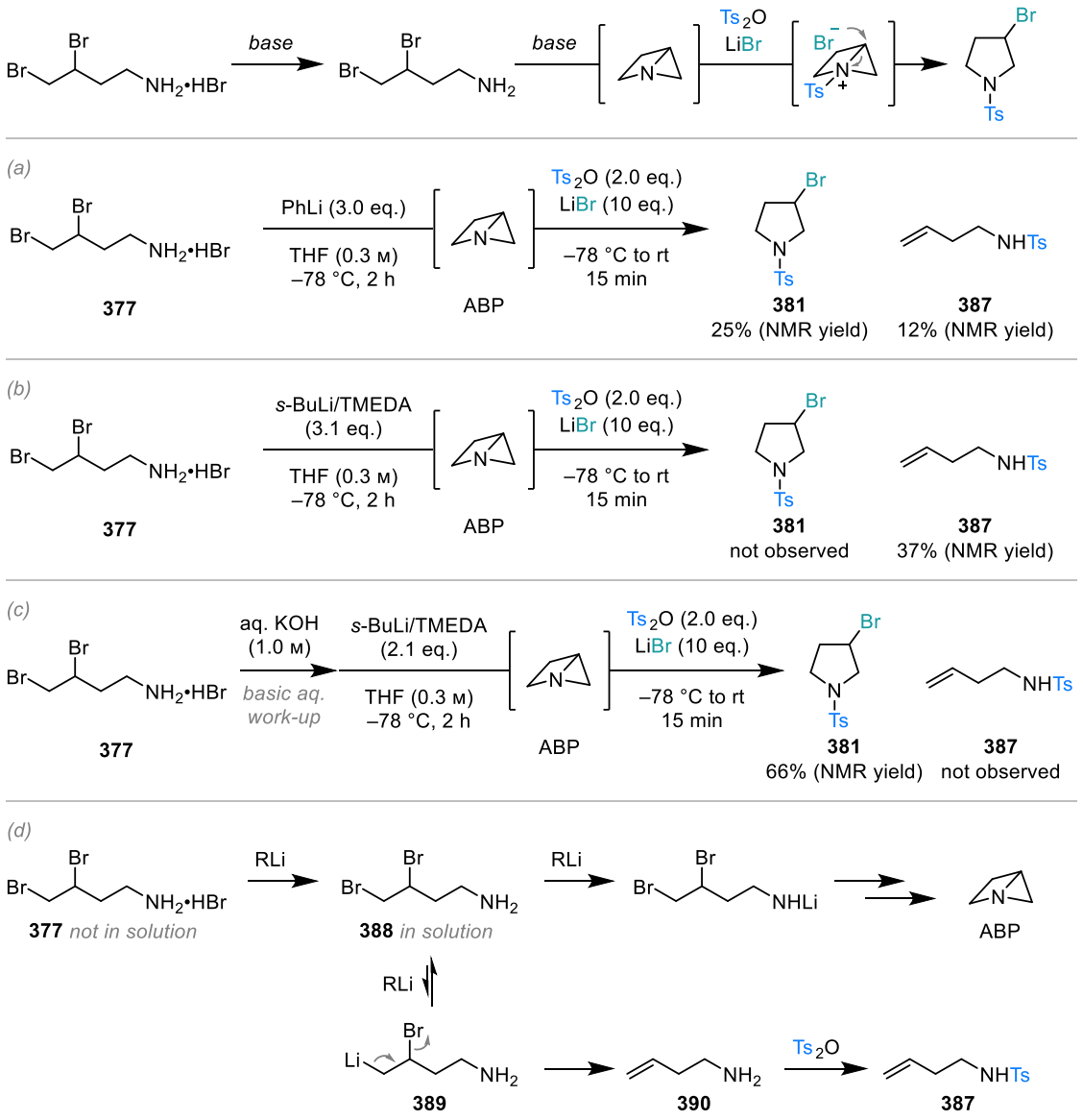


entry	T_1, t_1	T_2, t_2	T_3, t_3	^{1}H NMR yield (%)
1	–78 °C, 2 h	–20 °C, 5 min	–20 °C to rt, 90 min	68
2	–78 °C, 15 min	–20 °C, 5 min	–20 °C to rt, 90 min	74
3	–78 °C, 5 min	–20 °C, 5 min	–20 °C to rt, 90 min	59
4	–78 °C, 15 min	–20 °C, 5 min	–20 °C to rt, 15 min	70
5	–78 °C, 15 min	–20 °C, 5 min	–20 °C to rt, 30 min	66
6	–78 °C, 15 min	–78 °C to rt, 5 min	rt, 15 min	73

All reactions conducted on a 0.20 mmol scale. Yields were determined by ^{1}H NMR (400 MHz, $CDCl_3$) spectroscopic analysis using CH_2Br_2 as the internal standard.

With these optimised ABP ring-opening conditions in hand, dibromoamine ABP precursor **377** was investigated in order to compare its reactivity to the pyrrolidine-based precursors (Scheme 145). Treatment of **377** with 3 equivalents of phenyl lithium followed by lithium bromide and tosyl anhydride gave a disappointing 25% NMR yield of **381** (Scheme 145a). Interestingly the formation of alkene **387** was also observed. Changing the base to TMEDA-ligated *sec*-butyl

lithium exclusively gave alkene **387** (Scheme 145b). However, if the free base was liberated prior to being subjected to the reaction conditions, **381** could be observed in a 66% NMR yield (Scheme 145c).



*Scheme 145. Initial reactivity probes: using dibromoamine **377** to form ABP. (d) Proposed formation of side product **387**.*

Yields were determined by ^1H NMR (400 MHz, $CDCl_3$) spectroscopic analysis using CH_2Br_2 as the internal standard.

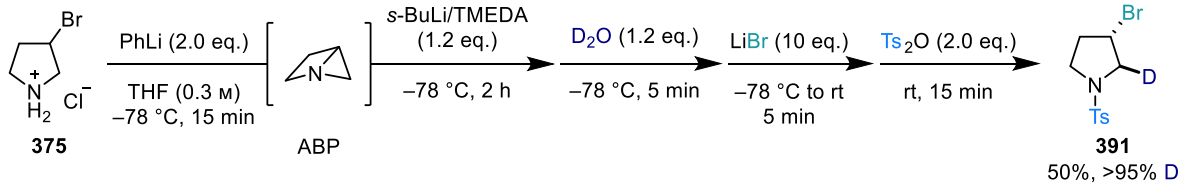
The formation of alkene **387** is proposed to occur from lithium-bromine exchange of **388** followed by elimination of **389** to give homoallyl amine **390**, which is then tosyl functionalised (Scheme 145d). Perhaps this occurs when using the hydrobromide salt starting material due to a slow initial heterogeneous deprotonation, leaving a high concentration of organolithium in solution compared to free amine **388** and thus favouring lithium-bromine exchange.

Since hydrobromide salt **377** had proven a poor precursor to ABP and its free base was sensitive to light and thus difficult to handle, the double displacement strategy for the formation of ABP was discarded.

4.5.3. Lithiation of 1-azabicyclo[2.1.0]pentane (ABP)

4.5.3.1. Lithiation-deuteration

Critical to the work in the Aggarwal group on the strain-release-driven reactivity of ABB is its selective bridgehead lithiation by TMEDA-ligated *sec*-butyl lithium, enabling the synthesis of 3-functionalised ABB compounds (see Section 4.3.3).[179] Investigations into the reactivity of ABP under the same conditions were thus conducted (Scheme 146). In order to probe the extent and location of lithiation, an electrophilic deuterium source, D_2O, was employed, followed by ABP ring-opening. Surprisingly, deuterium incorporation was observed in the 2-position of **391**, which was obtained in 50% yield with >95% deuterium incorporation.

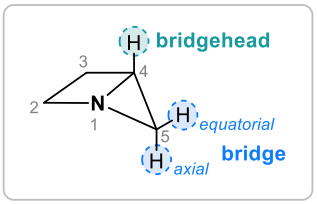


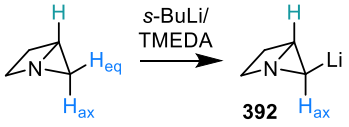
Scheme 146. Lithiation and deuteration of ABP.

Yield is of isolated product. Deuterium incorporation (% D) was determined by ^{1}H NMR (400 MHz, $CDCl_3$) spectroscopic analysis.

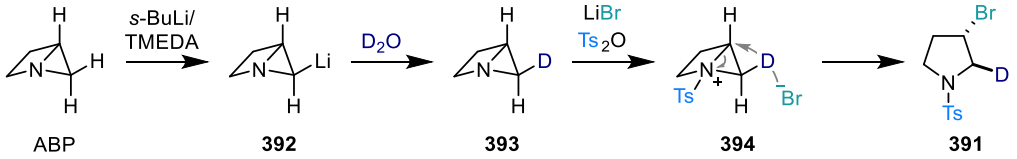
In this way, lithiation of ABP had occurred at the bridge position (Scheme 147). In addition, the product was formed exclusively as a single diastereomer, indicating that only one of the two bridge protons was selectively removed; the treatment of ABP with TMEDA-ligated *sec*-butyl lithium yields a disatereomerically pure organolithium (ABP-Li, **392**).

This lithiation was later confirmed to occur at the *pseudo*-equatorial position through X-ray diffraction analysis of a related product (see Scheme 151). Deuterium incorporation therefore occurred at this site (**393**). Bromide addition to activated ABP **394** occurs from the opposite face to the deuterium atom, owing to the orbital overlap requirements for the S_N2 reaction, giving ring-opened **391** as a single diastereomer (Scheme 148).





Scheme 147. Bridge lithiation of ABP.



*Scheme 148. Proposed mechanism for the formation of **391** as a single diastereomer.*

The extent and location of deuterium incorporation was determined by quantitative ^{1}H NMR spectroscopic analysis. Deuterium (^{2}D) has a spin of 1, compared to ^{1}H which has a spin of ½, and thus is quadrupolar. Deuterons will not be observed in a ^{1}H NMR spectrum and ^{1}H–^{2}D ^{3}J coupling constants are typically 1–2 Hz. By contrast, ^{13}C–^{2}D ^{2}J coupling constants are typically 20–25 Hz and this coupling interaction forms a 1:1:1 triplet for each coupled deuteron.

The evidence for the diastereoselective bridge lithiation is as follows: (a) a complete (>95%) depletion of the ^{1}H NMR signal for H_B (Figure 35a); (b) a change in the ^{1}H NMR peak shape of H_C with peak broadening, but no change in its integral (Figure 35a); (c) a 1:1:1 triplet is observed as the ^{13}C NMR signal for C_B (Figure 35b).

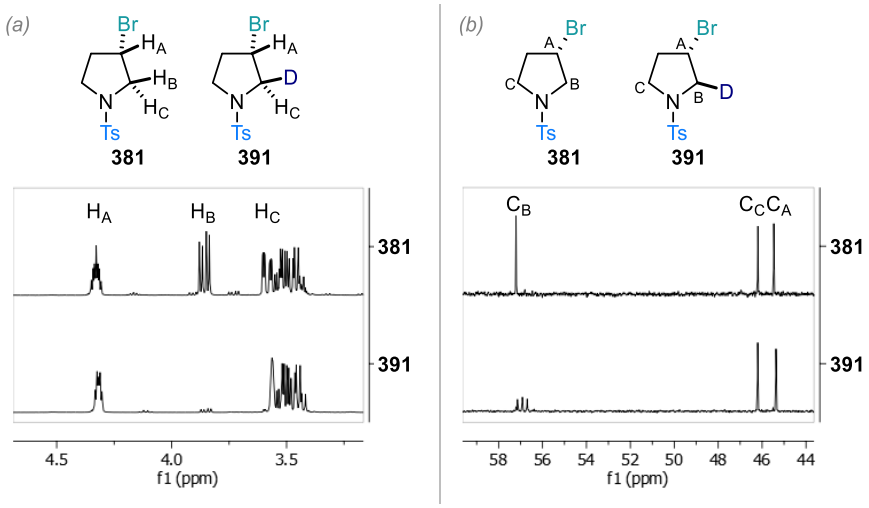


*Figure 35. Evidence of deuterium incorporation: comparison between the (a) ^{1}H NMR (400 MHz, $CDCl_3$) spectrum and (b) ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of **381** and **391**.*

The selectivity of the lithiation is surprising; in ABB there is complete selectivity for deprotonation at the bridgehead C3, whilst in ABP there is complete selectivity for deprotonation at the bridge C5 at the *pseudo*-equatorial position (Figure 36). The origin of this reversal in selectivity is unclear.

In the lithiation of aziridines, the pre-complexation of the organolithium with the nitrogen lone pair has been suggested as a prerequisite for the deprotonation (see Section 4.3.2). If analogy is drawn to this system, an organolithium-ABP complex could exist where lithiation is kinetically directed to the bridge site. This could be as a consequence of its closer proximity to the organolithium or its lower steric encumbrance when compared to the bridgehead site.

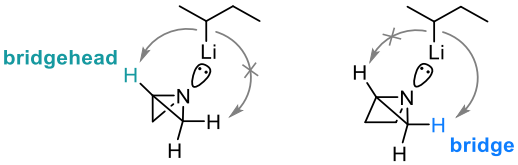
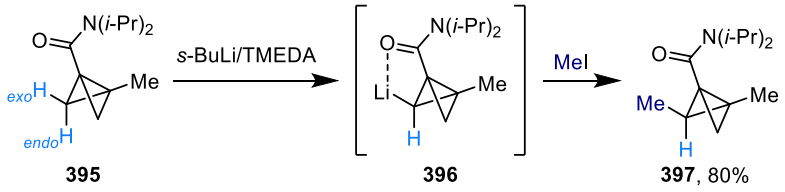


Figure 36. Contrasting selectivity in deprotonation of ABB and ABP.

The *pseudo*-equatorial bridge site is likely more sterically accessible than the corresponding axial site, resulting in a diastereoselective lithiation. This observation is in accordance with recent work from Anderson and co-workers on the bridge lithiation of bicyclo[1.1.0]butane **395** (Scheme 149).[191] The bridgehead amide group directs lithiation exclusively to the exo position (**396**), yielding bridge-functionalised **397**.

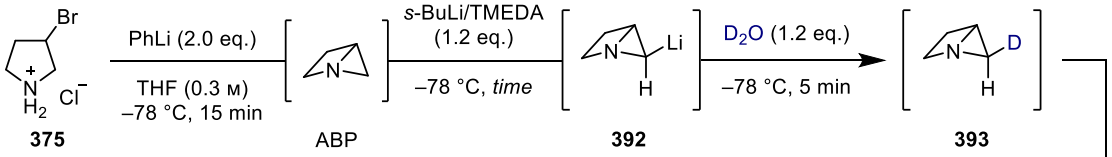


*Scheme 149. Anderson's bridge lithiation of bicyclo[1.1.0]butane **395**.*

Since the bridgehead is anticipated to be the thermodynamic site of deprotonation, owing to the bonding constraints imposed on the carbon sat at the junction between the aziridine and azetidine, clearly there are a multitude of complexation and steric effects at play here. A complete picture of their relative contributions to this unusual selectivity is yet to be formed.

A 2-hour lithiation time was confirmed to be necessary for full deuterium incorporation, however the yield of **391** decreased with increased lithiation time (Table 13; Entries 1–5). Omitting the TMEDA ligand reduced the extent of deuteration (Entry 6), likely as a result of poorer de-aggregation of the organolithium.

Table 13. Optimisation of reaction conditions for the lithiation of ABP.

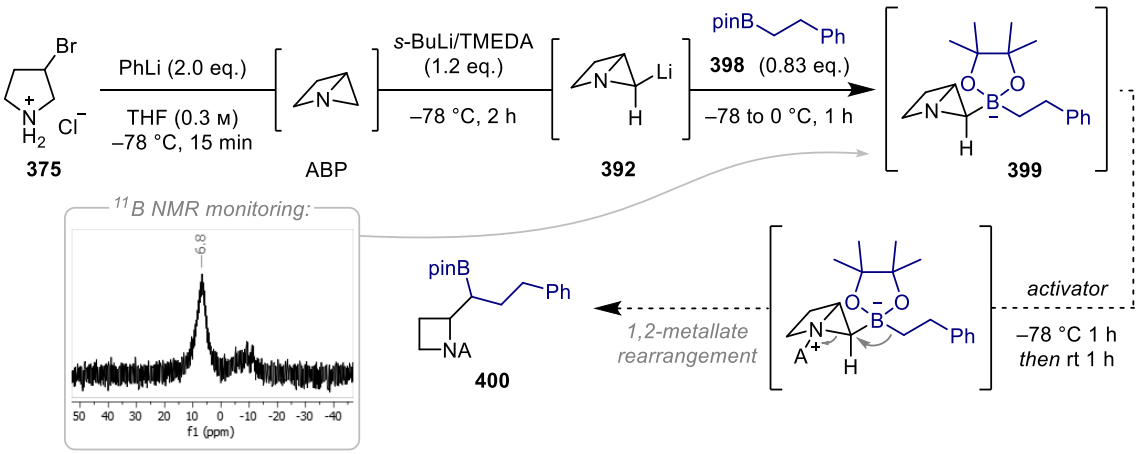


entry	time (min)	^{1}H NMR yield (%)	% D
1	15	66	50
2	60	59	76
3	90	57	89
4	120	50	>95
5	180	50	>95
6[a]	120	55	85

All reactions conducted on a 0.20 mmol scale. Yields were determined by ^{1}H NMR (400 MHz, $CDCl_3$) spectroscopic analysis using CH_2Br_2 as the internal standard. Deuterium incorporation (% D) was also determined by ^{1}H NMR spectroscopic analysis. [a] Without TMEDA.

4.5.3.2. Lithiation–borylation

Other electrophiles to trap novel organolithium species **392** were then investigated. Most appealing was trapping with a boronic ester which, by analogy to previous work in the Aggarwal group,[179] would yield boronate complex **399**, primed to undergo a 1,2-metallate rearrangement with ring-opening upon electrophilic activation of the nitrogen to give **400** (Scheme 150).



Scheme 150. Lithiation–borylation of ABP.

The addition of boronic ester **398** to an excess of ABP-Li (**392**) was confirmed to yield boronate complex **399** through ^{11}B NMR monitoring (δ_B = 6.8 ppm). A range of nitrogen activators for

the 1,2-metallate rearrangement were then trialled with concurrent ^{11}B NMR reaction monitoring to identify the fate of the boronate complex (Table 14). First, Brønsted acid activators were investigated. The addition of acetic acid, followed by Boc-protection of the corresponding azetidine, only returned boronic ester starting material **398** (Entry 1). The use of a stronger acid, tetrafluoroboric acid, gave a complex crude reaction mixture, with no identifiable products (Entry 2). Monitoring by ^{11}B NMR spectroscopic analysis indicated that some boronate complex remained prior to work-up, alongside boronic ester (BO_2R) and borinic ester (BOR_2). Activation by nitrogen acylation was also attempted. However, the addition of 1 equivalent of trifluoroacetic anhydride (TFAA) only returned **398** (Entry 3) and the addition of excess 2,2,2-trichloroethoxycarbonyl chloride (TrocCl) resulted in a complex crude reaction mixture (Entry 4). The addition of weakly acidic alcohol activators only returned **398** (Entries 5–7) and without any activation there was no transformation of boronate complex **399** (Entry 8). Unfortunately, under no activation mode was a proof of principle established for the 1,2-metallate rearrangement.

*Table 14. Activation of boronate complex **399** for the ring-opening 1,2-metallate rearrangement.*

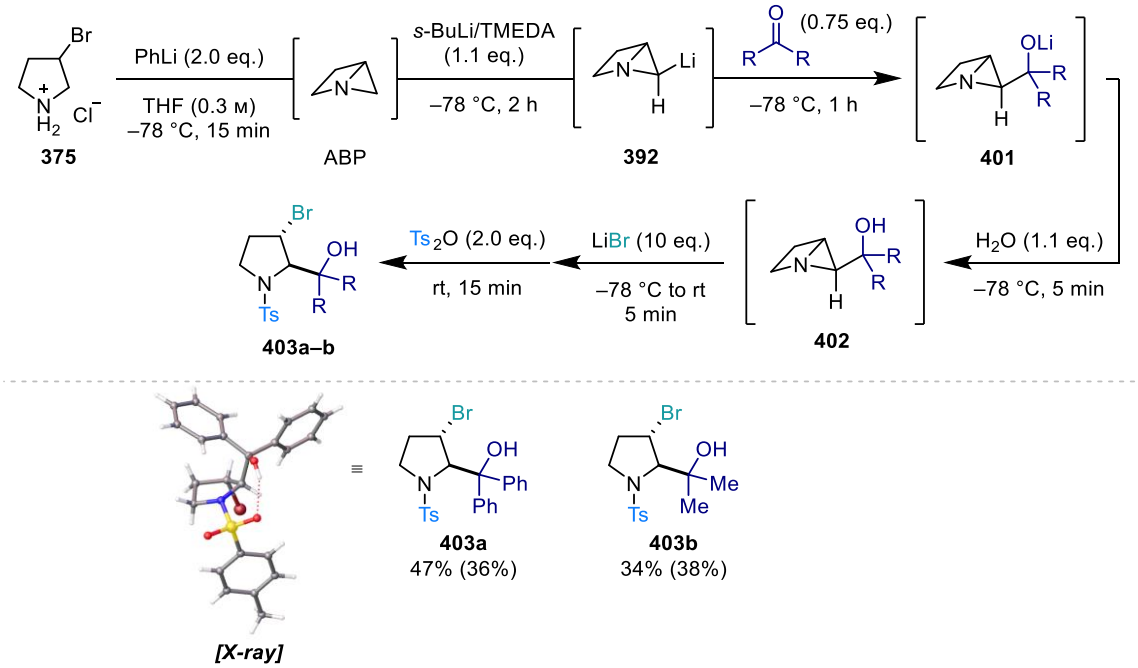
entry	activator (X eq.)	^{11}B NMR prior to work up	outcome
1	AcOH (2) (*then* Boc_2O/Et_3N)	boronic ester only	65% rsm
2	HBF_4 (2) (*then* Boc_2O/Et_3N)	boronate, boronic ester and borinic ester	*complex mixture*
3	TFAA (1)	1:1 boronate/boronic ester	40% rsm
4	TrocCl (2)	1:1:2 boronate/boronic ester/borinic ester	*complex mixture*
5	*t*-BuOH (2)	2:3 boronate/boronic ester	40% rsm
6	TFE (2)	1:1 boronate/boronic ester	66% rsm
7	phenol (2)	1:2 boronate/boronic ester	49% rsm
8	*none*	boronate only	-

*All reactions conducted on a 0.20 mmol scale. Yields were determined by ^{1}H NMR (400 MHz, $CDCl_3$) spectroscopic analysis using CH_2Br_2 as the internal standard. Reaction monitoring carried out through crude ^{11}B NMR (128 MHz) spectroscopic analysis. rsm = returned starting material **398**.*

4.5.3.3. Lithiation-trapping with ketones

The trapping of ABP-Li (**392**) with ketones was then examined (Scheme 151). The ketone was added to an excess of ABP-Li at –78 °C to generate lithium alkoxide **401**, which was then protonated upon addition of H_2O to give ABP carbinol **402**. ABP carbinol **402** was found to be unstable to aqueous work-up, however ring-opened product **403** could be isolated. Pleasingly, benzophenone-derived alcohol **403a** could be observed in 47% NMR yield as a single diastereomer. X-ray diffraction analysis of an analytically pure sample of **403a** confirmed the

trans relationship of the carbinol and bromide substituents on the pyrrolidine core. Moreover, acetone-derived alcohol **403b** could also be isolated in 38% yield, again as a single diastereomer. These yields were moderate but corresponded to a protocol involving numerous synthetic steps, assembling multiple functional groups with perfect selectivity.

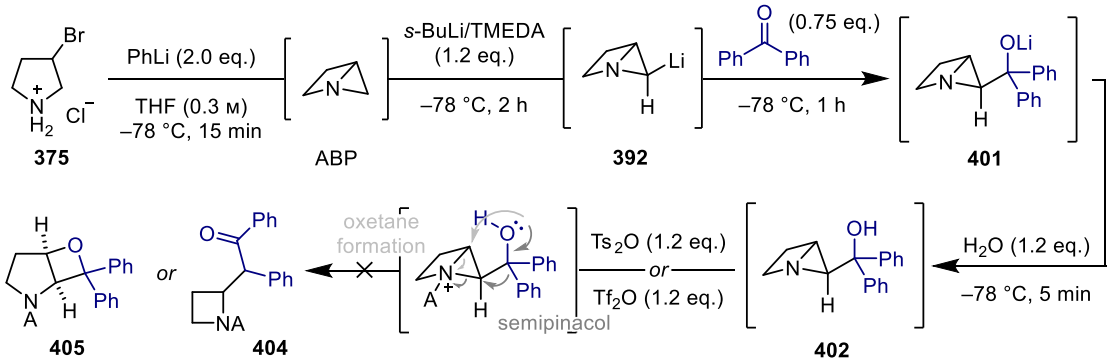


Scheme 151. Trapping of ABP-Li with ketones.

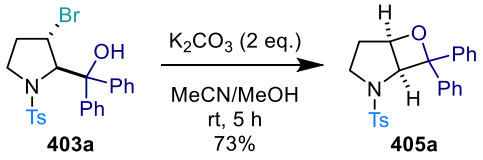
Yields were determined by ^{1}H NMR (400 MHz, $CDCl_3$) spectroscopic analysis using CH_2Br_2 as the internal standard. Isolated yield in parentheses.

Taking inspiration from previous work in the Aggarwal group,[180] it was proposed that direct activation of ABP carbinol **402** could either result in intramolecular cyclisation to oxetane **405**, or a semipinacol rearrangement with cleavage of the C–N aziridine bond to yield ketone **404** (Scheme 152). Unfortunately, under both tosyl anhydride and triflic anhydride activation conditions, no **404** or **405** were observed and a complex crude reaction mixture was obtained.

However, if pyrrolidine **403a** was treated with potassium carbonate,[180] ring-closure occurred with displacement of bromide to yield oxetane **405a** as a single *cis*-fused diastereomer in 73% isolated yield (Scheme 153).



*Scheme 152. Attempted in situ ring-opening reactivity of ABP carbinol **402**.*



*Scheme 153. Base-promoted ring closure of **403a** to oxetane **405a**.*

4.5.4. Alternative syntheses of 1-azabicyclo[2.1.0]pentane (ABP)

During initial investigations into the formation and reactivity of ABP, it became apparent that starting materials **373** and **375** were highly hygroscopic. It was confirmed through quantitative ^{1}H NMR spectroscopic analysis that a significant amount of water (~25 mol%) was being weighed into the reaction mixture alongside **373**/**375**. It is critical for the development of reproducible and reliable transformations that the precursor to ABP is bench-stable and water-free.

A library of related 3-substituted pyrrolidines was synthesised, altering the counterion in the amine salt, in order to compare their hygroscopicity (Figure 37). Unfortunately, all pyrrolidine salts proved hygroscopic regardless of the counterion. However, **406**, **407** and **408** could be stored as stock solutions in deuterated solvents, kept over 3 Å molecular sieves to enable water removal. Before use, the concentration of the stock solution was determined by adding a known amount of CH_2Br_2 (as the internal standard) to an aliquot of the stock solution for quantitative ^{1}H NMR spectroscopic analysis. With this strategy, pyrrolidine salts **406**, **407** and **408** could be investigated as ABP precursors without interference from erroneous water. Unfortunately, **373** and **375** were poorly soluble in a range of deuterated solvents and thus could not be reliably stored as stock solutions.

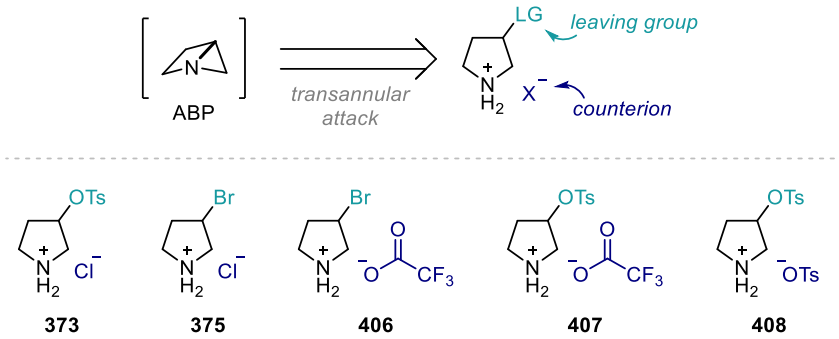
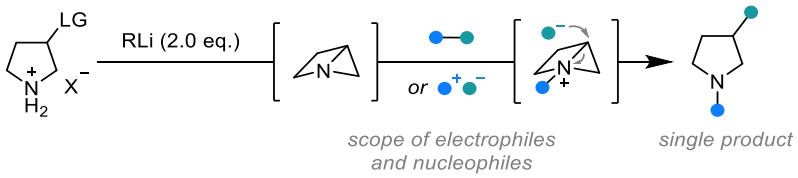


Figure 37. Changes to the ABP precursor: varying the leaving group and counterion.

4.5.5. Challenges in establishing a general ring-opening protocol

Having identified three new potential ABP precursors, **406**, **407** and **408** were investigated using the established ring-opening protocol with excess lithium bromide and tosyl anhydride. A more general ring-opening protocol was also sought (Scheme 154), exploring a range of nucleophiles and electrophiles which were not required to be in significant excess in order to yield a single ring-opened product. The main challenge here was anticipated to be suppressing both the formation of THF adducts and the re-addition of the leaving group. 2,2,2-Trichloroethoxycarbonyl chloride (TrocCl) was chosen as a suitable electrophile-nucleophile system; first the ABP nitrogen is acylated and then the liberated chloride anion can act as a nucleophile for the ring-opening of ABP. Despite there being an excess of acylating agent, the reaction mechanism means there will only be 1 equivalent of available chloride anion.

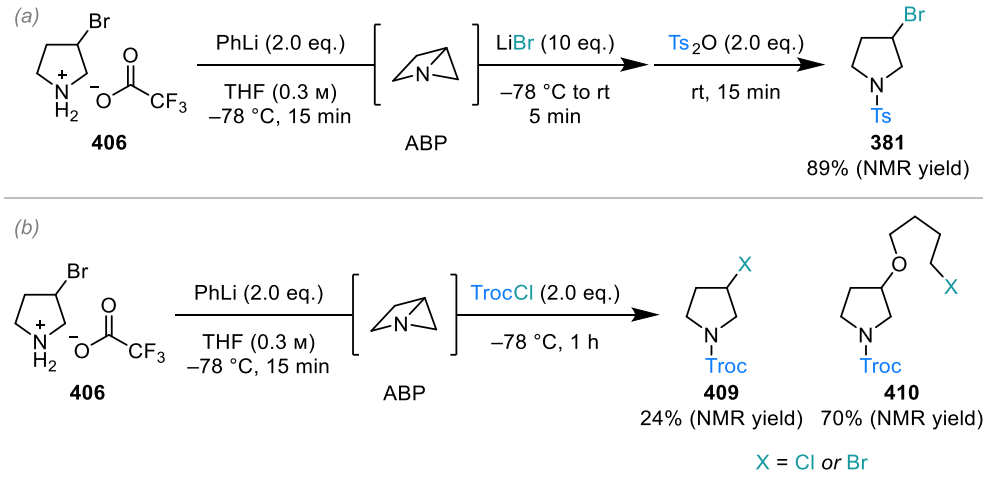


Scheme 154. General protocol for the ring-opening of ABP.

First, pyrrolidine **406**, stored as a stock solution in THF-d_8, was employed (Scheme 155). The THF-d_8 solvent was removed *in vacuo* and replaced by anhydrous THF prior to the reaction in order to enable identification of any THF adducts. Pleasingly, under the optimised LiBr/Ts_2O conditions, 3-bromo pyrrolidine **381** was observed in 89% NMR yield (Scheme 155a).

However, when adding TrocCl, a mixture of 4 products was observed, with **409** originating from the ring-opening of ABP by available halide anions, and **410** from ring-opening by THF

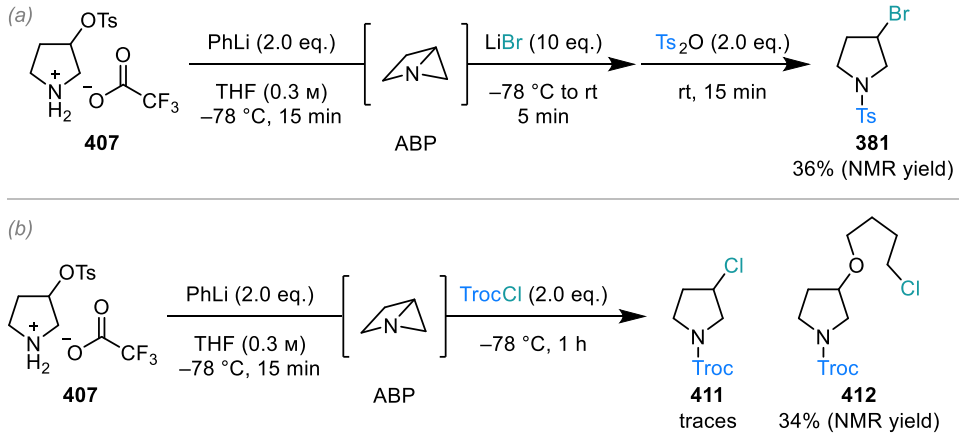
(Scheme 155b). The nucleophilic bromide leaving group is competing with the chloride nucleophile in both ABP ring-opening and THF ring-opening.



*Scheme 155. Pyrrolidine **406** as a precursor to ABP: ring-opening with (a) LiBr/Ts_2O and (b) TrocCl.*

Yields were determined by ^1H NMR (400 MHz, $CDCl_3$) spectroscopic analysis using CH_2Br_2 as the internal standard.

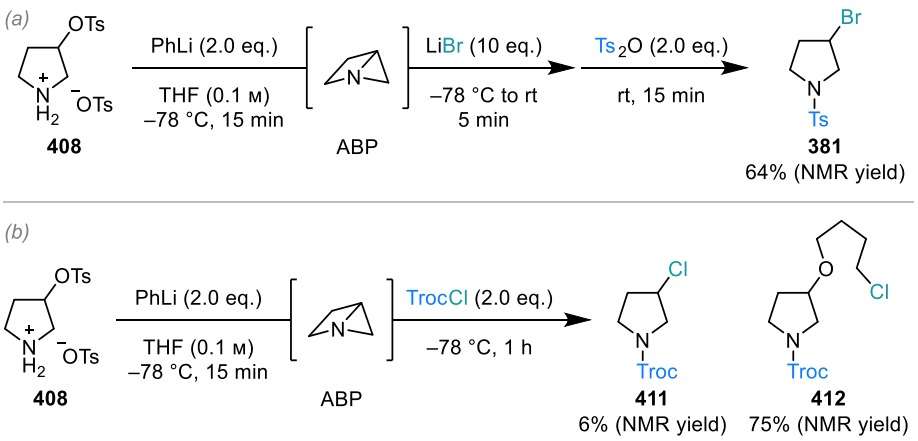
In order to simplify the product distribution, starting materials with both a non-nucleophilic leaving group and a non-nucleophilic counterion were investigated. Pyrrolidine **407**, stored as a stock solution in THF-d_8, performed poorly under both sets of reaction conditions (Scheme 156). It is not understood why **407** was a poor precursor to ABP.



*Scheme 156. Pyrrolidine **407** as a precursor to ABP: ring-opening with (a) LiBr/Ts_2O and (b) TrocCl.*

Yields were determined by ^1H NMR (400 MHz, $CDCl_3$) spectroscopic analysis using CH_2Br_2 as the internal standard.

Pleasingly, pyrrolidine **408**, stored as a stock solution in CD_2Cl_2, proved more successful (Scheme 157). 3-Bromo pyrrolidine **381** was formed in 64% NMR yield (Scheme 157a). Upon addition of TrocCl, 3-chloro pyrrolidine **411** was only observed in 6% NMR yield (Scheme 157b). Here, THF ring-opening dominated the reactivity, with **412** formed in 75% NMR yield. The overall high mass-balance of this transformation was encouraging.

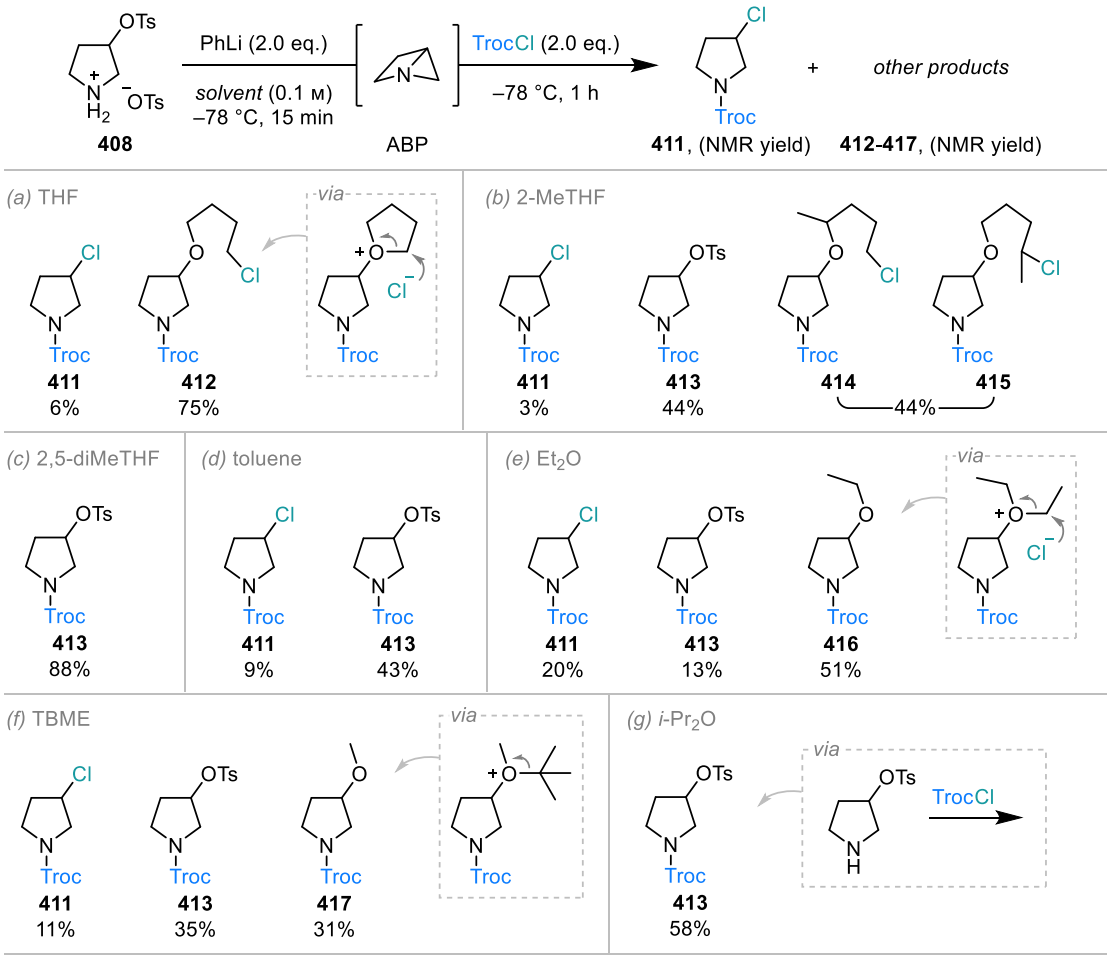


*Scheme 157. Pyrrolidine **408** as a precursor to ABP: ring-opening with (a) LiBr/Ts_2O and (b) TrocCl.*

Yields were determined by ^1H NMR (400 MHz, $CDCl_3$) spectroscopic analysis using CH_2Br_2 as the internal standard.

It was hypothesised that changing the reaction solvent from THF to a less nucleophilic alternative may limit solvent addition to ABP, and thus result in the formation of desired **411** only. A solvent screen was conducted, suspending starting material **408** in the required solvent, and then adding phenyl lithium followed by TrocCl (Scheme 158).

Increasing steric bulk, by moving from THF to 2-methyltetrahydrofuran (2-MeTHF), did not improve the product distribution, with traces of **411** observed (Scheme 158b). A 44% NMR yield of **414**/**415**, as a complex mixture of regioisomers and diastereomers, was observed, indicating that solvent addition had not been suppressed. 3-Tosyl pyrrolidine **413** was also observed in 44% NMR yield. It is believed that this species is formed through incomplete nitrogen deprotonation during ABP formation, likely due to the poor solubility of **408** in the reaction solvent. A more sterically hindered 2,5-dimethyltetrahydrofuran (2,5-diMeTHF) solvent did not enable any ABP formation, with 88% of **413** observed, again likely as a result of poor solubility (Scheme 158c). Performing the reaction in toluene gave a poor yield of **411**, alongside significant **413** (Scheme 158d). Acyclic ethereal solvents were then trialled. Employing diethyl ether as the reaction solvent gave a promising 20% NMR yield of 3-chloro pyrrolidine **411** (Scheme 158e). Surprisingly, significant formation 3-ethoxy pyrrolidine **416** was also observed. It is thought that this product arises from the addition of diethyl ether to the activated ABP, followed by displacement of one of the ethyl groups. More hindered ethereal solvents fared no better. Using a *tert*-butyl methyl ether (TBME) reaction solvent enabled some formation of **411** but limited solubility resulted in significant **413** formation (Scheme 158f). In addition, 3-methoxy pyrrolidine **417** was observed, presumably arising from *tert*-butyl loss following TBME addition to ABP. Starting material **408** was poorly soluble in diisopropyl ether, likely why **413** was the only observed product (Scheme 158g).



Scheme 158. Solvent screen for the ring-opening of ABP with TrocCl.

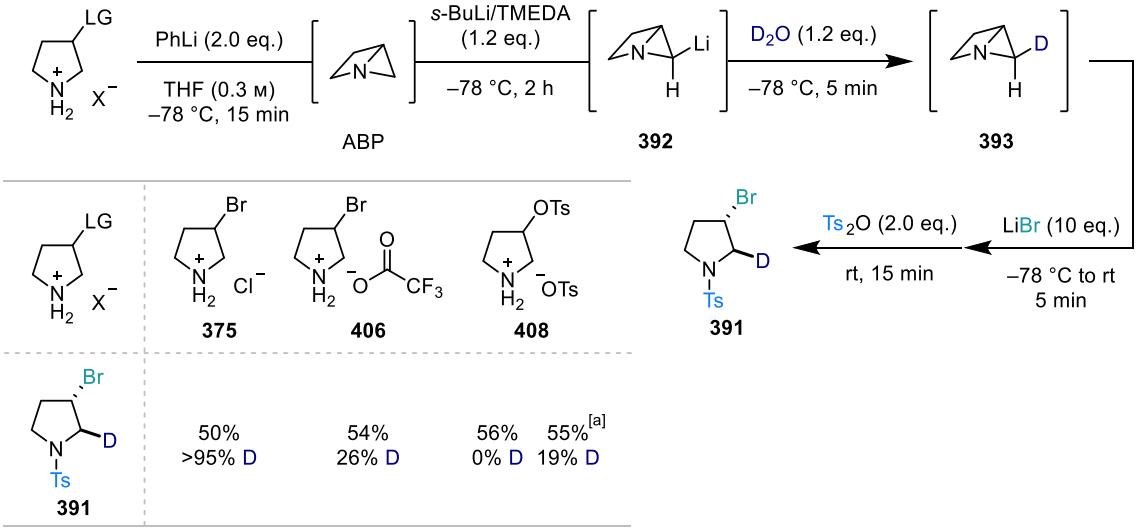
All reactions conducted on a 0.10 mmol scale. Yields were determined by ^{1}H NMR (400 MHz, $CDCl_3$) spectroscopic analysis using CH_2Br_2 as the internal standard.

Unfortunately, this solvent screen demonstrated the difficulties associated with establishing a general ring-opening protocol of ABP. There are significant challenges in balancing starting material solubility and solvent nucleophilicity. Unless the nucleophile is in available in significant excess, solvent ring-opening dominates. Thus, the range of possible nucleophiles is limited to external nucleophiles which are highly soluble in large excess in the reaction solvent.

4.5.6. Towards the diastereoselective synthesis of 2-functionalised 3-bromo pyrrolidines

Since a general ring-opening protocol had been challenging to establish, a general methodology for the synthesis of 2-functionalised 3-bromo pyrrolidines was sought, varying the electrophile with which ABP-Li (**392**) was trapped and then ring-opening the resultant 2-functionalised ABP with a bromide nucleophile.

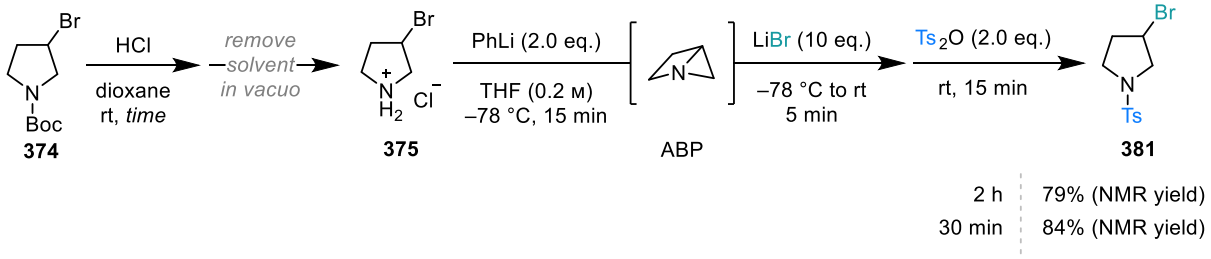
Initially, the new ABP precursors (**406**, **408**) were trialled in the model lithiation-deuteration reaction and compared to hydrochloride salt **375** (Scheme 159). Disappointingly, when using starting material **406** only 26% deuterium incorporation was observed. Moreover, when using **408**, deuterium incorporation could only be observed with a significant excess of TMEDA-ligated *sec*-butyl lithium. Since the only differences in the successful and unsuccessful systems were the identities of the leaving groups and counterions, it was hypothesised that the presence of trifluoroacetate and tosylate anions was problematic in the lithiation step. Perhaps unproductive lithium aggregates form between the *sec*-butyl lithium and these Lewis basic anions.[192]



Scheme 159. Investigating a range of ABP precursors in ABP-Li formation and deuteration.

All reactions conducted on a 0.10 mmol scale. Yields were determined by ^{1}H NMR (400 MHz, $CDCl_3$) spectroscopic analysis using CH_2Br_2 as the internal standard. Deuterium incorporation (% D) was also determined by ^{1}H NMR spectroscopic analysis. [a] With s-BuLi/TMEDA (3.1 eq.).

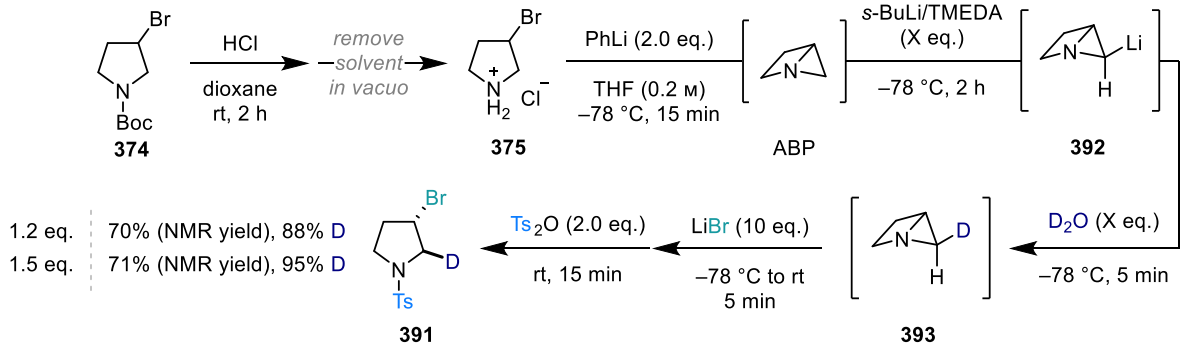
The hygroscopicity of hydrochloride salt **375**, however, limited its utility in the development of a general protocol. Its poor solubility meant that it could not be reliably stored as a stock solution over molecular sieves, and any attempts to dry the solid failed. It was proposed that *N*-Boc pyrrolidine **374** could act as a bench stable precursor to hydrochloride salt **375** (Scheme 160). If Boc deprotection and solvent removal occurred without exposure to air, dry **375** could be subjected to the reaction conditions. Despite involving an extra synthetic manipulation, this protocol proved high yielding, with ring-opened product **381** obtained in 84% NMR yield from **374**.



*Scheme 160. ABP formation and ring-opening starting from bench stable **374**.*

Yields were determined by ^{1}H NMR (400 MHz, $CDCl_3$) spectroscopic analysis using CH_2Br_2 as the internal standard.

Pleasingly, this new protocol enabled the synthesis of 2-deutero pyrrolidine **391** in 71% yield (from **374**) and with 95% deuterium incorporation when using 1.5 equivalents of TMEDA-ligated *sec*-butyl lithium for ABP lithiation (Scheme 161).



*Scheme 161. ABP lithiation and deuteration starting from bench stable **374**.*

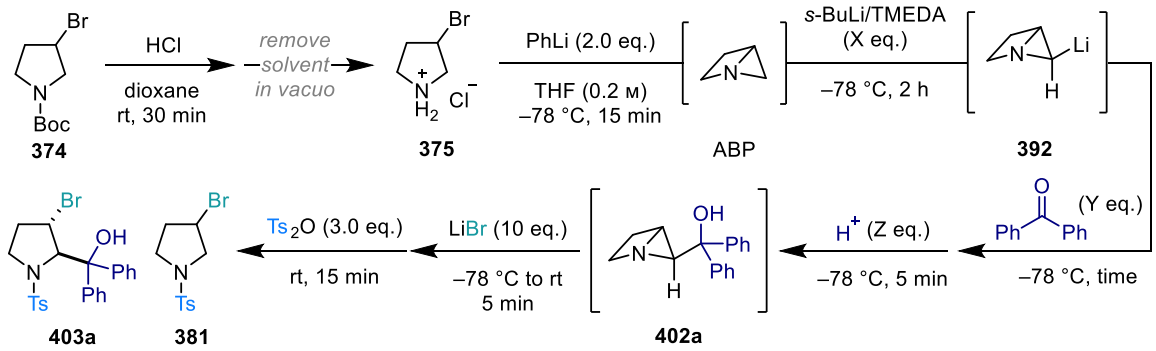
Yields were determined by ^{1}H NMR (400 MHz, $CDCl_3$) spectroscopic analysis using CH_2Br_2 as the internal standard. Deuterium incorporation (% D) was also determined by ^{1}H NMR spectroscopic analysis.

Having established conditions for the reliable formation of ABP-Li (**392**) from starting material **374**, its reaction with electrophiles was probed. First, the addition of benzophenone was investigated (Table 15). Again, following addition of the ketone to ABP-Li, the intermediate alkoxide was protonated to give ABP carbinol **402a**, which was then ring-opened.

In initial experiments, the ketone was added to an excess of ABP-Li, generated from the addition of 1.5 equivalents of TMEDA-ligated *sec*-butyl lithium to 1 equivalent of ABP. Unfortunately, only 29% of product **403a** was observed (Entry 1), alongside a 38% yield of **381**, formed as a result of the protonation of ABP-Li followed by ring-opening. This corresponds to a very poor mass balance of ABP-derived products (*n.b.* complete mass balance = 133%, due to reaction stoichiometry). Upon deuteration of ABP-Li, a 71% mass balance of pyrrolidine species was obtained. However, upon addition of benzophenone to ABP-Li, a 50% mass balance of pyrrolidine species was obtained. Since ABP-Li formation remained the same,

the discrepancy in mass balance is likely to arise from instability of intermediate ABP species under the reaction conditions.

Table 15. Optimisation of the addition of benzophenone to ABP-Li.

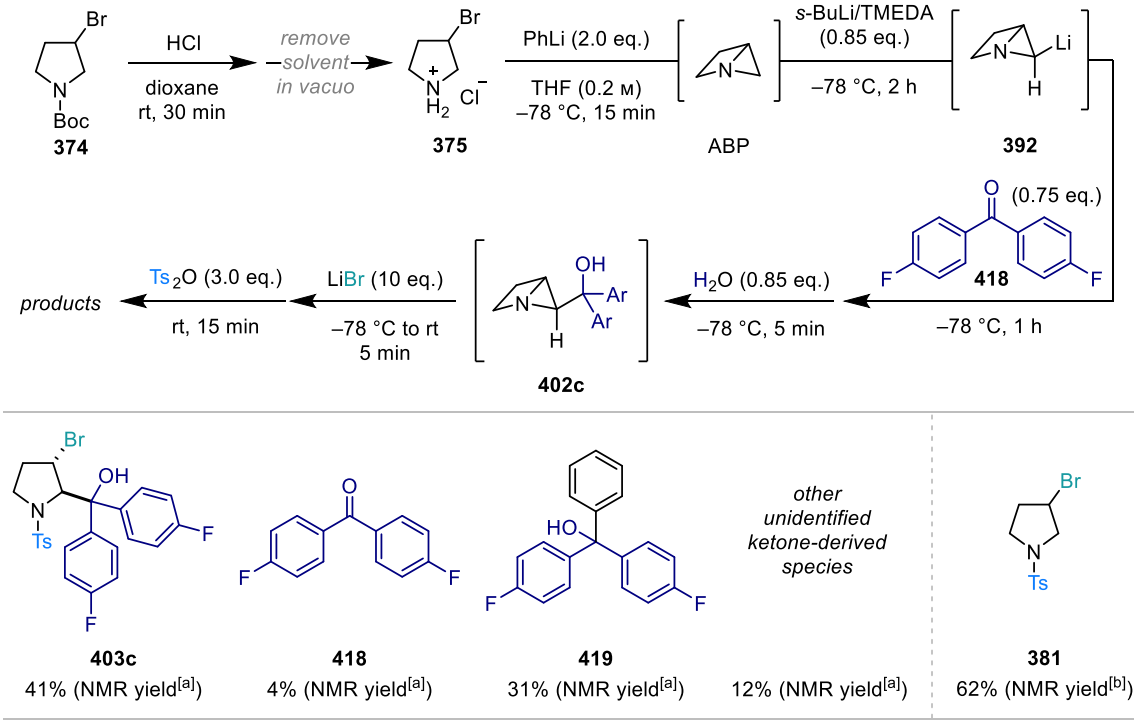


entry	*s*-BuLi/ TMEDA (X eq.)	ketone (Y eq.); time	proton source (Z eq.)	^{1}H NMR yield (%) **403a**	**381**
1	1.5	0.75; 1 h	H_2O; 1.0	29	38
2	1.5	0.75; 30 mins	H_2O; 1.0	36	40
3	1.5	0.75; 10 mins	H_2O; 1.0	14	51
4	1.5	0.75; 30 mins	MeOH; 1.0	29	27
5	1.5	0.75; 30 mins	*t*-BuOH; 1.0	20	44
6	0.85	0.75; 1 h	H_2O; 0.85	38	60
7	1.0	1.5; 1 h	H_2O; 1.0	39	13

All reactions conducted on a 0.20 mmol scale. Yields were determined by ^{1}H NMR (400 MHz, $CDCl_3$) spectroscopic analysis using CH_2Br_2 as the internal standard.

A reduction in reaction time to 30 minutes led to a slight increase in yield of **403a** (Entry 2), however 10 minutes proved too short a reaction time for sufficient electrophile trapping (Entry 3). There were no improvements in yield when trapping the alkoxide with other proton sources (Entries 4–5). An improvement in the mass balance came when substoichiometric amounts of TMEDA-ligated *sec*-butyl lithium were added to ABP (Entry 6). However, this did not significantly improve the yield of **403a**. In this case, it is likely that there is substoichiometric formation of ABP-Li with respect to the ketone, since previous experiments had highlighted the importance of excess TMEDA-ligated *sec*-butyl lithium in the formation of ABP-Li (see Scheme 161). Inverting the stoichiometry (*i.e.* with excess organolithium and excess ketone with respect to ABP) gave a poor mass balance of ABP-derived species but a similar yield of product **403a** (Entry 7). Again, this suggests an instability of the reaction intermediates under the reaction conditions.

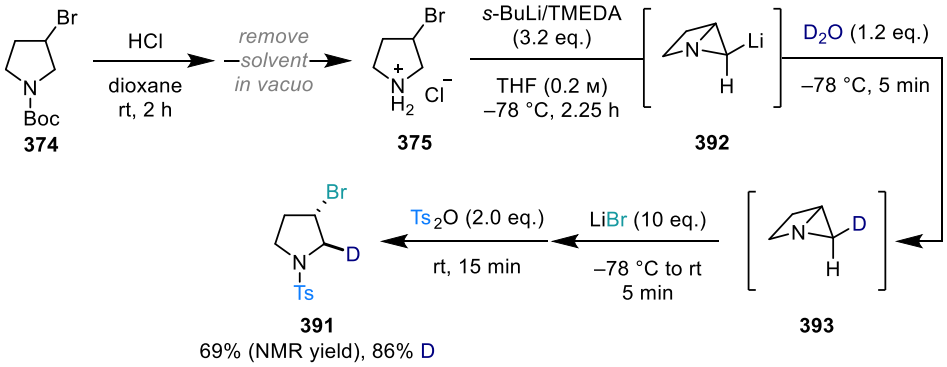
In order to further probe the origin of the poor reactivity between ABP-Li (**392**) and ketones, 4,4′-difluorobenzophenone (**418**) was employed instead of benzophenone (Scheme 162). This enabled reaction monitoring by ^{19}F NMR spectroscopy, allowing the fate of the ketone to be tracked. Under the optimised reaction conditions (Table 15; Entry 6), desired product **403c** was observed in 41% NMR yield, similar to that obtained with benzophenone. Only traces of ketone were returned, alongside traces of other unidentified ketone-derived species. The rest of the ketone had been transformed into triaryl alcohol **419**, formed in 31% NMR yield from addition of phenyl lithium to the ketone. Its formation indicated that the 2 equivalents of phenyl lithium added for ABP formation were not being fully consumed in the reaction time.



Scheme 162. Addition of 4,4′-difluorobenzophenone to ABP-Li to enable reaction monitoring by ^{19}F NMR spectroscopic analysis.

Yields were determined by [a] ^{19}F NMR (377 MHz, $CDCl_3$) spectroscopic analysis using C_6F_6 as the internal standard and [b] ^{1}H NMR (400 MHz, $CDCl_3$) spectroscopic analysis using CH_2Br_2 as the internal standard.

The use of TMEDA-ligated *sec*-butyl lithium for both the formation and lithiation of ABP was then investigated, since this simpler system would be easier to optimise through the use of only one organolithium base and thus one variable (Scheme 163). Pleasingly, 3.2 equivalents of base enabled ABP-Li (**392**) formation, with deuteration and ring-opening delivering the product (**391**) in 69% NMR yield with 86% deuterium incorporation.



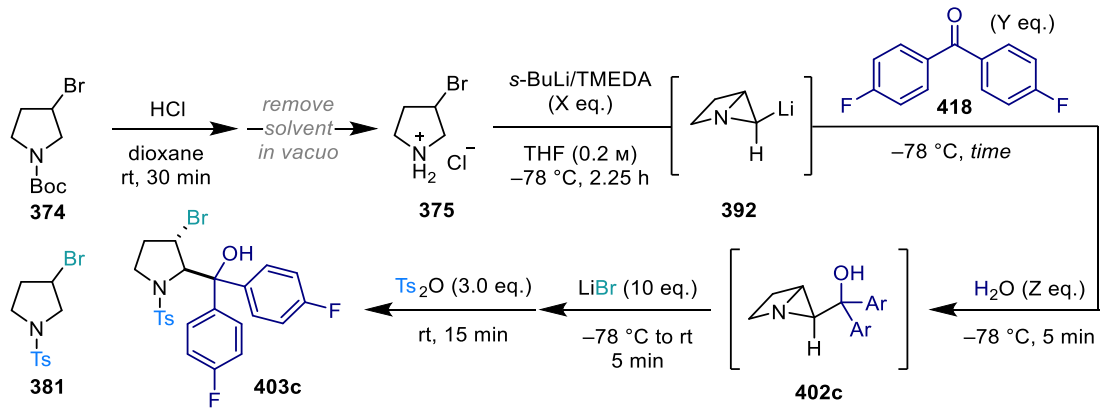
Scheme 163. ABP formation and lithiation using TMEDA-ligated sec-butyl lithium.

Yields were determined by ^{1}H NMR (400 MHz, $CDCl_3$) spectroscopic analysis using CH_2Br_2 as the internal standard. Deuterium incorporation (% D) was also determined by ^{1}H NMR spectroscopic analysis.

The addition of ABP-Li (**392**), now generated using only TMEDA-ligated *sec*-butyl lithium, to 4,4′-difluorobenzophenone (**418**) was then investigated (Table 16). Unfortunately, using 2.85 equivalents of TMEDA-ligated *sec*-butyl lithium (instead of 2 equivalents of phenyl lithium followed by 0.85 equivalents of TMEDA-ligated *sec*-butyl lithium; Table 15, Entry 6) delivered product **403c** in a similar yield alongside 30% returned ketone (Entry 1). The mass balance of ABP-derived products (*n.b.* complete mass balance = 133%) was promising, however the poor consumption of ketone **418** indicated substoichiometric formation of ABP-Li with respect to the ketone. Extended reaction times enabled further conversion of the ketone, but not exclusively to the desired product (Entry 2).

Inverting the stoichiometry (*i.e.* with excess organolithium and excess ketone with respect to ABP precursor **374**) again resulted in a poor mass balance of ABP-derived species and increased the consumption of the ketone (now in excess) to an array of unknown species (Entries 3–4). Through reaction monitoring by ^{19}F NMR spectroscopy, the existence of multiple decomposition pathways for the intermediate 2-functionalised ABP species was postulated, since no major ketone- or pyrrolidine-containing side product was obtained.

Table 16. Optimisation of the addition of 4,4'-difluorobenzophenone to ABP-Li generated using TMEDA-ligated sec-butyl lithium.



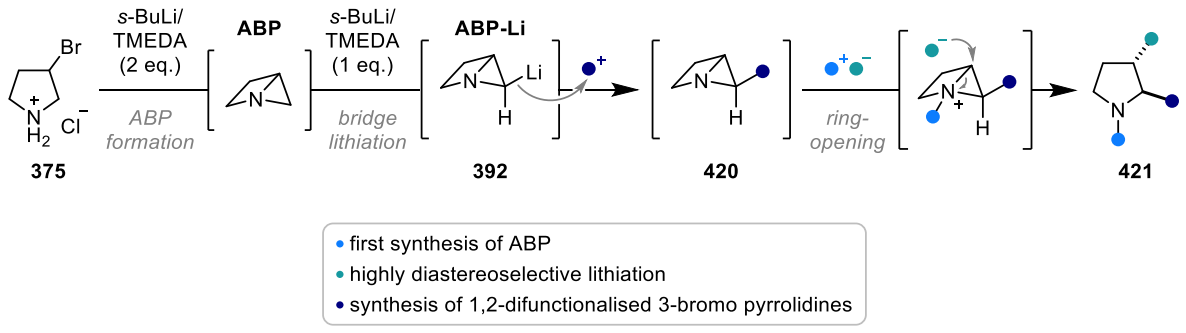
entry	*s*-BuLi/ TMEDA (X eq.)	ketone (Y eq.); time	H_2O (Z eq.)	^{19}F NMR yield (%)[a] **403c**	**418**	***other***	^{1}H NMR yield (%)[b] **381**
1	2.85	0.75; 1 h	0.85	36	30	14	71
2	2.85	0.75; 2 h	0.85	40	19	21	88
3	3.2	1.5; 1 h	1.2	33	52	44	18
4	3.5	1.5; 1 h	1.5	32	38	50	12

All reactions conducted on a 0.20 mmol scale. Yields were determined by [a] ^{19}F NMR (377 MHz, $CDCl_3$) spectroscopic analysis using C_6F_6 as the internal standard and [b] ^{1}H NMR (400 MHz, $CDCl_3$) spectroscopic analysis using CH_2Br_2 as the internal standard.

4.6. Conclusions and future work

4.6.1. Conclusions

The first synthesis of 1-azabicyclo[2.1.0]pentane (ABP) has been achieved and its lithiation, functionalisation and ring-opening reactions have been investigated (Scheme 164).



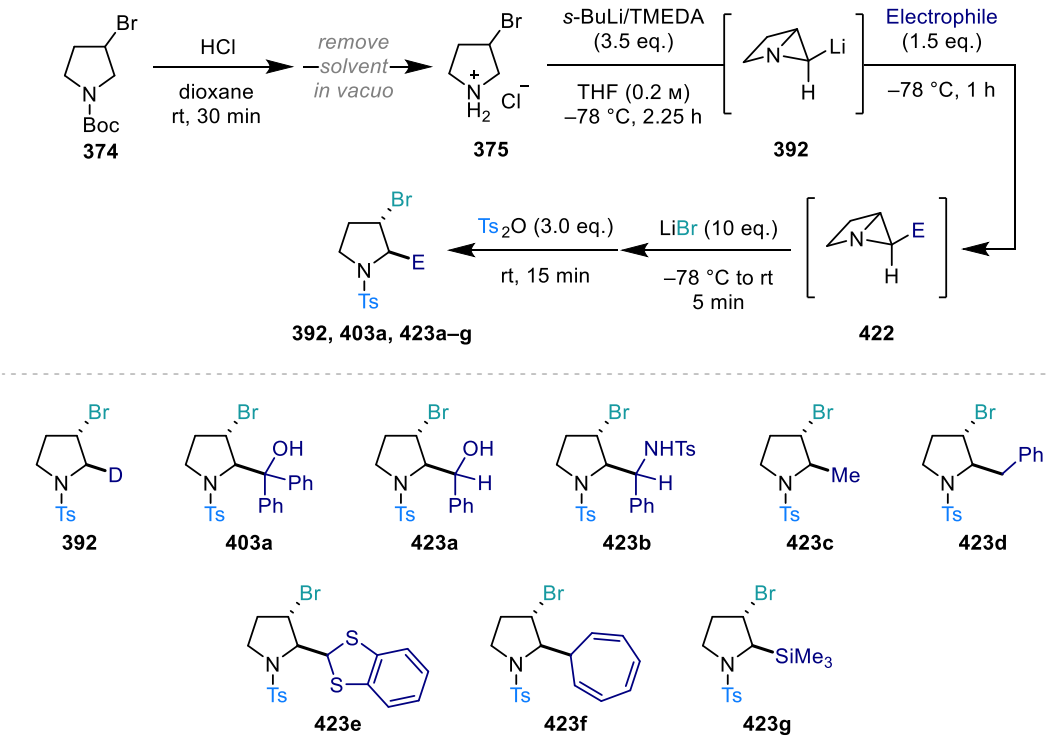
Scheme 164. Diastereoselective synthesis of 1,2,3-trifunctionalised pyrrolidines harnessing the reactivity of the novel, strained organolithium intermediate ABP-Li.

Lithiation of ABP occurred with unexpected selectivity; deprotonation occurred exclusively at the bridge position with selective removal of the *pseudo*-equatorial proton, yielding diastereomerically pure ABP-Li (**392**).

Unfortunately, the scope of the ring-opening step was narrow, since, upon activation, the strained, central bond in ABP was found to be highly reactive. The addition of the THF, the only suitable reaction solvent, to the 3-position of the activated ABP was only supressed in the presence of a large excess of external bromide nucleophile.

4.6.2. Future work

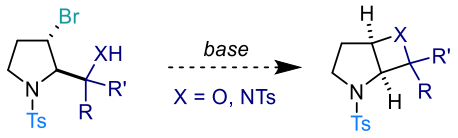
With conditions in hand which enable the synthesis of diastereomerically pure ABP-Li (**392**) from a bench stable starting material, a scope of electrophiles could be investigated (Scheme 165). The resultant 2-functionalised ABP (**422**) could then be ring-opened, delivering 1,2-difunctionalised 3-bromo pyrrolidines **423** as single diastereomers.



Scheme 165. Future work: electrophile scope for the synthesis of 1,2-difunctionalised 3-bromo pyrrolidines.

A range of carbonyl-derived electrophiles could be explored: benzophenone (to give **403a**), benzaldehyde (to give **423a**) and *N*-benzylidene-4-methylbenzenesulfonamide (to give **423b**). Whilst these transformations are likely to be moderately yielding, owing to the postulated instability of the ABP-containing intermediates under the reaction conditions, this multi-step protocol enables the formation of structurally complex pyrrolidine products with perfect

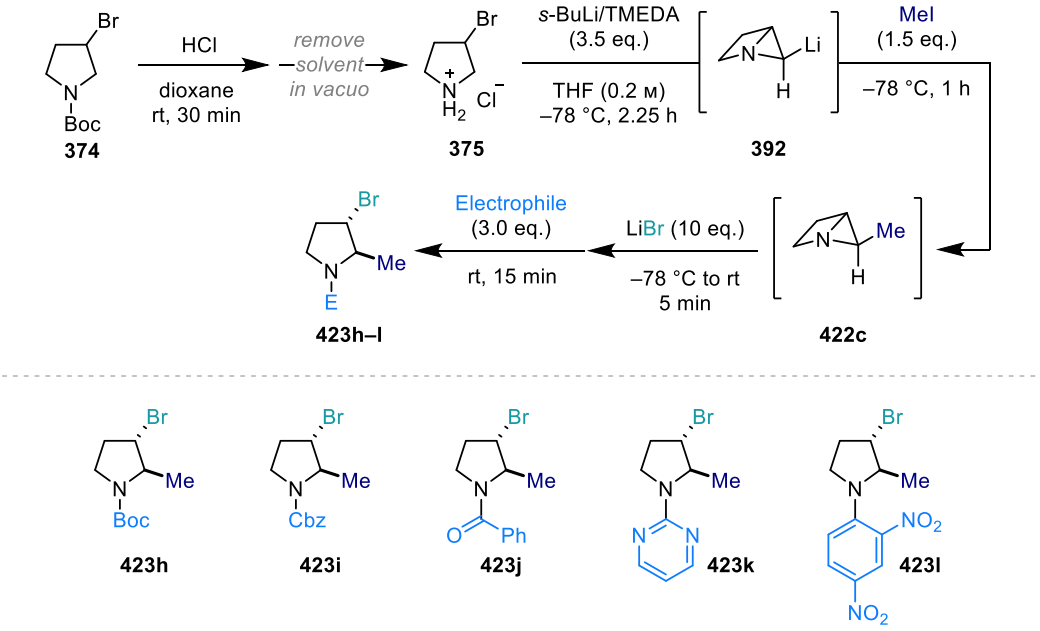
selectivity. Subsequent manipulation of the product alcohols/amines could enable the synthesis of diastereomerically pure fused oxetanes and azetidines (Scheme 166), a transformation for which a proof of principle has been established (see Scheme 153).



Scheme 166. Future work: base-promoted ring-closure to give fused oxetanes and azetidines.

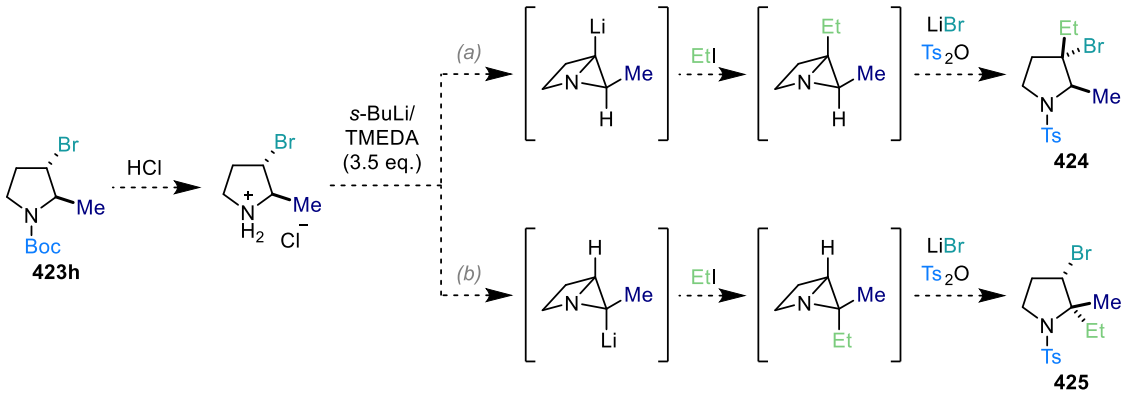
Additionally, alkyl halide electrophiles could be trialled, installing 2-alkyl functionality in the product pyrrolidines (**423c** from methyl iodide and **423d** from benzyl bromide). Other C–C bonds could be formed through the reaction of a highly electrophilic 1,3-benzodithiolylium cation (to give **423e**) or a tropylium cation (to give **423f**). Silylation of ABP-Li could also be attempted through the addition of chlorotrimethylsilane, yielding **423g**.

Moreover, a range of nitrogen functionalisation reactions could also be explored (Scheme 167). Carbamate formation would yield **423h** and **423i**, achieved through the reaction of **422c** with di-*tert*-butyl dicarbonate and benzyl chloroformate, respectively. Acylation of **422c** followed by ring-opening would yield **423j**. The propensity of **422c** to undergo S_NAr reactions with (hetero)arylhalides could also be investigated, giving *N*-arylated **423k** and **423l**.



Scheme 167. Future work: electrophile scope for the synthesis of 2-methyl 3-bromo N-functionalised pyrrolidines.

Furthermore, it would be interesting to explore whether removing the *pseudo*-equatorial proton at the bridge position of ABP would enable lithiation at the bridgehead to occur (Scheme 168a), or whether lithiation of the axial bridge proton would be favoured (Scheme 168b). This investigation could be possible by simply subjecting 2-methyl 3-bromo *N*-Boc pyrrolidine **423h** to the established reaction conditions. In this way, the tailored assembly of densely substituted pyrrolidines (**424**, **425**) could be possible.

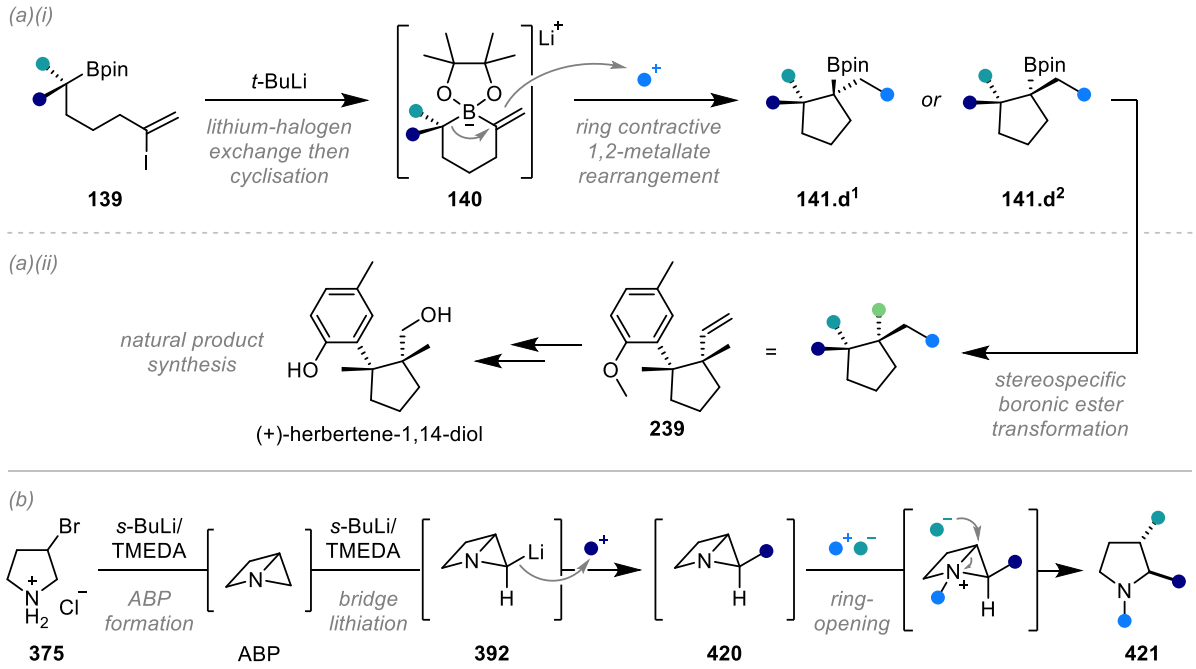


Scheme 168. Future work: lithiation of a 2-substituted ABP.

5. Conclusions and outlook

Two novel methodologies for the synthesis of highly decorated 5-membered rings have been developed, each with a particular focus on the stereocontrolled construction of contiguous stereocentres on the cyclic scaffold.

It was demonstrated that enantioenriched 6-membered cyclic alkenyl boronate complexes (**140**) can undergo a ring contractive 1,2-metallate rearrangement upon activation with a range of carbon- and heteroatom-based electrophiles (Scheme 169ai). This transformation was found to be enantiospecific and highly diastereoselective, enabling the synthesis of cyclopentyl boronic esters (**141**) bearing two contiguous fully substituted stereocentres. A remarkable solvent-induced diastereodivergence was observed in the case of some carbon-based electrophiles, allowing the synthesis of complementary diastereomeric pairs by simple variation of the reaction medium. A range of primary, secondary and tertiary boronic ester precursors (**139**) were synthesised in high enantiopurity using lithiation–borylation chemistry to introduce the stereocentre adjacent to boron and subjected to the reaction conditions.



Scheme 169. Overview of the developed methods for the organolithium-mediated assembly of 5-membered rings bearing contiguous stereocentres.

An investigation into the stereospecific transformation of the boronic ester functional handle was then undertaken (Scheme 169aii). It was found that tertiary boronic ester **141**, which bears an adjacent quaternary centre, is a poor substrate for many transition-metal-free C–C bond

forming reactions, likely owing to steric hindrance which limits the required borylation and 1,2-metallate rearrangement steps. However, olefination reactions proved highly successful, enabling the synthesis of cyclopentanes bearing two contiguous quaternary stereocentres with complete enantiospecificity.

Subsequently, a highly enantioenriched boronic ester, synthesised using this novel ring contractive methodology, was directly applied to the asymmetric total synthesis of sesquiterpene natural product (+)-herbertene-1,14-diol, with the synthetic route involving a key olefination/reductive ozonolysis reaction sequence for the functionalisation of the boronic ester handle.

A unique strategy for the synthesis of 1,2,3-trifunctionalised pyrrolidines was then developed, harnessing the reactivity of novel strain-release reagent 1-azabicyclo[2.1.0]pentane (ABP) (Scheme 169b). ABP was successfully generated for the first time, through treatment of 3-bromo pyrrolidine **375** with 2 equivalents of organolithium. When subjected to a further equivalent of TMEDA-ligated *sec*-butyl lithium, an unexpected regio- and diastereoselective bridge lithiation occurred, allowing the synthesis of diastereomerically pure ABP-Li (**392**) which could be trapped with a range of electrophiles. These functionalised ABP-containing compounds (**420**) were found to be unstable to aqueous work-up, and thus their ability to participate in ring-opening reactions was explored, varying the electrophilic nitrogen activator and the nucleophile. Due to the stereospecific nature of electrophilic trapping, the product 1,2,3-trifunctionalised pyrrolidines were formed as single diastereomers. The scope of this ring-opening was found to be undesirably narrow, owing to the high reactivity of ABP when activated by an electrophile, and thus addition of adventitious nucleophiles, such as the reaction solvent, gave rise to unwanted side products.

Future work shall focus on the development of the scope of this transformation, introducing variation at the two possible sites of diversity and enabling the synthesis of a library of diastereomerically pure 1,2-difunctionalised-3-bromo pyrrolidines.

6. Experimental

6.1. General experimental

6.1.1. Solvents, reagents and glassware

All manipulations were performed with oven-dried (130 °C for a minimum of 12 hours) or flame-dried glassware using standard Schlenk techniques under an atmosphere of nitrogen, unless otherwise stated. Room temperature (rt) refers to 15–25 °C.

All anhydrous solvents were commercially supplied or dried using an Anhydrous Engineering alumina column drying system (THF, toluene, Et_2O, MeCN, CH_2Cl_2). Reagents were purchased from commercial sources and used as received. 2,2,2-Trifluoroethanol (TFE) [CAS 75-89-8] was purchased from Sigma Aldrich and used as received unless otherwise stated. ***Exceptions***: *N*-bromosuccinimide (NBS) was recrystallised from boiling water. *N,N,N′,N′*-Tetramethylethylenediamine (TMEDA), triethylamine, and propionitrile (EtCN) were distilled over CaH_2 under an inert atmosphere at atmospheric pressure. Trifluoroacetic anhydride (TFAA) was distilled over P_2O_5 under an inert atmosphere at atmospheric pressure. All organolithium reagents were titrated against *N*-benzylbenzamide before use.[193] $MgBr_2$ (1 M in MeOH) was prepared from commercially available $MgBr_2$ which was dried for 2 hours (150 °C/0.1 mbar), cooled and dissolved in anhydrous MeOH under an inert atmosphere.[28]

6.1.2. Chromatography, spectroscopy and crystallography

Thin layer chromatography (TLC) was performed using Merck Kieselgel 60 F254 fluorescent treated silica, which was visualised under UV light, and/or by staining with aqueous basic potassium permanganate, ethanolic acidic *p*-anisaldehyde or aqueous acidic cerium ammonium molybdate (CAM) stain followed by heating.

Flash column chromatography was conducted using Sigma-Aldrich silica gel (60 Å, 230–400 mesh, 40-63 μm).

Nuclear magnetic resonance (NMR) spectra were recorded at various field strengths, as indicated, using Bruker 400 MHz, Varian VNMR 400 MHz, Varian VNMR 500 MHz, or Bruker Cryo 500 MHz for ^{1}H, ^{11}B, ^{13}C and ^{19}F acquisitions. All NMR spectra were recorded at 25 °C unless otherwise stated. Chemical shifts (δ) are reported in parts per million (ppm) and referenced: $CDCl_3$ (^{1}H: δ_H = 7.26 ppm; ^{13}C: δ_C = 77.0 ppm), CD_2Cl_2 (^{1}H: δ_H = 5.32 ppm; ^{13}C: δ_C = 53.5 ppm), CD_3OD (^{1}H: δ_H = 3.31 ppm; ^{13}C: δ_C = 49.0 ppm). Coupling constants (*J*)

are given in Hertz (Hz) and refer to apparent multiplicities (s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, hex = hextet, hept = heptet, m = multiplet, br = broad signal, dd = doublet of doublets, etc.). The ^{1}H NMR spectra are reported as follows: chemical shift (multiplicity, coupling constants, number of protons). NMR assignments were made with assistance from two-dimensional NMR spectroscopy (COSY, HSQC, HMBC). Exact assignments are made only when unambiguous, otherwise a general assignment is made. ^{1}H NMR yields were determined, unless otherwise stated, through quantitative ^{1}H NMR (400 MHz, $CDCl_3$) spectroscopic analysis using dibromomethane (CH_2Br_2) as the internal standard. ^{19}F NMR yields were determined, unless otherwise stated, through ^{19}F NMR (377 MHz, $CDCl_3$) spectroscopic analysis using hexafluorobenzene (C_6F_6) as the internal standard. Signals corresponding to diastereotopic atoms are distinguished by prime notation (*e.g.* H_A *vs* $H_{A'}$). Diastereomeric ratios (d.r.) were determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. Where the d.r. is high, NMR assignments are made for only the major diastereomer. When rotamers were observed by ^{1}H NMR spectroscopy, the distinguishable rotamer signals are given as the fraction of protons that they correspond to. When rotamers were observed by ^{13}C NMR spectroscopy, the distinguishable rotamers signals are assigned as two distinct signals.

High resolution mass spectra (HRMS) were recorded on a Bruker Daltonics MicrOTOF II by Electrospray Ionisation (ESI); a Thermo Scientific QExactive by Electron Ionisation (EI); a Thermo Scientific Orbitrap Elite by Electrospray Ionisation (ESI) or Atmospheric Pressure Chemical Ionisation (APCI); or a Bruker UltrafleXtreme by Matrix-assisted Laser Desorption/Ionisation (MALDI).

IR spectra were recorded neat as a thin film on a Perkin Elmer Spectrum One FT-IR. Selected absorption maxima (ν_{max}) are reported in wavenumbers (cm^{-1}). Broad (br) signals are indicated.

Chiral high-performance liquid chromatography (HPLC) analyses were performed on an Agilent 1100 system with Daicel Chiralpak IA, IB and IC columns with the isocratic gradient specified.

Chiral supercritical fluid chromatography (SFC) analyses were performed on a Waters (Thar) system with a Whelk-O1 column with the isocratic gradient specified.

Optical rotations ($[\alpha]_D^T$) were measured in CH_2Cl_2 (unless otherwise indicated) using a Bellingham & Stanley ADP 220 Polarimeter. Specific rotation values are given in (deg mL)/(g dm).

X-ray diffraction (XRD) experiments on **403a** were carried out at 100(2) K on a Bruker D8 Venture using Cu-K_α (λ = 1.54178 Å) radiation. Intensities were integrated in SAINT[194] and absorption corrections based on equivalent reflections were applied using SADABS.[195] The structure was solved using ShelXT[196] and refined by full matrix least squares against F^2 in ShelXL[197,198] using Olex2.[199] All of the non-hydrogen atoms were refined anisotropically. All of the hydrogen atoms were located geometrically and refined using a riding model, apart from the O-H proton which was located in the difference map and refined freely. The structure was refined as a racemic twin with a twin scale factor of 0.42(3).

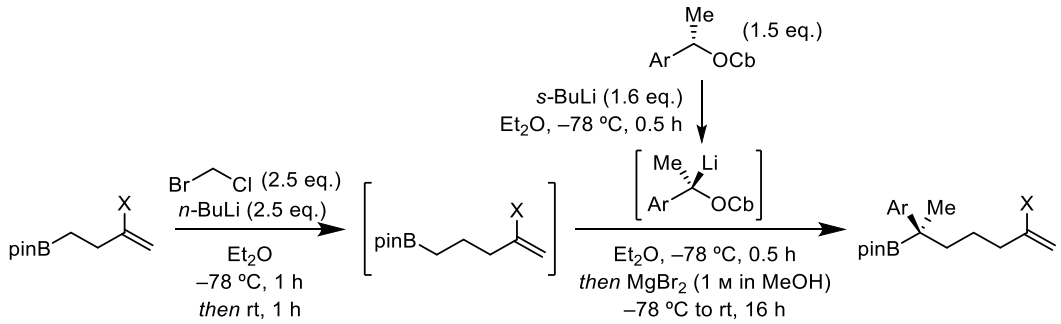
6.1.3. Naming of compounds

Compound names were generated by ChemDraw 20.0 software (PerkinElmer), following IUPAC nomenclature.

6.2. Synthetic procedures – Chapter 2

6.2.1. Synthesis of boronic ester starting materials

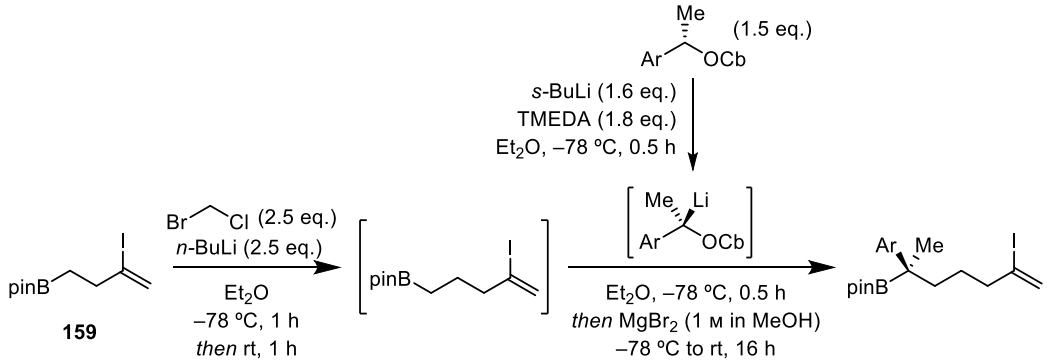
6.2.1.1. General procedure A: synthesis of tertiary boronic esters



According to a combination of modified literature procedures,[27,28,75] the boronic ester (1.0 eq.) was dissolved in anhydrous Et_2O (0.1 M) and the solution cooled to −78 °C (dry ice/acetone). Bromochloromethane (2.5 eq.) was added dropwise (~0.5 mL/min) to the solution, followed by *n*-butyl lithium (1.6 M in hexanes; 2.5 eq.) *via* syringe pump (0.03 mL/min). Following the addition, the reaction mixture was stirred at −78 °C for 1 hour and then warmed to rt and stirred at this temperature for 1 hour. The reaction mixture was filtered through a silica plug (eluting Et_2O) and concentrated *in vacuo*. The crude product was used without further purification.

The diisopropylcarbamate (1.5 eq.) was dissolved in anhydrous Et_2O (0.2 M) and the solution cooled to −78 °C (dry ice/acetone). *sec*-Butyl lithium (1.3 M in cyclohexane/hexane 92:8; 1.6 eq.) was added dropwise (~0.5 mL/min) to the solution. The reaction mixture was stirred at −78 °C for 30 minutes whereupon a solution of the crude boronic ester (1 M in Et_2O) was added dropwise. Following stirring at −78 °C for 30 minutes, $MgBr_2$ (1 M in MeOH; 1.8 eq.) was added at this temperature. The reaction mixture was then warmed to rt and stirred at this temperature overnight. Confirmation of full conversion to the boronic ester by ^{11}B NMR spectroscopy preceded quenching with water (10 mL/mmol) and the aqueous layer was extracted with Et_2O (3 × 10 mL/mmol). The combined organics were washed with brine (10 mL/mmol), dried over $MgSO_4$ and concentrated *in vacuo*. The crude reaction mixture was purified by flash column chromatography to give the product.

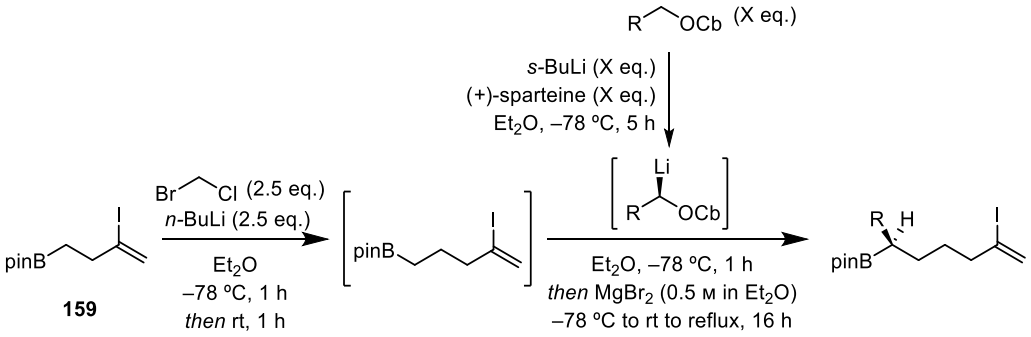
6.2.1.2. General procedure B: synthesis of tertiary boronic esters (with TMEDA)



According to a combination of modified literature procedures,[27,28,75] boronic ester **159** (1.0 eq.) was dissolved in anhydrous Et_2O (0.1 M) and the solution cooled to −78 °C (dry ice/acetone). Bromochloromethane (2.5 eq.) was added dropwise (~0.5 mL/min) to the solution, followed by *n*-butyl lithium (1.6 M in hexanes; 2.5 eq.) *via* syringe pump (0.03 mL/min). Following the addition, the reaction mixture was stirred at −78 °C for 1 hour and then warmed to rt and stirred at this temperature for 1 hour. The reaction mixture was filtered through a silica plug (eluting Et_2O) and concentrated *in vacuo*. The crude product was used without further purification.

The diisopropylcarbamate (1.5 eq.) was dissolved in anhydrous Et_2O (0.2 M) and the solution cooled to −78 °C (dry ice/acetone). TMEDA (1.8 eq.) was added dropwise (~0.5 mL/min) to the solution, followed by *sec*-butyl lithium (1.3 M in cyclohexane/hexane 92:8; 1.6 eq.). The reaction mixture was stirred at −78 °C for 30 minutes whereupon a solution of the crude boronic ester (1 M in Et_2O) was added dropwise (~0.5 mL/min). Following stirring at −78 °C for 30 minutes, $MgBr_2$ (1 M in MeOH; 1.8 eq.) was added at this temperature. The reaction mixture was then warmed to rt and stirred at this temperature overnight. Confirmation of full conversion to the boronic ester by ^{11}B NMR spectroscopy preceded quenching with water (10 mL/mmol) and the aqueous layer was extracted with Et_2O (3 × 10 mL/mmol). The combined organics were washed with brine (10 mL/mmol), dried over $MgSO_4$ and concentrated *in vacuo*. The crude reaction mixture was purified by flash column chromatography to give the product.

6.2.1.3. General procedure C: synthesis of secondary boronic esters



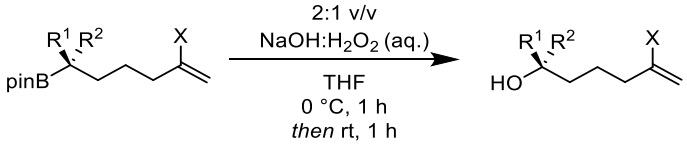
According to a combination of modified literature procedures,[21,75] boronic ester **159** (1.0 eq.) was dissolved in anhydrous Et_2O (0.1 M) and the solution cooled to −78 °C (dry ice/acetone). Bromochloromethane (2.5 eq.) was added dropwise (~0.5 mL/min) to the solution, followed by *n*-butyl lithium (1.6 M in hexanes; 2.5 eq.) *via* syringe pump (0.03 mL/min). Following the addition, the reaction mixture was stirred at −78 °C for 1 hour and then warmed to rt and stirred at this temperature for 1 hour. The reaction mixture was filtered through a silica plug (eluting Et_2O) and concentrated *in vacuo*. The crude product was used without further purification.

Enantioenriched: The carbamate (X eq.) and (+)-sparteine (X eq.) were dissolved in anhydrous Et_2O (0.1 M) and cooled to −78 °C (dry ice/acetone). *sec*-Butyl lithium (1.3 M in cyclohexane/hexane 92:8; X eq.) was added dropwise (~0.5 mL/min) to this mixture. The resultant mixture was stirred at −78 °C for 5 hours whereupon a solution of the crude boronic ester (1 M in Et_2O) was added dropwise (~0.5 mL/min). Following stirring at −78 °C for 1 hour, a solution of $MgBr_2$ in Et_2O [freshly made from stirring Mg turnings (2.5 eq.) and 1,2-dibromoethane (1.5 eq.) in Et_2O (0.5 M) at rt for 4 hours] was added at this temperature. The reaction mixture was stirred at −78 °C for a further 30 minutes whereupon it was warmed to rt, then heated to reflux and stirred at this temperature overnight. Confirmation of full conversion to the boronic ester by ^{11}B NMR spectroscopy preceded quenching the reaction mixture with 2 M aqueous HCl (10 mL/mmol). The organic layer was washed with 2 M aqueous HCl (4 × 10 mL/mmol) for the recovery of the (+)-sparteine and the combined aqueous washes were extracted with Et_2O (4 × 10 mL/mmol). The combined organics were washed with brine (10 mL/mmol), dried over $MgSO_4$ and concentrated *in vacuo*. The crude reaction mixture was purified by flash column chromatography to give the product.

Racemic: As above, replacing (+)-sparteine (1.5 eq.) with TMEDA (1.5 eq.). The work-up procedure can be simplified as follows: The reaction mixture was quenched with water

(10 mL/mmol) and the aqueous layer extracted with Et_2O (3 × 10 mL/mmol). The combined organics were washed with brine (10 mL/mmol), dried over $MgSO_4$ and concentrated *in vacuo*.

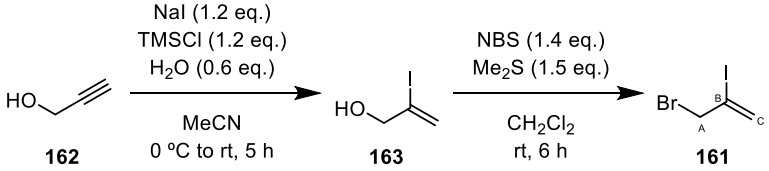
6.2.1.4. General procedure D: oxidation of boronic esters



According to a literature procedure,[75] the boronic ester (0.05 mmol, 1.0 eq.) was dissolved in THF (0.33 mL) and cooled to 0 °C (ice/water). A 2:1 v/v solution of 2 M aqueous NaOH (0.30 mL) and 30% w/w aqueous H_2O_2 (0.17 mL) was added dropwise (~0.5 mL/min) to the solution. The reaction mixture was allowed to stir at 0 °C for 1 hour, followed by warming to rt and stirring at rt for 1 hour. Completion of the reaction was confirmed by TLC monitoring, whereupon the reaction mixture was diluted with EtOAc (1 mL) and quenched with saturated aqueous $Na_2S_2O_3$ (1 mL). The aqueous layer was extracted with EtOAc (3 × 1 mL). The combined organics were washed with brine (1 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude reaction mixture was purified by flash column chromatography to give the product.

6.2.1.5. Characterisation of boronic ester starting materials

3-Bromo-2-iodoprop-1-ene (161)



According to a literature procedure,[75] sodium iodide (15.4 g, 103 mmol, 1.2 eq.) was dissolved in anhydrous MeCN (38 mL) and cooled to 0 °C (ice/water). Trimethylsilyl chloride (13.1 mL, 103 mmol, 1.2 eq.) was added dropwise (~1 mL/min) and the resultant solution stirred at 0 °C for 15 minutes. After which time, water (0.95 mL, 50 mmol, 0.6 eq.) was added dropwise (~1 mL/min), followed by **162** (5.0 mL, 86 mmol, 1.0 eq.) dropwise (~1 mL/min). The reaction mixture was warmed to rt over 1 hour (by halting the replenishment of the ice in the cooling bath) and then stirred at rt for 4 hours whereupon it was quenched with saturated aqueous $NaHCO_3$ (25 mL) and saturated aqueous $NaHSO_3$ (25 mL). The aqueous phase was extracted with Et_2O (3 × 50 mL) and the combined organics were washed with brine (50 mL), dried over

$MgSO_4$ and concentrated *in vacuo*. The crude reaction mixture was purified by flash column chromatography (pentane/Et_2O 20:1 to 10:1) to give **163** as a brown oil which was used in the subsequent step. *N*-Bromosuccinimide (11.2 g, 63 mmol, 1.4 eq.) was dissolved in anhydrous CH_2Cl_2 (16 mL) and cooled to –25 °C (cryostat). Dimethyl sulfide (4.9 mL, 67 mmol, 1.5 eq.) was added dropwise (~1 mL/min) to the solution. The reaction mixture was stirred at this temperature for 20 minutes whereupon **163** (8.24 g, 45 mmol, 1.0 eq.) in CH_2Cl_2 (4.5 mL) was added dropwise (~1 mL/min) and the resultant mixture warmed to rt. After 3 hours stirring at rt, the reaction mixture was diluted with pentane (20 mL) and poured over ice/water (20 mL). The organic phase was washed with brine (20 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude reaction mixture was purified by flash column chromatography (pentane) to give the alkenyl iodide product (7.27 g, 38% over 2 steps) as a bright red oil.

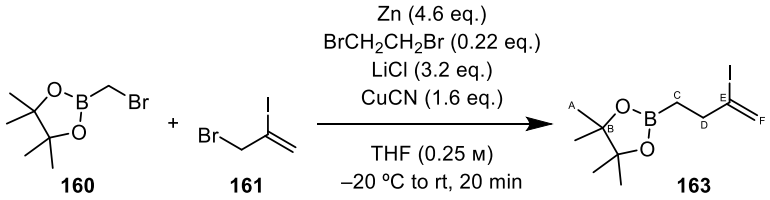
NMR Spectroscopy:

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 6.45 (dt, $^2J_{HH}$ = 1.9 Hz, $^4J_{HH}$ = 1.3 Hz, 1H, H_C), 5.88 (dt, $^2J_{HH}$ = 1.9 Hz, $^4J_{HH}$ = 0.5 Hz, 1H, H_C), 4.23 (dd, $^4J_{HH}$ = 1.3, 0.5 Hz, 2H, H_A) ppm;

^{13}C NMR (101 MHz, $CDCl_3$): δ_C 129.8 (C_C), 102.9 (C_B), 41.4 (C_A) ppm.

All recorded spectroscopic data matched those previously reported in the literature.[75]

2-(3-Iodobut-3-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (159)



According to a literature procedure,[75] zinc powder (4.87 g, 75 mmol, 4.6 eq.) was suspended in anhydrous THF (9 mL) at rt and 1,2-dibromoethane (0.31 mL, 3.6 mmol, 0.22 eq.) was added dropwise (~0.5 mL/min). To this suspension, **160** (4.3 mL, 24 mmol, 1.5 eq.) in anhydrous THF (24 mL) was added dropwise (~1 mL/min) *via* syringe pump (1.0 mL/min). Following this addition, the suspension was stirred for 30 minutes and then stirring was stopped and the zinc allowed to settle. In the meantime, dry lithium chloride (dried with a heat gun under vacuum and left to cool; 2.20 g, 52 mmol, 3.2 eq.) and copper(I) cyanide (2.32 g, 26 mmol, 1.6 eq.) were added to a flask which was then set under a nitrogen atmosphere, dissolved in anhydrous THF (32 mL) and cooled to −20 °C (cryostat). The organozinc solution was added *via* syringe pump (1.0 mL/min). Following the addition, the reaction mixture was stirred at

5 °C (ice/water) for 5 minutes and then cooled back to −20 °C whereupon **161** (4.00 g, 16 mmol, 1.0 eq.) was added *via* syringe pump (0.1 mL/min). After the addition was completed, the reaction mixture was warmed to rt and stirred at rt for 20 minutes and then quenched with water (120 mL) and Et_2O (60 mL). The aqueous phase was washed with Et_2O (2 × 30 mL). The combined organics were washed with brine (30 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude reaction mixture was purified by flash column chromatography (pentane/Et_2O 50:1, 25:1, 20:1) to give the product (3.89 g, 78%) as a pale-yellow oil.

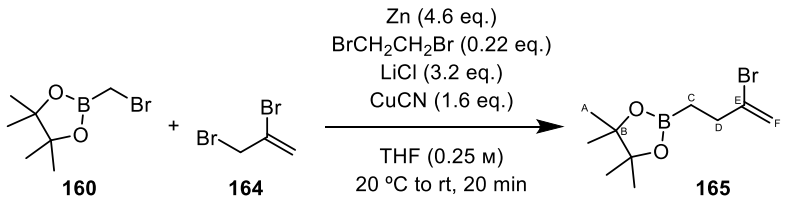
NMR Spectroscopy:

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 6.02 (apparent q, $^4J_{HH} = {}^2J_{HH}$ = 1.6 Hz, 1H, H_F), 5.64 (dt, $^2J_{HH}$ = 1.7 Hz, $^4J_{HH}$ = 0.8 Hz, 1H, $H_{F'}$), 2.65–2.37 (m, 2H, H_D), 1.25 (s, 12H, H_A), 1.06–0.90 (m, 2H, H_C) ppm;

^{13}C NMR (101 MHz, $CDCl_3$): δ_C 124.0 (C_F), 114.7 (C_E), 83.3 (C_B), 40.3 (C_D), 24.8 (C_A) ppm; C_C not observed due to quadrupolar relaxation.

All recorded spectroscopic data matched those previously reported in the literature.[75]

2-(3-Bromobut-3-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (165)



According to a literature procedure,[74] zinc powder (3.01 g, 46 mmol, 4.6 eq.) was suspended in anhydrous THF (5 mL) at rt and 1,2-dibromoethane (0.19 mL, 2.2 mmol, 0.22 eq.) was added dropwise (~0.5 mL/min). To this suspension **160** (2.7 mL, 15 mmol, 1.5 eq.) in anhydrous THF (14 mL) was added dropwise *via* syringe pump (1.0 mL/min). Following this addition, the suspension was stirred for 30 minutes and then stirring was stopped and the zinc allowed to settle. In the meantime, dry lithium chloride (dried with a heat gun under vacuum and left to cool; 1.36 g, 32 mmol, 3.2 eq.) and copper(I) cyanide (1.43 g, 16 mmol, 1.6 eq.) were added to a flask which was then set under a nitrogen atmosphere, dissolved in anhydrous THF (20 mL) and cooled to −20 °C (cryostat). The organozinc solution was added *via* syringe pump (1.0 mL/min). Following the addition, the reaction mixture was stirred at 5 °C for 5 minutes and then cooled back to −20 °C whereupon **164** (0.98 g, 10 mmol, 1.0 eq.) was added *via* syringe pump (0.1 mL/min). After the addition was completed, the reaction mixture was

warmed to rt and stirred at rt for 20 minutes and then quenched with water (80 mL) and Et_2O (40 mL). The aqueous phase was washed with Et_2O (2 × 30 mL). The combined organics were washed with brine (30 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude reaction mixture was purified by flash column chromatography (pentane then pentane/Et_2O 9:1) to give the product (1.23 g, 47 %) as a pale-yellow oil.

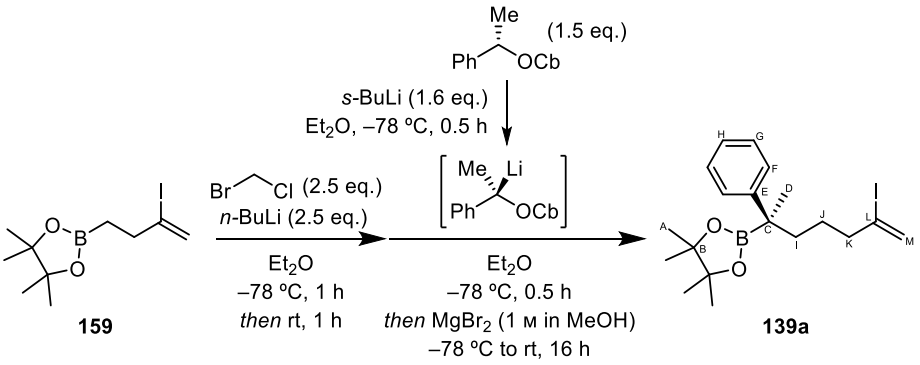
NMR Spectroscopy:

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 5.57 (apparent q, $^4J_{HH}$ = $^2J_{HH}$ = 1.4 Hz, 1H, H_F), 5.35 (d, $^2J_{HH}$ = 1.5 Hz, 1H, H_F), 2.59–2.50 (m, 2H, H_D), 1.24 (s, 12H, H_A), 1.09–1.01 (m, 2H, H_C) ppm;

^{13}C NMR (101 MHz, $CDCl_3$): δ_C 136.7 (C_F), 115.1 (C_E), 83.3 (C_B), 36.1 (C_C), 24.8 (C_A) ppm; C_C not observed due to quadrupolar relaxation.

All recorded spectroscopic data matched those previously reported in the literature.[74]

(*S*)-2-(6-Iodo-2-phenylhept-6-en-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (139a)



According to **General Procedure A**, boronic ester **159** (0.308 g, 1.0 mmol, 1.0 eq.) was reacted with bromochloromethane (0.16 mL, 2.5 mmol, 2.5 eq.) and *n*-butyl lithium (1.6 M in hexanes; 1.6 mL, 2.5 mmol, 2.5 eq.). The crude product was then reacted with (*S*)-1-phenylethyl diisopropylcarbamate[27] (0.374 g, 1.5 mmol, 1.5 eq.) and *sec*-butyl lithium (1.3 M in cyclohexane/hexane 92:8; 1.2 mL, 1.6 mmol, 1.6 eq.). The crude reaction mixture was purified by flash column chromatography (pentane/Et_2O 200:1 to 100:1) to give the product (0.270 g, 63% over 2 steps, 99:1 e.r.) as a colourless oil.

The e.r. of boronic ester **139a** could not be determined by chiral HPLC/SFC. Instead, the boronic ester was oxidised and the e.r. of alcohol **139a'** was determined.

R_f = 0.43 (pentane/Et_2O 95:5).

$[\alpha]_D^{25}$**:** –1 (*c* = 5.4, CH_2Cl_2).

NMR Spectroscopy:

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.35–7.21 (m, 4H, $H_{F,\,G}$), 7.17–7.08 (m, 1H, H_H), 5.98 (apparent q, $^4J_{HH}$ = $^2J_{HH}$ = 1.4 Hz, 1H, H_M), 5.69–5.61 (m, 1H, $H_{M'}$), 2.41–2.32 (m, 2H, $H_{K,\,K'}$), 1.86–1.60 (m, 2H, $H_{I,\,I'}$), 1.52–1.38 (m, 2H, $H_{J,\,J'}$), 1.36 (s, 3H, H_D), 1.22 (s, 6H, H_A), 1.21 (s, 6H, $H_{A'}$) ppm;

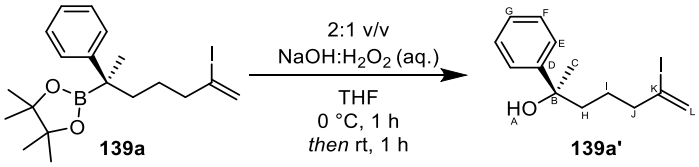
^{13}C NMR (101 MHz, $CDCl_3$): δ_C 147.1 (C_E), 128.1 (C_F *or* C_G), 126.8 (C_F *or* C_G), 125.2 (C_H *or* C_M), 125.1 (C_H *or* C_M), 112.6 (C_L), 83.4 (C_B), 46.0 (C_K), 38.1 (C_I), 25.3 (C_J), 24.6 (C_A), 21.6 (C_D) ppm; C_C not observed due to quadrupolar relaxation;

^{11}B NMR (128 MHz, $CDCl_3$): δ_B 32.9 ppm.

IR (film): ν_{max} 2977, 2925, 2852, 1616, 1467, 1379, 1312, 1140 cm^{-1}.

HRMS (ESI): m/z calc'd for $C_{19}H_{28}{}^{11}BINaO_2$ $[M+Na]^+$ 449.1123 found 449.1138.

(*R*)-6-Iodo-2-phenylhept-6-en-2-ol (139a')



According to **General Procedure D**, boronic ester **139a** (21 mg, 0.05 mmol, 1.0 eq.) was reacted with a 2 M aqueous solution of NaOH (0.33 mL) and aqueous H_2O_2 (30% w/w; 0.17 mL) at 0 °C in THF (0.33 mL). The crude reaction mixture was purified by flash column chromatography (pentane/EtOAc 9:1) to give the product (13 mg, 82%, 99:1 e.r.) as a colourless oil.

$\mathbf{R_f}$ = 0.32 (pentane/EtOAc 9:1).

$[\alpha]_D^{25}$**:** +8 (*c* = 2.8, CH_2Cl_2).

NMR Spectroscopy:

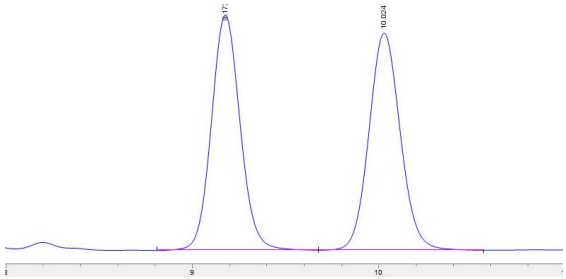
^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.47–7.40 (m, 2H, H_E), 7.39–7.31 (m, 2H, H_F), 7.28–7.21 (m, 1H, H_G), 5.97 (apparent q, $^4J_{HH}$ = $^2J_{HH}$ = 1.4 Hz, 1H, H_L), 5.67 (d, $^2J_{HH}$ = 1.5 Hz, 1H, $H_{L'}$), 2.37–2.29 (m, 2H, $H_{J,\,J'}$), 1.85–1.73 (m, 2H, $H_{H,\,H'}$), 1.58 (s, 3H, H_C), 1.55–1.45 (m, 1H, H_I), 1.45–1.31 (m, 1H, $H_{I'}$) ppm; H_A not observed;

^{13}C NMR (101 MHz, $CDCl_3$): δ_C 147.7 (C_D), 128.3 (C_F), 126.7 (C_G), 125.7 (C_L), 124.8 (C_E), 112.2 (C_K), 74.5 (C_B), 45.2 (C_J), 42.4 (C_H), 30.2 (C_C), 23.5 (C_I) ppm.

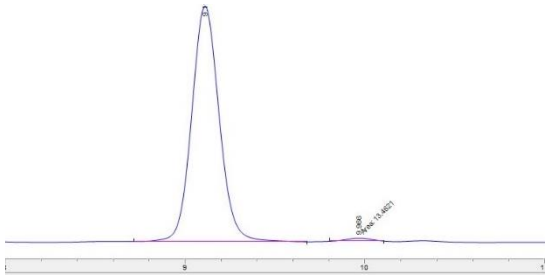
IR (film): ν_{max} 3414 (br), 2924, 1616, 1494, 1446, 1373, 1143, 1055 cm^{-1}.

HRMS (ESI): m/z calc'd for $C_{13}H_{17}INaO$ $[M+Na]^+$ 339.0216 found 399.0212.

Chiral HPLC (IC column, 99:1 hexane/IPA, 1 mL/min, rt, 325 nm): 9.1 min (major), 10.0 min (minor), 99:1 e.r.

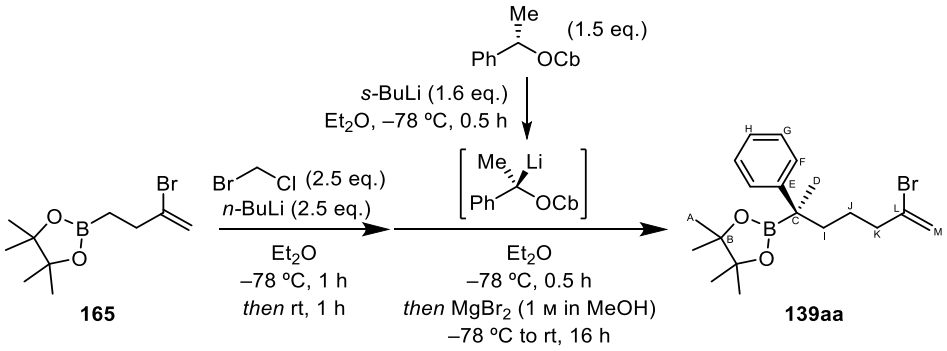


#	Time	Type	Area	Height	Width	Area%	Symmetry
1	9.173	BB	2270.3	212.3	0.1658	49.833	0.898
2	10.024	BB	2285.4	195.7	0.1818	50.167	0.898



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	9.11	BB	1126.1	105.8	0.1647	98.819	0.895
2	9.966	MM	13.5	1.4	0.1625	1.181	1.015

(*S*)-2-(6-Bromo-2-phenylhept-6-en-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (139aa)



According to **General Procedure A**, boronic ester **165** (0.600 g, 2.3 mmol, 1.0 eq.) was reacted with bromochloromethane (0.37 mL, 5.7 mmol, 2.5 eq.) and *n*-butyl lithium (1.6 M in hexanes; 3.6 mL, 5.7 mmol, 2.5 eq.). The crude product was then reacted with (*S*)-1-phenylethyl diisopropylcarbamate[27] (0.631 g, 2.5 mmol, 1.1 eq.) and *sec*-butyl lithium (1.3 M in cyclohexane/hexane 92:8; 2.8 mL, 3.7 mmol, 1.6 eq.). The crude reaction mixture was purified by flash column chromatography (pentane/Et_2O 50:1) to give the product (0.634 g, 73% over 2 steps, 99:1 e.r.) as a colourless oil.

The e.r. of boronic ester **139aa** could not be determined by chiral HPLC/SFC. Instead, the boronic ester was oxidised and the e.r. of alcohol **139aa'** was determined.

$\mathbf{R_f}$ = 0.64 (pentane/Et_2O 95:5).

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$**:** –3 (*c* = 5.4, CH_2Cl_2).

NMR Spectroscopy:

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.33–7.24 (m, 4H, $H_{F,\,G}$), 7.18–7.09 (m, 1H, H_H), 5.53 (apparent q, $^4J_{HH}$ = $^2J_{HH}$ = 1.4 Hz, 1H, H_M), 5.36 (d, $^2J_{HH}$ = 1.6 Hz, 1H, $H_{M'}$), 2.44–2.33 (m, 2H, $H_{K,\,K'}$), 1.86–1.74 (m, 1H, H_I), 1.73–1.61 (m, 1H, $H_{I'}$), 1.52–1.40 (m, 2H, $H_{J,\,J'}$), 1.35 (s, 3H, H_D), 1.21 (s, 6H, H_A), 1.20 (s, 6H, $H_{A'}$) ppm;

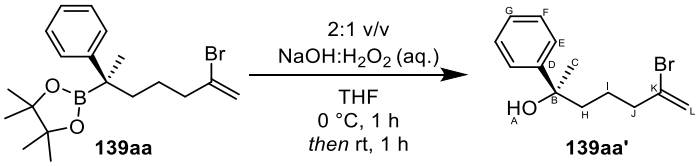
^{13}C NMR (101 MHz, $CDCl_3$): δ_C 147.1 (C_E), 134.8 (C_M), 128.1 (C_F *or* C_G), 126.8 (C_F *or* C_G), 125.1 (C_H), 116.3 (C_L), 83.4 (C_B), 42.1 (C_K), 38.2 (C_I), 24.6 (C_J), 24.2 (C_A), 21.6 (C_D) ppm; C_C not observed due to quadrupolar relaxation;

^{11}B NMR (128 MHz, $CDCl_3$): δ_B 33.1 ppm.

IR (film): ν_{max} 2977, 2945, 1629, 1467, 1379, 1349, 1312, 1141 cm^{-1}.

HRMS (ESI): m/z calc'd for $C_{19}H_{28}{}^{11}B^{79}BrNaO_2$ $[M+Na]^+$ 401.1261 found 401.1265.

(*R*)-6-Bromo-2-phenylhept-6-en-2-ol (139aa')



According to **General Procedure D**, boronic ester **139aa** (19 mg, 0.05 mmol, 1.0 eq.) was reacted with a 2 M aqueous solution of NaOH (0.33 mL) and aqueous H_2O_2 (30% w/w; 0.17 mL) at 0 °C in THF (0.33 mL). The crude reaction mixture was purified by flash column chromatography (pentane/EtOAc 9:1) to give the product (11 mg, 78%, 99:1 e.r.) as a colourless oil.

$\mathbf{R_f}$ = 0.36 (pentane/EtOAc 9:1).

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$**:** +5 (*c* = 2.5, CH_2Cl_2).

NMR Spectroscopy:

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.46–7.39 (m, 2H, H_E), 7.37–7.31 (m, 2H, H_F), 7.26–7.21 (m, 1H, H_G), 5.50 (apparent q, $^4J_{HH}$ = $^2J_{HH}$ = 1.3 Hz, 1H, H_L), 5.35 (d, $^2J_{HH}$ = 1.7 Hz, 1H, $H_{L'}$), 2.35 (td, $^3J_{HH}$ = 7.2 Hz, $^4J_{HH}$ = 1.1 Hz, 2H, $H_{J,\,J'}$), 1.82–1.74 (m, 2H, $H_{H,\,H'}$), 1.66 (br

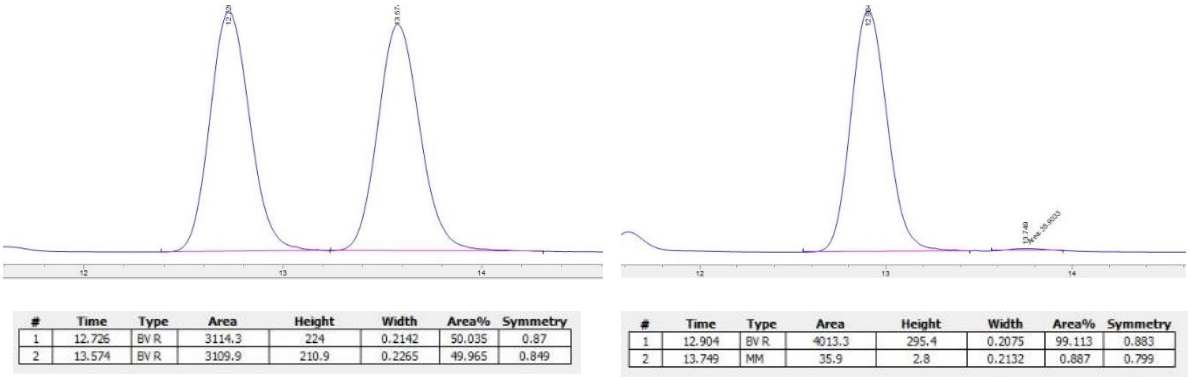
s, 1H, H_A), 1.62–1.48 (m, 1H, H_I), 1.57 (s, 3H, H_C), 1.48–1.35 (m, 1H, $H_{I'}$) ppm;

^{13}C NMR (101 MHz, $CDCl_3$): δ_C 147.7 (C_D), 134.4 (C_K), 128.3 (C_F), 126.8 (C_G), 124.8 (C_E), 116.9 (C_L), 74.6 (C_B), 42.7 (C_J), 41.4 (C_H), 30.3 (C_C), 22.4 (C_I) ppm.

IR (film): ν_{max} 3421 (br), 2949, 1629, 1494, 1446, 1374, 1151 cm^{-1}.

HRMS (ESI): m/z calc'd for $C_{13}H_{17}{}^{79}BrNaO$ $[M+Na]^+$ 291.0355 found 291.0356.

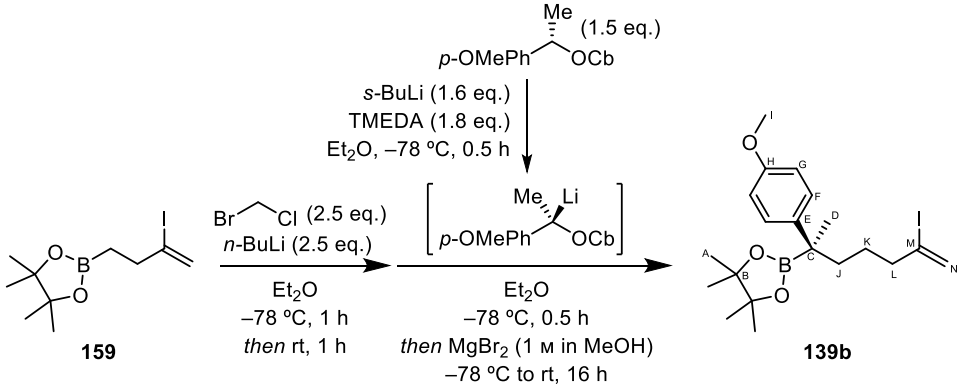
Chiral HPLC (IC column, 98:2 hexane/IPA, 0.5 mL/min, rt, 325 nm): 12.9 min (major), 13.7 min (minor), 99:1 e.r.



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	12.726	BV R	3114.3	224	0.2142	50.035	0.87
2	13.574	BV R	3109.9	210.9	0.2265	49.965	0.849

#	Time	Type	Area	Height	Width	Area%	Symmetry
1	12.904	BV R	4013.3	295.4	0.2075	99.113	0.883
2	13.749	MM	35.9	2.8	0.2132	0.887	0.799

(*S*)-2-(6-Iodo-2-(4-methoxyphenyl)hept-6-en-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (139b)



According to **General Procedure B**, boronic ester **159** (0.462 g, 1.5 mmol, 1.0 eq.) was reacted with bromochloromethane (0.24 mL, 3.8 mmol, 2.5 eq.) and *n*-butyl lithium (1.6 M in hexanes; 2.3 mL, 3.8 mmol, 2.5 eq.). The crude product was then reacted with (*S*)-1-(4-methoxyphenyl)ethyl diisopropylcarbamate[27] (0.629 g, 2.3 mmol, 1.5 eq.), TMEDA (0.40 mL, 2.7 mmol, 1.8 eq.) and *sec*-butyl lithium (1.3 M in cyclohexane/hexane 92:8; 1.9 mL, 2.4 mmol, 1.6 eq.). The crude reaction mixture was purified by flash column chromatography (pentane/Et_2O 9:1) to give the product (0.498 g, 73% over 2 steps, 95:5 e.r.) as a colourless oil.

The e.r. of boronic ester **139b** could not be determined by chiral HPLC/SFC. Instead, the boronic ester was oxidised and the e.r. of alcohol **139b'** was determined.

$\mathbf{R_f}$ = 0.31 (pentane/Et_2O 95:5).

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$**:** –3 (*c* = 5.0, CH_2Cl_2).

NMR Spectroscopy:

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.25–7.19 (m, 2H, H_F), 6.87–6.79 (m, 2H, H_G), 5.98 (apparent q, $^4J_{HH}$ = $^2J_{HH}$ = 1.4 Hz, 1H, H_N), 5.68–5.63 (m, 1H, $H_{N'}$), 3.78 (s, 3H, H_I), 2.42–2.30 (m, 2H, $H_{L, L'}$), 1.83–1.69 (m, 1H, H_J), 1.61 (ddd, J_{HH} = 13.1, 10.8, 5.7 Hz, 1H, $H_{J'}$), 1.52–1.36 (m, 2H, $H_{K, K'}$), 1.33 (s, 3H, H_D), 1.21 (s, 6H, H_A), 1.21 (s, 6H, $H_{A'}$) ppm;

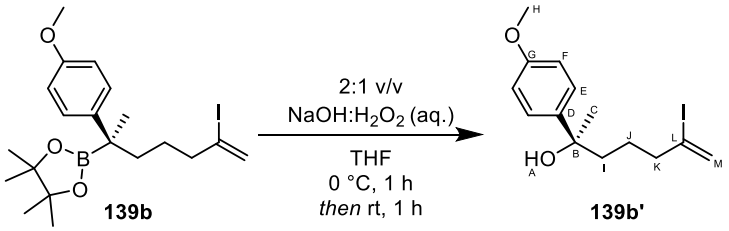
^{13}C NMR (101 MHz, $CDCl_3$): δ_C 157.2 (C_H), 139.1 (C_E), 127.7 (C_F), 125.2 (C_N), 113.5 (C_G), 112.7 (C_M), 83.3 (C_B), 55.2 (C_I), 46.1 (C_L), 38.3 (C_J), 25.4 (C_K), 24.7 (C_A), 24.6 ($C_{A'}$), 21.8 (C_D) ppm; C_C not observed due to quadrupolar relaxation;

^{11}B NMR (128 MHz, $CDCl_3$): δ_B 33.8 ppm.

IR (film): ν_{max} 2976, 2936, 1613, 1509, 1462, 1379, 1307, 1246, 1183, 1138 cm^{-1}.

HRMS (ESI): m/z calc'd for $C_{20}H_{34}{}^{11}BINO_3$ $[M+NH_4]^+$ 474.1675 found 474.1697.

(*R*)-6-Iodo-2-(4-methoxyphenyl)hept-6-en-2-ol (139b')



According to **General Procedure D**, boronic ester **139b** (23 mg, 0.05 mmol, 1.0 eq.) was reacted with a 2 M aqueous solution of NaOH (0.33 mL) and aqueous H_2O_2 (30% w/w; 0.17 mL) at 0 °C in THF (0.33 mL). The crude reaction mixture was purified by flash column chromatography (pentane/EtOAc 9:1) to give the product (14 mg, 83%, 95:5 e.r.) as a colourless oil.

$\mathbf{R_f}$ = 0.11 (pentane/EtOAc 9:1).

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$**:** +2 (*c* = 3.6, CH_2Cl_2).

NMR Spectroscopy:

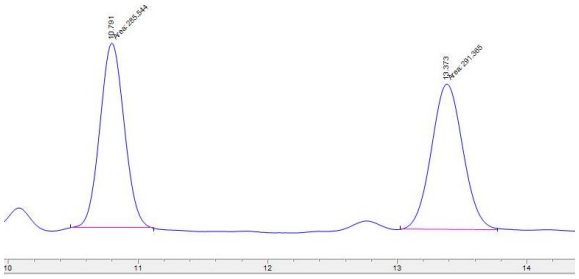
^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.39–7.30 (m, 2H, H_E), 6.92–6.84 (m, 2H, H_F), 5.97 (apparent q, $^4J_{HH}$ = $^2J_{HH}$ = 1.4 Hz, 1H, H_M), 5.67 (dt, $^2J_{HH}$ = 1.4 Hz, $^4J_{HH}$ = 0.6 Hz, 1H, $H_{M'}$), 3.81 (s, 3H, H_H), 2.36–2.29 (m, 2H, $H_{K, K'}$), 1.81–1.67 (m, 2H, $H_{I, I'}$), 1.56 (s, 3H, H_C), 1.53–1.37 (m, 2H, $H_{J, J'}$) ppm; H_A not observed;

^{13}C NMR (101 MHz, $CDCl_3$): δ_C 158.3 (C_G), 139.9 (C_D), 126.0 (C_E), 125.6 (C_M), 113.5 (C_F), 112.2 (C_L), 74.2 (C_B), 55.3 (C_H), 45.2 (C_K), 42.5 (C_I), 30.2 (C_C), 23.6 (C_J) ppm.

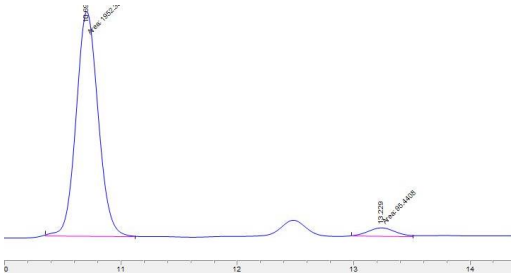
IR (film): ν_{max} 2933, 1608, 1511, 1289, 1246, 1180, 1034 cm^{-1}.

HRMS (ESI): m/z calc'd for $C_{14}H_{19}INaO_2$ $[M+Na]^+$ 369.0322 found 369.0330.

Chiral HPLC (IC column, 95:5 hexane/IPA, 1 mL/min, rt, 230 nm): 10.7 min (major), 13.2 min (minor), 95:5 e.r.

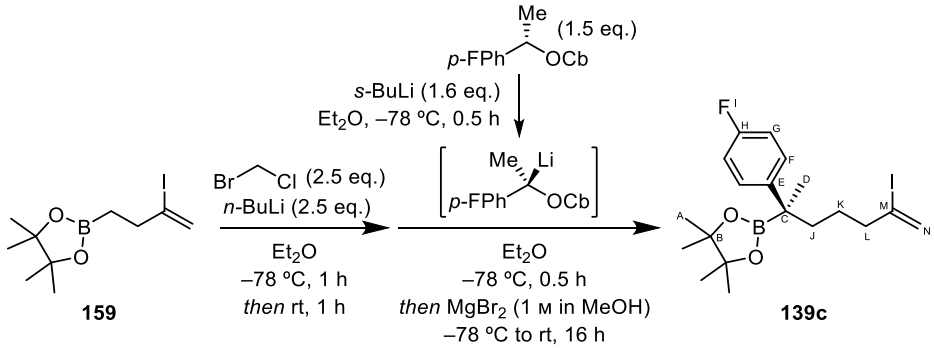


#	Time	Type	Area	Height	Width	Area%	Symmetry
1	10.791	MM	285.5	21.8	0.2179	49.495	0.94
2	13.373	MM	291.4	17.2	0.2821	50.505	0.94



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	10.699	MM	1952.3	148.2	0.2196	95.339	0.904
2	13.229	MM	95.4	5.7	0.2796	4.661	0.888

(S)-2-(2-(4-Fluorophenyl)-6-iodohept-6-en-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (139c)



According to **General Procedure A**, boronic ester **159** (0.462 g, 1.5 mmol, 1.0 eq.) was reacted with bromochloromethane (0.24 mL, 3.8 mmol, 2.5 eq.) and *n*-butyl lithium (1.6 M in hexanes; 2.3 mL, 3.8 mmol, 2.5 eq.). The crude product was then reacted with (*S*)-1-(4-fluorophenyl)ethyl diisopropylcarbamate[28] (0.602 g, 2.3 mmol, 1.5 eq.) and *sec*-butyl lithium (1.3 M in cyclohexane/hexane 92:8; 1.9 mL, 2.4 mmol, 1.6 eq.). The crude reaction

mixture was purified by flash column chromatography (pentane/Et_2O 50:1) to give the product (0.403 g, 61% over 2 steps, e.r. n.d.) as a colourless oil.

The e.r. of boronic ester **139c** could not be determined by chiral HPLC/SFC or by using Pirkle's chiral solvating agent.

$\mathbf{R_f}$ = 0.50 (pentane/Et_2O 95:5).

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$**:** –3 (*c* = 5.0, CH_2Cl_2).

NMR Spectroscopy:

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.31–7.21 (m, 2H, H_F), 7.01–6.91 (m, 2H, H_G), 5.98 (apparent q, $^4J_{HH}$ = $^2J_{HH}$ = 1.4 Hz, 1H, H_N), 5.66 (d, $^2J_{HH}$ = 1.5 Hz, 1H, H_N), 2.36 (apparent tt, $^3J_{HH}$ = 7.2 Hz, $^4J_{HH}$ = 1.6 Hz, 2H, $H_{L, L'}$), 1.80-1.69 (m, 1H, H_J), 1.67–1.58 (m, 1H, $H_{J'}$), 1.48–1.36 (m, 2H, $H_{K, K'}$), 1.33 (s, 3H, H_D), 1.21 (s, 6H, H_A), 1.21 (s, 6H, $H_{A'}$) ppm;

^{13}C NMR (101 MHz, $CDCl_3$): δ_C 161.2 (d, $^1J_{CF}$ = 242.9 Hz, C_H), 142.6 (d, $^4J_{CF}$ = 3.0 Hz, C_E), 128.2 (d, $^3J_{CF}$ = 7.6 Hz, C_F), 125.3 (C_N), 114.7 (d, $^2J_{CF}$ = 20.7 Hz, C_G), 112.5 (C_M), 83.5 (C_B), 45.9 (C_L), 38.2 (C_J), 25.2 (C_K), 24.6 (C_A), 24.6 ($C_{A'}$), 21.8 (C_D) ppm; C_C not observed due to quadrupolar relaxation;

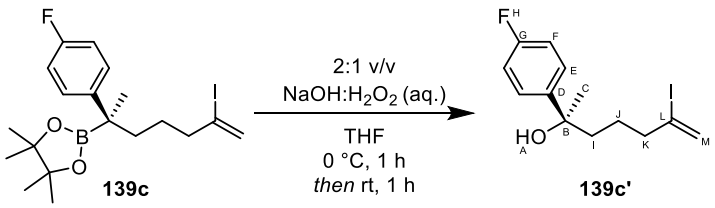
^{11}B NMR (128 MHz, $CDCl_3$): δ_B 33.7 ppm;

^{19}F NMR (377 MHz, $CDCl_3$): δ_F −118.9 ppm.

IR (film): ν_{max} 2977. 2931, 1616, 1508, 1466, 1380, 1350, 1316, 1231, 1141 cm^{-1}.

HRMS (ESI): m/z calc'd for $C_{19}H_{30}{}^{11}BFINO_2$ $[M+NH_4]^+$ 426.1475 found 462.1471.

(*R*)-2-(4-Fluorophenyl)-6-iodohept-6-en-2-ol (139c')



According to **General Procedure D**, boronic ester **139c** (22 mg, 0.05 mmol, 1.0 eq.) was reacted with a 2 M aqueous solution of NaOH (0.33 mL) and aqueous H_2O_2 (30% w/w; 0.17 mL) at 0 °C in THF (0.33 mL). The crude reaction mixture was purified by flash column chromatography (pentane/EtOAc 9:1) to give the product (15 mg, 87%, e.r. n.d.) as a colourless oil.

The e.r. of alcohol **139c'** could not be determined by chiral HPLC/SFC or by using Pirkle's chiral solvating agent.

$\mathbf{R_f}$ = 0.09 (pentane/EtOAc 9:1).

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$**:** +9 (*c* = 2.7, CH_2Cl_2).

NMR Spectroscopy:

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.46–7.34 (m, 2H, H_E), 7.08–6.96 (m, 2H, H_F), 5.98 (apparent q, $^4J_{HH}$ = $^2J_{HH}$ = 1.4 Hz, 1H, H_M), 5.67 (dd, $^2J_{HH}$ = 1.4 Hz, $^4J_{HH}$ = 0.7 Hz, 1H, $H_{M'}$), 2.35–2.30 (m, 2H, $H_{K, K'}$), 1.83–1.66 (m, 2H, $H_{I, I'}$), 1.62 (br s, 1H, H_A), 1.57 (s, 3H, H_C), 1.54–1.44 (m, 1H, H_J), 1.42–1.30 (m, 1H, $H_{J'}$) ppm;

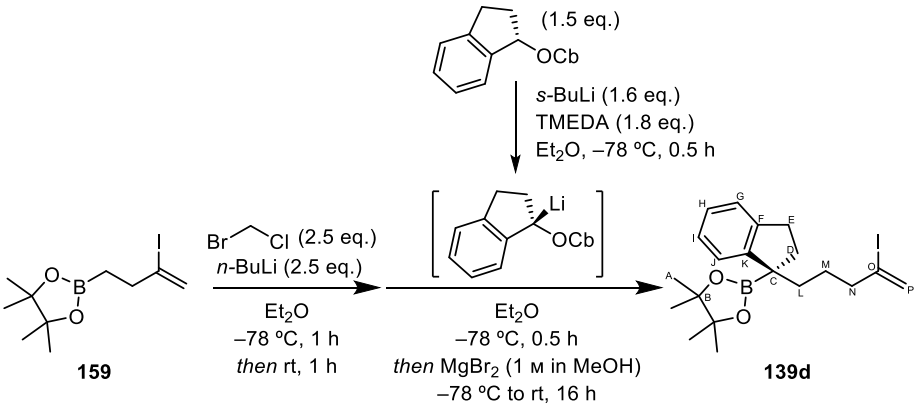
^{13}C NMR (101 MHz, $CDCl_3$): δ_C 161.7 (d, $^1J_{CF}$ = 244.6 Hz, C_G), 143.4 (d, $^4J_{CF}$ = 3.1 Hz, C_D), 126.5 (d, $^3J_{CF}$ = 7.9 Hz, C_E), 125.8 (C_M), 114.9 (d, $^2J_{CF}$ = 21.1 Hz, C_F), 112.1 (C_L), 74.2 (C_B), 45.1 (C_K), 42.5 (C_I), 30.4 (C_C), 23.4 (C_J) ppm;

^{19}F NMR (377 MHz, $CDCl_3$): δ_F −116.7 ppm.

IR (film): ν_{max} 3415 (br), 2943, 1602, 1510, 1226, 1160 cm^{-1}.

HRMS (ESI): m/z calc'd for $C_{13}H_{16}FINaO$ $[M+Na]^+$ 357.0122 found 357.0105.

(*R*)-2-(1-(4-Iodopent-4-en-1-yl)-2,3-dihydro-1*H*-inden-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (139d)



According to **General Procedure B**, boronic ester **159** (0.308 g, 1.0 mmol, 1.0 eq.) was reacted with bromochloromethane (0.16 mL, 2.5 mmol, 2.5 eq.) and *n*-butyl lithium (1.6 M in hexanes; 1.6 mL, 2.5 mmol, 2.5 eq.). The crude product was then reacted with (*S*)-2,3-dihydro-1*H*-inden-1-yl diisopropylcarbamate[27] (0.392 g, 1.5 mmol, 1.5 eq.), TMEDA (0.27 mL, 1.8 mmol, 1.8 eq.) and *sec*-butyl lithium (1.3 M in cyclohexane/hexane 92:8; 1.2 mL,

1.6 mmol, 1.6 eq.). The crude reaction mixture was purified by flash column chromatography (pentane/Et_2O 50:1) to give the product (0.268 g, 61% over 2 steps, 96:4 e.r.) as a colourless solid.

The e.r. of boronic ester **139d** could not be determined by chiral HPLC/SFC. Instead, the boronic ester was oxidised and the e.r. of alcohol **139d'** was determined.

$\mathbf{R_f}$ = 0.59 (pentane/Et_2O 95:5).

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$**:** +8 (*c* = 4.8, CH_2Cl_2).

NMR Spectroscopy:

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.25–7.20 (m, 1H, H_{Ar}), 7.20-7.16 (m, 1H, H_{Ar}), 7.14–7.05 (m, 2H, H_{Ar}), 6.00 (apparent q, $^4J_{HH}$ = $^2J_{HH}$ = 1.4 Hz, 1H, H_P), 5.69–5.63 (m, 1H, $H_{P'}$), 2.92 (apparent t, $^3J_{HH}$ = 7.4 Hz, 2H, $H_{E,E'}$), 2.47–2.30 (m, 3H, $H_{D,N,N'}$), 1.94–1.75 (m, 2H, $H_{D',L}$) 1.62–1.46 (m, 2H, $H_{M,M'}$), 1.47–1.36 (m, 1H, $H_{L'}$), 1.19 (s, 6H, H_A), 1.17 (s, 6H, $H_{A'}$) ppm;

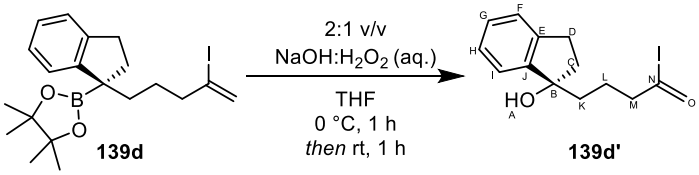
^{13}C NMR (101 MHz, $CDCl_3$): δ_C 148.8 (C_F), 143.7 (C_K), 125.9 (C_{Ar}), 125.7 (C_{Ar}), 125.3 (C_P), 124.3 (C_{Ar}), 124.1 (C_{Ar}), 112.6 (C_O), 83.3 (C_B), 45.9 (C_N), 36.8 (C_L), 34.0 (C_D), 31.6 (C_E), 26.7 (C_M), 24.7 (C_A) ppm; C_C not observed due to quadrupolar relaxation;

^{11}B NMR (128 MHz, $CDCl_3$): δ_B 33.3 ppm.

IR (film): ν_{max} 2976, 2934, 1616, 1370, 1313, 1263, 1213, 1165, 1141 cm^{-1}.

HRMS (ESI): m/z calc'd for $C_{20}H_{28}{}^{11}BINaO_2$ $[M+Na]^+$ 456.1569 found 456.1584.

(*S*)-1-(4-Iodopent-4-en-1-yl)-2,3-dihydro-1*H*-inden-1-ol (139d')



According to **General Procedure D**, boronic ester **139d** (22 mg, 0.05 mmol, 1.0 eq.) was reacted with a 2 M aqueous solution of NaOH (0.33 mL) and aqueous H_2O_2 (30% w/w; 0.17 mL) at 0 °C in THF (0.33 mL). The crude reaction mixture was purified by flash column chromatography (pentane/EtOAc 9:1) to give the product (11 mg, 70%, 96:4 e.r.) as a colourless oil.

$\mathbf{R_f}$ = 0.17 (pentane/EtOAc 9:1).

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$**:** –3 (*c* = 2.9, CH_2Cl_2).

NMR Spectroscopy:

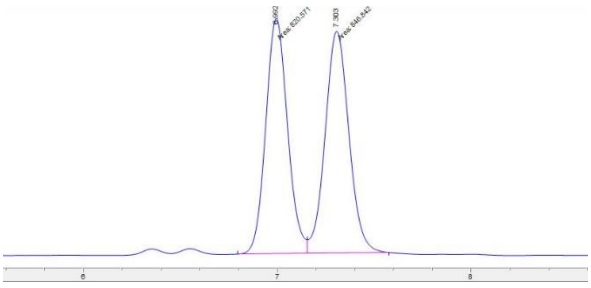
^{1}H NMR (400 MHz, CD_2Cl_2): δ_H 7.35–7.29 (m, 1H, H_{Ar}), 7.27–7.18 (m, 3H, H_{Ar}), 6.03 (apparent q, $^4J_{HH}$ = $^2J_{HH}$ = 1.4 Hz, 1H, H_O), 5.72–5.66 (m, 1H, $H_{O'}$), 3.00 (ddd, $^2J_{HH}$ = 16.1 Hz, $^3J_{HH}$ = 8.6, 4.9 Hz, 1H, H_D), 2.83 (ddd, $^2J_{HH}$ = 16.1 Hz, $^3J_{HH}$ = 8.2, 6.5 Hz, 1H, $H_{D'}$), 2.50–2.36 (m, 2H, $H_{M, M'}$), 2.31 (ddd, $^2J_{HH}$ = 13.2 Hz, $^3J_{HH}$ = 8.2, 4.9 Hz, 1H, H_C), 2.08 (ddd, $^2J_{HH}$ = 13.2 Hz, $^3J_{HH}$ = 8.6, 6.5 Hz, 1H, $H_{C'}$), 1.90-1.79 (m, 1H, H_K), 1.77 (s, 1H, H_A), 1.72–1.61 (m, 2H, $H_{K', L}$), 1.61–1.55 (m, 1H, $H_{L'}$) ppm;

^{13}C NMR (101 MHz, CD_2Cl_2): δ_C 147.6 (C_E *or* C_J), 143.1 (C_E *or* C_J), 128.1 (C_{Ar}), 126.5 (C_{Ar}), 125.5 (C_O), 124.9 (C_{Ar}), 122.7 (C_{Ar}), 112.4 (C_N), 83.3 (C_B), 45.4 (C_M), 40.0 (C_C), 38.7 (C_K), 29.4 (C_D), 23.9 (C_L) ppm.

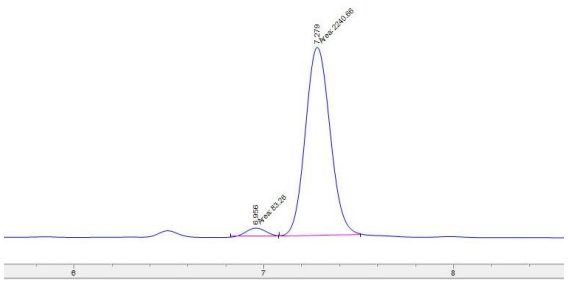
IR (film): ν_{max} 3372 (br), 2940, 2848, 1620, 1461, 1166, 1034 cm^{-1}.

HRMS (ESI): m/z calc'd for $C_{14}H_{17}INaO$ $[M+Na]^+$ 351.0216 found 351.0219.

Chiral HPLC (IC column, 95:5 hexane/IPA, 1 mL/min, rt, 254 nm): 7.0 min (minor), 7.3 min (major), 96:4 e.r.

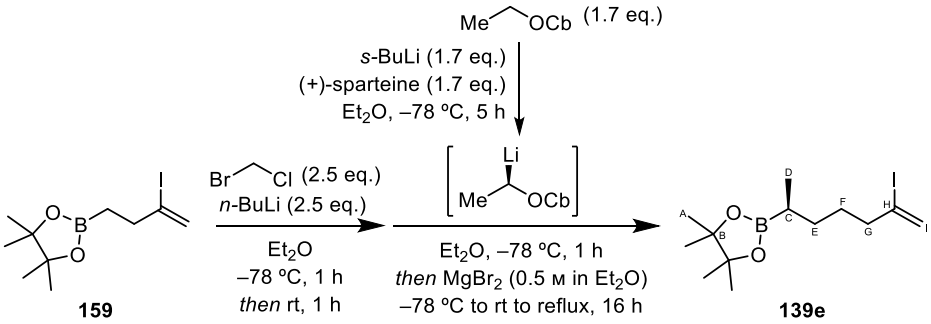


#	Time	Type	Area	Height	Width	Area%	Symmetry
1	6.992	MF	820.6	104.8	0.1305	49.212	0.897
2	7.303	FM	846.8	99	0.1426	50.788	0.914



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	6.956	MM	83.3	11.2	0.1237	3.583	0.888
2	7.279	MM	2240.7	246.6	0.1515	96.417	0.896

(S)-2-(6-Iodohept-6-en-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (139e)



According to **General Procedure C**, boronic ester **159** (0.308 g, 1.0 mmol, 1.0 eq.) was reacted with bromochloromethane (0.16 mL, 2.5 mmol, 2.5 eq.) and *n*-butyl lithium (1.6 M in hexanes; 1.6 mL, 2.5 mmol, 2.5 eq.). The crude product was then reacted with ethyl diisopropylcarbamate[22] (0.289 g, 1.7 mmol, 1.7 eq.), (+)-sparteine (380 μL, 1.7 mmol, 1.7 eq.) and *sec*-butyl lithium (1.3 M in cyclohexane/hexane 92:8; 1.3 mL, 1.7 mmol, 1.7 eq.). The crude reaction mixture was purified by flash column chromatography (pentane/Et_2O 100:1 to 50:1) to give the product (0.193 g, 55% over 2 steps, 98:2 e.r.) as a colourless oil.

The e.r. of boronic ester **139e** could not be determined by chiral HPLC/SFC. Instead, the boronic ester was oxidised and the e.r. of alcohol **139e'** was determined.

$\mathbf{R_f}$ = 0.70 (pentane/Et_2O 98:2).

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$**:** +5 (*c* = 5.0, CH_2Cl_2).

NMR Spectroscopy:

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 6.00 (apparent q, $^4J_{HH}$ = $^2J_{HH}$ = 1.4 Hz, 1H, H_I), 5.66 (dt, $^2J_{HH}$ = 1.3 Hz, $^4J_{HH}$ = 0.6 Hz, 1H, $H_{I'}$), 2.38 (td, $^3J_{HH}$ = 7.3 Hz, $^4J_{HH}$ = 1.4 Hz, 2H, $H_{G,\,G'}$), 1.58–1.48 (m, 2H, $H_{F,\,F'}$), 1.48–1.38 (m, 1H, H_E), 1.35–1.27 (m, 1H, $H_{E'}$), 1.24 (s, 12H, H_A), 1.06–0.94 (m, 4H, $H_{C,\,D}$) ppm;

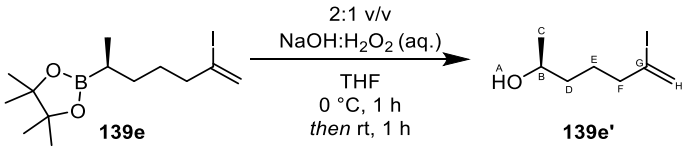
^{13}C NMR (101 MHz, $CDCl_3$): δ_C 125.1 (C_I), 112.8 (C_H), 82.9 (C_B), 45.6 (C_G), 31.8 (C_E), 28.5 (C_F), 24.8 (C_A), 24.8 ($C_{A'}$), 15.5 (C_D) ppm; C_C not observed due to quadrupolar relaxation;

^{11}B NMR (128 MHz, $CDCl_3$): δ_B 35.5 ppm.

IR (film): ν_{max} 2976, 2929, 2870, 1617, 1460, 1370, 1315, 1144 cm^{-1}.

HRMS (ESI): m/z calc'd for $C_{13}H_{24}{}^{11}BINaO_2$ $[M+Na]^+$ 373.0809 found 373.0806.

(*S*)-6-Iodohept-6-en-2-ol (139e')



According to **General Procedure D**, boronic ester **139e** (18 mg, 0.05 mmol, 1.0 eq.) was reacted with a 2 M aqueous solution of NaOH (0.33 mL) and aqueous H_2O_2 (30% w/w; 0.17 mL) at 0 °C in THF (0.33 mL). The crude reaction mixture was purified by flash column chromatography (pentane/EtOAc 9:1) to give the product (8 mg, 70%, 98:2 e.r.) as a colourless oil.

$\mathbf{R_f}$ = 0.14 (pentane/EtOAc 9:1).

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$**:** +3 (*c* = 2.7, CH_2Cl_2).

NMR Spectroscopy:

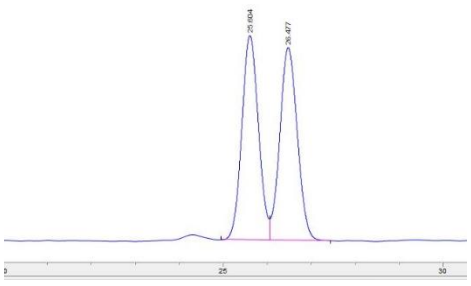
^{1}H NMR (400 MHz, $CDCl_3$): δ_H 6.03 (apparent q, $^4J_{HH}$ = $^2J_{HH}$ = 1.4 Hz, 1H, H_H), 5.70 (dd, $^2J_{HH}$ = 1.4 Hz, $^4J_{HH}$ = 0.7 Hz, 1H, $H_{H'}$), 3.89–3.76 (m, 1H, H_B), 2.41 (td, $^3J_{HH}$ = 7.2 Hz, $^4J_{HH}$ = 1.4 Hz, 2H, $H_{F, F'}$), 1.71–1.37 (m, 4H, $H_{D, D', E, E'}$), 1.21 (d, $^3J_{HH}$ = 6.2 Hz, 3H, H_C) ppm; H_A not observed;

^{13}C NMR (101 MHz, $CDCl_3$): δ_C 125.6 (C_H), 112.1 (C_G), 67.8 (C_B), 45.1 (C_F), 37.6 (C_D), 25.3 (C_E), 23.6 (C_C) ppm.

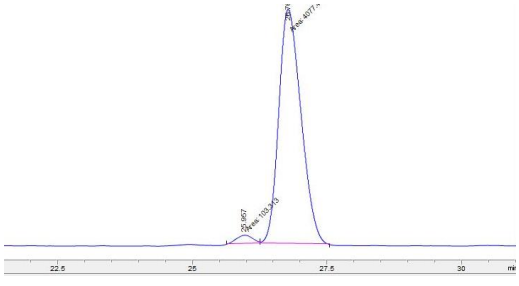
IR (film): ν_{max} 3362 (br), 2964, 2925, 1616, 1458, 1401, 1373, 1136 cm^{-1}.

HRMS (ESI): m/z calc'd for $C_7H_{13}INaO$ $[M+Na]^+$ 262.9909 found 262.9903.

Chiral HPLC (IB column, 99.5:0.5 hexane/IPA, 1 mL/min, rt, 254 nm): 26.0 min (minor), 26.8 min (major), 98:2 e.r.

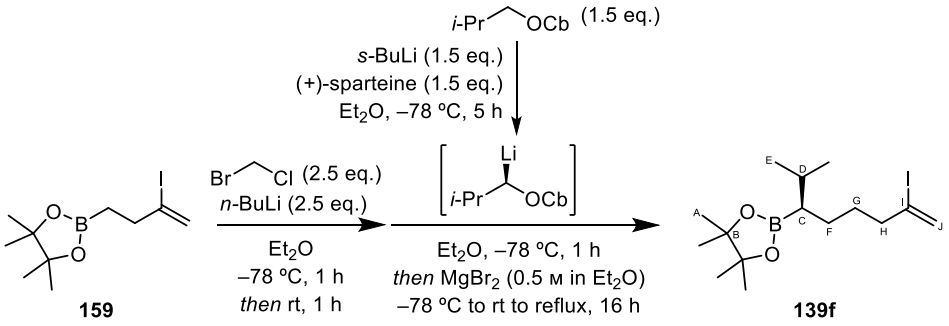


#	Time	Type	Area	Height	Width	Area%	Symmetry
1	25.604	BV	1551	59	0.3903	50.132	0.911
2	26.477	VB	1542.9	55.6	0.4221	49.868	0.894



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	25.957	MM	103.3	5	0.3454	2.471	0.997
2	26.764	MM	4077.4	141.8	0.4794	97.529	0.748

(R)-2-(7-Iodo-2-methyloct-7-en-3-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (139f)



According to **General Procedure C**, boronic ester **159** (0.308 g, 1.0 mmol, 1.0 eq.) was reacted with bromochloromethane (0.16 mL, 2.5 mmol, 2.5 eq.) and *n*-butyl lithium (1.6 M in hexanes; 1.6 mL, 2.5 mmol, 2.5 eq.). The crude product was then reacted with *iso*-butyl diisopropylcarbamate[22] (0.302 g, 1.5 mmol, 1.5 eq.), (+)-sparteine (350 μL, 1.5 mmol, 1.5 eq.) and *sec*-butyl lithium (1.3 M in cyclohexane/hexane 92:8; 1.2 mL, 1.5 mmol, 1.5 eq.). The crude reaction mixture was purified by flash column chromatography (pentane/Et_2O 100:1) to give the product (0.147 g, 39% over 2 steps, 95:5 e.r.) as a colourless oil.

The e.r. of boronic ester **139f** could not be determined by chiral HPLC/SFC. Instead, the boronic ester was oxidised and the e.r. of alcohol **139f'** was determined.

$\mathbf{R_f}$ = 0.57 (pentane/Et_2O 98:2).

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$**:** +5 (*c* = 5.0, CH_2Cl_2).

NMR Spectroscopy:

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 6.00 (apparent q, $^4J_{HH}$ = $^2J_{HH}$ = 1.4 Hz, 1H, H_J), 5.66 (dd, $^2J_{HH}$ = 1.3 Hz, $^4J_{HH}$ = 0.6 Hz, 1H, $H_{J'}$), 2.45–2.33 (m, 2H, $H_{H, H'}$), 1.70 (hept, $^3J_{HH}$ = 6.7 Hz, 1H, H_D), 1.57–1.49 (m, 1H, H_G), 1.48–1.31 (m, 3H, $H_{F, F', G'}$), 1.26 (s, 12H, H_A), 0.92 (d, $^3J_{HH}$ = 6.7 Hz, 3H, H_E), 0.91 (d, $^3J_{HH}$ = 6.7 Hz, 3H, $H_{E'}$) ppm;

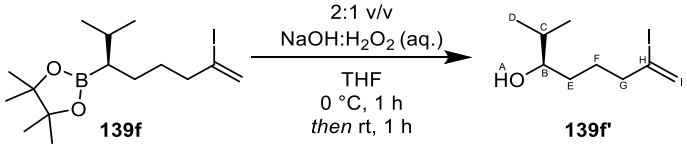
^{13}C NMR (101 MHz, $CDCl_3$): δ_C 125.1 (C_J), 112.8 (C_I), 82.9 (C_B), 45.7 (C_H), 29.6 (C_D), 29.1 (C_G), 27.8 (C_F), 25.0 (C_A), 24.9 ($C_{A'}$), 22.3 (C_E), 21.8 ($C_{E'}$) ppm; C_C not observed due to quadrupolar relaxation;

^{11}B NMR (128 MHz, $CDCl_3$): δ_B 33.6 ppm.

IR (film): ν_{max} 3423, 2960, 2925, 2858, 1617, 1459, 1380, 1315, 1260, 1216, 1144 cm^{-1}.

HRMS (ESI): m/z calc'd for $C_{15}H_{29}O_2{}^{11}BI$ $[M+H]^+$ 379.1300 found 379.1308.

(*R*)-7-Iodo-2-methyloct-7-en-3-ol (139f')



According to **General Procedure D**, boronic ester **139f** (19 mg, 0.05 mmol, 1.0 eq.) was reacted with a 2 M aqueous solution of NaOH (0.33 mL) and aqueous H_2O_2 (30% w/w; 0.17 mL) at 0 °C in THF (0.33 mL). The crude reaction mixture was purified by flash column chromatography (pentane/EtOAc 9:1) to give the product (12 mg, 90%, 95:5 e.r.) as a colourless oil.

R_f = 0.17 (pentane/EtOAc 9:1).

$[\alpha]_D^{25}$: +9 (*c* = 2.7, CH_2Cl_2).

NMR Spectroscopy:

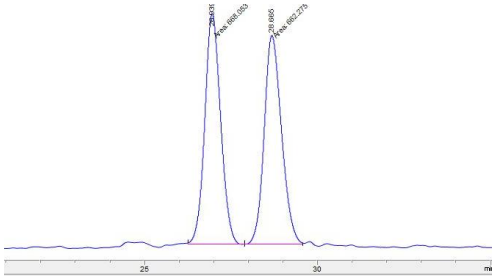
^{1}H NMR (400 MHz, $CDCl_3$): δ_H 6.03 (apparent q, $^4J_{HH}$ = $^2J_{HH}$ = 1.4 Hz, 1H, H_I), 5.70 (dd, $^2J_{HH}$ = 1.4 Hz, $^4J_{HH}$ = 0.7 Hz, 1H, $H_{I'}$), 3.38 (ddd, $^3J_{HH}$ = 8.6, 5.2, 3.5 Hz, 1H, H_B), 2.46–2.38 (m, 2H, $H_{G, G'}$), 1.78–1.60 (m, 2H, $H_{C, F}$), 1.60-1.43 (m, 2H, $H_{E, F'}$), 1.43–1.31 (m, 1H, $H_{E'}$), 0.92 (d, $^3J_{HH}$ = 6.8 Hz, 3H, H_D), 0.91 (d, $^3J_{HH}$ = 6.8 Hz, 3H, $H_{D'}$) ppm; H_A not observed;

^{13}C NMR (101 MHz, $CDCl_3$): δ_C 125.5 (C_I), 112.4 (C_H), 76.4 (C_B), 45.2 (C_G), 33.6 (C_C), 32.6 (C_E), 25.5 (C_F), 18.9 (C_D), 17.1 ($C_{D'}$) ppm.

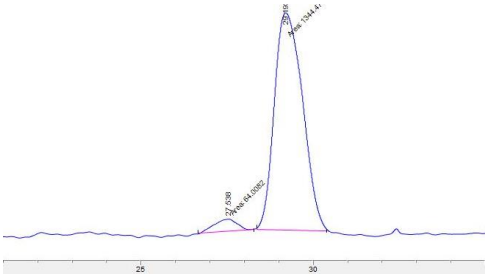
IR (film): ν_{max} 3374 (br), 2957, 2872, 1616, 1459, 1385, 1261, 1173, 1139 cm^{-1}.

HRMS (ESI): m/z calc'd for $C_9H_{17}INaO$ $[M+Na]^+$ 291.0216 found 291.0208.

Chiral HPLC (IA column, 99.9:0.1 hexane/IPA, 1 mL/min, rt, 254 nm): 27.5 min (minor), 29.2 (major), 95:5 e.r.

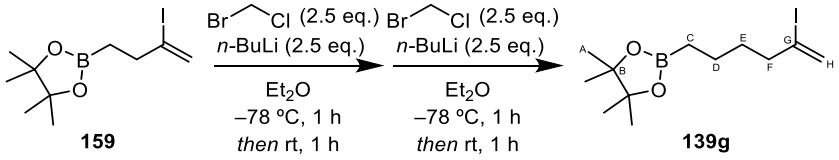


#	Time	Type	Area	Height	Width	Area%	Symmetry
1	26.939	BB	1200.5	37.8	0.4419	50.323	0.847
2	28.664	BB	1185.1	34.2	0.4595	49.677	0.757



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	27.526	MM	115.4	2.4	0.8099	4.547	1.515
2	29.191	MM	2422.7	42.4	0.9524	95.453	0.676

2-(5-Iodohex-5-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (139g)



159 **139g**

According to a modified literature procedure,[75] boronic ester **159** (0.616 g, 2.0 mmol, 1.0 eq.) was dissolved in anhydrous Et_2O (20 mL) and cooled to −78 °C (dry ice/acetone). Bromochloromethane (0.32 mL, 5.0 mmol, 2.5 eq.) was added dropwise (~0.5 mL/min). To the resultant mixture *n*-butyl lithium (1.6 M in hexanes; 3.1 mL, 5.0 mmol, 2.5 eq.) was added *via* syringe pump (0.03 mL/min). Following the addition, the reaction mixture was stirred at −78 °C for 1 hour and then warmed to rt and stirred at this temperature for 1 hour. The reaction mixture was filtered through a silica plug (eluting Et_2O) and concentrated *in vacuo*. The crude product was used without further purification. The above procedure was then repeated to yield the crude twice homologated boronic ester which was purified by flash column chromatography (pentane/CH_2Cl_2 9:1) to give the product (0.376 g, 56% over 2 steps) as a colourless oil.

$\mathbf{R_f}$ = 0.40 (pentane/Et_2O 98:2).

NMR Spectroscopy:

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 6.00 (apparent q, $^4J_{HH}$ = $^2J_{HH}$ = 1.4 Hz, 1H, H_H), 5.67 (dt, $^2J_{HH}$ = 1.4 Hz, $^4J_{HH}$ = 0.6 Hz, 1H, $H_{H'}$), 2.41–2.33 (m, 2H, H_F), 1.56–1.47 (m, 2H, H_E), 1.47–1.37 (m, 2H, H_D), 1.25 (s, 12H, H_A), 0.79 (t, $^3J_{HH}$ = 7.7 Hz, 2H, H_C) ppm;

^{13}C NMR (101 MHz, $CDCl_3$): δ_C 125.1 (C_H), 112.7 (C_G), 83.0 (C_B), 45.2 (C_F), 31.7 (C_E), 24.9 (C_A), 24.8 ($C_{A'}$), 22.7 (C_D) ppm; C_C not observed due to quadrupolar relaxation;

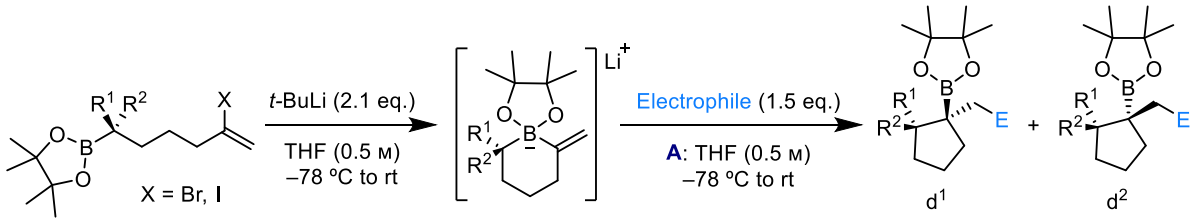
^{11}B NMR (128 MHz, $CDCl_3$): δ_B 33.7 ppm.

IR (film): ν_{max} 2987, 2931, 2862, 1617, 1378, 1320, 1145 cm^{-1}.

HRMS (ESI): m/z calc'd for $C_{12}H_{22}{}^{11}BIO_2Na$ $[M+Na]^+$ 359.0652 found 359.0655.

6.2.2. Synthesis of cyclopentyl boronic esters

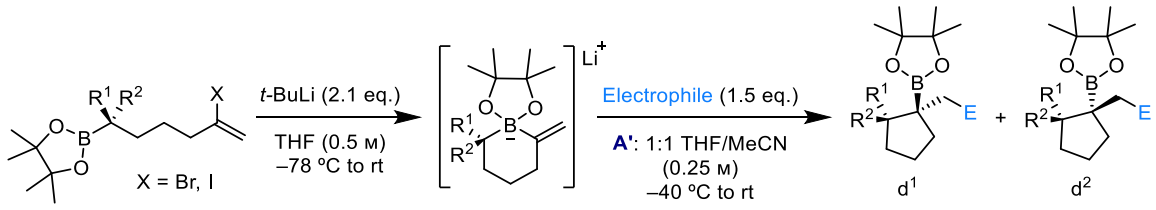
6.2.2.1. General procedure E: electrophile-induced ring contraction of 6-membered cyclic alkenyl boronate complexes in THF



tert-Butyl lithium[a] (in pentane, 0.42 mmol, 2.1 eq.) was added dropwise (~0.5 mL/min) to a solution of the starting boronic ester (0.20 mmol, 1.0 eq.) in anhydrous THF (0.40 mL, 0.5 M) at −78 °C (dry ice/acetone) and allowed to stir at this temperature for 1 hour. The cooling bath was removed, and the reaction was stirred at rt for a further 1 hour before being cooled again to −78 °C (dry ice/acetone) whereupon the electrophile[b] (0.30 mmol, 1.5 eq.) was added. The reaction mixture was stirred at −78 °C for 2 hours and slowly warmed to rt overnight (the replenishment of dry ice in the cooling bath was halted). The reaction mixture was diluted with Et_2O (5 mL) and quenched with water[c] (5 mL). The aqueous layer was extracted with Et_2O (3 × 5 mL) and the combined organics washed with brine (5 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude residue was analysed by ^1H NMR to determine in what diastereomeric ratio the product was formed. The crude reaction mixture was then purified by flash column chromatography.

[a] *tert*-Butyl lithium should be titrated before use.[193] [b] Electrophiles sufficiently soluble in THF were added as 1 M solutions in THF, those with partial solubility were quickly added directly into the flask. [c] To be replaced with 0.5 M aqueous NaOH when using Eschenmoser's salt as the electrophile.

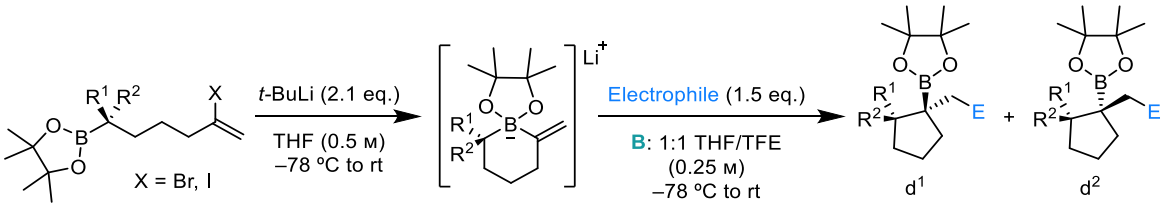
6.2.2.2. General procedure F: electrophile-induced ring contraction of 6-membered cyclic alkenyl boronate complexes in 1:1 THF/MeCN



tert-Butyl lithium[a] (in pentane, 0.42 mmol, 2.1 eq.) was added dropwise (~0.5 mL/min) to a solution of the starting boronic ester (0.20 mmol, 1.0 eq.) in anhydrous THF (0.40 mL, 0.5 M) at −78 °C (dry ice/acetone) and allowed to stir at this temperature for 1 hour. The cooling bath was removed, and the reaction was stirred at rt for a further 1 hour before being cooled to −40 °C (cryostat) whereupon anhydrous MeCN (0.40 mL) was added followed by the electrophile[b] (0.30 mmol, 1.5 eq.). The reaction mixture was stirred at −40 °C for 2 hours and slowly warmed to rt overnight (the cryostat was turned off). The reaction mixture was diluted with Et_2O (5 mL) and quenched with water (5 mL). The aqueous layer was extracted with Et_2O (3 × 5 mL) and the combined organics washed with brine (5 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude residue was analysed by ^1H NMR to determine in what diastereomeric ratio the product was formed. The crude reaction mixture was then purified by flash column chromatography.

[a] *tert*-Butyl lithium should be titrated before use.[193] [b] Electrophiles sufficiently soluble in THF were added as 1 M solutions in THF, those with partial solubility were quickly added directly into the flask.

6.2.2.3. General procedure G: electrophile-induced ring contraction of 6-membered cyclic alkenyl boronate complexes in 1:1 THF/TFE

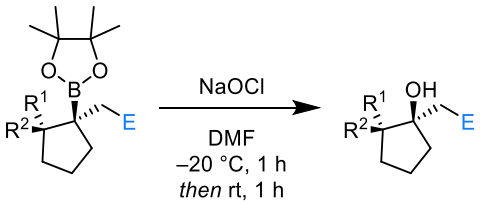


tert-Butyl lithium[a] (in pentane, 0.42 mmol, 2.1 eq.) was added dropwise (~0.5 mL/min) to a solution of the starting boronic ester (0.20 mmol, 1.0 eq.) in anhydrous THF (0.40 mL, 0.5 M) at −78 °C (dry ice/acetone) and allowed to stir at this temperature for 1 hour. The cooling bath was removed, and the reaction was stirred at rt for a further 1 hour before being cooled again

to −78 °C (dry ice/acetone) whereupon 2,2,2-trifluoroethanol (TFE) (0.40 mL) was added followed by the electrophile[b] (0.30 mmol, 1.5 eq.). The reaction mixture was stirred at −78 °C for 2 hours and slowly warmed to rt overnight (the replenishment of dry ice in the cooling bath was halted). The reaction mixture was diluted with Et_2O (5 mL) and quenched with water[c] (5 mL). The aqueous layer was extracted with Et_2O (3 × 5 mL) and the combined organics washed with brine (5 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude residue was analysed by ^1H NMR to determine in what diastereomeric ratio the product was formed. The crude reaction mixture was then purified by flash column chromatography.

[a] *tert*-Butyl lithium should be titrated before use.[193] [b] Electrophiles sufficiently soluble in THF were added as 1 M solutions in THF, those with partial solubility were quickly added directly into the flask. [c] To be replaced with 0.5 M aqueous NaOH when using Eschenmoser's salt as the electrophile.

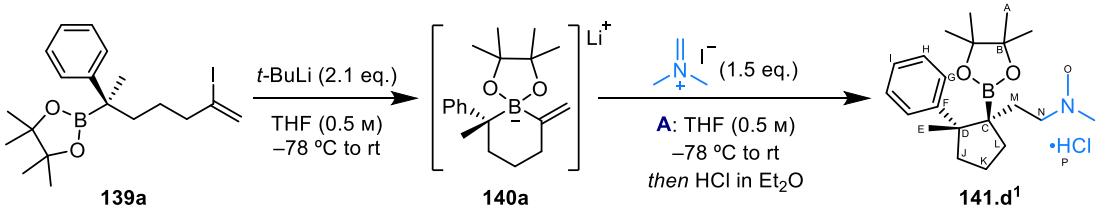
6.2.2.4. General procedure H: oxidation of cyclopentyl boronic esters



According to a literature procedure,[88] the boronic ester (0.05 mmol, 1.0 eq.) was dissolved in DMF (0.65 mL) and cooled to −20 °C (cryostat). Aqueous NaOCl (8% available chlorine, 0.14 mL) was added dropwise (~0.5 mL/min). The reaction mixture was allowed to stir at this temperature for 1 hour followed by stirring at rt for 1 hour whereupon it was then diluted with Et_2O (2 mL) and quenched with saturated aqueous $Na_2S_2O_3$ (2 mL). The aqueous layer was extracted with Et_2O (3 × 2 mL) and the combined organics washed with brine (2 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude reaction mixture was then purified by flash column chromatography.

6.2.2.5. Substrate scope: characterisation of cyclopentyl boronic esters

_N,N_-Dimethyl-2-((1*S*,2*S*)-2-methyl-2-phenyl-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclopentyl)ethan-1-amine hydrochloride salt (141a.d[1])



According to **General Procedure E**, boronic ester **139a** (85 mg, 0.20 mmol, 1.0 eq.; 99:1 e.r.) was allowed to react with *tert*-butyl lithium (1.6 M in pentane, 0.27 mL, 0.42 mmol, 2.1 eq.) and *N*,*N*-dimethylmethyleneiminium iodide (56 mg, 0.30 mmol, 1.5 eq.) to give a crude residue (89:11 d.r. by crude ^{1}H NMR spectroscopic analysis) which was dissolved in Et_2O (*ca.* 0.5 mL) and then HCl (2 M in Et_2O; 110 µL, 0.22 mmol, 1.1 eq.) was added. The white precipitate formed was collected *via* suction filtration and dried under high vacuum to afford the boronic ester (57 mg, 73%, 89:11 d^1/d^2, >98:2 e.r., 100% e.s.) as a white foam.

The same procedure was repeated on a 2.35 mmol scale (1.00 g of boronic ester **139a**) to give **141a.d[1]** (0.721 g, 78%, 90:10 d^1/d^2, >98:2 e.r., 100% e.s.) as a white foam.

R_f = 0.20 for both diastereomers (CH_2Cl_2/MeOH 9:1).

$[\alpha]_D^{25}$: –3 (*c* = 5.7, CH_2Cl_2).

NMR Spectroscopy: *Assignments made for the major diastereomer.*

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 12.02 (s, 1H, H_P), 7.37–7.32 (m, 2H, H_G), 7.32–7.25 (m, 2H, H_H), 7.21–7.14 (m, 1H, H_I), 2.90–2.70 (m, 2H, H_N), 2.59 (d, $^3J_{HH}$ = 4.8 Hz, 3H, H_O), 2.47 (d, $^3J_{HH}$ = 4.8 Hz, 3H, $H_{O'}$), 2.42–2.30 (m, 1H, H_J), 2.19–2.05 (m, 1H, H_L), 2.04–1.87 (m, 2H, $H_{K, K'}$), 1.87–1.78 (m, 1H, $H_{J'}$), 1.59–1.44 (m, 2H, $H_{L', M}$), 1.36 (s, 3H, H_E), 1.30 (s, 6H, H_A), 1.30 (s, 6H, $H_{A'}$), 1.17–1.06 (m, 1H, $H_{M'}$) ppm;

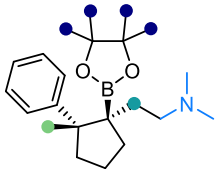
^{13}C NMR (101 MHz, $CDCl_3$): δ_C 147.2 (C_F), 128.0 (C_H), 127.3 (C_G), 125.9 (C_I), 83.8 (C_B), 55.5 (C_N), 53.5 (C_D), 42.5 (C_O), 41.1 ($C_{O'}$), 37.8 (C_J), 32.5 (C_L), 28.6 (C_E), 27.4 (C_M), 25.2 (C_A), 25.0 ($C_{A'}$), 21.9 (C_K) ppm; C_C not observed due to quadrupolar relaxation;

^{11}B NMR (128 MHz, $CDCl_3$): δ_B 33.6 ppm.

IR (film): ν_{max} 3398 (br), 2973, 2596, 1471, 1372, 1313, 1142 cm^{-1}.

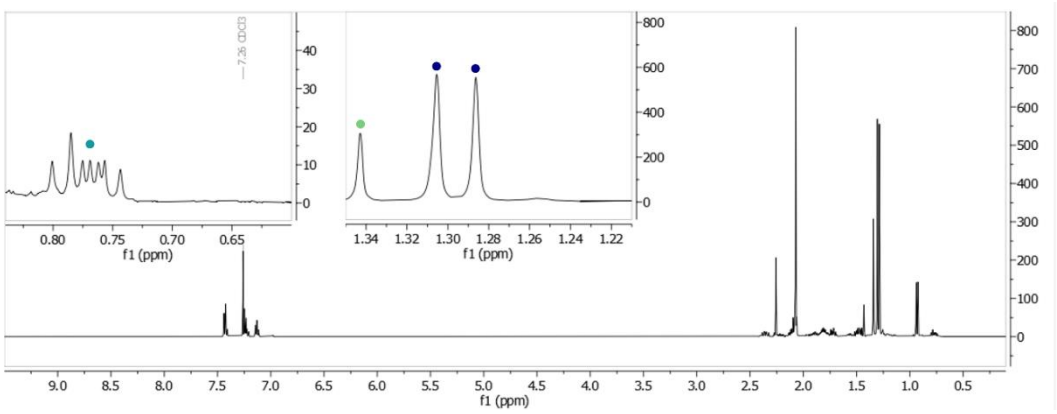
HRMS (ESI): m/z calc'd for $C_{22}H_{37}{}^{11}BNO_2$ $[M+H]^+$ 358.2916 found 358.2912.

Chiral solvating agent: The enantiopurity of boronic ester **141a.d[1]** was determined using Pirkle's alcohol ((*R*)-(–)-1-(9-anthryl)-2,2,2-trifluoroethanol) NMR shift reagent (1.0 eq, rt, $CDCl_3$, 0.05 M), >98:2 e.r. A portion of the HCl salt was converted to free amine **182a.d[1]** by washing with 0.5 M aqueous NaOH and extracting with Et_2O for e.r. determination.

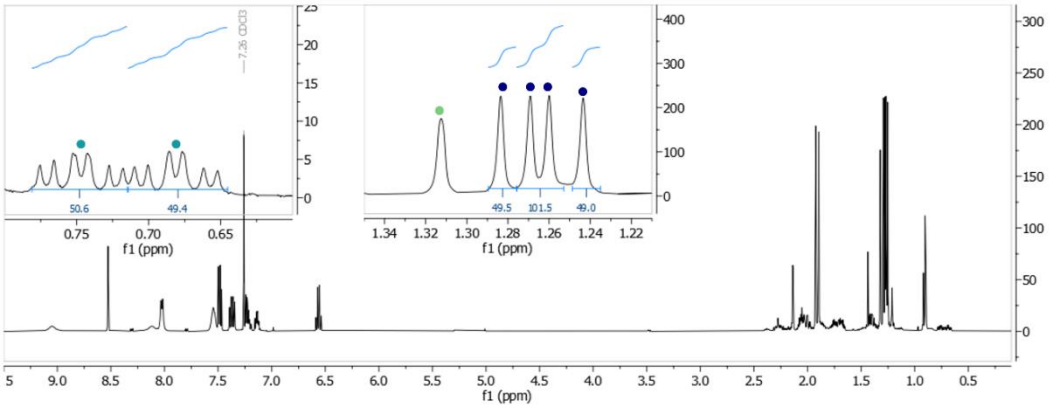


182a.d[1]

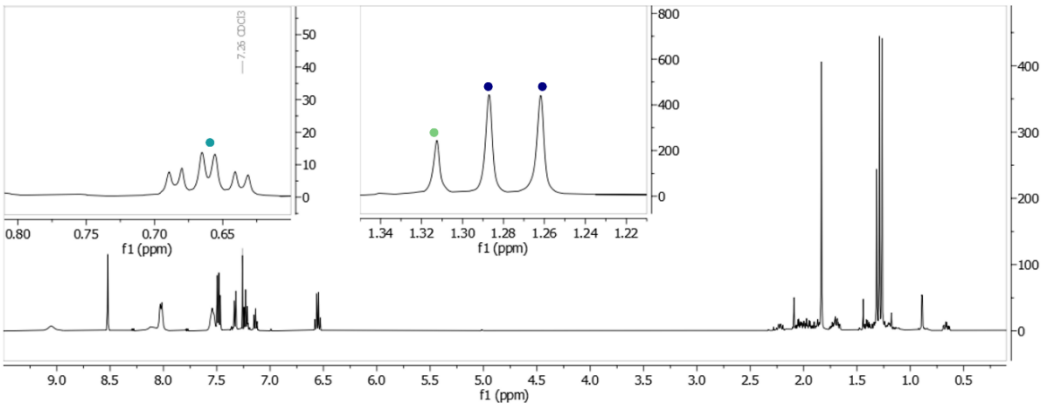
^{1}H NMR (500 MHz, $CDCl_3$) expansion of **(±)-182a.d[1]** only:



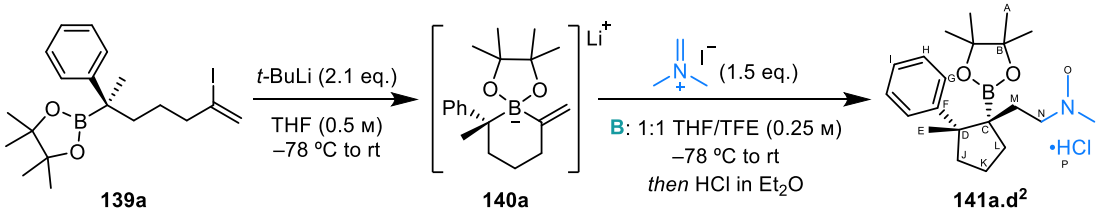
^{1}H NMR (500 MHz, $CDCl_3$) expansion of **(±)-182a.d[1]** with Pirkle's alcohol:



^{1}H NMR (500 MHz, $CDCl_3$) expansion of **182a.d^1** with Pirkle's alcohol:



***N*,*N*-Dimethyl-2-((1*R*,2*S*)-2-methyl-2-phenyl-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclopentyl)ethan-1-amine hydrochloride salt (141a.d^2)**



According to **General Procedure G**, boronic ester **139a** (85 mg, 0.20 mmol, 1.0 eq.; 99:1 e.r.) was allowed to react with *tert*-butyl lithium (1.6 M in pentane, 0.27 mL, 0.42 mmol, 2.1 eq.) and *N*,*N*-dimethylmethyleneiminium iodide (56 mg, 0.30 mmol, 1.5 eq.) to give a crude residue (86:14 d.r. by crude ^{1}H NMR spectroscopic analysis) which was dissolved in Et_2O (*ca.* 0.5 mL) and then HCl (2 M in Et_2O; 110 µL, 0.22 mmol, 1.1 eq.) was added. The white precipitate formed was collected *via* suction filtration and dried under high vacuum to afford the boronic ester (71 mg, 99%, 14:86 d^1/d^2, >98:2 e.r., 100% e.s.) as a white foam.

$\mathbf{R_f}$ = 0.20 for both diastereomers (CH_2Cl_2/MeOH 9:1).

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$**:** –2 (*c* = 6.8, CH_2Cl_2).

NMR Spectroscopy: *Assignments made for the major diastereomer.*

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 12.05 (s, 1H, H_P), 7.37–7.32 (m, 2H, H_G), 7.23–7.17 (m, 2H, H_H), 7.14–7.07 (m, 1H, H_I), 3.08–2.87 (m, 2H, H_N), 2.77 (s, 3H, H_O), 2.76 (s, 3H, $H_{O'}$), 2.66–2.57 (m, 1H, H_J), 2.27 (apparent td, J_{HH} = 11.7, 4.7 Hz, 1H, H_M), 2.01–1.73 (m, 4H, $H_{K,\,K',\,L,\,M'}$), 1.73–1.60 (m, 1H, $H_{J'}$), 1.60-1.39 (m, 1H, $H_{L'}$), 1.21 (s, 3H, H_E), 0.90 (s, 6H, H_A), 0.82 (s, 6H, $H_{A'}$) ppm;

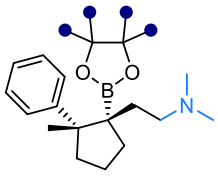
^{13}C NMR (101 MHz, $CDCl_3$): δ_C 147.8 (C_F), 127.9 (C_H), 126.7 (C_G), 126.0 (C_I), 83.2 (C_B), 56.9 (C_N), 51.1 (C_D), 43.6 (C_O), 41.6 ($C_{O'}$), 38.3 (C_J), 32.8 (C_L), 28.0 (C_M), 24.8 (C_A), 24.7 ($C_{A'}$), 24.5 (C_E), 21.0 (C_K) ppm; C_C not observed due to quadrupolar relaxation;

^{11}B NMR (128 MHz, $CDCl_3$): δ_B 33.6 ppm.

IR (film): ν_{max} 3405 (br), 2968, 2660, 1474, 1372, 1316, 1142 cm^{-1}.

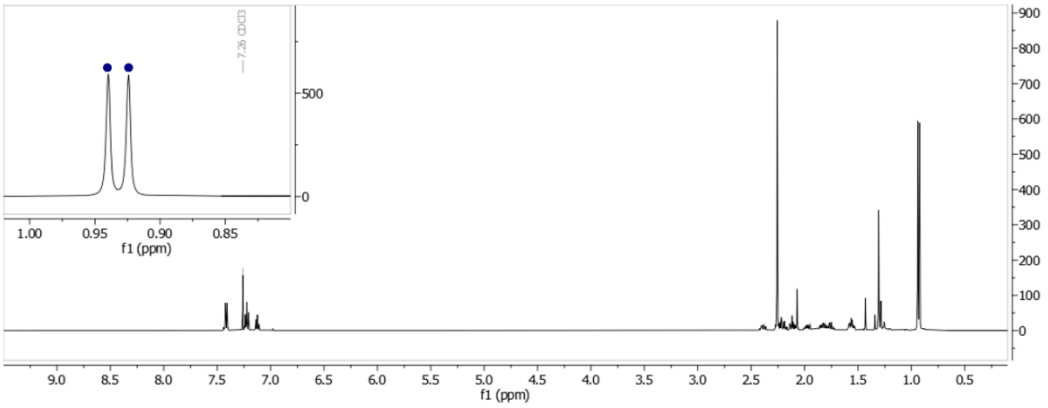
HRMS (ESI): m/z calc'd for $C_{22}H_{37}{}^{11}BNO_2$ $[M+H]^+$ 358.2912 found 358.2908.

Chiral solvating agent: The enantiopurity of boronic ester **141a.d^2** was determined using Pirkle's alcohol ((*R*)-(–)-1-(9-anthryl)-2,2,2-trifluoroethanol) NMR shift reagent (1.0 eq, rt, $CDCl_3$, 0.05 M), >98:2 e.r. A portion of the HCl salt was converted to free amine **182a.d^2** by washing with 0.5 M aqueous NaOH and extracting with Et_2O for e.r. determination.

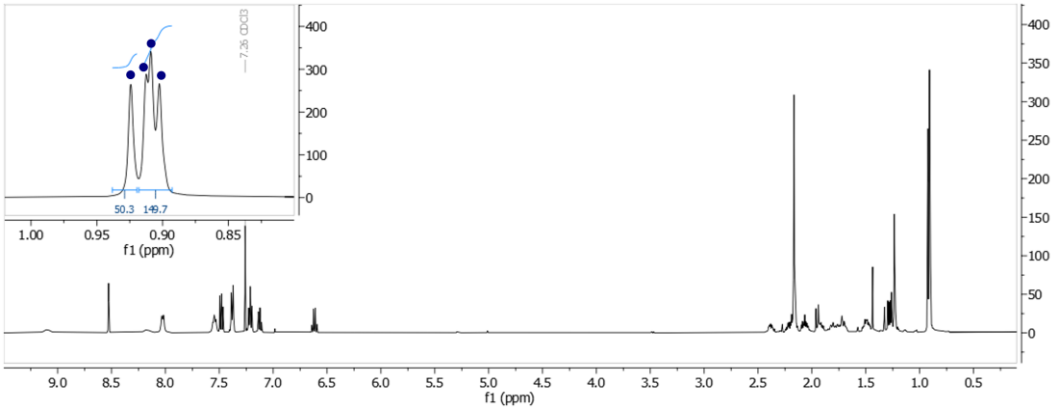


182a.d^2

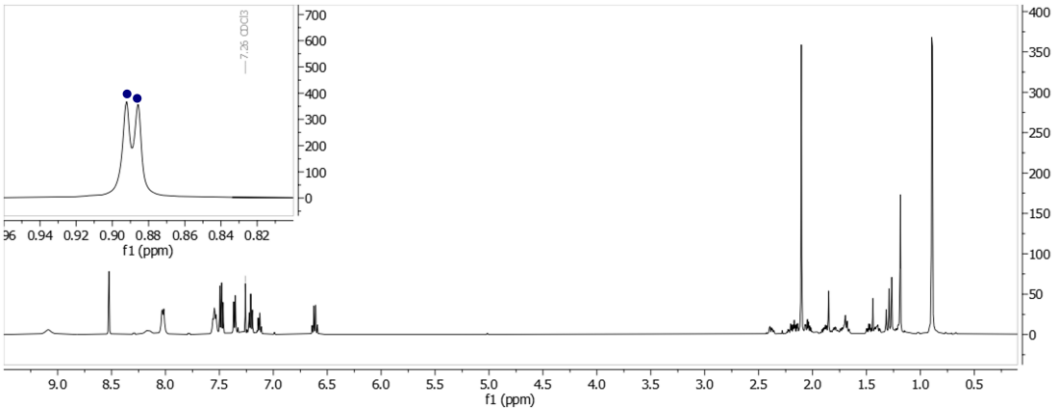
^{1}H NMR (500 MHz, $CDCl_3$) expansion of **(±)-182a.d^2** only:



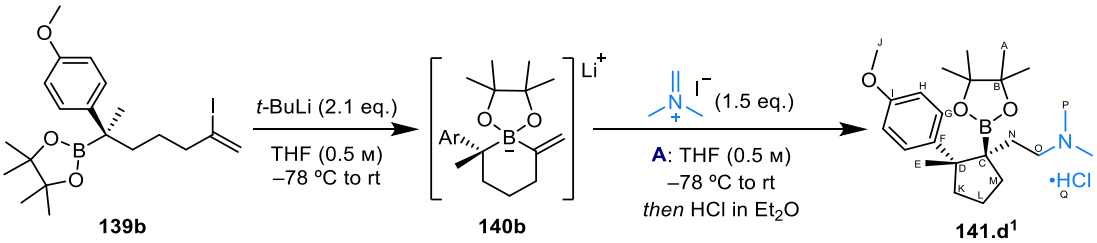
^{1}H NMR (500 MHz, $CDCl_3$) expansion of **(±)-182a.d^2** with Pirkle's alcohol:



^{1}H NMR (500 MHz, $CDCl_3$) expansion of **182a.d^2** with Pirkle's alcohol:



2-((1*S*,2*S*)-2-(4-Methoxyphenyl)-2-methyl-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclopentyl)-*N*,*N*-dimethylethan-1-amine hydrochloride salt (141b.d^1)



According to **General Procedure E**, boronic ester **139b** (91 mg, 0.20 mmol, 1.0 eq.; 95:5 e.r.) was allowed to react with *tert*-butyl lithium (1.7 M in pentane, 0.25 mL, 0.42 mmol, 2.1 eq.) and *N*,*N*-dimethylmethyleneiminium iodide (56 mg, 0.30 mmol, 1.5 eq.) to give a crude residue (94:6 d.r. by crude ^{1}H NMR spectroscopic analysis) which was dissolved in Et_2O (*ca.* 0.5 mL) and then HCl (2 M in Et_2O; 110 µL, 0.22 mmol, 1.1 eq.) was added. The white precipitate formed was collected *via* suction filtration and dried under high vacuum to afford the boronic ester (83 mg, 98%, 94:6 d^1/d^2, 95:5 e.r., 100% e.s.) as a white foam.

R_f = 0.63 for both diastereomers (CH_2Cl_2/MeOH 9:1).

$[\alpha]_D^{25}$: –1 (*c* = 6.1, CH_2Cl_2).

NMR Spectroscopy: *Assignments made for the major diastereomer.*

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 11.98 (s, 1H, H_Q), 7.24–7.19 (m, 2H, H_G), 6.80–6.74 (m, 2H, H_H), 3.75 (s, 3H, H_J), 2.87–2.67 (m, 2H, H_O) 2.56 (d, $^3J_{HH}$ = 4.9 Hz, 3H, H_P), 2.45 (d, $^3J_{HH}$ = 4.9 Hz, 3H, $H_{P'}$), 2.33–2.20 (m, 1H, H_K), 2.05 (ddd, J_{HH} = 13.1, 9.5, 5.3 Hz, 1H, H_M), 1.98–1.81 (m, 2H, $H_{L, L'}$), 1.75 (ddd, J_{HH} = 12.6, 9.2, 3.8 Hz, 1H, $H_{K'}$), 1.50 (apparent td, J_{HH} = 12.7, 5.4 Hz, 1H, H_N), 1.46–1.39 (m, 1H, $H_{M'}$), 1.29 (s, 3H, H_E), 1.25 (s, 6H, H_A),

1.24 (s, 6H, $H_{A'}$), 1.07 (apparent td, J_{HH} = 12.6, 4.8 Hz, 1H, $H_{N'}$) ppm;

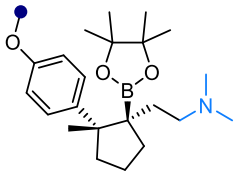
^{13}C NMR (101 MHz, $CDCl_3$): δ_C 157.5 (C_I), 139.1 (C_F), 128.3 (C_G), 113.2 (C_H), 83.8 (C_B), 55.6 (C_O), 55.2 (C_J), 52.8 (C_D), 42.5 (C_P), 41.1 ($C_{P'}$), 38.0 (C_K), 32.5 (C_M), 28.6 (C_E), 27.5 (C_N), 25.2 (C_A), 25.0 ($C_{A'}$), 22.0 (C_L) ppm; C_C not observed due to quadrupolar relaxation;

^{11}B NMR (128 MHz, $CDCl_3$): δ_B 33.2 ppm.

IR (film): ν_{max} 3406 (br), 2967, 2645, 1610, 1513, 1468, 1371, 1312, 1253, 1141 cm^{-1}.

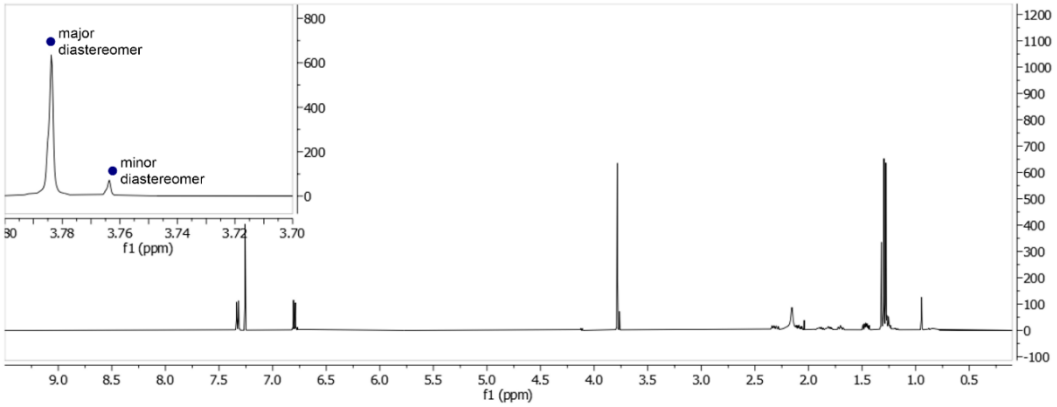
HRMS (ESI): m/z calc'd for $C_{23}H_{39}{}^{11}BNO_3$ $[M+H]^+$ 388.3022 found 388.3032.

Chiral solvating agent: The enantiopurity of boronic ester **141b.d[1]** was determined using Pirkle's alcohol ((*R*)-(–)-1-(9-anthryl)-2,2,2-trifluoroethanol) NMR shift reagent (2.0 eq, rt, $CDCl_3$, 0.03 M), 95:5 e.r. A portion of the HCl salt was converted to free amine **182b.d[1]** by washing with 0.5 M aqueous NaOH and extracting with Et_2O for e.r. determination.

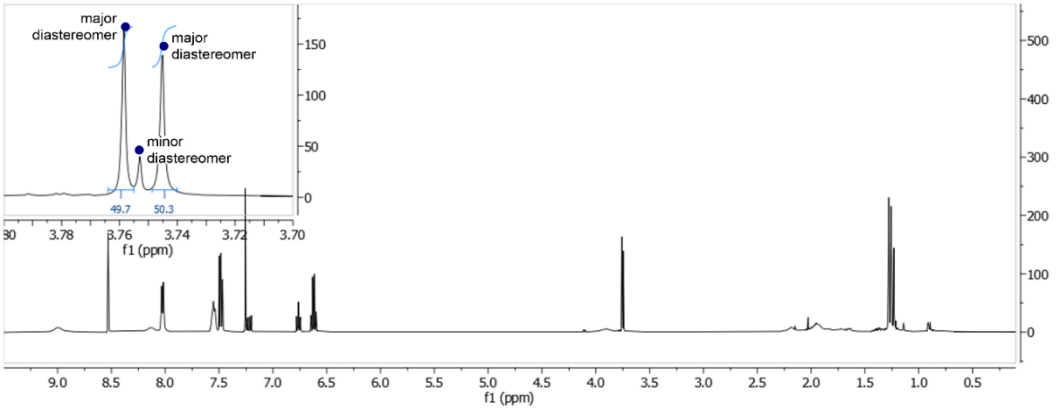


182b.d[1]

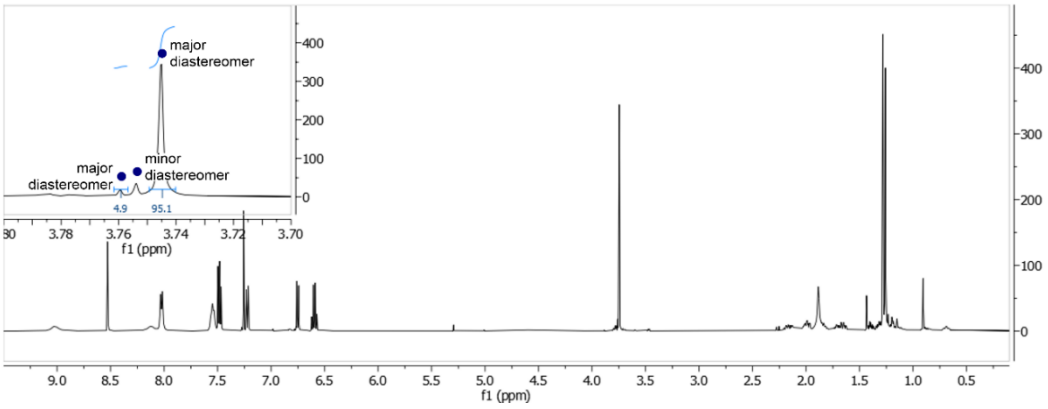
^{1}H NMR (500 MHz, $CDCl_3$) expansion of **(±)-182b.d[1]** only:



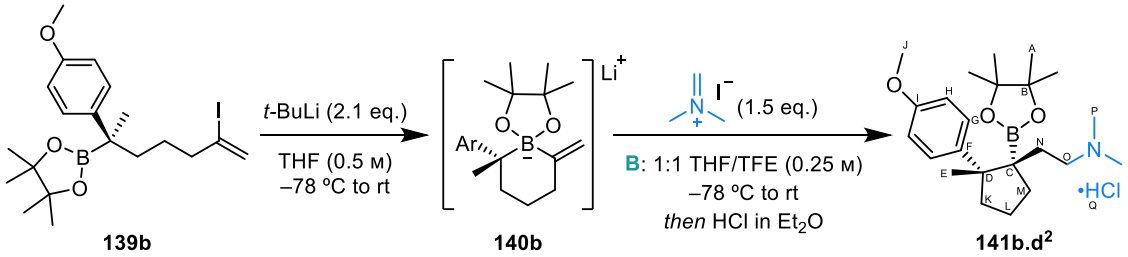
^{1}H NMR (500 MHz, $CDCl_3$) expansion of **(±)-182b.d[1]** with Pirkle's alcohol:



^{1}H NMR (500 MHz, $CDCl_3$) expansion of **182b.d^1** with Pirkle's alcohol:



2-((1*R*,2*S*)-2-(4-Methoxyphenyl)-2-methyl-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclopentyl)-*N*,*N*-dimethylethan-1-amine hydrochloride salt (141b.d^2)



According to **General Procedure G**, boronic ester **139b** (91 mg, 0.20 mmol, 1.0 eq.; 95:5 e.r.) was allowed to react with *tert*-butyl lithium (1.7 M in pentane, 0.25 mL, 0.42 mmol, 2.1 eq.) and *N*,*N*-dimethylmethyleneiminium iodide (56 mg, 0.30 mmol, 1.5 eq.) to give a crude residue (89:11 d.r. by crude ^{1}H NMR spectroscopic analysis) which was dissolved in Et_2O (*ca.* 0.5 mL) and then HCl (2 M in Et_2O; 110 µL, 0.22 mmol, 1.1 eq.) was added. The white precipitate formed was collected *via* suction filtration and dried under high vacuum to afford the boronic ester (82 mg, 96%, 11:89 d^1/d^2, 95:5 e.r., 100% e.s.) as a white foam.

$\mathbf{R_f}$ = 0.63 for both diastereomers (CH_2Cl_2/MeOH 9:1).

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$: –2 (*c* = 6.0, CH_2Cl_2).

NMR Spectroscopy: *Assignments made for the major diastereomer.*

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 12.15 (s, 1H, H_Q), 7.29–7.23 (m, 2H, H_G), 6.76–6.71 (m, 2H, H_H), 3.71 (s, 3H, H_J), 3.05–2.87 (m, 2H, H_O), 2.76 (d, $^3J_{HH}$ = 4.8 Hz, 6H, H_P), 2.62–2.51 (m, 1H, H_K), 2.28–2.19 (m, 1H, H_N), 1.98–1.69 (m, 4H, $H_{L,\,L',\,M,\,N'}$), 1.64 (ddd, J_{HH} = 12.0, 7.4, 2.6 Hz, 1H, $H_{K'}$), 1.51 (ddd, J_{HH} = 11.1, 9.2, 5.0 Hz, 1H, $H_{M'}$), 1.18 (s, 3H, H_E), 0.92 (s, 6H, H_A), 0.85 (s, 6H, $H_{A'}$) ppm;

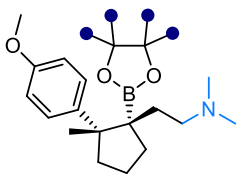
^{13}C NMR (101 MHz, $CDCl_3$): δ_C 157.8 (C_I), 140.0 (C_F), 127.8 (C_G), 113.2 (C_H), 83.1 (C_B), 56.9 (C_O), 55.3 (C_J), 50.4 (C_D), 43.5 (C_P), 41.7 ($C_{P'}$), 38.5 (C_K), 32.8 (C_M), 28.0 (C_N), 24.8 (C_A), 24.8 ($C_{A'}$), 24.5 (C_E), 21.0 (C_L) ppm; C_C not observed due to quadrupolar relaxation;

^{11}B NMR (128 MHz, $CDCl_3$): δ_B 33.2 ppm.

IR (film): ν_{max} 3406 (br), 2967, 2645, 1610, 1513, 1468, 1371, 1312, 1253, 1187, 1141 cm^{-1}.

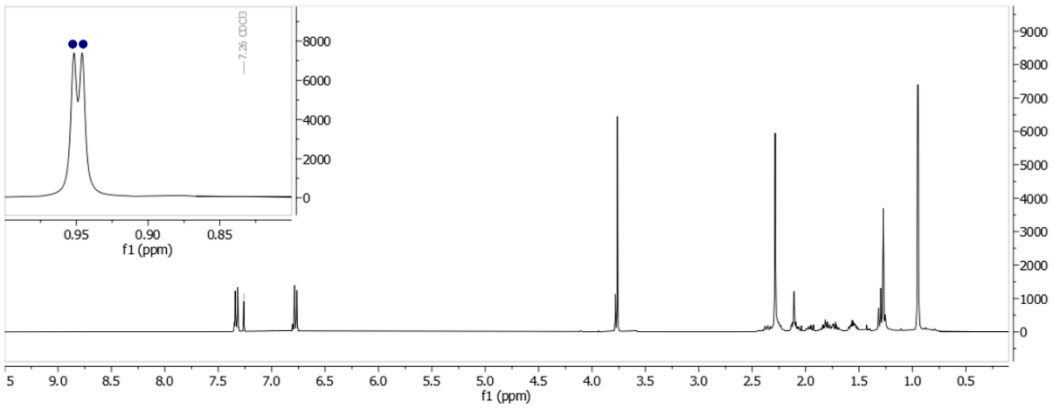
HRMS (ESI): m/z calc'd for $C_{23}H_{39}{}^{11}BNO_3$ $[M+H]^+$ 388.3018 found 388.3013.

Chiral solvating agent: The enantiopurity of boronic ester **141b.d^2** was determined using Pirkle's alcohol ((*R*)-(–)-1-(9-anthryl)-2,2,2-trifluoroethanol) NMR shift reagent (3.0 eq, rt, $CDCl_3$, 0.04 M), 95:5 e.r. A portion of the HCl salt was converted to free amine **182b.d^2** by washing with 0.5 M aqueous NaOH and extracting with Et_2O for e.r. determination.

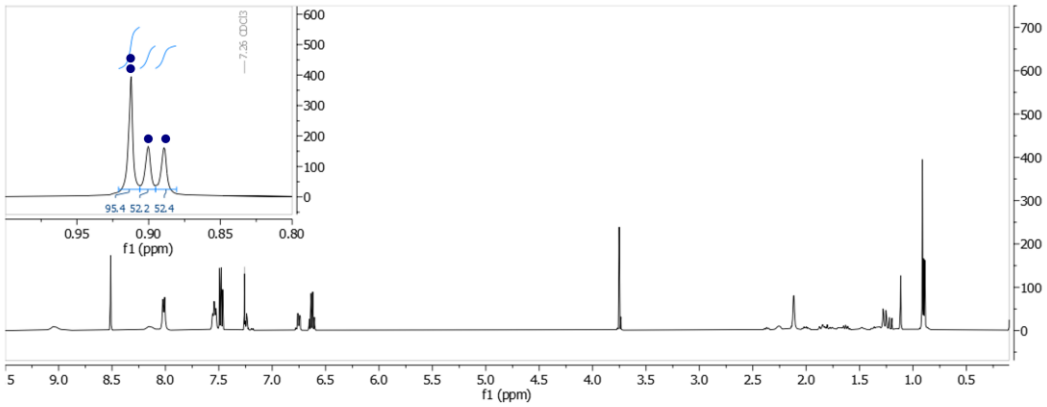


182b.d^2

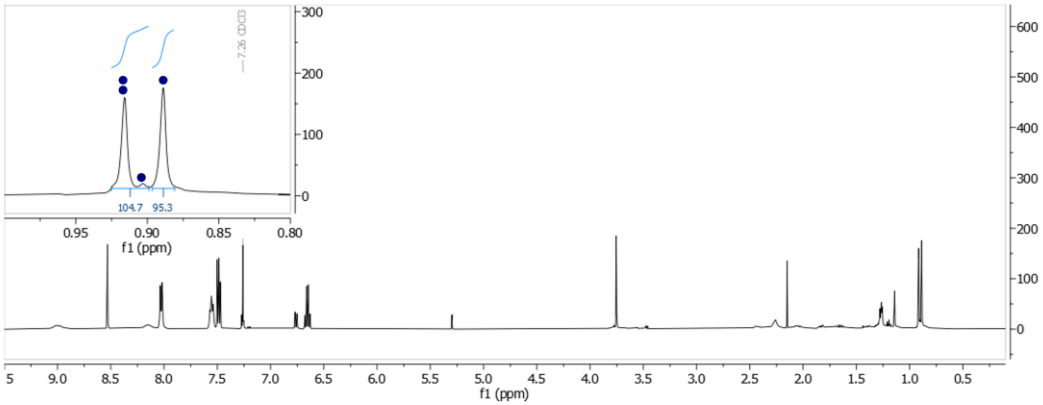
^{1}H NMR (500 MHz, $CDCl_3$) expansion of **(±)-182b.d^2** only:



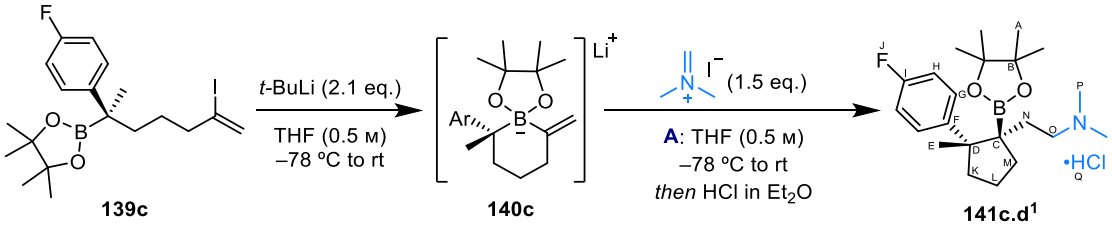
^{1}H NMR (500 MHz, $CDCl_3$) expansion of **(±)-182b.d^2** with Pirkle's alcohol:



^{1}H NMR (500 MHz, $CDCl_3$) expansion of **182b.d^2** with Pirkle's alcohol:



2-((1*S*,2*S*)-2-(4-Fluorophenyl)-2-methyl-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclopentyl)-*N*,*N*-dimethylethan-1-amine hydrochloride salt (141c.d^1)



According to **General Procedure E**, boronic ester **139c** (89 mg, 0.20 mmol, 1.0 eq.; e.r. n.d.) was allowed to react with *tert*-butyl lithium (1.7 M in pentane, 0.25 mL, 0.42 mmol, 2.1 eq.) and *N*,*N*-dimethylmethyleneiminium iodide (56 mg, 0.30 mmol, 1.5 eq.) to give a crude residue (80:20 d.r. by crude ^{1}H NMR spectroscopic analysis) which was dissolved in Et_2O (*ca.* 0.5 mL) and then HCl (2 M in Et_2O; 110 µL, 0.22 mmol, 1.1 eq.) was added. The white precipitate formed was collected *via* suction filtration and dried under high vacuum to afford the boronic ester (74 mg, 90%, 80:20 d^1/d^2, e.r. n.d.) as a white foam.

The e.r. of boronic ester **141c.d^1** could not be determined by chiral HPLC/SFC or by using Pirkle's chiral solvating agent.

$\mathbf{R_f}$ = 0.59 for both diastereomers (CH_2Cl_2/MeOH 9:1).

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$**:** –3 (*c* = 6.1, CH_2Cl_2).

NMR Spectroscopy: *Assignments made for the major diastereomer.*

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 12.05 (s, 1H, H_Q), 7.37–7.20 (m, 2H, H_G), 6.98–6.85 (m, 2H, H_H), 2.85–2.68 (m, 2H, H_O), 2.58 (d, $^3J_{HH}$ = 5.0 Hz, 3H, H_P), 2.47 (d, $^3J_{HH}$ = 5.0 Hz, 3H, $H_{P'}$), 2.34–2.18 (m, 1H, H_K), 2.07 (ddd, J_{HH} = 13.3, 9.3, 5.7 Hz, 1H, H_M), 1.98–1.82

(m, 2H, $H_{L,\,L'}$), 1.76 (ddd, J_{HH} = 12.7, 8.9, 3.9 Hz, 1H, $H_{K'}$), 1.54–1.40 (m, 2H, $H_{M',\,N}$), 1.28 (s, 3H, H_E), 1.25 (s, 6H, H_A), 1.25 (s, 6H, $H_{A'}$), 1.13–1.02 (m, 1H, $H_{N'}$) ppm;

^{13}C NMR (101 MHz, $CDCl_3$): δ_C 161.0 (d, $^1J_{CF}$ = 244.7 Hz, H_I), 142.9 (d, $^4J_{CF}$ = 3.3 Hz, H_F), 128.9 (d, $^3J_{CF}$ = 7.5 Hz, H_G), 114.6 (d, $^2J_{CF}$ = 20.7 Hz, H_H), 83.9 (C_B), 55.7 (C_O), 53.1 (C_D), 42.7 (C_P), 41.2 ($C_{P'}$), 37.9 (C_K), 32.2 (C_M), 28.7 (C_E), 27.6 (C_N), 25.2 (C_A), 24.9 ($C_{A'}$), 21.8 (C_L) ppm; C_C not observed due to quadrupolar relaxation;

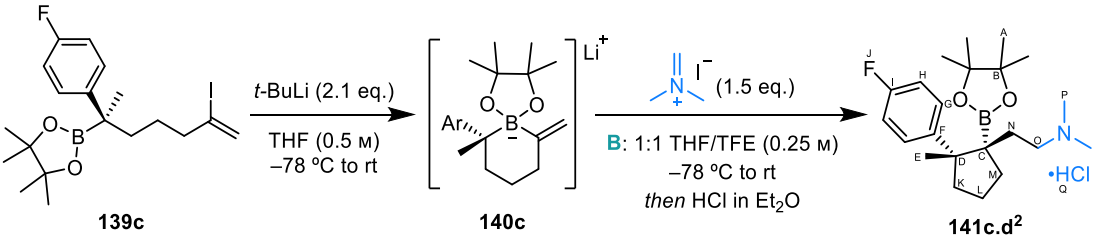
^{11}B NMR (128 MHz, $CDCl_3$): δ_B 33.6 ppm;

^{19}F NMR (377 MHz, $CDCl_3$): δ_F −117.8 ppm.

IR (film): ν_{max} 3402 (br), 2968, 2633, 1510, 1472, 1368, 1314, 1166, 1229, 1166, 1141 cm^{-1}.

HRMS (ESI): m/z calc'd for $C_{22}H_{36}{}^{11}BFNO_2$ $[M+H]^+$ 376.2822 found 376.2821.

2-((1*R*,2*S*)-2-(4-Fluorophenyl)-2-methyl-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclopentyl)-*N*,*N*-dimethylethan-1-amine hydrochloride salt (141c.d^2)



According to **General Procedure G**, boronic ester **139c** (89 mg, 0.20 mmol, 1.0 eq.; e.r. n.d.) was allowed to react with *tert*-butyl lithium (1.7 M in pentane, 0.25 mL, 0.42 mmol, 2.1 eq.) and *N*,*N*-dimethylmethyleneiminium iodide (56 mg, 0.30 mmol, 1.5 eq.) to give a crude residue (93:7 d.r. by crude ^{1}H NMR spectroscopic analysis) which was dissolved in Et_2O (*ca.* 0.5 mL) and then HCl (2 M in Et_2O; 110 µL, 0.22 mmol, 1.1 eq.) was added. The white precipitate formed was collected *via* suction filtration and dried under high vacuum to afford the boronic ester (79 mg, 96%, 7:93 d^1/d^2, e.r. n.d.) as a white foam.

The e.r. of boronic ester **141c.d^2** could not be determined by chiral HPLC/SFC or by using Pirkle's chiral solvating agent.

R_f = 0.59 for both diastereomers (CH_2Cl_2/MeOH 9:1).

$[\alpha]_D^{25}$: –4 (*c* = 5.9, CH_2Cl_2).

NMR Spectroscopy: *Assignments made for the major diastereomer.*

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.34–7.27 (m, 2H, H_G), 6.92–6.84 (m, 2H, H_H), 2.96–2.79 (m, 2H, H_O), 2.71 (s, 6H, H_P), 2.59–2.47 (m, 1H, H_K), 2.21 (apparent td, J_{HH} = 11.8, 5.0 Hz, 1H, H_N), 1.98–1.83 (m, 2H, $H_{M, N'}$), 1.83–1.70 (m, 2H, $H_{L, L'}$), 1.66 (ddd, J_{HH} = 12.0, 7.4, 2.8 Hz, 1H, $H_{K'}$), 1.53 (ddd, J_{HH} = 11.6, 9.5, 5.5 Hz, 1H, $H_{M'}$), 1.19 (s, 3H, H_E), 0.91 (s, 6H, H_A), 0.85 (s, 6H, $H_{A'}$) ppm;

^{13}C NMR (101 MHz, $CDCl_3$): δ_C 161.2 (d, $^{1}J_{CF}$ = 244.4 Hz, C_I), 143.8 (d, $^{4}J_{CF}$ = 3.3 Hz, C_F), 128.3 (d, $^{3}J_{CF}$ = 7.5 Hz, C_G) 114.4 (d, $^{2}J_{CF}$ = 20.5 Hz, C_H), 83.2 (C_B), 57.0 (C_O), 50.6 (C_D), 42.9 (C_P), 38.6 (C_K), 32.7 (C_M), 28.4 (C_N), 24.8 (C_A), 24.7 ($C_{A'}$), 24.7 (C_E), 20.9 (C_L) ppm; C_C not observed due to quadrupolar relaxation;

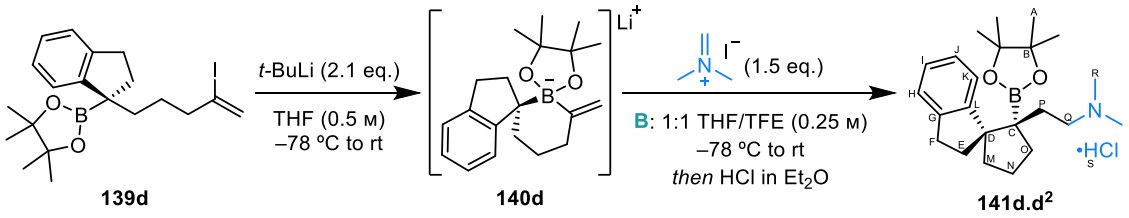
^{11}B NMR (128 MHz, $CDCl_3$): δ_B 33.6 ppm;

^{19}F NMR (377 MHz, $CDCl_3$): δ_F −117.6 ppm.

IR (film): ν_{max} 3401 (br), 2968, 2657, 1602, 1510, 1475, 1372, 1317, 1229, 1165, 1141 cm^{-1}.

HRMS (ESI): m/z calc'd for $C_{22}H_{36}{}^{11}BFNO_2$ $[M+H]^+$ 376.2818 found 376.2814.

***N*,*N*-dimethyl-2-((1*R*,2*R*)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2',3'-dihydrospiro[cyclopentane-1,1'-inden]-2-yl)ethan-1-amine hydrochloride salt (141d.d^2)**



According to **General Procedure G**, boronic ester **139d** (88 mg, 0.20 mmol, 1.0 eq.; 96:4 e.r.) was allowed to react with *tert*-butyl lithium (1.7 M in pentane, 0.25 mL, 0.42 mmol, 2.1 eq.) and *N*,*N*-dimethylmethyleneiminium iodide (56 mg, 0.30 mmol, 1.5 eq.) to give a crude residue (>95:5 d.r. by crude ^{1}H NMR spectroscopic analysis) which was dissolved in Et_2O (*ca.* 0.5 mL) and then HCl (2 M in Et_2O; 110 µL, 0.22 mmol, 1.1 eq.) was added. The white precipitate formed was collected *via* suction filtration and dried under high vacuum to afford the boronic ester (77 mg, 94%, 5:95< d^1/d^2, 96:4 e.r., 100% e.s.) as a white foam.

R_f = 0.38 for both diastereomers (CH_2Cl_2/MeOH 9:1).

$[\alpha]_D^{25}$: +22 (*c* = 6.5, CH_2Cl_2)

NMR Spectroscopy: *Assignments made for the major diastereomer.*

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 12.17 (s, 1H, H_S), 7.22–7.15 (m, 1H, H_{Ar}), 7.11–6.96 (m, 3H, H_{Ar}), 3.01–2.83 (m, 2H, $H_{F, Q}$), 2.80–2.58 (m, 2H, $H_{F', Q'}$), 2.72 (d, $^{3}J_{HH}$ = 4.9 Hz, 3H, H_R) 2.68 (d, $^{3}J_{HH}$ = 4.9 Hz, 3H, $H_{R'}$), 2.37 (ddd, J_{HH} = 12.8, 8.3, 6.2 Hz, 1H, H_E), 2.21–2.10 (m, 1H, H_O), 2.04–1.88 (m, 2H, $H_{M, P}$), 1.85–1.69 (m, 5H, $H_{E', M', N, N', P'}$), 1.60 (ddd, J_{HH} = 13.8, 8.6, 5.1 Hz, 1H, $H_{O'}$), 0.94 (s, 6H, H_A), 0.89 (s, 6H, $H_{A'}$) ppm;

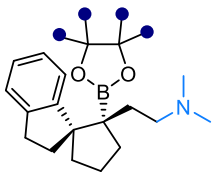
^{13}C NMR (101 MHz, $CDCl_3$): δ_C 149.3 (C_G *or* C_L), 143.6 (C_G *or* C_L), 126.6 (C_{Ar}), 125.8 (C_{Ar}), 124.5 (C_{Ar}), 124.4 (C_{Ar}), 83.4 (C_B), 62.0 (C_D), 56.4 (C_Q), 43.2 (C_R), 41.9 ($C_{R'}$), 38.7 (C_M), 35.2 (C_E), 31.9 (C_O), 31.0 (C_F), 27.7 (C_P), 25.0 (C_A), 24.7 ($C_{A'}$), 21.6 (C_N) ppm; C_C not observed due to quadrupolar relaxation;

^{11}B NMR (128 MHz, $CDCl_3$): δ_B 32.8 ppm.

IR (film): ν_{max} 3410 (br), 2957, 2463, 1474, 1372, 1311, 1261, 1141 cm^{-1}.

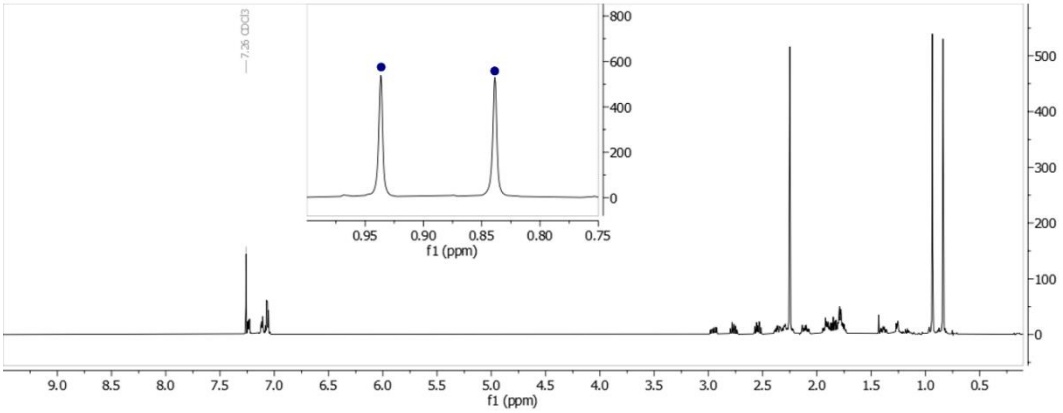
HRMS (ESI): m/z calc'd for $C_{23}H_{37}{}^{11}BNO_2$ $[M+H]^+$ 370.2916 found 370.2929.

Chiral solvating agent: The enantiopurity of boronic ester **141d.d^2** was determined using Pirkle's alcohol ((*R*)-(–)-1-(9-anthryl)-2,2,2-trifluoroethanol) NMR shift reagent (2.0 eq, rt, $CDCl_3$, 0.04 M), 96:4 e.r. A portion of the HCl salt was converted to free amine **182d.d^2** by washing with 0.5 M aqueous NaOH and extracting with Et_2O for e.r. determination.

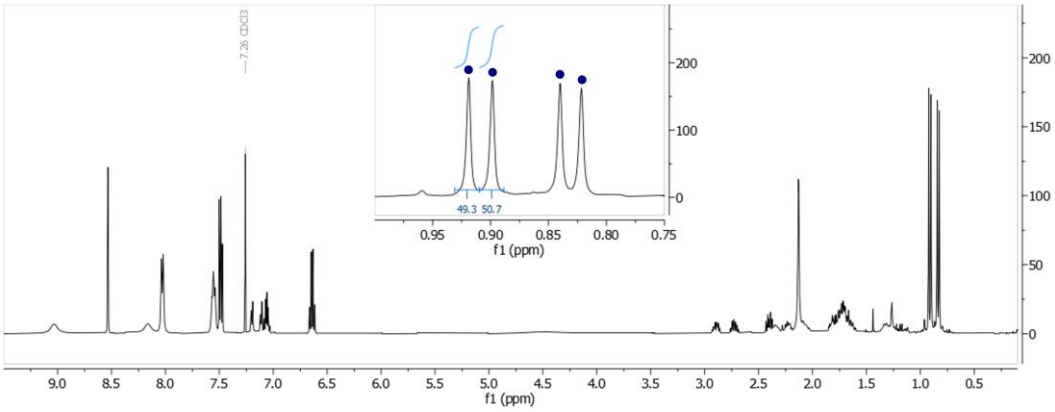


182d.d^2

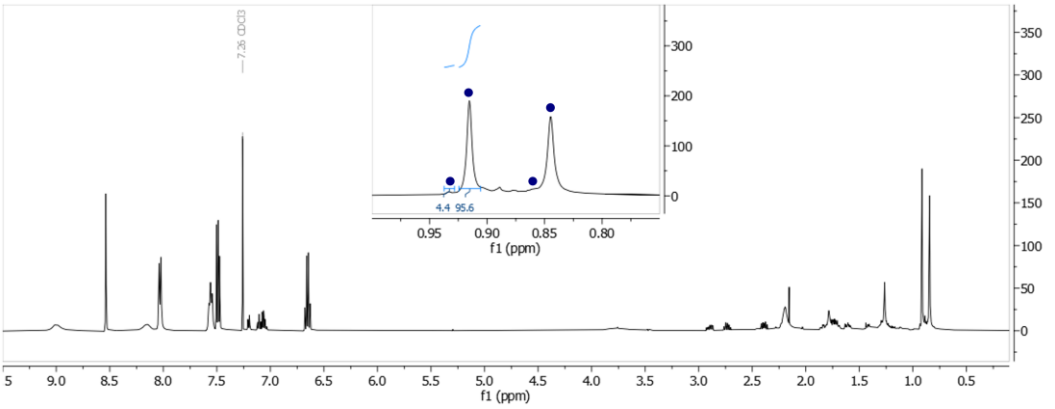
^{1}H NMR (500 MHz, $CDCl_3$) expansion of **(±)-182d.d^2** only:



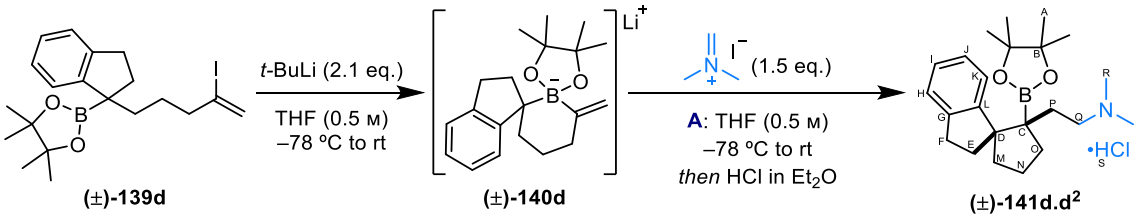
^{1}H NMR (500 MHz, $CDCl_3$) expansion of **(±)-182d.d^2** with Pirkle's alcohol:



^{1}H NMR (500 MHz, $CDCl_3$) expansion of **182d.d^2** with Pirkle's alcohol:

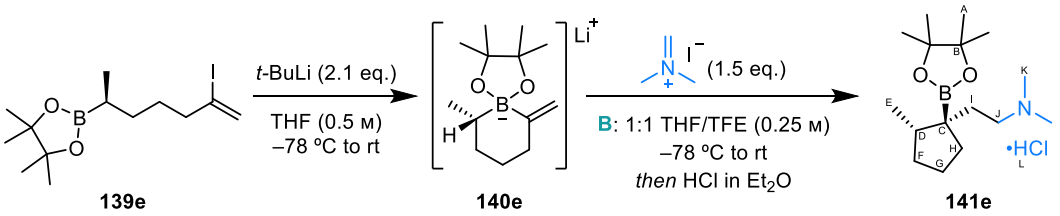


Racemic test reaction:



According to **General Procedure E**, boronic ester **(±)-139d** (44 mg, 0.10 mmol, 1.0 eq.) was allowed to react with *tert*-butyl lithium (1.7 M in pentane, 0.12 mL, 0.21 mmol, 2.1 eq.) and *N*,*N*-dimethylmethyleneiminium iodide (28 mg, 0.15 mmol, 1.5 eq.) to give a crude residue (>95:5 d.r. by crude ^{1}H NMR spectroscopic analysis) which was dissolved in Et_2O (*ca.* 0.3 mL) and then HCl (2 M in Et_2O; 55 µL, 0.11 mmol, 1.1 eq.) was added. The white precipitate formed was collected *via* suction filtration and dried under high vacuum to afford the racemic boronic ester (38 mg, 94%, 5:95< d^1/d^2) as a white foam.

***N*,*N*-Dimethyl-2-((1*S*,2*S*)-2-methyl-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclopentyl)ethan-1-amine hydrochloride salt (141e)**



139e 140e 141e

According to **General Procedure G**, boronic ester **139e** (70 mg, 0.20 mmol, 1.0 eq.; 98:2 e.r.) was allowed to react with *tert*-butyl lithium (1.7 M in pentane, 0.25 mL, 0.42 mmol, 2.1 eq.) and *N*,*N*-dimethylmethyleneiminium iodide (56 mg, 0.30 mmol, 1.5 eq.) to give a crude residue (94:6 d.r. by crude GCMS) which was dissolved in Et_2O (*ca.* 0.5 mL) and then HCl (2 M in Et_2O; 110 µL, 0.22 mmol, 1.1 eq.) was added. The white precipitate formed was collected *via* suction filtration and dried under high vacuum to afford the boronic ester (58 mg, 91%, 94:6 d.r., 98:2 e.r., 100% e.s.) as a white foam.

R_f = 0.20 for both diastereomers (CH_2Cl_2/MeOH 9:1).

$[\alpha]_D^{25}$: +3 (*c* = 6.4, CH_2Cl_2).

NMR Spectroscopy: *Assignments made for the major diastereomer.*

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 12.09 (s, 1H, H_L), 3.06–2.92 (m, 2H, H_J), 2.74 (d, $^3J_{HH}$ = 4.9 Hz, 3H, H_K), 2.73 (d, $^3J_{HH}$ = 4.9 Hz, 3H, $H_{K'}$), 2.02 (ddd, J_{HH} = 11.4, 10.8, 5.8 Hz, 1H, H_I), 1.87–1.62 (m, 3H, $H_{F,\ G,\ H}$), 1.60–1.42 (m, 3H, $H_{D,\ G',\ I'}$), 1.36–1.25 (m, 1H, $H_{F'}$), 1.24–1.17 (m, 1H, $H_{H'}$), 1.17 (s, 12H, H_A), 0.93 (d, $^3J_{HH}$ = 6.9 Hz, 3H, H_E) ppm;

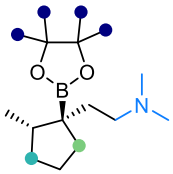
^{13}C NMR (101 MHz, $CDCl_3$): δ_C 82.7 (C_B), 56.3 (C_J), 45.4 (C_D), 43.0 (C_K), 41.8 ($C_{K'}$), 34.7 (C_H), 34.0 (C_F), 31.8 (C_I), 25.1 (C_A), 24.9 ($C_{A'}$), 22.9 (C_G), 17.3 (C_E) ppm; C_C not observed due to quadrupolar relaxation;

^{11}B NMR (128 MHz, $CDCl_3$): δ_B 33.4 ppm.

IR (film): ν_{max} 3402 (br), 2952, 2868, 1644, 1470, 1372, 1315, 1141 cm^{-1}.

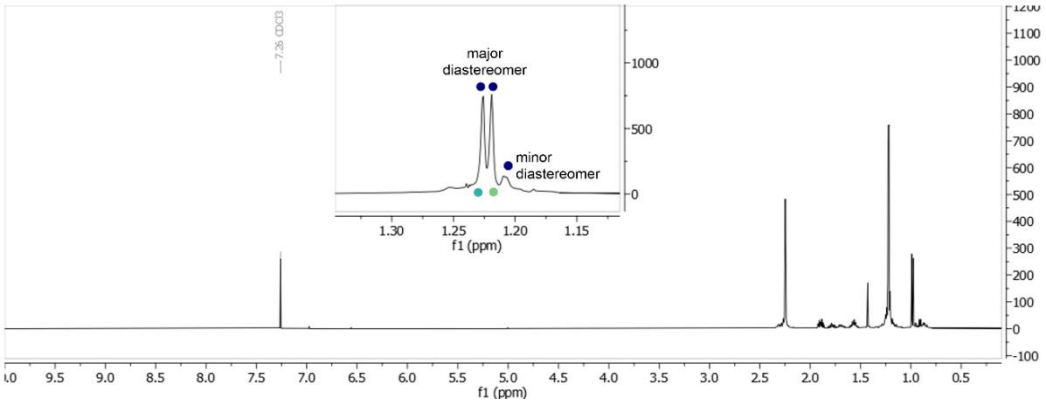
HRMS (ESI): m/z calc'd for $C_{16}H_{33}{}^{11}BNO_2$ $[M+H]^+$ 282.2602 found 282.2611.

Chiral solvating agent: The enantiopurity of boronic ester **141e** was determined using Pirkle's alcohol ((*R*)-(–)-1-(9-anthryl)-2,2,2-trifluoroethanol) NMR shift reagent (2.0 eq, rt, $CDCl_3$, 0.05 M), 98:2 e.r. A portion of the HCl salt was converted to free amine **182e** by washing with 0.5 M aqueous NaOH and extracting with Et_2O for e.r. determination.

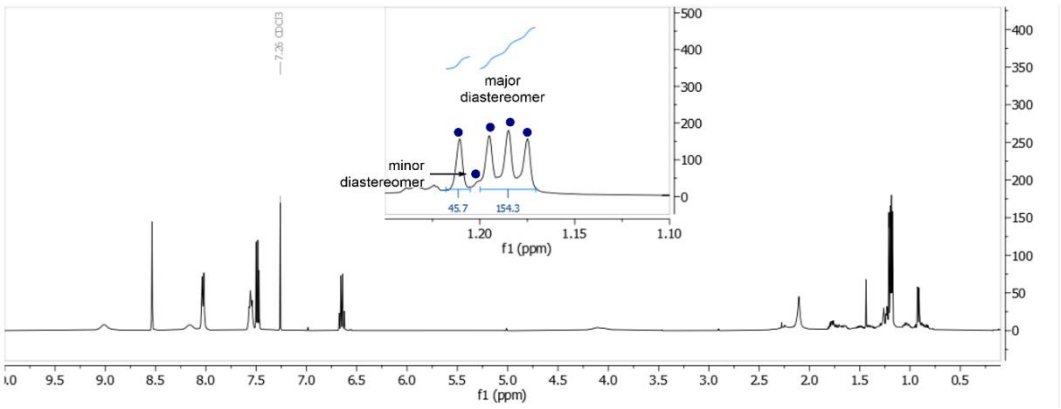


182e

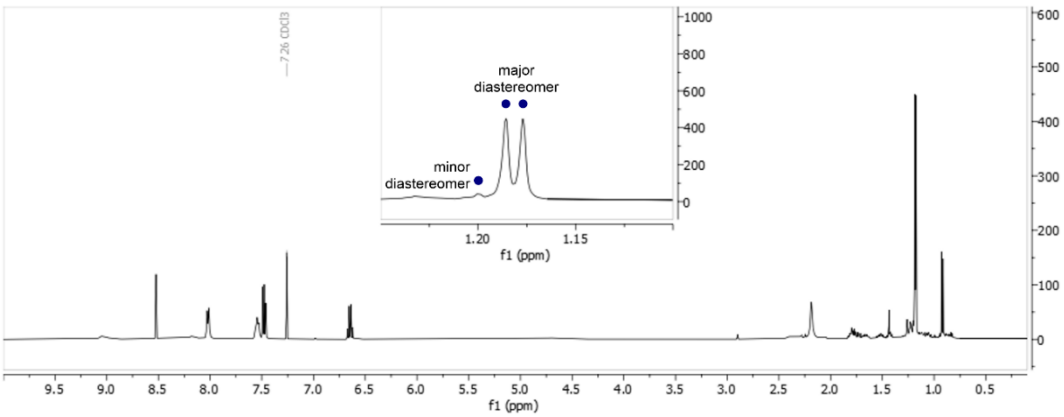
^{1}H NMR (500 MHz, $CDCl_3$) expansion of **(±)-182e** only:



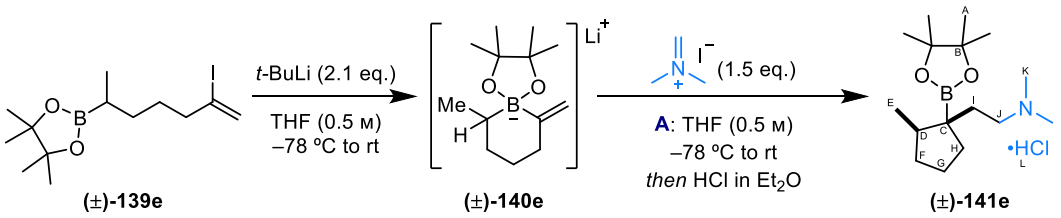
^{1}H NMR (500 MHz, $CDCl_3$) expansion of **(±)-182e** with Pirkle's alcohol:



^{1}H NMR (500 MHz, $CDCl_3$) expansion of **182e** with Pirkle's alcohol:

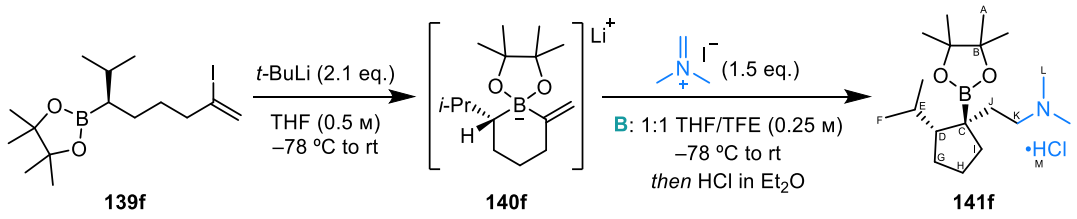


Racemic test reaction:



According to **General Procedure E**, boronic ester **(±)-139e** (70 mg, 0.20 mmol, 1.0 eq.) was allowed to react with *tert*-butyl lithium (1.7 M in pentane, 0.25 mL, 0.42 mmol, 2.1 eq.) and *N*,*N*-dimethylmethyleneiminium iodide (56 mg, 0.30 mmol, 1.5 eq.) to give a crude residue (93:7 d.r. by crude GCMS) which was dissolved in Et_2O (*ca.* 0.5 mL) and then HCl (2 M in Et_2O; 110 µL, 0.22 mmol, 1.1 eq.) was added. The white precipitate formed was collected *via* suction filtration and dried under high vacuum to afford the racemic boronic ester (54 mg, 84%, 93:7 d.r.) as a white foam.

2-((1*S*,2*R*)-2-Isopropyl-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclopentyl)-*N*,*N*-dimethylethan-1-amine hydrochloride salt (141f)



According to **General Procedure G**, boronic ester **139f** (76 mg, 0.20 mmol, 1.0 eq.; 95:5 e.r.) was allowed to react with *tert*-butyl lithium (1.7 M in pentane, 0.25 mL, 0.42 mmol, 2.1 eq.) and *N*,*N*-dimethylmethyleneiminium iodide (56 mg, 0.30 mmol, 1.5 eq.) to give a crude residue (>95:5 d.r. by crude GCMS) which was dissolved in Et_2O (*ca.* 0.5 mL) and then HCl (2 M in Et_2O; 110 µL, 0.22 mmol, 1.1 eq.) was added. The white precipitate formed was collected *via* suction filtration and dried under high vacuum to afford the boronic ester (54 mg, 78%, >95:5 d.r., 95:5 e.r., 100% e.s.) as a white foam.

$\mathbf{R_f}$ = 0.24 for both diastereomers (CH_2Cl_2/MeOH 9:1).

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$**:** +7 (*c* = 5.4, CH_2Cl_2).

NMR Spectroscopy: *Assignments made for the major diastereomer.*

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 12.03 (s, 1H, H_M), 3.14–3.04 (m, 1H, H_K), 3.04–2.92 (m, 1H, $H_{K'}$), 2.76–2.66 (m, 6H, H_L), 2.13 (apparent td, J_{HH} = 12.3, 4.3 Hz, 1H, H_J), 1.87–1.71

(m, 2H, $H_{G, I}$), 1.70–1.44 (m, 4H, $H_{E, H, H', J'}$), 1.40–1.19 (m, 3H, $H_{D, G', I'}$), 1.18 (s, 6H, H_A), 1.17 (s, 6H, $H_{A'}$), 0.91 (d, $^3J_{HH}$ = 6.6 Hz, 3H, H_F), 0.82 (d, $^3J_{HH}$ = 6.6 Hz, 3H, $H_{F'}$) ppm;

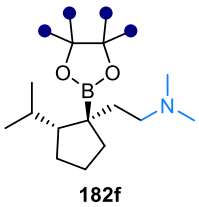
^{13}C NMR (101 MHz, $CDCl_3$): δ_C 83.3 (C_B), 58.6 (C_D), 56.2 (C_K), 43.1 (C_L), 41.7 ($C_{L'}$), 35.9 (C_I), 33.1 (C_J), 32.0 (C_E), 31.5 (C_G), 24.9 (C_A), 24.9 ($C_{A'}$), 23.6 (C_H), 23.3 (C_F), 22.6 ($C_{F'}$) ppm; C_C not observed due to quadrupolar relaxation;

^{11}B NMR (128 MHz, $CDCl_3$): δ_B 33.7 ppm.

IR (film): ν_{max} 3340 (br), 2955, 2870, 1634, 1473, 1372, 1311, 1258, 1166 cm^{-1}.

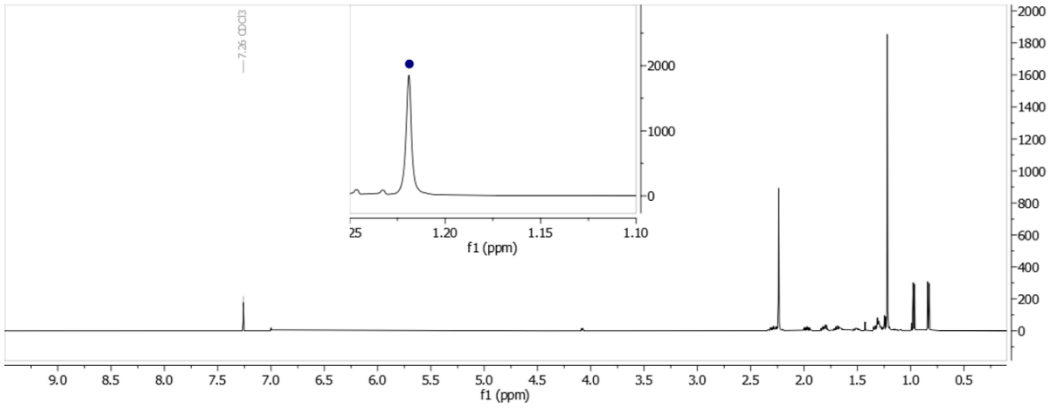
HRMS (ESI): m/z calc'd for $C_{18}H_{37}{}^{11}BNO_2$ $[M+H]^+$ 310.2915 found 310.2919.

Chiral solvating agent: The enantiopurity of boronic ester **141f** was determined using Pirkle's alcohol ((*R*)-(–)-1-(9-anthryl)-2,2,2-trifluoroethanol) NMR shift reagent (2.0 eq, rt, $CDCl_3$, 0.05 M), 95:5 e.r. A portion of the HCl salt was converted to free amine **182f** by washing with 0.5 M aqueous NaOH and extracting with Et_2O for e.r. determination.

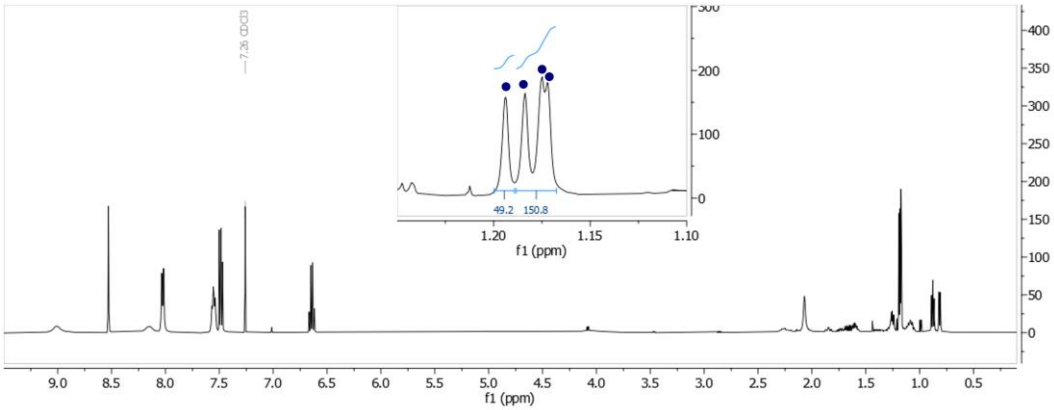


182f

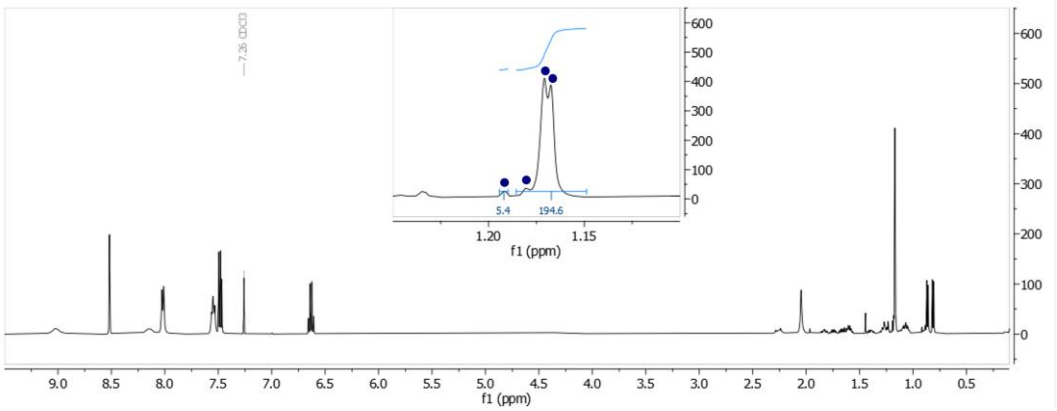
^{1}H NMR (500 MHz, $CDCl_3$) expansion of **(±)-182f** only:



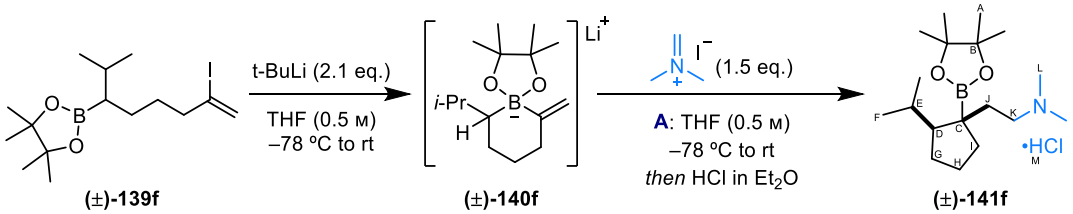
^{1}H NMR (500 MHz, $CDCl_3$) expansion of **(±)-182f** with Pirkle's alcohol:



^{1}H NMR (500 MHz, $CDCl_3$) expansion of **182f** with Pirkle's alcohol:

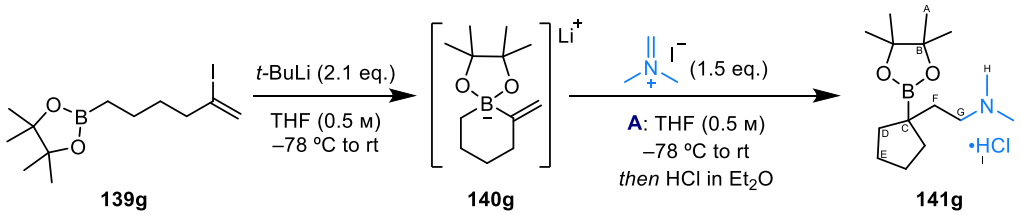


Racemic test reaction:



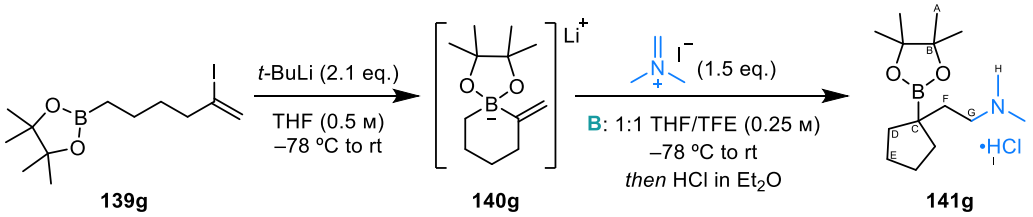
According to **General Procedure E**, boronic ester **(±)-139f** (38 mg, 0.10 mmol, 1.0 eq.) was allowed to react with *tert*-butyl lithium (1.5 M in pentane, 0.14 mL, 0.21 mmol, 2.1 eq.) and *N*,*N*-dimethylmethyleneiminium iodide (28 mg, 0.15 mmol, 1.5 eq.) to give a crude residue (91:9 d.r. by crude ^{1}H NMR spectroscopic analysis) which was dissolved in Et_2O (*ca.* 0.3 mL) and then HCl (2 M in Et_2O; 55 µL, 0.11 mmol, 1.1 eq.) was added. The white precipitate formed was collected *via* suction filtration and dried under high vacuum to afford the racemic boronic ester (24 mg, 68%, 91:9 d.r.) as a white foam.

N,*N*-Dimethyl-2-(1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclopentyl)ethan-1-amine hydrochloride salt (141g)



According to **General Procedure E**, boronic ester **139g** (67 mg, 0.20 mmol, 1.0 eq.) was allowed to react with *tert*-butyl lithium (1.8 M in pentane, 0.24 mL, 0.42 mmol, 2.1 eq.) and *N*,*N*-dimethylmethyleneiminium iodide (56 mg, 0.30 mmol, 1.5 eq.) to give a crude residue which was dissolved in Et_2O (*ca.* 0.5 mL) and then HCl (2 M in Et_2O; 110 µL, 0.22 mmol,

1.1 eq.) was added. The white precipitate formed was collected *via* suction filtration and dried under high vacuum to afford the boronic ester (33 mg, 55%) as a white foam.



According to **General Procedure G**, boronic ester **139g** (67 mg, 0.20 mmol, 1.0 eq.) was allowed to react with *tert*-butyl lithium (1.8 M in pentane, 0.24 mL, 0.42 mmol, 2.1 eq.) and *N*,*N*-dimethylmethyleneiminium iodide (56 mg, 0.30 mmol, 1.5 eq.) to give a crude residue which was dissolved in Et_2O (*ca.* 0.5 mL) and then HCl (2 M in Et_2O; 110 µL, 0.22 mmol, 1.1 eq.) was added. The white precipitate formed was collected *via* suction filtration and dried under high vacuum to afford the boronic ester (32 mg, 52%) as a white foam.

$\mathbf{R_f}$ = 0.20 (CH_2Cl_2/MeOH 9:1).

NMR Spectroscopy:

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 12.26 (s, 1H, H_I), 3.07–2.88 (m, 2H, H_G), 2.75 (s, 3H, H_H), 2.74 (s, 3H, $H_{H'}$), 1.83–1.72 (m, 4H, $H_{D,\,F,\,F'}$), 1.63–1.55 (m, 4H, $H_{E,\,E'}$), 1.35–1.20 (m, 2H, $H_{D'}$), 1.19 (s, 12H, H_A) ppm;

^{13}C NMR (101 MHz, $CDCl_3$): δ_C 83.5 (C_B), 56.3 (C_G), 42.5 (C_H), 35.2 (C_D), 31.3 (C_F), 25.1 (C_E), 24.7 (C_A) ppm; C_C not observed due to quadrupolar relaxation;

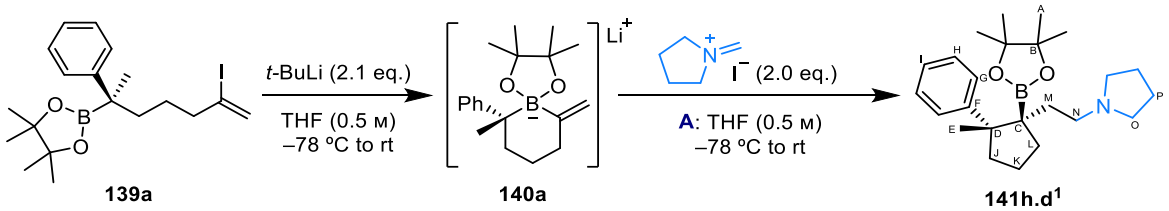
^{11}B NMR (128 MHz, $CDCl_3$): δ_B 33.7 ppm.

IR (film): ν_{max} 3371, 2929 (br), 2859, 2604, 1737, 1379, 1318, 1260, 1144 cm^{-1}.

HRMS (ESI): m/z calc'd for $C_{15}H_{31}{}^{11}BNO_2$ $[M+H]^+$ 268.2445 found 268.2455.

6.2.2.6. Electrophile scope: characterisation of cyclopentyl boronic esters

1-(2-((1*S*,2*S*)-2-Methyl-2-phenyl-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclopentyl)ethyl)pyrrolidine (141h.d[1])



According to **General Procedure E**, boronic ester **139a** (85 mg, 0.20 mmol, 1.0 eq.; 99:1 e.r.) was allowed to react with *tert*-butyl lithium (1.6 M in pentane, 0.26 mL, 0.42 mmol, 2.1 eq.) and the 1-methylenepyrrolidin-1-ium iodide[200] (84 mg, 0.40 mmol, 2.0 eq.) to give a crude residue (82:18 d.r. by crude ^{1}H NMR spectroscopic analysis) which was purified by flash column chromatography (9:1 pentane/CH_2Cl_2) to afford the boronic ester (21 mg, 27%, 82:18 d^1/d^2, >98:2 e.r., 100% e.s.) as a colourless oil.

$\mathbf{R_f}$ = 0.20 for both diastereomers (CH_2Cl_2/MeOH 9:1).

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$**:** –2 (*c* = 3.0, CH_2Cl_2).

NMR Spectroscopy: *Assignments made for the major diastereomer.*

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.45–7.39 (m, 2H, H_G), 7.28–7.20 (m, 2H, H_H), 7.17–7.08 (m, 1H, H_I), 2.42–2.29 (m, 6H, $H_{J,\,N,\,O}$), 2.21 (apparent td, J_{HH} = 11.6, 4.6 Hz, 1H, $H_{N'}$), 2.12 (ddd, J_{HH} = 13.1, 9.7, 4.8 Hz, 1H, H_L), 1.95–1.77 (m, 2H, $H_{K,\,K'}$), 1.75–1.70 (m, 1H, $H_{J'}$), 1.70–1.65 (m, 4H, H_P), 1.56–1.46 (m, 2H, $H_{L',\,M}$), 1.34 (s, 3H, H_E), 1.30 (s, 6H, H_A), 1.28 (s, 6H, $H_{A'}$), 0.86 (apparent td, J_{HH} = 12.2, 4.6 Hz, 1H, $H_{M'}$) ppm;

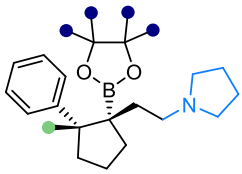
^{13}C NMR (101 MHz, $CDCl_3$): δ_C 147.9 (C_F), 127.9 (C_G), 127.5 (C_H), 125.2 (C_I), 83.2 (C_B), 54.8 (C_N), 54.2 (C_O), 53.0 (C_D), 38.3 (C_J), 34.0 (C_M), 32.2 (C_L), 28.7 (C_E), 25.3 (C_A), 25.0 ($C_{A'}$), 24.7 (C_P), 23.3 (C_K) ppm; C_C not observed due to quadrupolar relaxation;

^{11}B NMR (128 MHz, $CDCl_3$): δ_B 33.2 ppm.

IR (film): ν_{max} 2952, 2874, 2787, 1601, 1444, 1370, 1308, 1204, 1143 cm^{-1}.

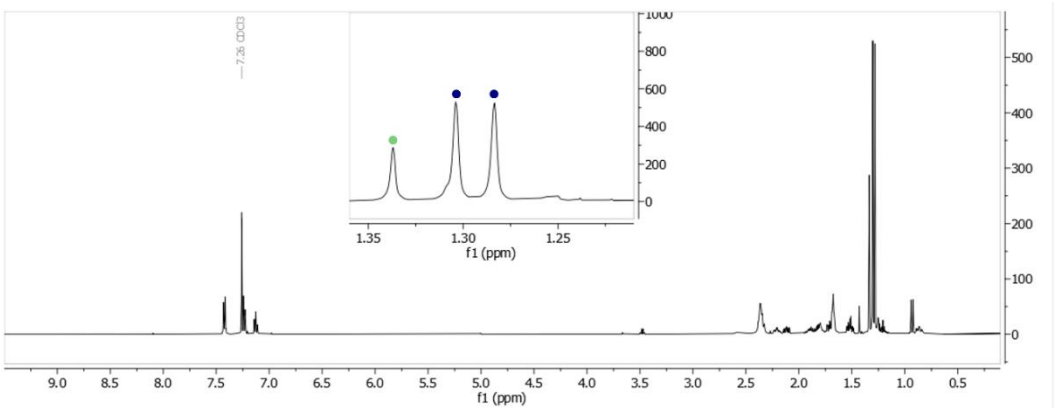
HRMS (ESI): m/z calc'd for $C_{24}H_{39}{}^{11}BNO_2$ $[M+H]^+$ 384.3073 found 384.3086.

Chiral solvating agent: The enantiopurity of boronic ester **141h.d[1]** was determined using Pirkle's alcohol ((*R*)-(–)-1-(9-anthryl)-2,2,2-trifluoroethanol) NMR shift reagent (2.0 eq, rt, $CDCl_3$, 0.05 M), >98:2 e.r.

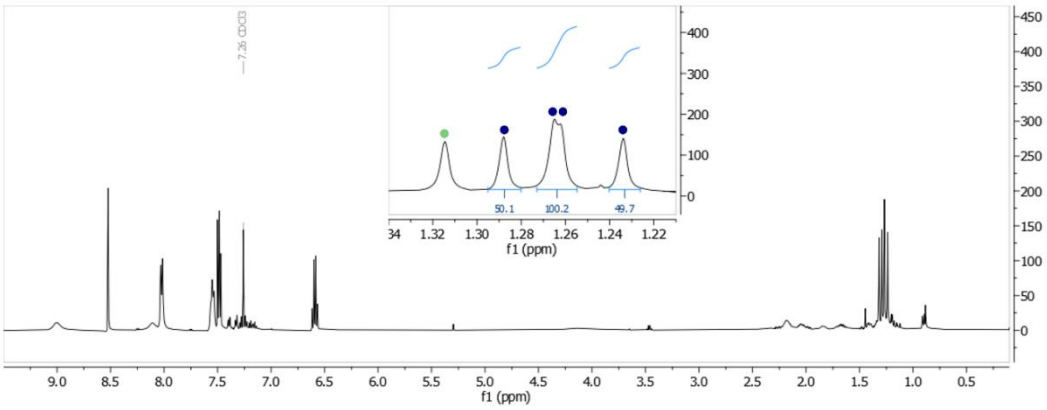


141h.d[1]

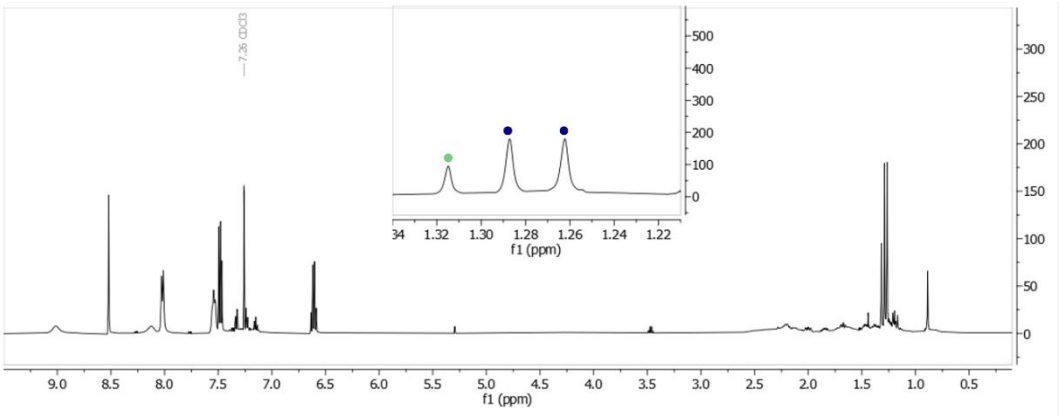
^{1}H NMR (500 MHz, $CDCl_3$) expansion of **(±)-141h.d[1]** only:



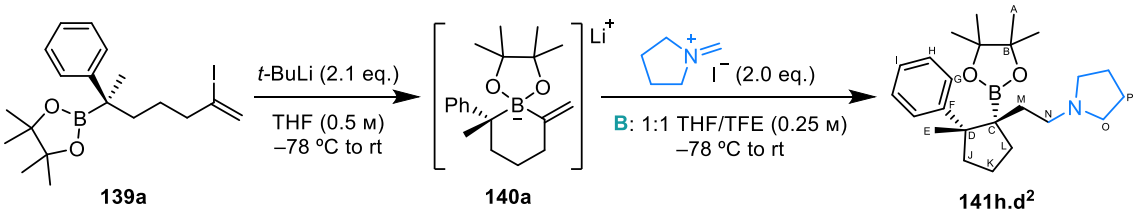
^{1}H NMR (500 MHz, $CDCl_3$) expansion of **(±)-141h.d[1]** with Pirkle's alcohol:



^{1}H NMR (500 MHz, $CDCl_3$) expansion of **141h.d[1]** with Pirkle's alcohol:



1-(2-((1*R*,2*S*)-2-Methyl-2-phenyl-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclopentyl)ethyl)pyrrolidine (141h.d^2)



According to **General Procedure G**, boronic ester **139a** (85 mg, 0.20 mmol, 1.0 eq.; 99:1 e.r.) was allowed to react with *tert*-butyl lithium (1.6 M in pentane, 0.26 mL, 0.42 mmol, 2.1 eq.) and the pyrrolidine-derived iminium salt[200] (84 mg, 0.40 mmol, 2.0 eq.) to give a crude residue (82:18 d.r. by crude ^{1}H NMR spectroscopic analysis) which was purified by flash column chromatography (9:1 pentane/CH_2Cl_2) to afford the boronic ester (46 mg, 60%, 18:82 d^1/d^2, >98:2 e.r., 100% e.s.) as a colourless oil.

$\mathbf{R_f}$ = 0.20 for both diastereomers (CH_2Cl_2/MeOH 9:1).

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$**:** –1 (*c* = 8.0, CH_2Cl_2).

NMR Spectroscopy: *Assignments made for the major diastereomer.*

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.44–7.38 (m, 2H, H_G), 7.25–7.19 (m, 2H, H_H), 7.14–7.09 (m, 1H, H_I), 2.61–2.44 (m, 5H, $H_{N,\,O}$), 2.42–2.26 (m, 2H, $H_{J,\,N'}$), 2.18 (apparent td, J_{HH} = 12.1, 4.2 Hz, 1H, H_M), 1.98 (ddd, J_{HH} = 12.8, 9.0, 7.3 Hz, 1H, H_L), 1.87–1.70 (m, 7H, $H_{J',\,K,\,K',\,P}$), 1.68–1.55 (m, 2H, $H_{L',\,M'}$), 1.31 (s, 3H, H_E), 0.94 (s, 6H, H_A), 0.92 (s, 6H, $H_{A'}$) ppm;

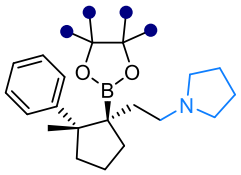
^{13}C NMR (101 MHz, $CDCl_3$): δ_C 149.5 (C_F), 127.5 (C_H), 127.2 (C_G), 125.5 (C_I), 82.6 (C_B), 55.1 (C_N), 54.4 (C_O), 51.3 (C_D), 38.7 (C_J), 33.1 (C_M), 31.9 (C_L), 25.2 (C_A), 24.7 ($C_{A'}$), 24.5 (C_E), 23.4 (C_P), 21.6 (C_K) ppm; C_C not observed due to quadrupolar relaxation;

^{11}B NMR (128 MHz, $CDCl_3$): δ_B 33.2 ppm.

IR (film): ν_{max} 2960, 2788, 1443, 1371, 1310, 1210, 1139, 1032 cm^{-1}.

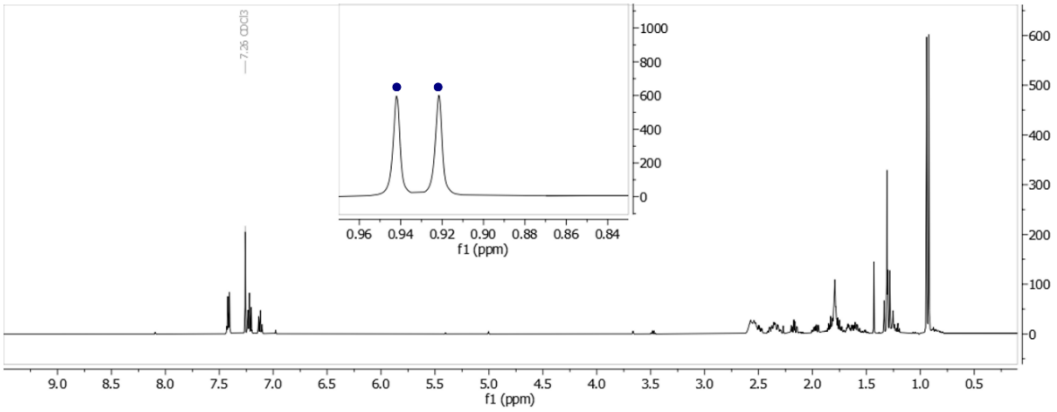
HRMS (ESI): m/z calc'd for $C_{24}H_{39}{}^{11}BNO_2$ $[M+H]^+$ 384.3067 found 384.3068.

Chiral solvating agent: The enantiopurity of boronic ester **141h.d²** was determined using Pirkle's alcohol ((*R*)-(–)-1-(9-anthryl)-2,2,2-trifluoroethanol) NMR shift reagent (2.0 eq, rt, $CDCl_3$, 0.04 M), >98:2 e.r.

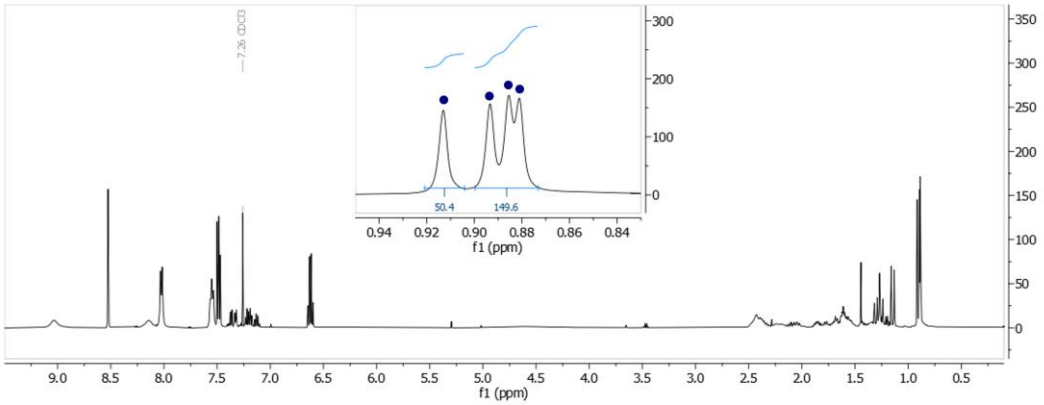


141h.d²

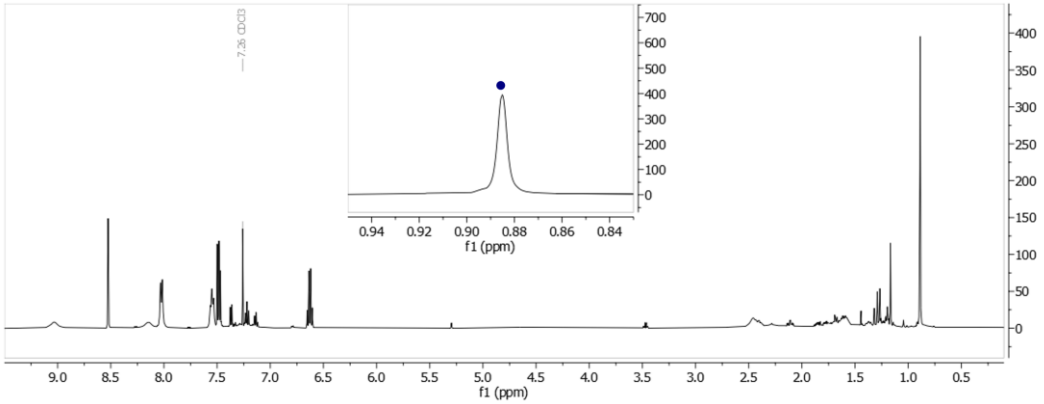
^{1}H NMR (500 MHz, $CDCl_3$) expansion of **(±)-141h.d²** only:



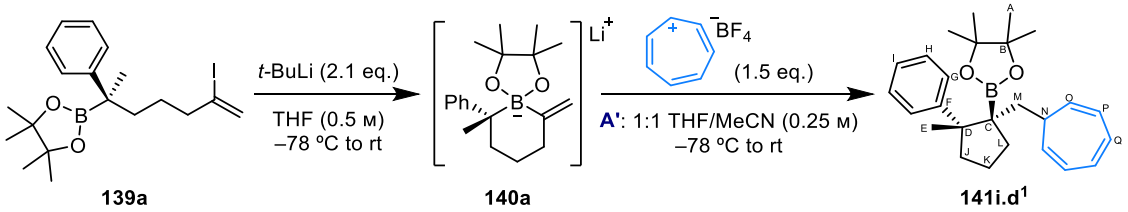
^{1}H NMR (500 MHz, $CDCl_3$) expansion of **(±)-141h.d²** with Pirkle's alcohol:



^{1}H NMR (500 MHz, $CDCl_3$) expansion of **141h.d²** with Pirkle's alcohol:



2-((1*S*,2*S*)-1-(Cyclohepta-2,4,6-trien-1-ylmethyl)-2-methyl-2-phenylcyclopentyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (141i.d[1])



According to **General Procedure F**, boronic ester **139a** (85 mg, 0.20 mmol, 1.0 eq.; 99:1 e.r.) was allowed to react with *tert*-butyl lithium (1.6 M in pentane, 0.27 mL, 0.42 mmol, 2.1 eq.) and tropylium tetrafluoroborate (53 mg, 0.30 mmol, 1.5 eq.) to give a crude residue (94:6 d.r. by crude ^{1}H NMR spectroscopic analysis) which was purified by flash column chromatography (100:1 pentane/Et_2O) to afford the boronic ester (34 mg, 44%, 94:6 d^1/d^2, 99:1 e.r., 100% e.s.) as a colourless oil. Boronic ester **185** was isolated as a side product.

The e.r. of boronic ester **141i.d[1]** could not be determined by chiral HPLC/SFC. Instead, the boronic ester was oxidised and the e.r. of alcohol **141i'.d[1]** was determined.

$\mathbf{R_f}$ = 0.43 for both diastereomers (pentane/CH_2Cl_2 9:1).

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$**:** +15 (*c* = 6.0, CH_2Cl_2).

NMR Spectroscopy: *Assignments made for the major diastereomer.*

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.49–7.45 (m, 2H, H_G), 7.35–7.27 (m, 2H, H_H), 7.22–7.16 (m, 1H, H_I), 6.65–6.54 (m, 2H, H_Q), 6.08–6.01 (m, 2H, H_P), 5.10 (dd, $^3J_{HH}$ = 9.2, 5.7 Hz, 1H, H_O), 5.24 (dd, $^3J_{HH}$ = 9.2, 5.7 Hz, 1H, $H_{O'}$), 2.48–2.34 (m, 1H, H_J), 2.19–2.07 (m, 1H, H_L), 2.03–1.79 (m, 3H, $H_{K, K', M}$), 1.79–1.71 (m, 1H, $H_{J'}$), 1.71–1.59 (m, 1H $H_{L'}$), 1.36 (s, 3H, H_E), 1.28–1.14 (m, 2H, $H_{M', N}$), 1.24 (s, 6H, H_A), 1.20 (s, 6H, $H_{A'}$) ppm;

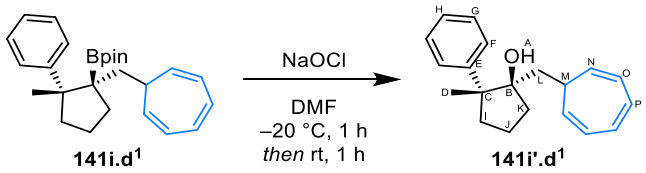
^{13}C NMR (101 MHz, $CDCl_3$): δ_C 148.1 (C_F), 130.8 (C_Q), 130.5 ($C_{Q'}$), 127.9 (C_O), 127.9 (C_G), 127.5 (C_H), 127.4 ($C_{O'}$), 125.3 (C_I), 123.1 (C_P), 123.1 ($C_{P'}$), 83.3 (C_B), 53.4 (C_D), 39.4 (C_M), 38.9 (C_N), 38.4 (C_J), 32.5 (C_L), 28.9 (C_E), 25.0 (C_A), 25.0 ($C_{A'}$), 22.1 (C_K) ppm; C_C not observed due to quadrupolar relaxation;

^{11}B NMR (128 MHz, $CDCl_3$): δ_B 34.6 ppm.

IR (film): ν_{max} 2975, 2929, 2873 1444, 1370, 1308, 1143 cm^{-1}.

HRMS (ESI): m/z calc'd for $C_{26}H_{36}{}^{11}BO_2$ $[M+H]^+$ 391.2808 found 391.2793.

(1*R*,2*R*)-1-(Cyclohepta-2,4,6-trien-1-ylmethyl)-2-methyl-2-phenylcyclopentan-1-ol (141i'.d^1)



According to **General Procedure H**, boronic ester **141i.d^1** (23 mg, 0.06 mmol, 94:6 d^1/d^2, 1.0 eq.) was allowed to react with aqueous NaOCl (0.16 mL) in DMF (0.77 mL) to give a crude residue which was purified by flash column chromatography (100:3 pentane/EtOAc) to give the alcohol (8 mg, 49%, 94:6 d^1/d^2, 99:1 e.r.) as a colourless oil.

R$_f$ = 0.48 for both diastereomers (pentane/EtOAc 9:1).

$[\alpha]_D^{25}$**:** +2 (*c* = 3.5, CH_2Cl_2).

NMR Spectroscopy: *Assignments made for the major diastereomer.*

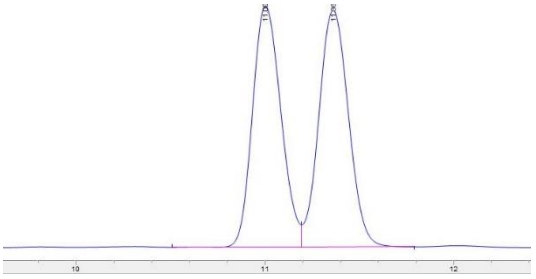
^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.46–7.40 (m, 2H, H_F), 7.35–7.28 (m, 2H, H_G), 7.24–7.17 (m, 1H, H_H), 6.72–6.56 (m 2H, H_P), 6.18–6.01 (m 2H, H_O), 5.17 (dd, $^3J_{HH}$ = 9.3, 5.6 Hz, 1H, H_N), 4.96 (dd, $^3J_{HH}$ = 9.3, 5.6 Hz, H_N), 2.36–2.22 (m, 1H, H_I), 2.03–1.87 (m, 3H, $H_{I', J, K}$), 1.86–1.68 (m, 3H, $H_{J', K', L}$), 1.68–1.58 (m, 1H, H_M), 1.51–1.43 (m, 1H, $H_{L'}$), 1.41 (s, 3H, H_D) ppm; H_A not observed;

^{13}C NMR (101 MHz, $CDCl_3$): δ_C 147.3 (C_E), 131.0 (C_P), 130.8 ($C_{P'}$), 127.9 (C_F), 127.1 (C_G), 126.7 (C_N), 126.1 ($C_{N'}$), 125.9 (C_H), 123.8 (C_O), 123.7 ($C_{O'}$), 84.9 (C_B), 52.4 (C_C), 40.2 (C_L), 35.9 (C_I), 35.8 (C_K), 35.6 (C_M), 23.8 (C_D), 19.1 (C_J) ppm.

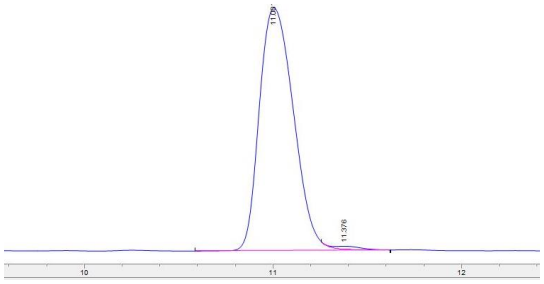
IR (film): ν_{max} 3582 (br), 2959, 2924, 1723, 1600, 1496, 1464, 1375, 1261, 1092, 1031 cm^{-1}.

HRMS (ESI): m/z calc'd for $C_{20}H_{24}ONa$ $[M+Na]^+$ 303.1719 found 303.1730.

Chiral HPLC (IB column, 97:3 hexane/IPA, 0.5 mL/min, rt, 230 nm): 11.0 min (major), 11.4 min (minor), 99:1 e.r.

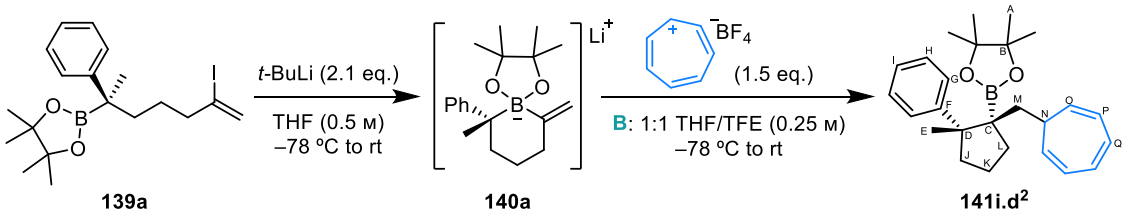


#	Time	Type	Area	Height	Width	Area%	Symmetry
1	11.003	VV R	4124.9	394	0.1651	49.453	0.811
2	11.362	VB	4216.1	386.3	0.1698	50.547	0.896



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	11.001	BV R	8684.1	689.6	0.2004	98.915	0.71
2	11.376	VB E	95.3	9.5	0.144	1.085	0.552

2-((1*R*,2*S*)-1-(Cyclohepta-2,4,6-trien-1-ylmethyl)-2-methyl-2-phenylcyclopentyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (141i.d^2)



139a **140a** **141i.d^2**

According to **General Procedure G**, boronic ester **139a** (85 mg, 0.20 mmol, 1.0 eq.; 99:1 e.r.) was allowed to react with *tert*-butyl lithium (1.6 M in pentane, 0.27 mL, 0.42 mmol, 2.1 eq.) and tropylium tetrafluoroborate (53 mg, 0.30 mmol, 1.5 eq.) to give a crude residue (83:17 d.r. by crude ^{1}H NMR spectroscopic analysis) which was purified by flash column chromatography (100:1 pentane/Et_2O) to afford the boronic ester (54 mg, 69%, 17:83 d^1/d^2, 99:1 e.r., 100% e.s.) as a colourless oil.

The e.r. of boronic ester **141i.d^2** could not be determined by chiral HPLC/SFC. Instead, the boronic ester was oxidised and the e.r. of alcohol **141i'.d^2** was determined.

R$_f$ = 0.43 for both diastereomers (pentane/CH_2Cl_2 9:1).

$[\alpha]_D^{25}$: –17 (*c* = 9.4, CH_2Cl_2).

NMR Spectroscopy: *Assignments made for the major diastereomer.*

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.46–7.41 (m, 2H, H_G), 7.29–7.23 (m, 2H, H_H), 7.19–7.10 (m, 1H, H_I), 6.71–6.57 (m, 2H, H_Q), 6.19–6.08 (m, 2H, H_P), 5.31 (dd, $^3J_{HH}$ = 9.2, 5.7 Hz, 1H, H_O), 5.25 (dd, $^3J_{HH}$ = 9.2, 5.7 Hz, 1H, $H_{O'}$), 2.44 (dd, J_{HH} = 13.0, 4.3 Hz, 1H, H_M), 2.41–2.31 (m, 1H, H_J), 2.01–1.77 (m, 5H, $H_{J', K, K', L, M'}$), 1.78–1.70 (m, 1H, $H_{L'}$), 1.41 (s, 3H, H_E), 1.34–1.27 (m, 1H, H_N), 0.93 (s, 6H, H_A), 0.88 (s, 6H, $H_{A'}$) ppm;

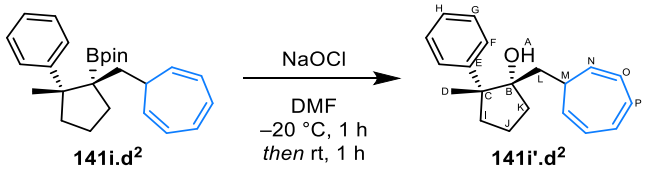
^{13}C NMR (101 MHz, $CDCl_3$): δ_C 150.3 (C_F), 130.9 (C_Q), 130.6 ($C_{Q'}$), 127.9 (C_O), 127.6 (C_H), 127.3 (C_G), 127.2 ($C_{O'}$), 125.5 (C_I), 123.4 (C_P), 123.3 ($C_{P'}$), 82.3 (C_B), 51.6 (C_D), 39.0 (C_N), 38.7 (C_J), 38.1 (C_M), 32.0 (C_L), 25.1 (C_A), 24.9 ($C_{A'}$), 24.3 (C_E), 21.9 (C_K) ppm; C_C not observed due to quadrupolar relaxation;

^{11}B NMR (128 MHz, $CDCl_3$): δ_B 34.6 ppm.

IR (film): ν_{max} 2974, 2872, 1443, 1372, 1311, 1142 cm^{-1}.

HRMS (ESI): m/z calc'd for $C_{26}H_{36}{}^{11}BO_2$ $[M+H]^+$ 391.2803 found 391.2802.

(1*S*,2*R*)-1-(Cyclohepta-2,4,6-trien-1-ylmethyl)-2-methyl-2-phenylcyclopentan-1-ol (141i'.d^2)



According to **General Procedure H**, boronic ester **141i.d^2** (19 mg, 0.05 mmol, 17:83 d^1/d^2, 1.0 eq.) was allowed to react with aqueous NaOCl (0.14 mL) in DMF (0.65 mL) to give a crude residue which was purified by flash column chromatography (100:3 pentane/EtOAc) to give the alcohol (6 mg, 41%, 17:83 d^1/d^2, 99:1 e.r.) as a colourless oil.

$\mathbf{R_f}$ = 0.48 for both diastereomers (pentane/EtOAc 9:1).

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$**:** –32 (*c* = 2.3, CH_2Cl_2).

NMR Spectroscopy: *Assignments made for the major diastereomer.*

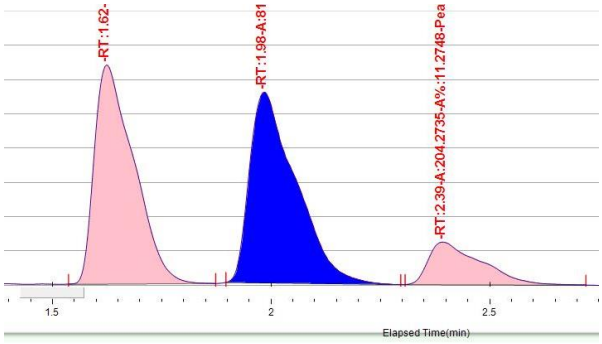
^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.57–7.48 (m, 2H, H_F), 7.41–7.34 (m, 2H, H_G), 7.32–7.24 (m, 1H, H_H), 6.68–6.56 (m, 2H, H_P), 6.18–6.03 (m, 2H, H_O), 5.23–5.10 (m, 2H, H_N), 2.81–2.66 (m, 1H, H_I), 2.18–2.10 (m, 1H, H_L), 2.01–1.70 (m, 6H, $H_{J,\ J',\ K,\ K',\ L',\ M}$), 1.64–1.55 (m, 1H, $H_{I'}$), 1.36 (s, 3H, H_D) ppm; H_A not observed;

^{13}C NMR (101 MHz, $CDCl_3$): δ_C 142.9 (C_E), 130.9 (C_P), 130.8 ($C_{P'}$), 128.2 (C_G), 128.1 (C_F), 126.7 (C_N), 126.6 (C_H), 126.3 ($C_{N'}$), 123.9 (C_O), 123.7 ($C_{O'}$), 84.4 (C_B), 53.9 (C_C), 39.2 (C_L), 36.0 (C_K), 35.6 ($C_{I,\ M}$), 23.6 (C_D), 19.5 (C_J) ppm.

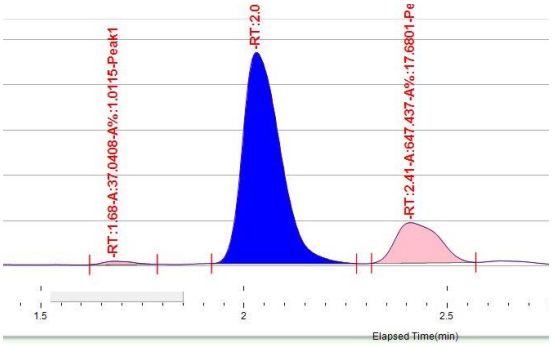
IR (film): ν_{max} 3457 (br), 2964, 2935, 1600, 1497, 1443, 1379, 1034 cm^{-1}.

HRMS (ESI): m/z calc'd for $C_{20}H_{23}$ $[M+H–H_2O]^+$ 263.1794 found 263.1794.

Chiral SFC (Whelk-O1 column, iso 5% hexane/IPA 10%, 4 mL/min, 125 bar): 1.7 min (d^2, minor enantiomer), 2.0 min (d^2, major enantiomer), 2.4 min (d^1, both enantiomers), 99:1 e.r.

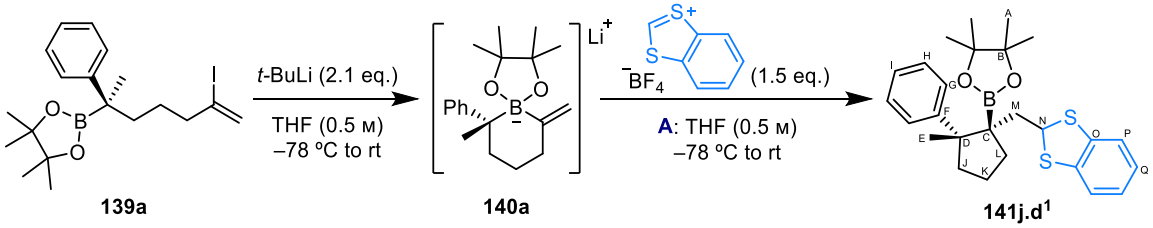


Signal	Peak Name	Area Percent	Area	Retention Time	Height
MaxAbsorbance	Peak1	43.8426	794.3291	1.62 min	127.8296
	Peak2	44.8826	813.1703	1.98 min	111.3337
	Peak3	11.2748	204.2735	2.39 min	24.8371



Signal	Peak Name	Area Percent	Area	Retention Time	Height
MaxAbsorbance	Peak1	1.0115	37.0408	1.68 min	7.4534
	Peak2	81.3084	2977.4771	2.03 min	466.7121
	Peak3	17.6801	647.437	2.41 min	89.1287

2-((1*S*,2*S*)-1-(Benzo[d][1,3]dithiol-2-ylmethyl)-2-methyl-2-phenylcyclopentyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (141j.d^1)



According to **General Procedure E**, boronic ester **139a** (85 mg, 0.20 mmol, 1.0 eq.; 99:1 e.r.) was allowed to react with *tert*-butyl lithium (1.7 M in pentane, 0.25 mL, 0.42 mmol, 2.1 eq.) and 1,3-benzodithiolium tetrafluoroborate (72 mg, 0.30 mmol, 1.5 eq.) to give a crude residue (86:14 d.r. by crude ^{1}H NMR spectroscopic analysis) which was purified by flash column chromatography (100:1 pentane/Et_2O) to afford the boronic ester (24 mg, 26%, 86:14 d^1/d^2, 99:1 e.r., 100% e.s.) as a colourless oil.

The e.r. of boronic ester **141j.d^1** could not be determined by chiral HPLC/SFC. Instead, the boronic ester was oxidised and the e.r. of alcohol **141j'.d^1** was determined.

$\mathbf{R_f}$ = 0.25 for both diastereomers (pentane/CH_2Cl_2 9:1).

$[\alpha]_D^{25}$**:** –8 (*c* = 1.2, CH_2Cl_2).

NMR Spectroscopy: *Assignments made for the major diastereomer.*

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.40–7.34 (m, 2H, H_G), 7.29–7.23 (m, 2H, H_H), 7.18–7.12

(m, 1H, H_I), 7.11–7.05 (m, 2H, H_P *or* H_Q), 6.95–6.89 (m, 2H, H_P *or* H_Q), 4.98 (dd, $^3J_{HH}$ = 8.4, 4.6 Hz, 1H, H_N), 2.35–2.18 (m, 2H, $H_{J,L}$), 2.11 (dd, $^2J_{HH}$ = 14.6 Hz, $^3J_{HH}$ = 4.6 Hz, 1H, H_M), 2.01–1.82 (m, 2H, $H_{K,K'}$), 1.81–1.67 (m, 2H, $H_{J',L'}$), 1.53 (dd, $^2J_{HH}$ = 14.6 Hz, $^3J_{HH}$ = 8.4 Hz, 1H, $H_{M'}$), 1.34 (s, 6H, H_A), 1.32 (s, 9H, $H_{A',E}$) ppm;

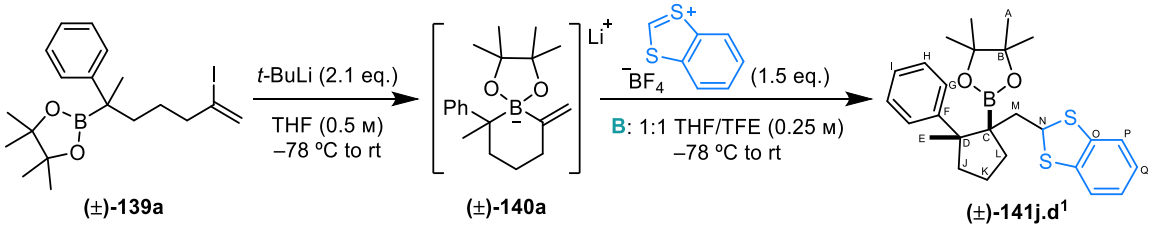
^{13}C NMR (101 MHz, $CDCl_3$): δ_C 147.7 (C_F), 138.4 (C_O), 138.1 ($C_{O'}$), 127.8 (C_H), 127.7 (C_G), 125.6 (C_I), 125.2 (C_P *or* C_Q), 125.1 (C_P *or* C_Q), 122.1 (C_P *or* C_Q), 121.9 (C_P *or* C_Q), 83.6 (C_B), 54.1 (C_D *or* C_N), 54.0 (C_D *or* C_N), 43.4 (C_M), 38.1 (C_J), 32.6 (C_L), 29.0 (C_E), 25.3 (C_A), 25.1 ($C_{A'}$), 21.8 (C_K) ppm; C_C not observed due to quadrupolar relaxation;

^{11}B NMR (128 MHz, $CDCl_3$): δ_B 33.3 ppm.

IR (film): ν_{max} 2973, 2874, 1444, 1361, 1309, 1208, 1140 cm^{-1}.

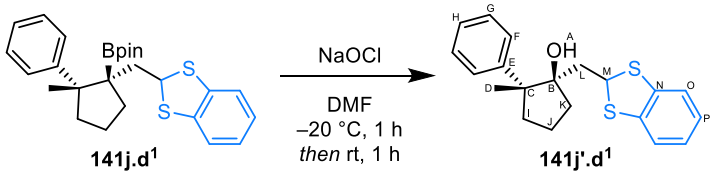
HRMS (ESI): m/z calc'd for $C_{26}H_{33}{}^{11}BNaO_2S_2$ $[M+Na]^+$ 475.1912 found 475.1912.

Racemic test reaction:



According to **General Procedure G**, boronic ester **(±)-139a** (43 mg, 0.10 mmol, 1.0 eq.) was allowed to react with *tert*-butyl lithium (1.7 M in pentane, 0.12 mL, 0.24 mmol, 2.1 eq.) and 1,3-benzodithiolium tetrafluoroborate (36 mg, 0.15 mmol, 1.5 eq.) to give a crude residue (54:46 d.r. by crude ^{1}H NMR spectroscopic analysis) which was purified by flash column chromatography (100:1 pentane/Et_2O) to afford the racemic boronic ester (20 mg, 44%, 54:46 d^1/d^2) as a colourless oil.

(1*R*,2*R*)-1-(Benzo[*d*][1,3]dithiol-2-ylmethyl)-2-methyl-2-phenylcyclopentan-1-ol (141j'.d^1)



According to **General Procedure H**, boronic ester **141j.d^1** (12 mg, 0.03 mmol, 86:14 d^1/d^2, 1.0 eq.) was allowed to react with aqueous NaOCl (0.07 mL) in DMF (0.34 mL) to give a crude

residue which was purified by flash column chromatography (95:5 pentane/EtOAc) to give the alcohol (5 mg, 59%, 86:14 d^1/d^2, 99:1 e.r.) as a colourless oil.

R_f = 0.36 (d^2), 0.13 (d^1) (pentane/EtOAc 9:1).

$[\alpha]_D^{25}$: +3 (*c* = 1.6, CH_2Cl_2).

NMR Spectroscopy: *Assignments made for the major diastereomer.*

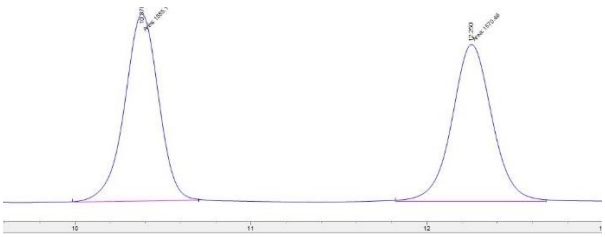
^{1}H NMR (500 MHz, $CDCl_3$): δ_H 7.37–7.33 (m, 2H, H_F *or* H_G), 7.32–7.24 (m, 2H, H_F *or* H_G), 7.22–7.17 (m, 1H, H_H), 7.15–7.09 (m, 2H, H_Q *or* H_P), 7.01–6.92 (m, 2H, H_Q *or* H_P), 5.13 (dd, $^3J_{HH}$ = 7.8, 5.6 Hz, 1H, H_M), 2.29–2.20 (m, 1H, H_I *or* H_K), 2.12 (dd, $^2J_{HH}$ = 14.9 Hz, $^3J_{HH}$ = 7.8 Hz, 1H, H_L), 2.02–1.90 (m, 2H, H_I *or* H_K), 1.89–1.81 (m, 1H, H_I *or* H_K), 1.77 (dd, $^2J_{HH}$ = 14.9 Hz, $^3J_{HH}$ = 5.6 Hz, 1H, $H_{L'}$), 1.40 (s, 3H, H_D), 1.27–1.23 (m, 2H, $H_{J, J'}$) ppm; H_A not observed;

^{13}C NMR (125 MHz, $CDCl_3$): δ_C 146.4 (C_E), 138.0 (C_N), 137.4 ($C_{N'}$), 128.1 (C_{Ar}), 126.9 (C_{Ar}), 126.2 (C_{Ar}), 125.4 (C_{Ar}), 122.2 (C_{Ar}), 122.1 (C_{Ar}), 84.4 (C_B), 52.6 (C_C *or* C_M), 51.3 (C_C *or* C_M), 44.2 (C_L), 36.0 (C_I *or* C_K), 35.6 (C_I *or* C_K), 23.5 (C_D), 19.2 (C_J) ppm.

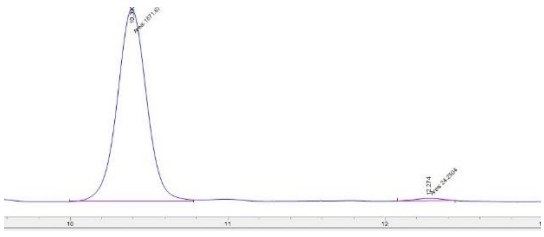
IR (film): ν_{max} 3498 (br), 3056, 2961, 2877, 1496, 1444, 1374, 1118, 1031 cm^{-1}.

HRMS (ESI): m/z calc'd for $C_{20}H_{22}NaOS_2$ $[M+Na]^+$ 365.1004 found 365.1011.

Chiral HPLC (IA column, 97:3 hexane/IPA, 1 mL/min, rt, 230 nm): 10.4 min (major), 12.3 min (minor), 99:1 e.r.

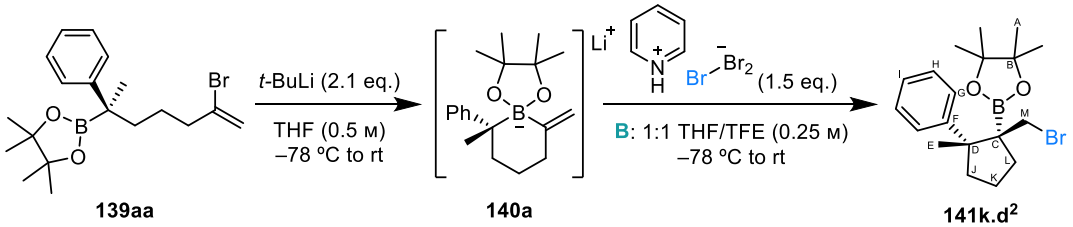


#	Time	Type	Area	Height	Width	Area%	Symmetry
1	10.378	MM	1585.1	117.5	0.2248	50.232	1.041
2	12.25	MM	1570.5	98.5	0.2657	49.768	0.947



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	10.39	MM	1871.7	144	0.2166	98.721	0.961
2	12.274	MM	24.3	2	0.2066	1.279	1.045

2-((1*S*,2*S*)-1-(Bromomethyl)-2-methyl-2-phenylcyclopentyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (141k.d^2)



According to **General Procedure G**, boronic ester **139aa** (76 mg, 0.20 mmol, 1.0 eq.; 99:1 e.r.) was allowed to react with *tert*-butyl lithium (1.6 M in pentane, 0.26 mL, 0.42 mmol, 2.1 eq.) and pyridinium tribromide (96 mg, 0.30 mmol, 1.5 eq.) to give a crude residue (>95:5 d.r. by crude ^{1}H NMR spectroscopic analysis) which was purified by flash column chromatography (100:1 pentane/Et_2O) to afford the boronic ester (43 mg, 57%, 5:95< d^1/d^2, 99:1 e.r., 100% e.s.) as a white solid.

R_f = 0.37 for both diastereomers (pentane/EtOAc 95:5).

$[\alpha]_D^{25}$: –7 (*c* = 8.6, CH_2Cl_2).

NMR Spectroscopy: *Assignments made for the major diastereomer.*

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.39–7.33 (m, 2H, H_G), 7.29–7.22 (m, 2H, H_H), 7.20–7.13 (m, 1H, H_I), 4.08 (d, $^2J_{HH}$ = 8.6 Hz, 1H, H_M), 3.54 (d, $^2J_{HH}$ = 8.6 Hz, 1H, $H_{M'}$), 2.52–2.36 (m, 1H, H_J), 2.28–2.16 (m, 1H, H_L), 2.01–1.79 (m, 4H, $H_{J', K, K', L'}$), 1.37 (s, 3H, H_E), 1.00 (s, 6H, H_A), 0.97 (s, 6H, $H_{A'}$) ppm;

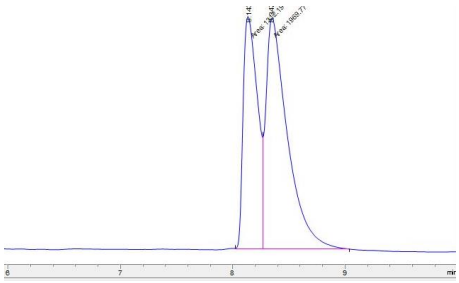
^{13}C NMR (101 MHz, $CDCl_3$): δ_C 148.4 (C_F), 127.8 (C_H), 127.0 (C_G), 126.0 (C_I), 83.4 (C_B), 52.1 (C_D), 41.6 (C_M), 39.7 (C_J), 33.0 (C_L), 25.2 (C_A), 24.7 ($C_{A'}$), 24.0 (C_E), 21.3 (C_K) ppm; C_C not observed due to quadrupolar relaxation;

^{11}B NMR (128 MHz, $CDCl_3$): δ_B 31.5 ppm.

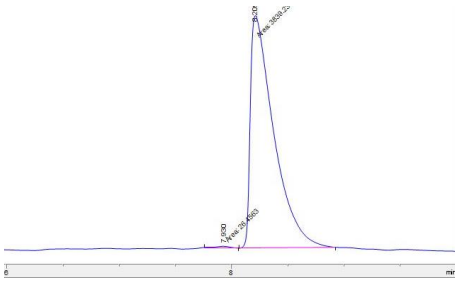
IR (film): ν_{max} 2974, 2875, 1444, 1371, 1324, 1237, 1210, 1142, 1032 cm^{-1}.

HRMS (ESI): m/z calc'd for $C_{19}H_{28}O_2{}^{11}B^{79}BrNa$ $[M+Na]^+$ 401.1261 found 401.1272.

Chiral HPLC (IB column, 100:0 hexane/IPA, 0.7 mL/min, rt, 254 nm): 7.9 min (minor), 8.2 min (major), 99:1 e.r.

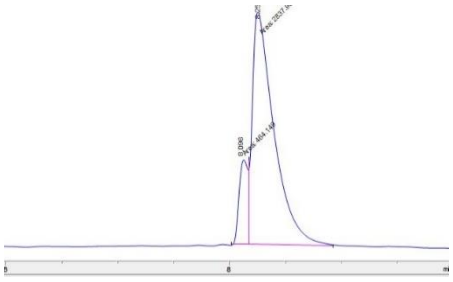


#	Time	Type	Area	Height	Width	Area%	Symmetry
1	8.143	MF	1312.2	147.7	0.148	39.982	0.436
2	8.347	FM	1969.8	146.6	0.224	60.018	0.336



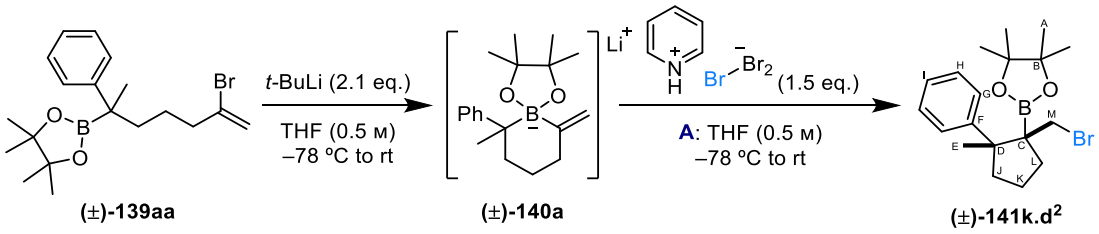
#	Time	Type	Area	Height	Width	Area%	Symmetry
1	7.93	MM	26.5	2.3	0.19	0.684	1.05
2	8.209	MM	3839.2	265.7	0.2408	99.316	0.25

The identity of the minor enantiomeric peak was confirmed by spiking a small amount of the racemic compound into the enantioenriched sample so that the minor enantiomeric peak became more pronounced:



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	8.096	MF	464.1	77.7	0.0996	14.056	0.872
2	8.25	FM	2838	213.8	0.2213	85.944	0.357

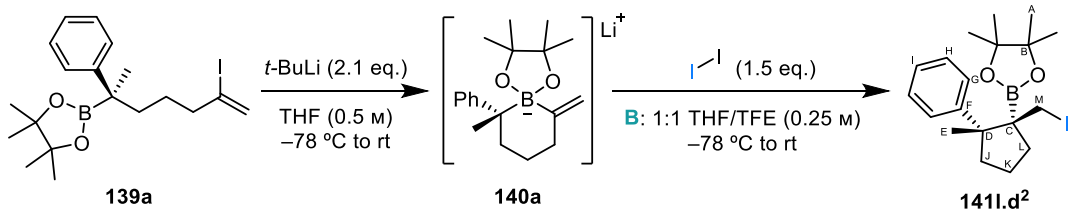
Racemic test reaction:



(±)-139aa **(±)-140a** **(±)-141k.d²**

According to **General Procedure E**, boronic ester **(±)-139aa** (38 mg, 0.10 mmol, 1.0 eq.) was allowed to react with *tert*-butyl lithium (1.8 M in pentane, 0.12 mL, 0.21 mmol, 2.1 eq.) and pyridinium tribromide (48 mg, 0.15 mmol, 1.5 eq.) to give a crude residue (93:7 d.r. by crude ^{1}H NMR spectroscopic analysis) which was purified by flash column chromatography (100:1 pentane/Et_2O) to afford the racemic boronic ester (11 mg, 30%, 7:93 d^1/d^2) as a white solid.

2-((1*S*,2*S*)-1-(Iodomethyl)-2-methyl-2-phenylcyclopentyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (141l.d^2)



According to **General Procedure G**, boronic ester **139a** (85 mg, 0.20 mmol, 1.0 eq.; 99:1 e.r.) was allowed to react with *tert*-butyl lithium (1.7 M in pentane, 0.25 mL, 0.42 mmol, 2.1 eq.) and iodine (1 M in THF; 76 mg, 0.30 mmol, 1.5 eq.) to give a crude residue (>95:5 d.r. by crude ^{1}H NMR spectroscopic analysis) which was purified by flash column chromatography (4:1 pentane/CH_2Cl_2) to afford the boronic ester (58 mg, 68%, 5:95< d^1/d^2, 99:1 e.r., 100% e.s.) as a white solid (*n.b.* traces of the elimination product were observed).

R_f = 0.28 (d^2), 0.13 (d^1) (pentane/CH_2Cl_2 9:1).

$[\alpha]_D^{25}$: –7 (*c* = 9.8, CH_2Cl_2).

NMR Spectroscopy: *Assignments made for the major diastereomer.*

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.32–7.24 (m, 2H, H_G), 7.23–7.13 (m, 2H, H_H), 7.13–7.03 (m, 1H, H_I), 3.82 (d, $^2J_{HH}$ = 8.2 Hz, 1H, H_M), 3.31 (d, $^2J_{HH}$ = 8.2 Hz, 1H, $H_{M'}$), 2.45–2.34 (m, 1H, H_J), 2.23–2.10 (m, 1H, H_L), 1.91–1.73 (m, 4H, $H_{J', K, K', L'}$), 1.27 (s, 3H, H_E), 0.92 (s, 12H, H_A) ppm;

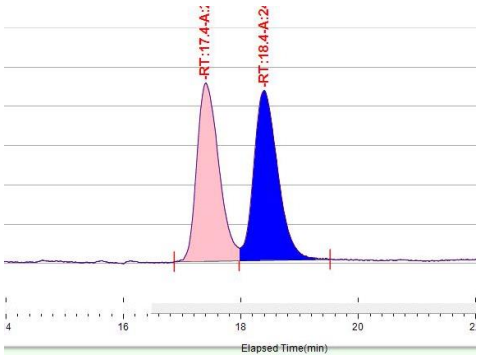
^{13}C NMR (101 MHz, $CDCl_3$): δ_C 148.3 (C_F), 127.8 (C_G), 126.8 (C_H), 126.0 (C_I), 83.4 (C_B), 51.6 (C_D), 39.7 (C_J), 36.0 (C_L), 25.3 (C_A), 24.9 ($C_{A'}$), 23.9 (C_E), 20.9 (C_K), 16.9 (C_M) ppm; C_C not observed due to quadrupolar relaxation;

^{11}B NMR (128 MHz, $CDCl_3$): δ_B 31.6 ppm.

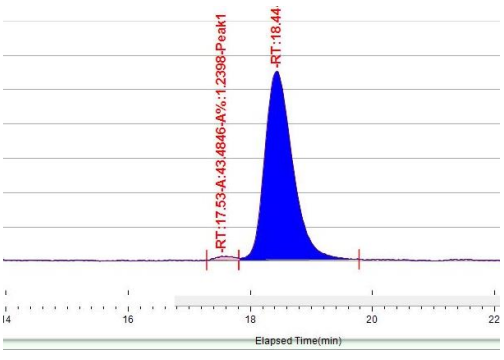
IR (film): ν_{max} 2922, 2853, 1463, 1372, 1319, 1140 cm^{-1}.

HRMS (ESI): m/z calc'd for $C_{19}H_{28}O_2{}^{11}BNaI$ $[M+Na]^+$ 449.1123 found 449.1136.

Chiral SFC (Whelk-O1 column, iso 2% hexane, 2 mL/min, 100 bar): 17.5 min (minor), 18.4 min (major), 99:1 e.r.

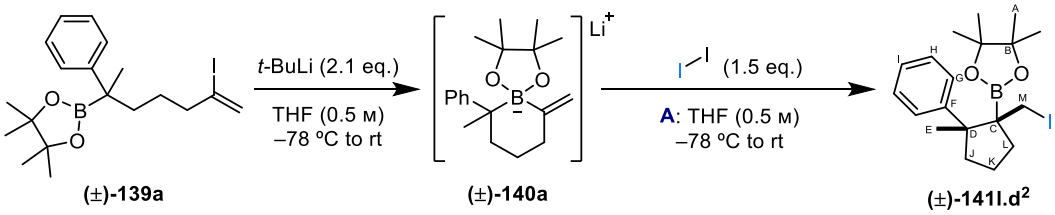


Signal	Peak Name	Area Percent	Area	Retention Time	Height
MaxAbsorbance	Peak1	48.9494	2353.8686	17.4 min	90.7954
	Peak2	51.0506	2454.9097	18.4 min	86.5248



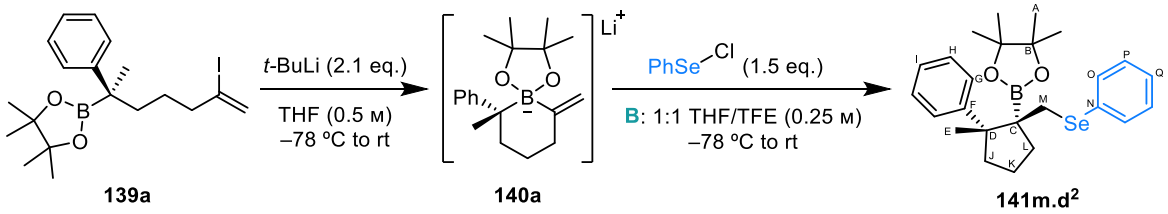
Signal	Peak Name	Area Percent	Area	Retention Time	Height
MaxAbsorbance	Peak1	1.2398	43.4846	17.53 min	2.305
	Peak2	98.7602	3464.0186	18.44 min	109.8198

Racemic test reaction:



According to **General Procedure E**, boronic ester **(±)-139a** (43 mg, 0.10 mmol, 1.0 eq.) was allowed to react with *tert*-butyl lithium (1.7 M in pentane, 0.13 mL, 0.21 mmol, 2.1 eq.) and iodine (1 M in THF; 38 mg, 0.15 mmol, 1.5 eq.) to give a crude residue (93:7 d.r. by crude ^{1}H NMR spectroscopic analysis) which was purified by flash column chromatography (4:1 pentane/CH_2Cl_2) to afford the racemic boronic ester (28 mg, 66%, 7:93 d^1/d^2) as a white solid (*n.b.* traces of the elimination product were observed).

4,4,5,5-Tetramethyl-2-((1*S*,2*S*)-2-methyl-2-phenyl-1-((phenylselanyl)methyl)cyclopentyl)-1,3,2-dioxaborolane (141m.d^2)



According to a modified **General Procedure G**, boronic ester **139a** (85 mg, 0.20 mmol, 1.0 eq.; 99:1 e.r.) was allowed to react with *tert*-butyl lithium (1.7 M in pentane, 0.25 mL, 0.42 mmol, 2.1 eq.) and phenylselenyl chloride (1 M in THF; 58 mg, 0.30 mmol, 1.5 eq.) with the addition of *degassed* TFE to give a crude residue (85:15 d.r. by crude ^{1}H NMR spectroscopic analysis) which was purified by flash column chromatography (1000:1 to 100:1

pentane/Et_2O) to afford the boronic ester (35 mg, 38%, 15:85 d^1/d^2, 99:1 e.r., 100% e.s.) as a colourless oil.

$\mathbf{R_f}$ = 0.26 (d^2), 0.14 (d^1) (pentane/CH_2Cl_2 9:1).

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$**:** –7 (*c* = 9.8, CH_2Cl_2).

NMR Spectroscopy: *Assignments made for the major diastereomer.*

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.61–7.56 (m, 2H, H_O), 7.43–7.38 (m, 2H, H_G), 7.30–7.21 (m, 5H, $H_{H,\,P,\,Q}$), 7.19–7.12 (m, 1H, H_I), 3.60 (d, $^2J_{HH}$ = 10.1 Hz, 1H, H_M), 3.16 (d, $^2J_{HH}$ = 10.1 Hz, 1H, $H_{M'}$), 2.50–2.37 (m, 1H, H_J), 2.28–2.15 (m, 1H, H_L), 1.93–1.67 (m, 4H, $H_{J',\,K,\,K',\,L'}$), 1.36 (s, 3H, H_E), 1.02 (s, 6H, H_A), 0.97 (s, 6H, $H_{A'}$) ppm;

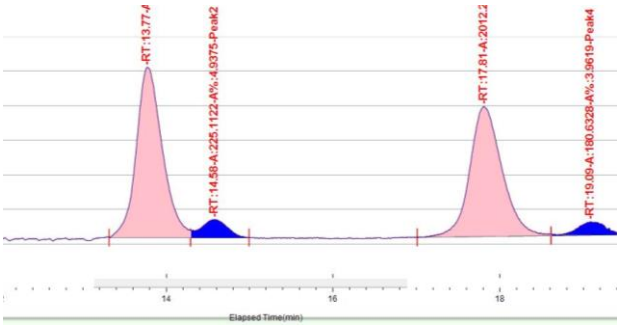
^{13}C NMR (101 MHz, $CDCl_3$): δ_C 148.9 (C_F), 132.8 (C_O), 128.9 (C_H *or* C_P), 127.7 (C_H *or* C_P), 127.0 (C_G), 126.5 (C_Q), 125.8 (C_I), 83.2 (C_B), 52.1 (C_D), 39.2 (C_J), 36.0 (C_M), 33.5 (C_L), 25.1 (C_A), 24.9 ($C_{A'}$), 24.2 (C_E), 21.6 (C_K) ppm; C_C not observed due to quadrupolar relaxation;

^{11}B NMR (128 MHz, $CDCl_3$): δ_B 32.8 ppm;

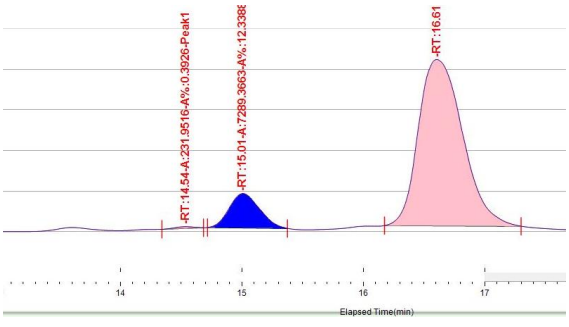
IR (film): ν_{max} 2958, 2926, 1579, 1477, 1371, 1315, 1142 cm^{-1}.

HRMS (APCI): m/z calc'd for $C_{25}H_{33}{}^{11}BO_2{}^{80}Se$ $[M]^+$ 457.1812 found 457.1799.

Chiral SFC (Whelk-O1 column, iso 2% hexane, 4 mL/min, 125 bar): 13.8 min (d^2, minor enantiomer), 14.6 min (d^1, major enantiomer), 17.8 min (d^2, major enantiomer), 19.1 min (d^1, minor enantiomer), 99:1 e.r.

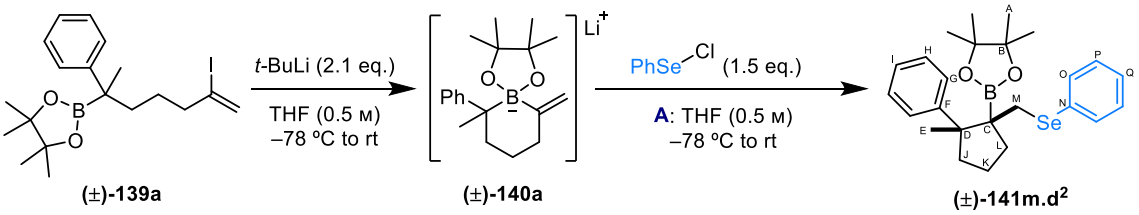


Signal	Peak Name	Area Percent	Area	Retention Time	Height
MaxAbsorbance	Peak1	46.9652	2141.2438	13.77 min	98.7685
	Peak2	4.9375	225.1122	14.58 min	10.4978
	Peak3	44.1354	2012.2253	17.81 min	75.3307
	Peak4	3.9619	180.6328	19.09 min	7.7193



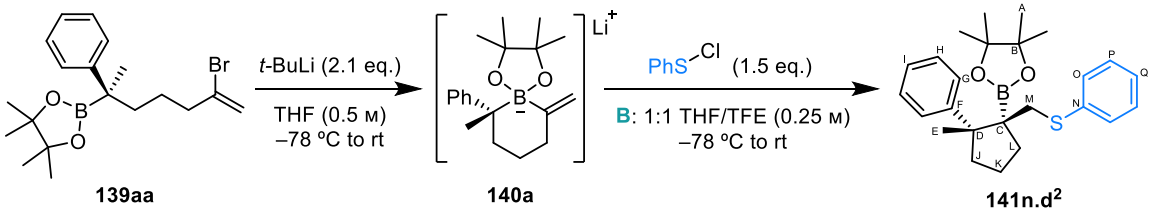
Signal	Peak Name	Area Percent	Area	Retention Time	Height
MaxAbsorbance	Peak1	0.3926	231.9516	14.54 min	21.4512
	Peak2	12.3388	7289.3663	15.01 min	423.939
	Peak3	87.2686	51555.3807	16.61 min	2048.6532

Racemic test reaction:



According to **General Procedure E**, boronic ester **(±)-139a** (49 mg, 0.12 mmol, 1.0 eq.) was allowed to react with *tert*-butyl lithium (1.7 M in pentane, 0.14 mL, 0.24 mmol, 2.1 eq.) and phenylselenyl chloride (1 M in THF; 33 mg, 0.17 mmol, 1.5 eq.) to give a crude residue (56:44 d.r. by crude ^{1}H NMR spectroscopic analysis) which was purified by flash column chromatography (20:1 pentane/Et_2O) to afford the racemic boronic ester (10 mg, 20%, 44:56 d^1/d^2) as a colourless oil.

4,4,5,5-Tetramethyl-2-((1*S*,2*S*)-2-methyl-2-phenyl-1-((phenylthio)methyl)cyclopentyl)-1,3,2-dioxaborolane (141n.d^2)



According to **General Procedure G**, boronic ester **139aa** (76 mg, 0.20 mmol, 1.0 eq.; 99:1 e.r.) was allowed to react with *tert*-butyl lithium (1.6 M in pentane, 0.27 mL, 0.42 mmol, 2.1 eq.) and freshly prepared phenylsulfenyl chloride[201] (1 M in THF; 43 mg, 0.30 mmol, 1.5 eq.) to give a crude residue (83:17 d.r. by crude ^{1}H NMR spectroscopic analysis) which was purified by flash column chromatography (200:1 to 100:1 pentane/Et_2O) to afford the boronic ester (62 mg, 76%, 17:83 d^1/d^2, 99:1 e.r., 100% e.s.) as a white solid.

The e.r. of boronic ester **141n.d^2** could not be determined by chiral HPLC/SFC. Instead, the boronic ester was oxidised and the e.r. of alcohol **141n'.d^2** was determined.

R_f = 0.61 for both diastereomers (pentane/Et_2O 95:5).

$[\alpha]_D^{25}$: +37 (*c* = 5.2, CH_2Cl_2).

NMR Spectroscopy: *Assignments made for the major diastereomer.*

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.45–7.34 (m, 4H, $H_{G,\,O}$), 7.31–7.18 (m, 4H, $H_{H,\,P}$), 7.20–7.10 (m, 2H, $H_{I,\,Q}$), 3.50 (d, $^{2}J_{HH}$ = 10.4 Hz, 1H, H_M), 3.15 (d, $^{2}J_{HH}$ = 10.4 Hz, 1H, $H_{M'}$), 2.46–2.32 (m, 1H, H_J), 2.21–2.09 (m, 1H, H_L), 1.95–1.70 (m, 4H, $H_{J',\,K,\,K',\,L'}$), 1.41 (s, 3H, H_E), 1.02 (s, 6H, H_A), 0.94 (s, 6H, $H_{A'}$) ppm;

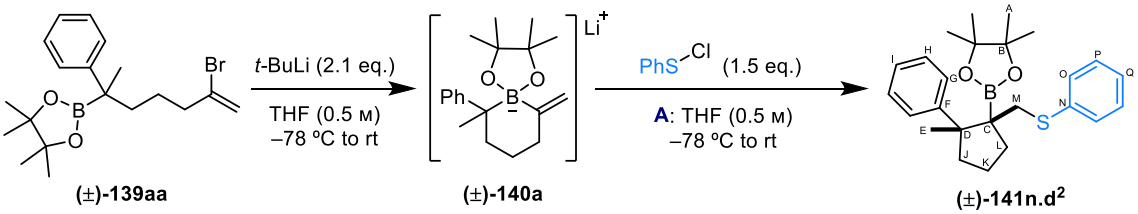
^{13}C NMR (101 MHz, $CDCl_3$): δ_C 149.1 (C_F), 139.0 (C_N), 129.5 (C_G *or* C_O), 128.8 (C_H *or* C_P), 127.8 (C_H *or* C_P), 127.2 (C_G *or* C_O), 125.9 (C_I *or* C_Q), 125.7 (C_I *or* C_Q), 83.3 (C_B), 52.0 (C_D), 40.7 (C_M), 39.3 (C_J), 32.1 (C_L), 25.3 (C_A), 24.9 ($C_{A'}$), 24.3 (C_E), 22.0 (C_K) ppm; C_C not observed due to quadrupolar relaxation;

^{11}B NMR (128 MHz, $CDCl_3$): δ_B 32.2 ppm.

IR (film): ν_{max} 2974, 2875, 1583, 1480, 1370, 1317,1210, 1141, 1026 cm^{-1}.

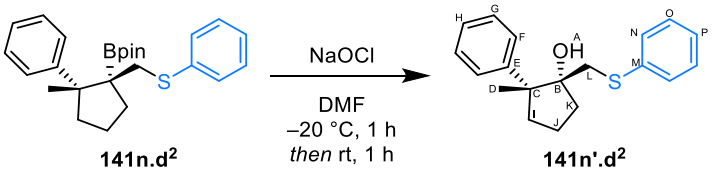
HRMS (ESI): m/z calc'd for $C_{25}H_{33}{}^{11}BNaO_2S$ $[M+Na]^+$ 431.2191 found 431.2192.

Racemic test reaction:



According to **General Procedure E**, boronic ester **(±)-139aa** (38 mg, 0.10 mmol, 1.0 eq.) was allowed to react with *tert*-butyl lithium (1.6 M in pentane, 0.13 mL, 0.21 mmol, 2.1 eq.) and phenylsulfenyl chloride[201] (1 M in THF; 22 mg, 0.15 mmol, 1.5 eq.) to give a crude residue (82:18 d.r. by crude ^{1}H NMR spectroscopic analysis) which was purified by flash column chromatography (200:1 to 100:1 pentane/Et_2O) to afford the racemic boronic ester (18 mg, 44%, 18:82 d^1/d^2) as a white solid.

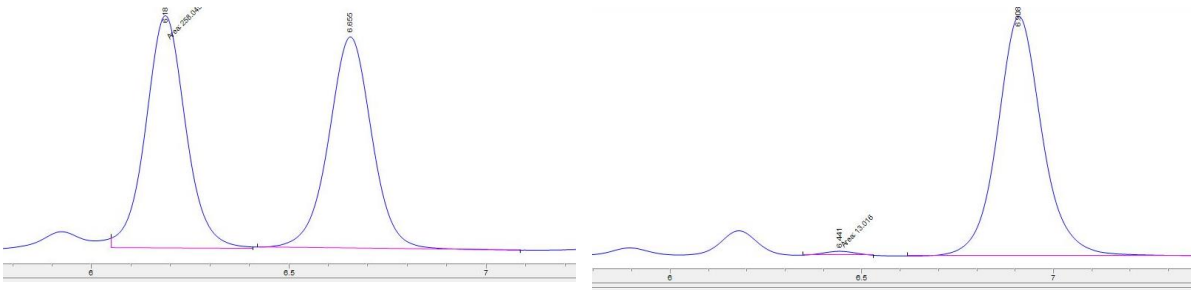
(1*R*,2*R*)-2-Methyl-2-phenyl-1-((phenylthio)methyl)cyclopentan-1-ol (141n'.d^2)



According to **General Procedure H**, boronic ester **141n.d^2** (19 mg, 0.05 mmol, 17:83 d^1/d^2, 1.0 eq.) was allowed to react with aqueous NaOCl (0.14 mL) in DMF (0.65 mL) to give a crude residue which was purified by flash column chromatography (95:5 pentane/EtOAc) to give the alcohol (4 mg, 30%, 17:83 d^1/d^2, 99:1 e.r.) as a colourless oil, along with recovered starting

material (8 mg, 41%). The alcohol was air-sensitive, and thus full characterisation was not obtained and the sample was immediately analysed by Chiral HPLC.

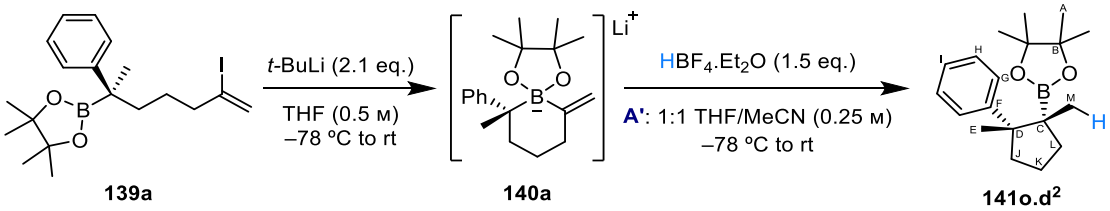
Chiral HPLC (IA column, 99:1 hexane/IPA, 1 mL/min, rt, 254 nm): 6.4 min (minor), 6.9 min (major), 99:1 e.r.



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	6.186	MM	258	36.4	0.1182	50.661	0.936
2	6.655	BB	251.3	33	0.1154	49.339	0.985

#	Time	Type	Area	Height	Width	Area%	Symmetry
1	6.441	MM	13	2.2	0.0989	1.233	1.052
2	6.908	BB	1042.9	128	0.1231	98.767	0.897

2-((1*S*,2*S*)-1,2-Dimethyl-2-phenylcyclopentyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (141o.d^2)



According to **General Procedure F**, boronic ester **139a** (85 mg, 0.20 mmol, 1.0 eq.; 99:1 e.r.) was allowed to react with *tert*-butyl lithium (1.5 M in pentane, 0.28 mL, 0.42 mmol, 2.1 eq.) and tetrafluoroboric acid diethyl ether complex (41 μL, 0.30 mmol, 1.5 eq.) to give a crude residue (86:14 d.r. by GCMS) which was purified by flash column chromatography (9:1 pentane/CH_2Cl_2) to afford the boronic ester (32 mg, 53%, 14:86 d^1/d^2, 99:1 e.r., 100% e.s.) as a colourless oil.

The e.r. of boronic ester **141o.d^2** could not be determined by chiral HPLC/SFC. Instead, the boronic ester was oxidised and the e.r. of alcohol **141o'.d^2** was determined.

R$_f$ = 0.20 for both diastereomers (pentane/CH_2Cl_2 9:1).

$[\alpha]_D^{25}$**:** –10 (*c* = 6.0, CH_2Cl_2).

NMR Spectroscopy: *Assignments made for the major diastereomer.*

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.43–7.36 (m, 2H, H_G), 7.25–7.18 (m, 2H, H_H), 7.18–7.07 (m, 1H, H_I), 2.59–2.43 (m, 1H, H_J), 2.04–1.93 (m, 1H, H_L), 1.90–1.73 (m, 3H, $H_{J', K, K'}$), 1.54–1.42 (m, 1H, $H_{L'}$), 1.25 (s, 3H, H_E), 1.19 (s, 3H, H_M), 0.97 (s, 6H, H_A), 0.93 (s, 6H, $H_{A'}$) ppm;

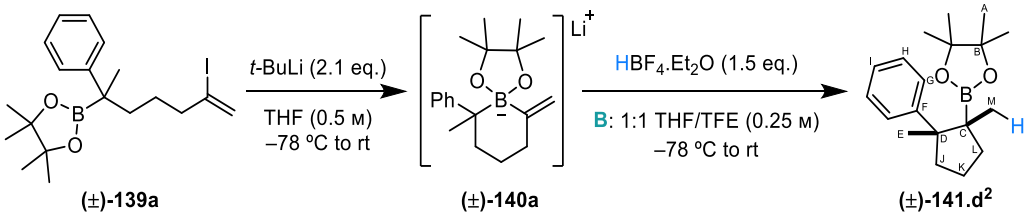
^{13}C NMR (101 MHz, $CDCl_3$): δ_C 150.5 (C_F), 127.6 (C_H), 126.7 (C_G), 125.3 (C_I), 82.4 (C_B), 50.2 (C_D), 39.2 (C_J), 36.7 (C_L), 24.9 (C_E), 24.6 (C_A), 24.5 ($C_{A'}$), 21.4 (C_K), 20.3 (C_M) ppm; C_C not observed due to quadrupolar relaxation;

^{11}B NMR (128 MHz, $CDCl_3$): δ_B 33.9 ppm.

IR (film): ν_{max} 2974, 1444, 1355, 1306, 1146 cm^{-1}.

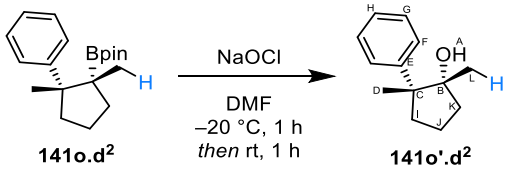
HRMS (ESI): m/z calc'd for $C_{19}H_{30}{}^{11}BO_2$ $[M+H]^+$ 301.2337 found 301.2330.

Racemic test reaction:



According to **General Procedure G**, boronic ester **(±)-139** (80 mg, 0.19 mmol, 1.0 eq.) was allowed to react with *tert*-butyl lithium (1.6 M in pentane, 0.27 mL, 0.42 mmol, 2.1 eq.) and tetrafluoroboric acid diethyl ether complex (41 μL, 0.30 mmol, 1.5 eq.) to give a crude residue (73:27 d.r. by GCMS) which was purified by flash column chromatography (9:1 pentane/CH_2Cl_2) to afford the boronic ester (17 mg, 29%, 27:73 d^1/d^2) as a colourless oil.

(1*R*,2*R*)-1,2-Dimethyl-2-phenylcyclopentan-1-ol (141o'.d^2)



According to **General Procedure H**, boronic ester **141o.d^2** (14 mg, 0.05 mmol, 14:86 d^1/d^2, 1.0 eq.) was allowed to react with aqueous NaOCl (0.14 mL) in DMF (0.65 mL) to give a crude residue which was purified by flash column chromatography (pentane then 3:1 pentane/Et_2O) to give the alcohol (d^2: 4 mg; d^1: <0.5 mg; 45%, 99:1 e.r.) as a colourless oil.

R_f = 0.36 (d^2), 0.25 (d^1) (pentane/EtOAc 9:1).

$[\alpha]_D^{25}$: –24 (*c* = 2.2, CH_2Cl_2).

NMR Spectroscopy: *Assignments made for the major diastereomer.*

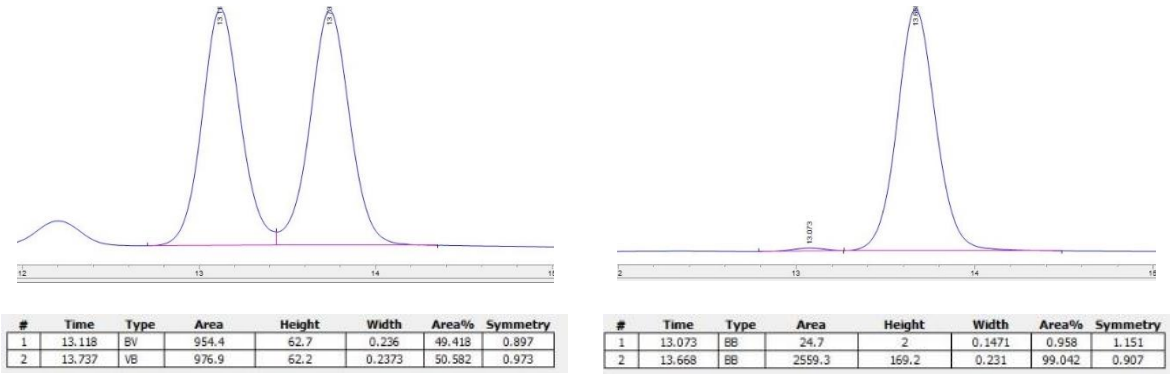
^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.53–7.47 (m, 2H, H_F), 7.41–7.31 (m, 2H, H_G), 7.30–7.21 (m, 1H, H_H), 2.79–2.67 (m, 1H, H_I), 1.99–1.86 (m, 3H, $H_{J,\ K,\ K'}$), 1.86–1.73 (m, 1H, $H_{J'}$), 1.69–1.59 (m, 1H, $H_{I'}$), 1.32 (s, 3H, H_D), 1.26 (s, 3H, H_L), 0.90 (s, 1H, H_A) ppm;

^{13}C NMR (101 MHz, $CDCl_3$): δ_C 143.5 (C_E), 128.2 (C_G), 127.8 (C_F), 126.5 (C_H), 82.5 (C_B), 52.9 (C_C), 38.4 (C_K), 35.8 (C_I), 24.2 (C_D), 22.9 (C_L), 19.3 (C_J) ppm.

IR (film): ν_{max} 3446 (br), 2962, 2928, 1600, 1497, 1443, 1371, 1136 cm^{-1}.

HRMS (ESI): m/z calc'd for $C_{13}H_{18}ONa$ $[M+Na]^+$ 213.1250 found 213.1260.

Chiral HPLC (IA column, 97:3 hexane/IPA, 0.5 mL/min, rt, 230 nm): 13.1 min (minor), 13.7 min (major), 99:1 e.r.



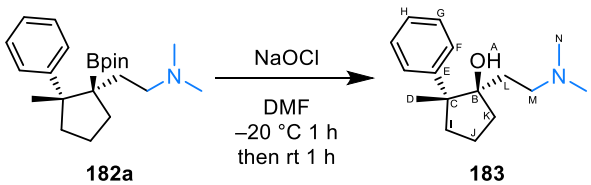
#	Time	Type	Area	Height	Width	Area%	Symmetry
1	13.118	BV	954.4	62.7	0.236	49.418	0.897
2	13.737	VB	976.9	62.2	0.2373	50.582	0.973

#	Time	Type	Area	Height	Width	Area%	Symmetry
1	13.073	BB	24.7	2	0.1471	0.958	1.151
2	13.668	BB	2559.3	169.2	0.231	99.042	0.907

6.2.3. Functionalisation of cyclopentyl boronic esters

A portion of HCl salt **141a** was converted to free amine **182a** by washing with 0.5 M aqueous NaOH and extracting with Et_2O. Free amine **182a** was used as a 9:1 mixture of diastereomers.

(1*R*,2*R*)-1-(2-(Dimethylamino)ethyl)-2-methyl-2-phenylcyclopentan-1-ol (183)



According to a literature procedure,[88] boronic ester **182a** (37 mg, 0.10 mmol, 1.0 eq.; 9:1 d^1/d^2, >98:2 e.r.) was dissolved in DMF (1.2 mL) and cooled to −20 °C (cryostat). Aqueous NaOCl (8% available chlorine, 0.26 mL) was added dropwise (~0.5 mL/min) to this solution. The

reaction mixture was allowed to stir at this temperature for 1 hour and then at rt for 1 hour whereupon it was then diluted with Et_2O (2 mL) and quenched with saturated aqueous $Na_2S_2O_3$ (2 mL). The aqueous layer was extracted with Et_2O (3 × 2 mL), and the combined organics washed with brine (2 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude reaction mixture was then purified by flash column chromatography (CH_2Cl_2 then 9:1 CH_2Cl_2:MeOH) to give the alcohol (11 mg, 48%, 8:1 d.r., >98:2 e.r., 100% e.s.) as a colourless oil.

$\mathbf{R_f}$ = 0.24 (CH_2Cl_2/MeOH 9:1).

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$**:** –8 (*c* = 1.6, CH_2Cl_2).

NMR Spectroscopy: *Assignments made for the major diastereomer.*

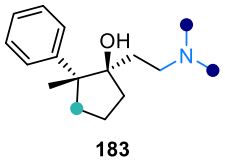
^{1}H NMR (500 MHz, $CDCl_3$): δ_H 7.52–7.45 (m, 2H, H_F), 7.35–7.24 (m, 2H, H_G), 7.23–7.14 (m, 1H, H_H), 2.78 (apparent td, J_{HH} = 12.4, 3.2 Hz, 1H, H_M), 2.21 (s, 8H, $H_{I,\ M',\ N}$), 2.03–1.82 (m, 4H, $H_{I',\ J,\ K,\ K'}$), 1.73–1.63 (m, 1H, $H_{J'}$), 1.58–1.48 (m, 1H, H_L), 1.39 (s, 3H, H_D), 1.25 (br s, 1H, H_A), 0.94–0.89 (m, 1H, $H_{L'}$) ppm;

^{13}C NMR (125 MHz, $CDCl_3$): δ_C 148.2 (C_E), 127.7 (C_G), 127.1 (C_F), 125.6 (C_H), 84.7 (C_B), 56.3 (C_M), 51.7 (C_C), 44.7 (C_N), 35.6 (C_K), 35.0 (C_I), 30.4 (C_L), 24.1 (C_D), 18.5 (C_J) ppm.

IR (film): ν_{max} 3681 (br), 3357 (br), 2924, 2857, 1464, 1377, 1054 cm^{-1}.

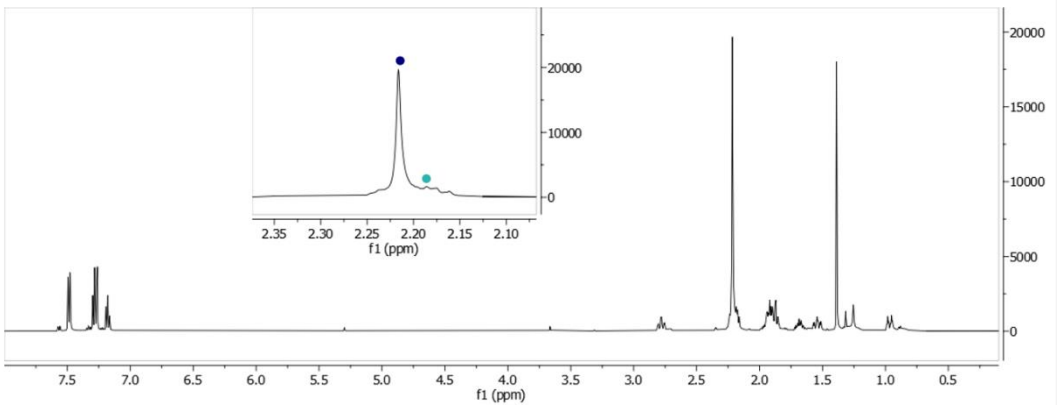
HRMS (ESI): m/z calc'd for $C_{16}H_{25}NO$ $[M+H]^+$ 248.2009 found 248.2021.

Chiral solvating agent: The enantiopurity of boronic ester **183** was determined using Pirkle's alcohol ((*R*)-(–)-1-(9-anthryl)-2,2,2-trifluoroethanol) NMR shift reagent (3.0 eq, rt, $CDCl_3$, 0.05 M), >98:2 e.r.

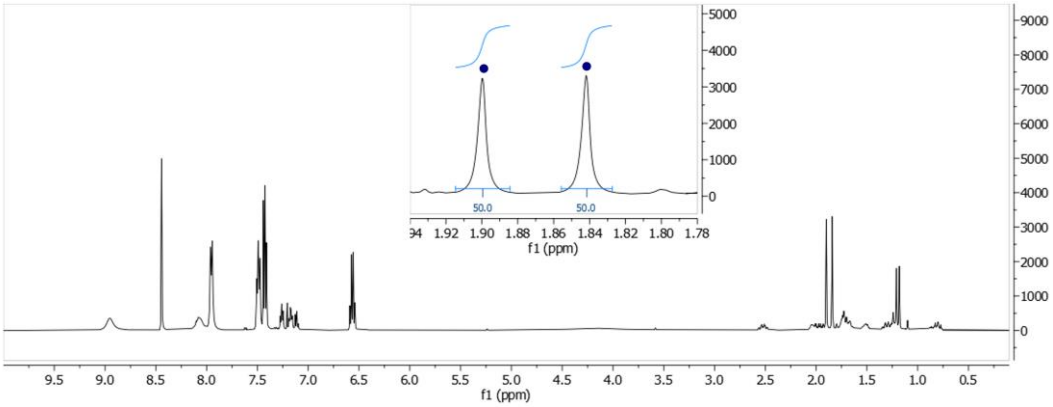


183

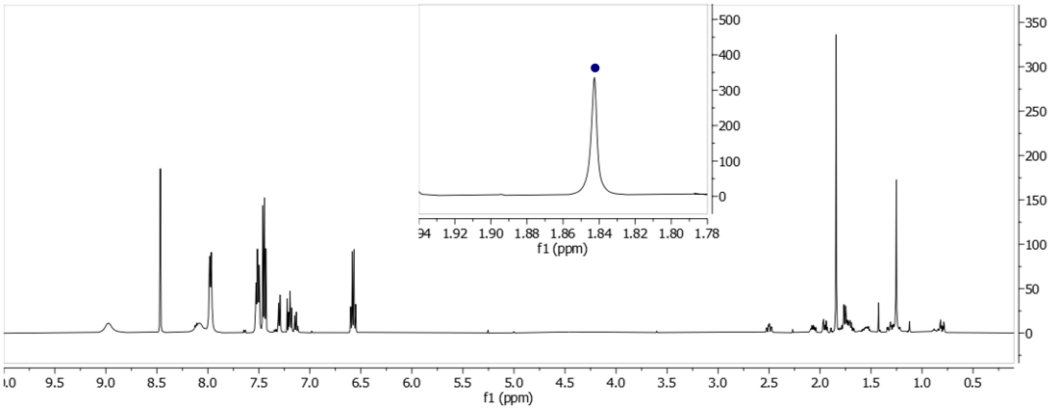
^{1}H NMR (500 MHz, $CDCl_3$) expansion of **(±)-183** only:



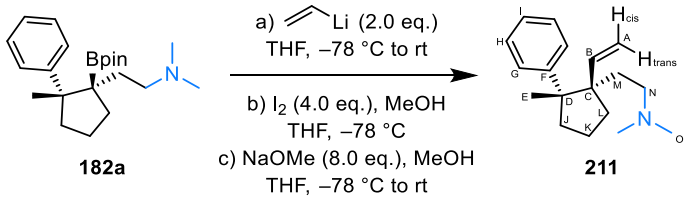
^{1}H NMR (500 MHz, $CDCl_3$) expansion of **(±)-183** with Pirkle's alcohol:



^{1}H NMR (500 MHz, $CDCl_3$) expansion of **183** with Pirkle's alcohol:



***N*,*N*-Dimethyl-2-((1*S*,2*S*)-2-methyl-2-phenyl-1-vinylcyclopentyl)ethan-1-amine (211)**



According to a modified literature procedure,[15] boronic ester **182a** (36 mg, 0.10 mmol, 1.0 eq.; 9:1 d^1/d^2, >98:2 e.r.) was dissolved in anhydrous THF (1.6 mL) and cooled to –78 °C (dry ice/acetone). Vinyllithium[a] (0.62 M in THF; 0.32 mL, 0.20 mmol, 2.0 eq.) was then added dropwise (~0.5 mL/min). The reaction mixture was warmed to rt and stirred at this temperature for 30 minutes. It was then cooled to –78 °C and a solution of iodine (102 mg, 0.40 mmol, 4.0 eq.) in MeOH (1.3 mL) was added dropwise (~0.5 mL/min). The reaction mixture was stirred at –78 °C for 30 minutes whereupon NaOMe (0.5 M in MeOH; 1.6 mL, 0.8 mmol, 8.0 eq.) was added dropwise (~0.5 mL/min). The reaction mixture was warmed to rt and stirred for an hour, then it was quenched with a saturated aqueous solution of $Na_2S_2O_3$ (5 mL). The

aqueous layer was extracted with Et_2O (3 × 5 mL), and the combined organic extracts were washed with brine (5 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude reaction mixture was purified by flash column chromatography (19:1:1 pentane/EtOAc/NEt_3) to yield the alkene (20 mg, 77%, 8:1 d.r., >98:2 e.r., 100% e.s.) as a colourless oil.

[a] Vinyllithium (in THF) was prepared according to a literature procedure and titrated against *N*-benzylbenzamide before use.[40]

R_f = 0.12 (pentane/EtOAc/NEt_3 100:5:5).

$[\alpha]_D^{25}$: –30 (*c* = 4.1, CH_2Cl_2).

NMR Spectroscopy: *Assignments made for the major diastereomer.*

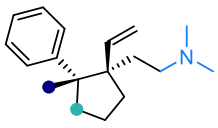
^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.29–7.24 (m, 2H, H_G), 7.22–7.17 (m, 2H, H_H), 7.12–7.06 (m, 1H, H_I), 5.76 (dd, $^3J_{HH(trans)}$ = 17.6 Hz, $^3J_{HH(cis)}$ = 11.0 Hz, 1H, H_B), 5.10 (dd, $^3J_{HH(cis)}$ = 11.0 Hz, $^2J_{HH}$ = 1.6 Hz, 1H, H_{Acis}), 4.93 (dd, $^3J_{HH(trans)}$ = 17.6 Hz, $^2J_{HH}$ = 1.6 Hz, 1H, H_{Atrans}), 2.51–2.41 (m, 1H, H_J), 1.99 (s, 6H, H_O), 1.95–1.86 (m, 3H, $H_{L,\ N,\ N'}$), 1.84–1.74 (m, 2H, $H_{K,\ K'}$), 1.67–1.52 (m, 2H, $H_{J',\ L'}$), 1.17 (s, 3H, H_E), 1.13–1.05 (m, 1H, H_M), 1.01–0.91 (m, 1H, $H_{M'}$) ppm;

^{13}C NMR (101 MHz, $CDCl_3$): δ_C 146.1 (C_F), 142.4 (C_B), 127.6 (C_H), 127.5 (C_G), 125.7 (C_I), 114.0 (C_A), 56.4 (C_N), 53.2 (C_C), 52.1 (C_D), 45.6 (C_O), 35.8 (C_J), 33.0 (C_M), 29.9 (C_L), 25.2 (C_E), 20.0 (C_K) ppm.

IR (film): ν_{max} 3396 (br), 2957, 2879, 2814, 2762, 1633, 1497, 1462, 1378 cm^{-1}.

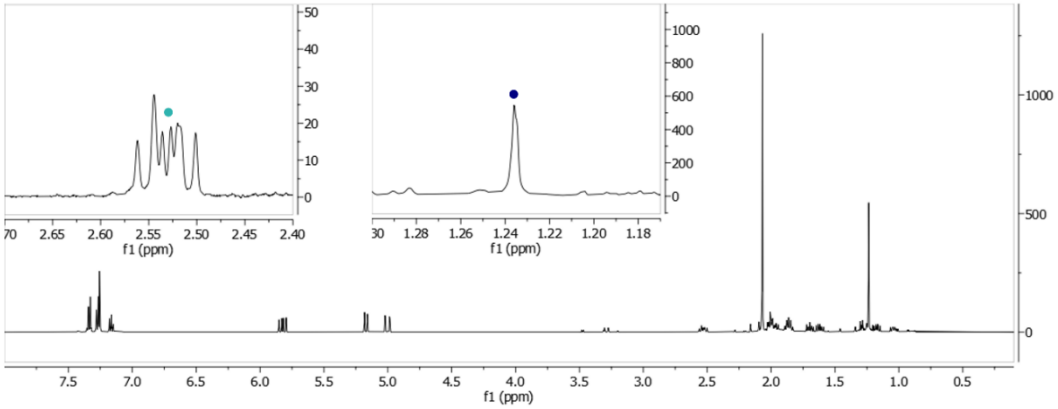
HRMS (ESI): m/z calc'd for $C_{18}H_{28}N$ $[M+H]^+$ 258.2216 found 258.2222.

Chiral solvating agent: The enantiopurity of boronic ester **211** was determined using Pirkle's alcohol ((*R*)-(–)-1-(9-anthryl)-2,2,2-trifluoroethanol) NMR shift reagent (1.0 eq, rt, $CDCl_3$, 0.05 M), >98:2 e.r.

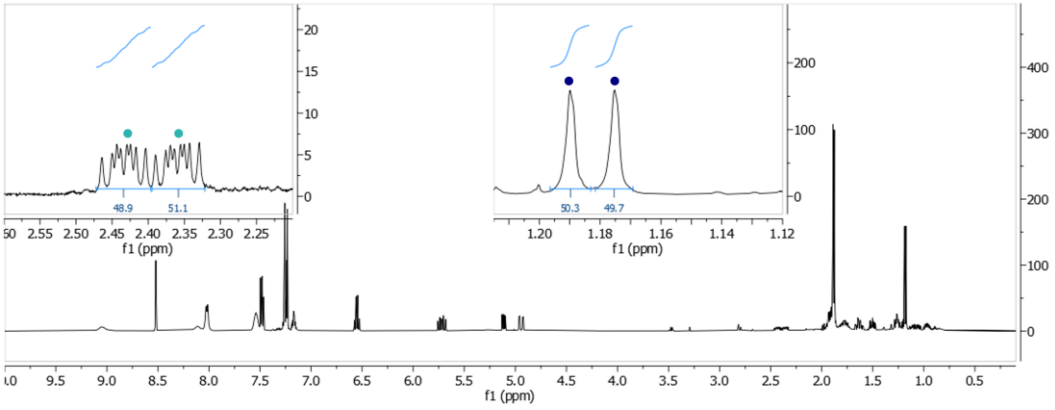


211

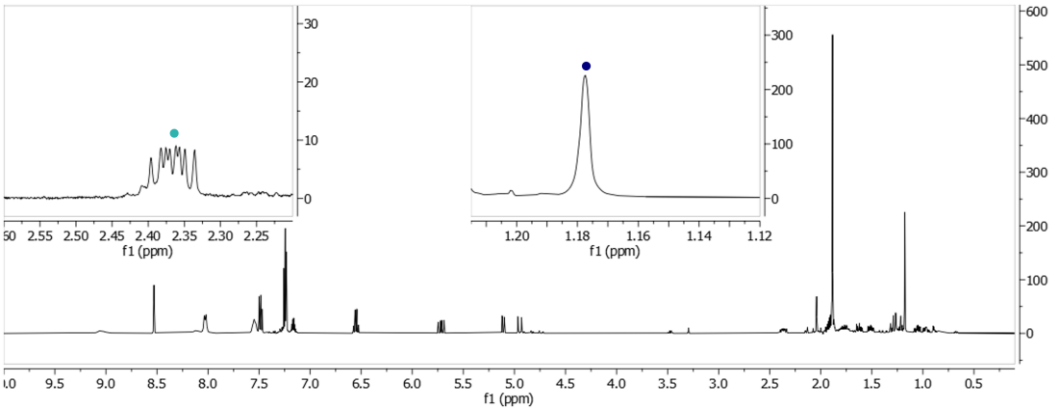
^{1}H NMR (500 MHz, $CDCl_3$) expansion of **(±)-211** only:



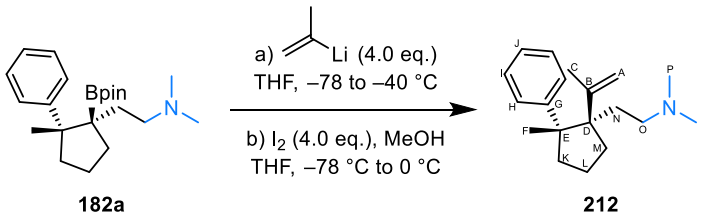
^{1}H NMR (500 MHz, $CDCl_3$) expansion of **(±)-211** with Pirkle's alcohol:



^{1}H NMR (500 MHz, $CDCl_3$) expansion of **211** with Pirkle's alcohol:



***N*,*N*-Dimethyl-2-((1*S*,2*R*)-2-methyl-2-phenyl-1-(prop-1-en-2-yl)cyclopentyl)ethan-1-amine (212)**



182a **212**

According to a literature procedure,[115] 2-bromopropene (36 μL, 0.40 mmol, 4 eq.) was dissolved in anhydrous THF (0.40 mL) and cooled to –78 °C (dry ice/acetone). *tert*-Butyl lithium (1.7 M in pentane; 0.47 mL, 0.8 mmol, 8 eq.) was then added dropwise (~0.5 mL/min). The reaction mixture was stirred at –78 °C for 30 minutes whereupon a solution of boronic ester **182a** (36 mg, 0.10 mmol, 1.0 eq.; 9:1 d^1/d^2, >98:2 e.r.) in anhydrous THF (0.40 mL) was added dropwise (~0.5 mL/min). Following stirring at –78 °C for 1 hour, the reaction mixture was warmed to –40 °C (cryostat) and stirred at this temperature for an additional hour. The reaction mixture was then cooled to –78 °C and a solution of iodine (102 mg, 0.40 mmol, 4 eq.) in MeOH (1.6 mL) was added dropwise (~0.5 mL/min). The reaction mixture was stirred at –78 °C for 30 minutes followed by 0 °C for 30 minutes, whereupon a 5% w/v aqueous solution of $Na_2S_2O_3$ (3 mL) was added at 0 °C and the reaction mixture immediately warmed to rt. The biphasic mixture was stirred at rt for 1 hour, then the phases were separated at the aqueous layer extracted with Et_2O (3 × 5 mL). The combined organic extracts were washed with brine (5 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude residue (44% **212** and 12% **182a** by quantitative ^{1}H NMR spectroscopic analysis) was purified by flash column chromatography (100:5:5 pentane/EtOAc/NEt_3) to give the product (>98:2 e.r., 100% e.s.) as an inseperable mixture with **182a** (7:1 **212**/**182a**).

*Characterisation given for a 7:1 mixture of **212**/**182a**.*

R_f = 0.12 (pentane/EtOAc/NEt_3 100:5:5).

$[\alpha]_D^{25}$: –52 (*c* = 3.4, CH_2Cl_2).

NMR Spectroscopy: *Assignments made for the major diastereomer of the major product.*

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.46–7.42 (m, 2H, H_H), 7.28–7.21 (m, 2H, H_I), 7.18–7.12 (m, 1H, H_J), 4.88 (br d, $^2J_{HH}$ = 1.5 Hz, 1H, H_A), 4.56 (d, $^2J_{HH}$ = 1.7 Hz, 1H, $H_{A'}$), 2.53–2.42 (m, 1H, H_K), 2.12 (s, 6H, H_P), 2.18–2.03 (m, 2H, H_O & H_M *or* H_N), 2.02–1.77 (m, 3H,

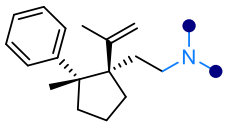
$H_{L,\,L',\,O'}$), 1.77–1.65 (m, 1H, $H_{K'}$), 1.50 (s, 3H, H_C), 1.47–1.42 (m, 3H, H_M *or* H_N), 1.29 (s, 3H, H_F) ppm;

^{13}C NMR (101 MHz, $CDCl_3$): δ_C 147.5 (C_B), 145.5 (C_G), 128.9 (C_H), 127.2 (C_I), 125.8 (C_J), 113.3 (C_A), 56.7 (C_O), 56.2 (C_D), 52.1 (C_E), 45.8 (C_P), 38.9 (C_K), 32.5 (C_M *or* C_N), 32.3 (C_M *or* C_N), 25.2 (C_F), 22.4 (C_C), 20.4 (C_L) ppm.

IR (film): ν_{max} 2955, 2814, 2761, 1630, 1560, 1461, 1377, 1144 cm^{-1}.

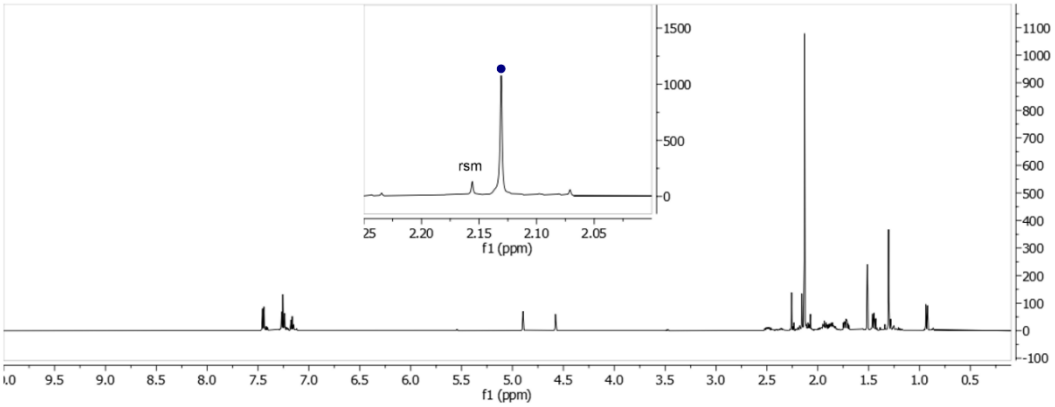
HRMS (ESI): m/z calc'd for $C_{19}H_{29}N$ $[M+H]^+$ 272.2373 found 272.2372.

Chiral solvating agent: The enantiopurity of boronic ester **212** was determined using Pirkle's alcohol ((*R*)-(–)-1-(9-anthryl)-2,2,2-trifluoroethanol) NMR shift reagent (2.0 eq, rt, $CDCl_3$, 0.05 M), >98:2 e.r.

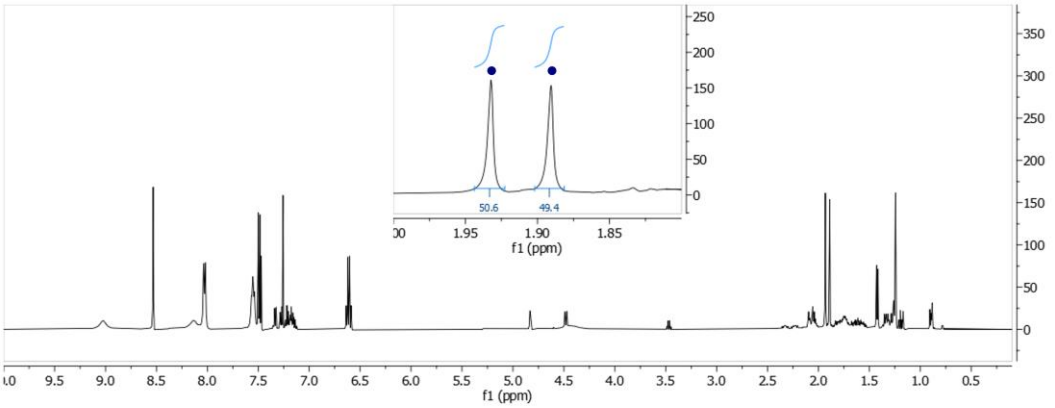


212

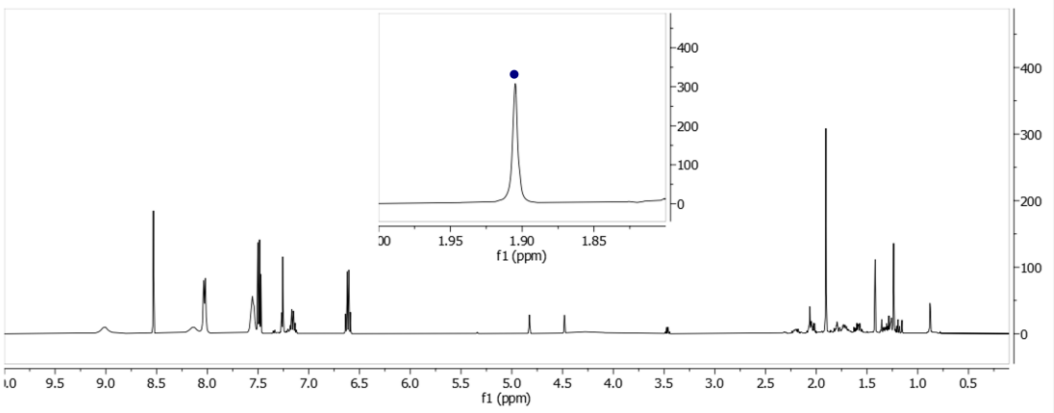
^{1}H NMR (500 MHz, $CDCl_3$) expansion of **(±)-212** only:



^{1}H NMR (500 MHz, $CDCl_3$) expansion of **(±)-212** with Pirkle's alcohol:

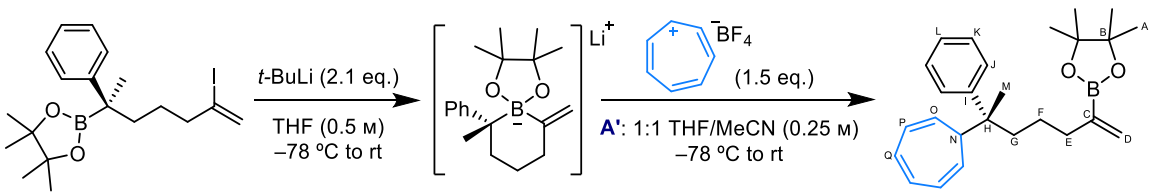


^{1}H NMR (500 MHz, $CDCl_3$) expansion of **212** with Pirkle's alcohol:



6.2.4. Miscellaneous compounds

(*S*)-2-(6-(Cyclohepta-2,4,6-trien-1-yl)-6-phenylhept-1-en-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (185)



According to **General Procedure F**, boronic ester **139a** (85 mg, 0.20 mmol, 1.0 eq.) was allowed to react with *tert*-butyl lithium (1.6 M in pentane, 0.27 mL, 0.42 mmol, 2.1 eq.) and tropylium tetrafluoroborate (53 mg, 0.30 mmol, 1.5 eq.) to give a crude residue which was purified by flash column chromatography (100:1 pentane/Et_2O) to afford boronic ester **185** (16 mg, 21%, 93:7 e.r., 88% e.s.) alongside boronic ester **141i.d[1]**.

The e.r. of boronic ester **185** could not be determined by chiral HPLC/SFC. Instead, the boronic ester was oxidised and the e.r. of ketone **185'** was determined.

$\mathbf{R_f}$ = 0.19 (pentane/CH_2Cl_2 9:1).

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$**:** +17 (*c* = 2.4, CH_2Cl_2).

NMR Spectroscopy:

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.23–7.15 (m, 4H, $H_{J,\ K}$), 7.15–7.01 (m, 1H, H_L), 6.63–6.50 (m, 2H, H_Q), 6.15 (dd, $^3J_{HH}$ = 10.0, 5.0 Hz, 1H, H_P), 5.99 (dd, $^3J_{HH}$ = 9.4, 4.3 Hz, 1H, $H_{P'}$), 5.61 (d, $^2J_{HH}$ = 3.6 Hz, 1H, H_D), 5.43–5.40 (m, 1H, $H_{D'}$), 5.37 (dd, $^3J_{HH}$ = 9.5,

5.8 Hz, 1H, H_O), 5.04 (dd, $^3J_{HH}$ = 9.5, 5.8 Hz, 1H, $H_{O'}$), 2.03–1.91 (m, 2H, $H_{E,\ E'}$), 1.85–1.60 (m, 3H, $H_{G,\ G',\ N}$), 1.40 (s, 3H, H_M), 1.22–1.13 (m, 1H, H_F), 1.12 (s, 12H, H_A), 1.05–0.91 (m, 1H, $H_{F'}$) ppm;

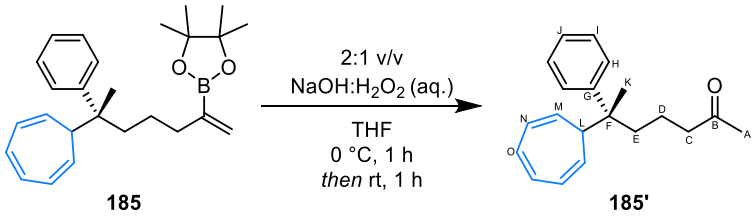
^{13}C NMR (101 MHz, $CDCl_3$): δ_C 146.5 (C_I), 130.8 (C_Q), 130.5 ($C_{Q'}$), 128.8 (C_D), 128.0 (C_J *or* C_K), 127.0 (C_J *or* C_K), 125.6 (C_L), 124.8 (C_P), 124.4 (C_O), 124.2 ($C_{P'}$), 123.4 ($C_{O'}$), 83.3 (C_B), 48.4 (C_N), 41.9 (C_H), 40.7 (C_G), 36.0 (C_E), 24.7 (C_A), 24.7 ($C_{A'}$), 23.4 (C_F), 20.7 (C_M) ppm; C_C not observed due to quadrupolar relaxation;

^{11}B NMR (128 MHz, $CDCl_3$): δ_B 29.4 ppm.

IR (film): ν_{max} 2976, 2933, 1616, 1444, 1370, 1308, 1142 cm^{-1}.

HRMS (ESI): m/z calc'd for $C_{26}H_{35}{}^{11}BNaO_2$ $[M+Na]^+$ 413.2627 found 413.2624.

(*S*)-6-(Cyclohepta-2,4,6-trien-1-yl)-6-phenylheptan-2-one (185')



According to **General Procedure D**, boronic ester **185** (10 mg, 0.03 mmol, 1.0 eq.) was reacted with a 2 M aqueous solution of NaOH (0.17 mL) and aqueous H_2O_2 (30% w/w; 0.08 mL) at 0 °C in THF (0.15 mL). The product (5 mg, 70%, 93:7 e.r.) was isolated as a colourless oil after purification by flash column chromatography (pentane/EtOAc 9:1).

R_f = 0.32 (pentane/EtOAc 9:1).

$[\alpha]_D^{25}$: +46 (*c* = 2.0, CH_2Cl_2).

NMR Spectroscopy:

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.27–7.20 (m, 4H, $H_{H,\ I}$), 7.15–7.09 (m, 1H, H_J), 6.64–6.54 (m, 2H, H_O), 6.20–6.14 (m, 1H, H_N), 6.04–5.95 (m, 1H, $H_{N'}$), 5.36 (dd, $^3J_{HH}$ = 9.5, 5.8 Hz, 1H, H_M), 5.03 (dd, $^3J_{HH}$ = 9.5, 5.8 Hz, 1H, $H_{M'}$), 2.22 (t, $^3J_{HH}$ = 7.3 Hz, 2H, H_C), 1.95 (s, 3H, H_A), 1.79–1.63 (m, 3H, $H_{E,\ E',\ L}$), 1.43 (s, 3H, H_K), 1.38–1.26 (m, 1H, H_D), 1.20–1.05 (m, 1H, $H_{D'}$) ppm;

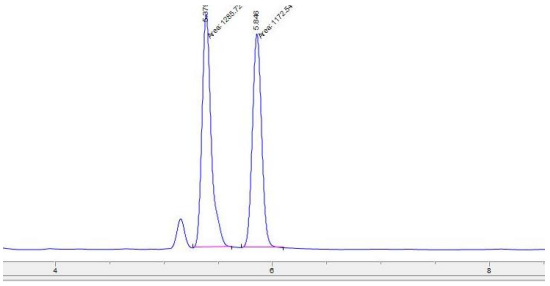
^{13}C NMR (101 MHz, $CDCl_3$): δ_C 208.9 (C_B), 146.0 (C_G), 130.9 (C_O), 130.5 ($C_{O'}$), 128.2 (C_H *or* C_I), 126.9 (C_H *or* C_I), 125.9 (C_J), 125.0 (C_N), 124.3 ($C_{N'}$), 124.1 (C_M), 122.9 ($C_{M'}$),

48.3 (C_L), 44.2 (C_C), 41.9 (C_F), 40.7 (C_E), 29.7 (C_A), 20.4 (C_K), 18.4 (C_D) ppm.

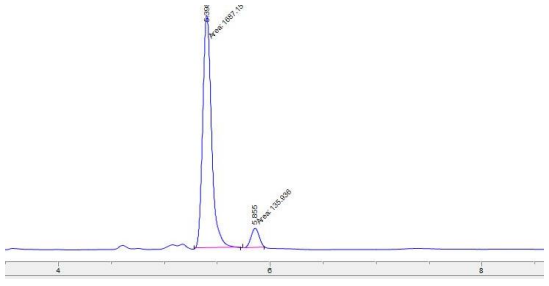
IR (film): ν_{max} 3002, 2949, 1714 (C=O), 1498, 1445, 1359, 1161 cm^{-1}.

HRMS (ESI): m/z calc'd for $C_{20}H_{24}O$ $[M+H]^+$ 281.1900 found 281.1894.

Chiral HPLC (IB column, 90:10 hexane/IPA, 1 mL/min, rt, 254 nm): 5.4 min (major), 5.8 (minor), 93:7 e.r.

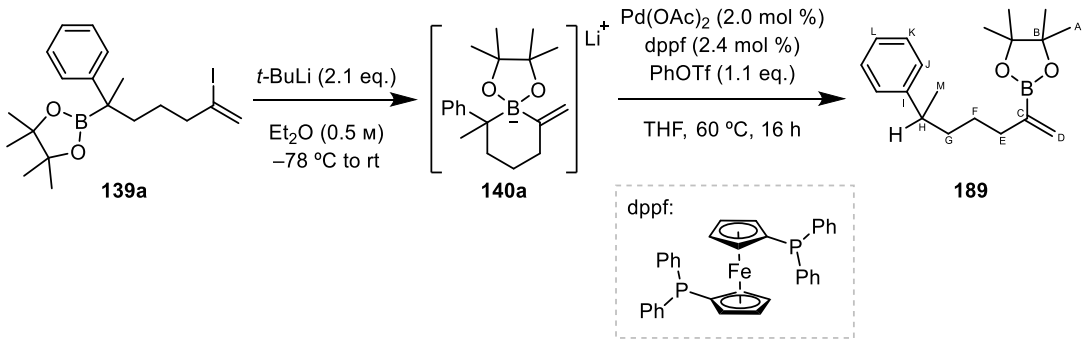


#	Time	Type	Area	Height	Width	Area%	Symmetry
1	5.379	MM	1285.7	218.4	0.0981	52.302	0.652
2	5.846	MM	1172.5	200.1	0.0977	47.698	0.867



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	5.398	MM	1687.2	288.9	0.0973	92.544	0.811
2	5.855	MM	135.9	24.6	0.0921	7.456	1.028

4,4,5,5-Tetramethyl-2-(6-phenylhept-1-en-2-yl)-1,3,2-dioxaborolane (189)



According to a modified literature procedure,[59] boronic ester **139a** (41 mg, 0.10 mmol, 1.0 eq.) was dissolved in anhydrous Et_2O (0.20 mL) and cooled to −78 °C (dry ice/acetone). *tert*-Butyl lithium (1.5 M in pentane, 0.14 mL, 0.21 mmol, 2.1 eq.) was then added dropwise (~0.5 mL/min). The resultant mixture was stirred at −78 °C for 1 hour before warming to rt and stirring at this temperature for a further 1 hour. The solvent was then removed *in vacuo* at rt. A stock solution of anhydrous THF (0.50 mL), palladium(II) acetate (2 mg, 0.01 mmol) and 1,1'-bis(diphenylphosphino)ferrocene (7 mg, 0.012 mmol) were added to a separate oven-dried Schlenk-tube equipped with a stirring bar. This solution was allowed to stir at rt for 20 min prior to the transfer of 0.10 mL of the stock solution to the boronate complex. Anhydrous THF (0.30 mL) and phenyl triflate (18 µL, 0.11 mmol, 1.1 eq.) were then sequentially added to the reaction mixture. The reaction was allowed to stir at 60 °C overnight whereupon, after cooling

to rt, the crude material was filtered through a silica plug (eluting Et_2O) and concentrated *in vacuo*. The crude reaction mixture was purified by flash column chromatography (7:1 to 5:1 pentane/CH_2Cl_2) to give **189** (14 mg, 45%) as a colourless oil.

NMR Spectroscopy:

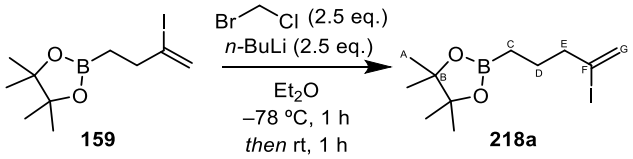
^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.40–7.29 (m, 2H, H_K), 7.30–7.18 (m, 3H, $H_{J, L}$), 5.81 (br d, $^2J_{HH}$ = 3.5 Hz, $^4J_{HH}$ = 1.0 Hz, 1H, H_D), 5.63 (br d, $^2J_{HH}$ = 3.5 Hz, 1H, $H_{D'}$), 2.82–2.69 (m, 1H, H_H), 2.28–2.11 (m, 2H, H_E), 1.72–1.55 (m, 2H, H_G), 1.53–1.35 (m, 2H, H_F), 1.32–1.29 (m, 15H, $H_{A, M}$) ppm;

^{13}C NMR (101 MHz, $CDCl_3$): δ_C 147.9 (C_I), 128.9 (C_D), 128.2 (C_K), 127.0 (C_J), 125.7 (C_L), 83.3 (C_B), 39.8 (C_H), 38.0 (C_G), 35.4 (C_E), 27.3 (C_F), 24.7 (C_A), 24.7 ($C_{A'}$), 22.2 (C_M) ppm; C_C not observed due to quadrupolar relaxation.

6.2.5. Extension to the synthesis of cyclobutyl boronic esters

6.2.5.1. Synthesis of boronic ester starting materials

(*S*)-2-(6-Iodo-2-(2-methoxy-5-methylphenyl)hept-6-en-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (218a)



According to a literature procedure,[75] boronic ester **159** (0.307 g, 1.0 mmol, 1.0 eq.) was dissolved in anhydrous Et_2O (10 mL) and cooled to −78 °C (dry ice/acetone). Bromochloromethane (0.16 mL, 2.5 mmol, 2.5 eq.) was added dropwise (~0.5 mL/min) to the solution, followed by *n*-butyl lithium (1.6 M in hexanes; 1.6 mL, 2.5 mmol, 2.5 eq.) *via* syringe pump (0.012 mL/min). Following the addition, the reaction mixture was stirred at −78 °C for 1 hour and then warmed to rt and stirred at this temperature for 1 hour. The reaction mixture was filtered through a silica plug (eluting Et_2O) and concentrated *in vacuo*. The crude reaction mixture was purified by flash column chromatography (pentane) to give the product (0.250 g, 78%) as a colourless oil.

NMR Spectroscopy:

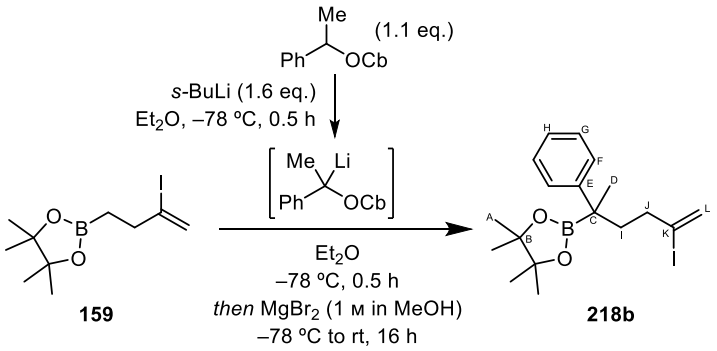
^{1}H NMR (400 MHz, $CDCl_3$): δ_H 6.00 (apparent q, $^4J_{HH}$ = $^2J_{HH}$ = 1.4 Hz, 1H, H_G), 5.68

(dd, $^{2}J_{HH}$ = 1.4 Hz, $^{4}J_{HH}$ = 0.6 Hz, 1H, $H_{G'}$), 2.40 (tdd, $^{3}J_{HH}$ = 7.3 Hz, $^{4}J_{HH}$ = 1.4, 0.6 Hz, 2H, H_E), 1.67–1.58 (m, 2H, H_D), 1.25 (s, 12H, H_A), 0.82–0.74 (m, 2H, H_C) ppm;

^{13}C NMR (101 MHz, $CDCl_3$): δ_C 125.4 (C_G), 112.4 (C_F), 83.0 (C_B), 47.7 (C_E), 24.8 (C_A), 23.5 (C_D) ppm; C_C not observed due to quadrupolar relaxation.

All recorded spectroscopic data matched those previously reported in the literature.[75]

2-(5-Iodo-2-phenylhex-5-en-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (218b)



1-Phenylethyl diisopropylcarbamate[27] (0.549 g, 2.2 mmol, 1.1 eq.) was dissolved in anhydrous Et_2O (9 mL) and the solution cooled to −78 °C (dry ice/acetone). *sec*-Butyl lithium (1.3 M in cyclohexane/hexane 92:8; 2.3 mL, 3.2 mmol, 1.6 eq.) was added dropwise (~0.5 mL/min) to the solution. The reaction mixture was stirred at −78 °C for 30 minutes whereupon boronic ester **159** (1 M in Et_2O; 0.616 g, 2.0 mmol, 1.0 eq.) was added dropwise (~0.5 mL/min). Following stirring at −78 °C for 30 minutes, $MgBr_2$ (1 M in MeOH; 3.6 mL, 3.6 mmol, 1.8 eq.) was added at this temperature. The reaction mixture was then warmed to rt and stirred at this temperature overnight. The reaction mixture was then quenched with water (10 mL) and the aqueous layer extracted with Et_2O (3 × 10 mL). The combined organics were washed with brine (10 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude reaction mixture was purified by flash column chromatography (pentane/Et_2O 200:1 to 100:1) to give the product (0.634 g, 76%) as a colourless oil.

NMR Spectroscopy:

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.35–7.23 (m, 4H, $H_{F, G}$) 7.19–7.10 (m, 1H, H_H), 5.96 (apparent q, $^{4}J_{HH}$ = $^{2}J_{HH}$ = 1.4 Hz, 1H, H_L), 5.63 (d, $^{2}J_{HH}$ = 1.5 Hz, 1H, H_L), 2.39–2.17 (m, 2H, $H_{J, J'}$), 2.04–1.92 (m, 2H, $H_{I, I'}$), 1.36 (s, 3H, H_D), 1.21 (s, 6H, H_A), 1.20 (s, 6H, $H_{A'}$) ppm;

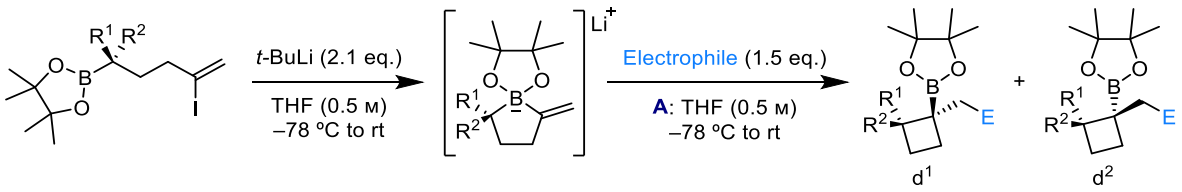
^{13}C NMR (101 MHz, $CDCl_3$): δ_C 146.3 (C_E), 128.2 (C_F *or* C_G), 126.8 (C_F *or* C_G), 125.3

(C_H), 124.8 (C_L), 112.8 (C_K), 83.5 (C_B), 41.8 (C_J), 39.1 (C_I), 24.6 (C_A), 21.5 (C_D) ppm; C_C not observed due to quadrupolar relaxation.

All recorded spectroscopic data matched those previously reported in the literature.[75]

6.2.5.2. Attempted synthesis of cyclobutyl boronic esters

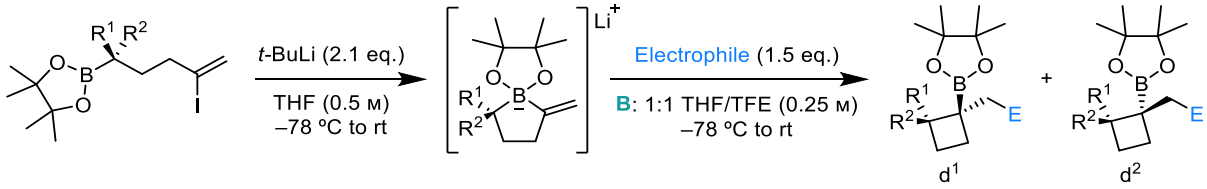
6.2.5.3. General procedure I: electrophile-induced ring contraction of 5-membered cyclic alkenyl boronate complexes in THF



tert-Butyl lithium[a] (in pentane, 0.21 mmol, 2.1 eq.) was added dropwise (~0.5 mL/min) to a solution of the starting boronic ester (0.10 mmol, 1.0 eq.) in anhydrous THF (0.20 mL, 0.5 M) at −78 °C (dry ice/acetone) and allowed to stir at this temperature for 1 hour. The cooling bath was removed, and the reaction was stirred at rt for a further 1 hour before being cooled again to −78 °C (dry ice/acetone) whereupon the electrophile[b] (0.15 mmol, 1.5 eq.) was added. The reaction mixture was stirred at −78 °C for 2 hours and slowly warmed to rt overnight (the replenishment of dry ice in the cooling bath was halted). The reaction mixture was diluted with Et_2O (5 mL) and quenched with water[c] (5 mL). The aqueous layer was extracted with Et_2O (3 × 5 mL) and the combined organics washed with brine (5 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude residue was analysed by ^1H NMR to determine in what diastereomeric ratio the product was formed. The crude product was then purified by flash column chromatography.

[a] *tert*-Butyl lithium should be titrated before use.[193] [b] Electrophiles sufficiently soluble in THF were added as 1 M solutions in THF, those with partial solubility were quickly added directly into the flask. [c] To be replaced with 0.5 M aqueous NaOH when using Eschenmoser's salt as the electrophile.

6.2.5.4. General procedure J: electrophile-induced ring contraction of 5-membered cyclic alkenyl boronate complexes in 1:1 THF/TFE

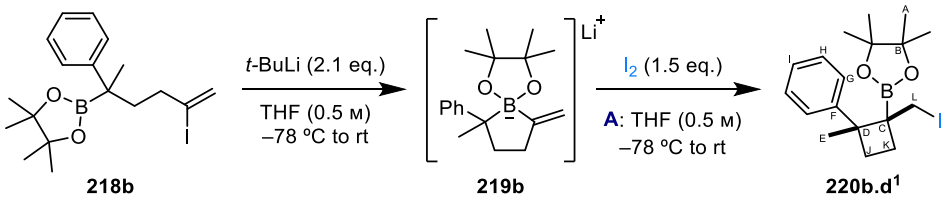


tert-Butyl lithium[a] (in pentane, 0.21 mmol, 2.1 eq.) was added dropwise (~0.5 mL/min) to a solution of the starting boronic ester (0.10 mmol, 1.0 eq.) in anhydrous THF (0.20 mL, 0.5 M) at −78 °C (dry ice/acetone) and allowed to stir at this temperature for 1 hour. The cooling bath was removed, and the reaction was stirred at rt for a further 1 hour before being cooled again to −78 °C (dry ice/acetone) whereupon 2,2,2-trifluoroethanol (TFE) (0.40 mL) was added followed by the electrophile[b] (0.30 mmol, 1.5 eq.). The reaction mixture was stirred at −78 °C for 2 hours and slowly warmed to rt overnight (the replenishment of dry ice in the cooling bath was halted). The reaction mixture was diluted with Et_2O (5 mL) and quenched with water[c] (5 mL). The aqueous layer was extracted with Et_2O (3 × 5 mL) and the combined organics washed with brine (5 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude residue was analysed by ^1H NMR to determine in what diastereomeric ratio the product was formed. The crude product was then purified by flash column chromatography.

[a] *tert*-Butyl lithium should be titrated before use.[193] [b] Electrophiles sufficiently soluble in THF were added as 1 M solutions in THF, those with partial solubility were quickly added directly into the flask. [c] To be replaced with 0.5 M aqueous NaOH when using Eschenmoser's salt as the electrophile.

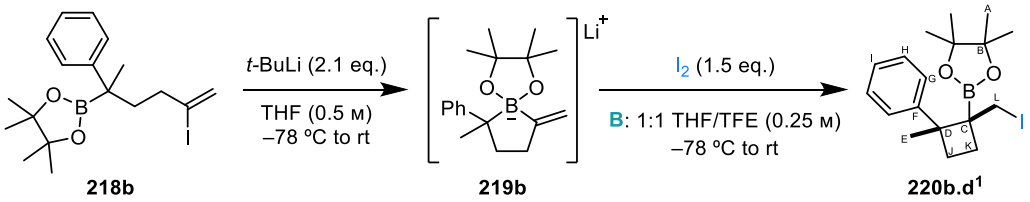
6.2.5.5. Characterisation of cyclobutyl boronic esters

2-(1-(Iodomethyl)-2-methyl-2-phenylcyclobutyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (220b)



According to **General Procedure I**, boronic ester **218b** (41 mg, 0.10 mmol, 1.0 eq.) was allowed to react with *tert*-butyl lithium (1.8 M in pentane, 0.12 mL, 0.21 mmol, 2.1 eq.) and

iodine (1 M in THF; 38 mg, 0.15 mmol, 1.5 eq.) to give a crude residue (78:22 d.r. by crude ^{1}H NMR spectroscopic analysis) which was purified by flash column chromatography (4:1 pentane/CH_2Cl_2) to afford the boronic ester (19 mg, 47%, 78:22 d^1/d^2) as a white solid.



According to **General Procedure J**, boronic ester **218b** (41 mg, 0.10 mmol, 1.0 eq.) was allowed to react with *tert*-butyl lithium (1.8 M in pentane, 0.12 mL, 0.21 mmol, 2.1 eq.) and iodine (1 M in THF; 38 mg, 0.15 mmol, 1.5 eq.) to give a crude residue (87:13 d.r. by crude ^{1}H NMR spectroscopic analysis) which was purified by flash column chromatography (4:1 pentane/CH_2Cl_2) to afford the boronic ester (21 mg, 51%, 87:13 d^1/d^2) as a white solid.

Characterisation given for a mixture of diastereomers (78:22 d^1/d^2).

R_f = 0.24 (d^1), 0.16 (d^2) (pentane/CH_2Cl_2 4:1).

NMR Spectroscopy: *Assignments made for the major diastereomer.*

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.25–7.20 (m, 2H, H_{Ar}), 7.15–7.09 (m, 3H, H_{Ar}), 3.76 (d, $^2J_{HH}$ = 8.1 Hz, 1H, H_L), 3.56 (d, $^2J_{HH}$ = 8.1 Hz, 1H, $H_{L'}$), 2.58 (apparent q, $^3J_{HH}$ = $^2J_{HH}$ = 9.6 Hz, 1H, H_J), 2.15–2.06 (m, 1H, H_K), 1.79–1.60 (m, 2H, $H_{J',K'}$), 1.32 (s, 3H, H_E), 0.93 (s, 6H, H_A), 0.80 (s, 6H, $H_{A'}$) ppm;

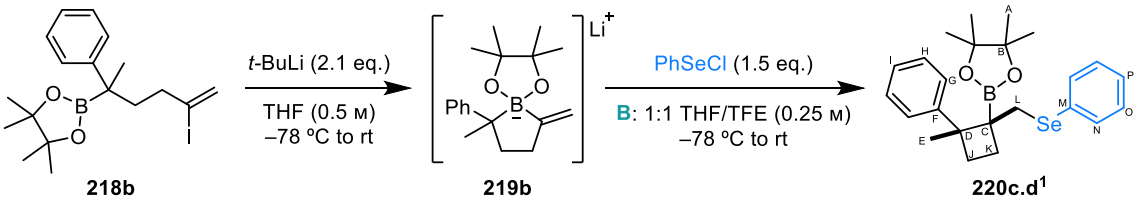
^{13}C NMR (101 MHz, $CDCl_3$): δ_C 149.41 (C_F), 127.8 (C_{Ar}), 125.8 (C_{Ar}), 125.8 (C_{Ar}), 83.5 (C_B), 48.5 (C_D), 28.0 (C_K), 27.3 (C_J), 26.2 (C_E), 24.9 (C_A), 24.2 ($C_{A'}$), 15.4 (C_L) ppm; C_C not observed due to quadrupolar relaxation;

^{11}B NMR (128 MHz, $CDCl_3$): δ_B 32.2 ppm.

IR (film): ν_{max} 2977, 2870, 1601, 1445 1373, 1321, 1140 cm^{-1}.

HRMS (ESI): m/z calc'd for $C_{18}H_{26}{}^{11}BINaO_2$ $[M+Na]^+$ 435.0966 found 435.0947.

4,4,5,5-Tetramethyl-2-(2-methyl-2-phenyl-1-((phenylselanyl)methyl)cyclobutyl)-1,3,2-dioxaborolane (220c)



According to **General Procedure J**, boronic ester **218b** (41 mg, 0.10 mmol, 1.0 eq.) was allowed to react with *tert*-butyl lithium (1.7 M in pentane, 0.12 mL, 0.21 mmol, 2.1 eq.) and phenylselenyl chloride (1 M in THF; 29 mg, 0.15 mmol, 1.5 eq.) to give a crude residue (49%, 65:35 d.r. by quantitative ^{1}H NMR spectroscopic analysis). Purification by flash column chromatography (200:1 pentane/Et_2O) was attempted, but traces of an alkene impurity proved inseparable.

Characterisation given for a mixture of diastereomers (65:35 d^1/d^2).

NMR Spectroscopy: *Assignments made for the major diastereomer.*

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.56–7.49 (m, 2H, H_{Ar}), 7.27–7.20 (m, 1H, H_{Ar}), 7.19–7.12 (m, 5H, H_{Ar}), 7.11–7.00 (m, 2H, H_{Ar}), 3.48 (d, $^{2}J_{HH}$ = 10.4 Hz, 1H, H_L), 3.24 (d, $^{2}J_{HH}$ = 10.4 Hz, 1H, $H_{L'}$), 2.58–2.51 (m, 1H, H_J *or* H_K), 2.13–2.05 (m, 1H, H_J *or* H_K), 1.70–1.59 (m, 2H, H_J *or* H_K), 1.30–1.28 (s, 3H, H_E), 0.87 (s, 6H, H_A), 0.73 (s, 6H, $H_{A'}$) ppm;

^{13}C NMR (101 MHz, $CDCl_3$): δ_C 150.0 (C_F), 133.1 (C_{Ar}), 128.8 (C_{Ar}), 128.1 (C_{Ar}), 127.8 (C_{Ar}), 126.6 (C_{Ar}), 125.8 (C_{Ar}), 83.3 (C_B), 48.6 (C_D), 35.1 (C_L), 29.1 (C_J *or* C_K), 26.3 (C_E), 26.0 (C_J *or* C_K), 24.9 (C_A), 24.2 ($C_{A'}$) ppm; C_C not observed due to quadrupolar relaxation;

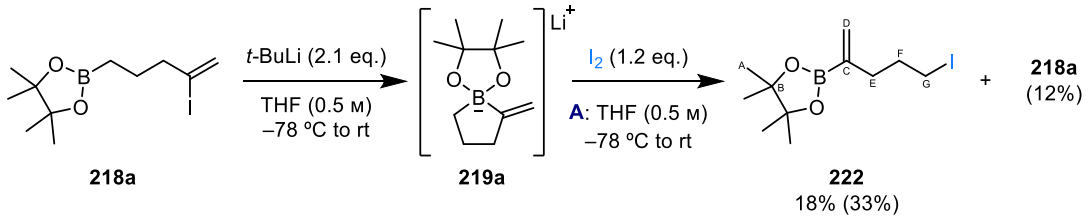
^{11}B NMR (128 MHz, $CDCl_3$): δ_B 33.0 ppm.

IR (film): ν_{max} 2977, 1601, 1445, 1373, 1321, 1140 cm^{-1}.

HRMS (ESI): m/z calc'd for $C_{24}H_{31}{}^{11}BNa^{80}SeO_2$ $[M+Na]^+$ 465.1480 found 465.1466.

6.2.5.6. Characterisation of key side products

2-(5-Iodopent-1-en-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (222)



According to a modified **General Procedure I**, boronic ester **218a** (64 mg, 0.20 mmol, 1.0 eq.) was allowed to react with *tert*-butyl lithium (1.7 M in pentane, 0.25 mL, 0.42 mmol, 2.1 eq.) and iodine (1 M in THF; 64 mg, 0.24 mmol, 1.2 eq.) to give a crude residue (33% **222** and 12% **218a** by quantitative ^{1}H NMR spectroscopic analysis) which was purified by flash column chromatography (4:1 pentane/CH_2Cl_2) to afford boronic ester **222** (13 mg, 18%) as a colourless oil.

$\mathbf{R_f}$ = 0.20 (pentane/CH_2Cl_2 4:1).

NMR Spectroscopy:

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 5.87–5.78 (m, 1H, H_D), 5.69–5.63 (m, 1H, H_D), 3.17 (t, $^{3}J_{HH}$ = 7.1 Hz, 2H, H_G), 2.28–2.20 (m, 2H, H_E), 2.03–1.91 (m, 2H, H_F), 1.26 (s, 12H, H_A) ppm;

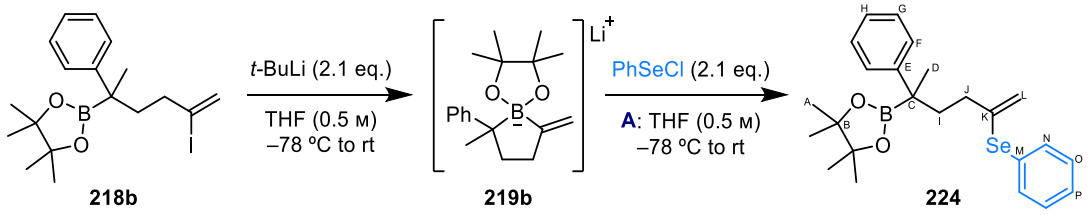
^{13}C NMR (101 MHz, $CDCl_3$): δ_C 130.5 (C_D), 83.9 (C_B), 36.0 (C_E), 32.9 (C_F), 24.8 (C_A), 6.7 (C_G) ppm; C_C not observed due to quadrupolar relaxation;

^{11}B NMR (128 MHz, $CDCl_3$): δ_B 29.5 ppm.

IR (film): ν_{max} 2978, 2928, 1615, 1426, 1370, 1310, 1220, 1142 cm^{-1}.

HRMS (ESI): m/z calc'd for $C_{11}H_{20}{}^{11}BINaO_2$ $[M+Na]^+$ 345.0495 found 345.0479.

4,4,5,5-Tetramethyl-2-(2-phenyl-5-(phenylselanyl)hex-5-en-2-yl)-1,3,2-dioxaborolane (224)



According to a modified **General Procedure I**, boronic ester **218b** (37 mg, 0.10 mmol, 1.0 eq.) was allowed to react with *tert*-butyl lithium (1.7 M in pentane; 0.12 mL, 0.21 mmol, 2.1 eq.) and phenylselenyl chloride (1 M in THF; 40 mg, 0.21 mmol, 2.1 eq.) to give a crude residue which was purified by flash column chromatography (pentane/Et_2O 200:1 to 100:1) to afford the boronic ester (15 mg, 36%) as a colourless oil.

$\mathbf{R_f}$ = 0.20 (pentane/Et_2O 9:1).

NMR Spectroscopy:

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.56–7.46 (m, 2H, H_{Ar}), 7.32–7.19 (m, 7H, H_{Ar}), 7.17–7.07 (m, 1H, H_{Ar}), 5.47 (br t, J_{HH} = 1.3 Hz, 1H, H_L), 5.09 (br s, 1H, H_L), 2.28–2.10 (m, 2H, $H_{J, J'}$), 2.10–1.92 (m, 2H, $H_{I, I'}$), 1.29 (s, 3H, H_D), 1.17 (s, 6H, H_A), 1.16 (s, 6H, $H_{A'}$) ppm;

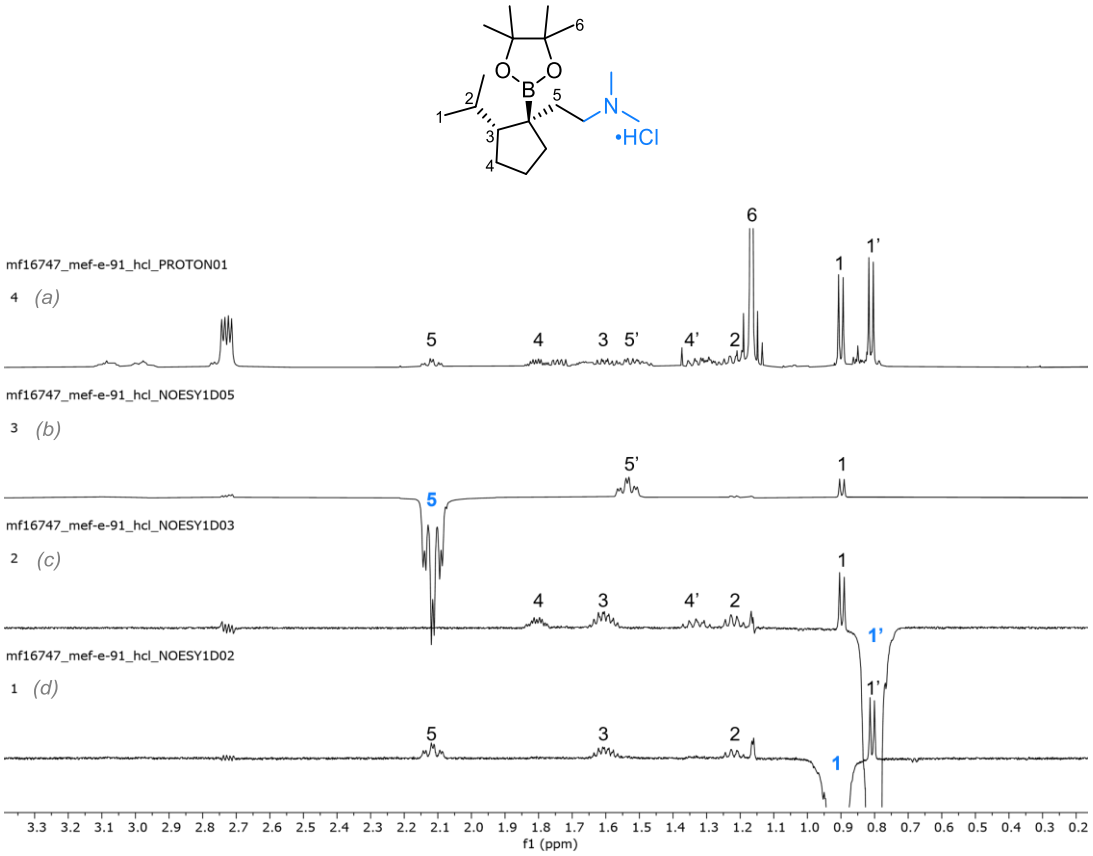
^{13}C NMR (101 MHz, $CDCl_3$): δ_C 146.6 (C_{Ar}), 144.0 (C_L), 134.7 (C_{Ar}), 129.2 (C_{Ar}), 129.2 (C_{Ar}), 128.1 (C_{Ar}), 127.6 (C_{Ar}), 126.8 (C_{Ar}), 125.1 (C_{Ar}), 116.0 (C_K), 83.4 (C_B), 38.9 (C_J), 34.5 (C_I), 24.6 (C_A), 21.6 (C_D) ppm; C_C not observed due to quadrupolar relaxation;

IR (film): ν_{max} 2975, 2924, 2853, 1610, 1476, 1379, 1314, 1144 cm^{-1}.

HRMS (Nanospray): m/z calc'd for $C_{24}H_{31}{}^{11}BNa^{80}SeO_2$ $[M+Na]^+$ 465.1480 found 465.1472.

6.2.6. One dimensional ^{1}H nOe experiments for the determination of relative stereochemistry

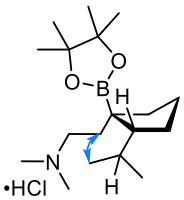
2-((1*S*,2*R*)-2-Isopropyl-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclopentyl)-*N*,*N*-dimethylethan-1-amine hydrochloride salt (141e)



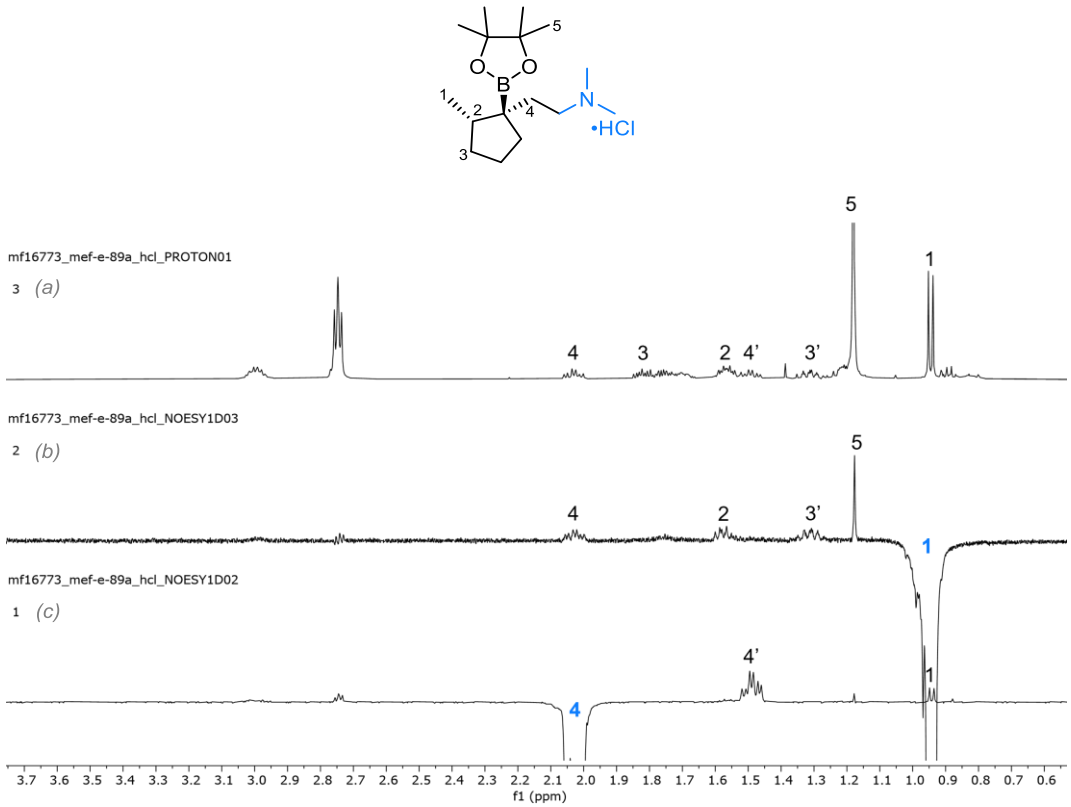
*Supplementary Figure 1. 1D ^{1}H nOe experiments for **141e**. (a) ^{1}H NMR (500 MHz, $CDCl_3$) spectrum of **141e**; (b) Irradiation of CH^{5}_{2}; (c) Irradiation of $CH^{1'}_{3}$; (d) Irradiation of $CH^{'}_{3}$.*

Key observations:

- Irradiation of C**H**$^{5}_{2}$: Observable nOe correlation with H^1 protons but no significant correlation with H^3.
- Irradiation of C**H**$^{1}_{3}$: Observable nOe correlation with H^5 but no significant correlation with H^6.
- Irradiation of C**H**$^{1'}_{3}$: Observable nOe correlation with H^4 but no significant correlation with H^5.



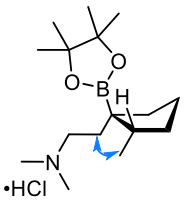
***N*,*N*-Dimethyl-2-((1*S*,2*S*)-2-methyl-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclopentyl)ethan-1-amine hydrochloride salt (141f)**



*Supplementary Figure 2. 1D ^{1}H nOe experiments for **141f**. (a) ^{1}H NMR (500 MHz, $CDCl_3$) spectrum of **141f**; (b) Irradiation of CH^{1}_{3}; (c) Irradiation of CH^{4}_{2}.*

Key observations:

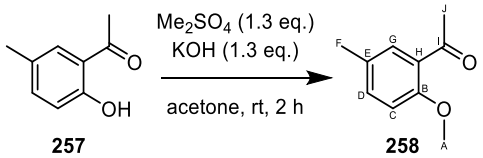
- Irradiation of C**H**$^{1}_{3}$: Observable nOe correlation with H^{4} proton and slight correlation with H^{5}.
- Irradiation of C**H**$^{4}_{2}$: Observable nOe correlation with H^{1} but no significant correlation with H^{2}.



6.3. Synthetic procedures – Chapter 3

6.3.1. Asymmetric total synthesis of (+)-herbertene-1,14-diol

1-(2-Methoxy-5-methylphenyl)ethan-1-one (258)



According to a modified literature procedure,[74] 1-(2-hydroxy-5-methylphenyl)ethan-1-one **257** (5.00 g, 33 mmol, 1.0 eq.) was dissolved in anhydrous acetone (70 mL) at rt and potassium hydroxide (2.43 g, 43 mmol, 1.3 eq.) was added followed by dimethyl sulfate (4.1 mL, 43 mmol, 1.3 eq.) dropwise (~1 mL/min). The reaction mixture was stirred at rt for 2 hours. Completion of the reaction was confirmed by TLC monitoring, whereupon a 1 M aqueous solution of NaOH (100 mL) was added. The aqueous phase was extracted with Et_2O (3 × 100 mL) and the combined organics were washed with brine (100 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude reaction mixture was purified by flash column chromatography (pentane/EtOAc 20:1) to give the product (5.17 g, 95%) as a colourless oil.

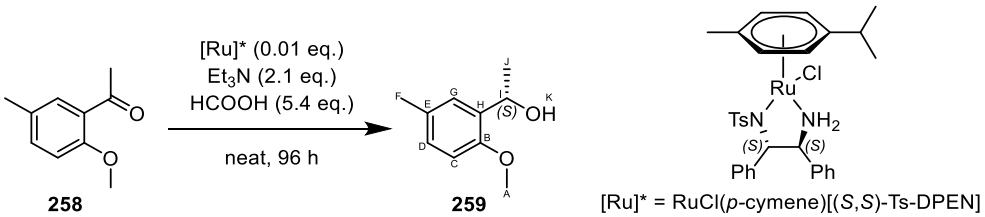
NMR Spectroscopy:

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.53 (d, $^4J_{HH}$ = 2.5 Hz, 1H, H_G), 7.26 (dd, $^3J_{HH}$ = 8.4 Hz, $^4J_{HH}$ = 2.5 Hz, 1H, H_D), 6.86 (d, $^3J_{HH}$ = 8.4 Hz, 1H, H_C), 3.88 (s, 3H, H_A), 2.60 (s, 3H, H_J), 2.30 (s, 3H, H_F) ppm;

^{13}C NMR (101 MHz, $CDCl_3$): δ_C 200.1 (C_I), 157.0 (C_B), 134.1 (C_D), 130.6 (C_G), 129.9 (C_E), 128.0 (C_H), 111.6 (C_C), 55.6 (C_A), 31.8 (C_J), 20.2 (C_F) ppm.

All recorded spectroscopic data matched those previously reported in the literature.[202]

(*S*)-1-(2-Methoxy-5-methylphenyl)ethan-1-ol (259)



According to a modified literature procedure,[74] formic acid (6.1 mL, 162 mmol, 5.4 eq.) was added to triethylamine (8.8 mL, 63 mmol, 2.1 eq.) at 0 °C (ice/water). The reaction mixture was warmed to room temperature whereupon ketone **258** (4.92 g, 30 mmol, 1.0 eq.) was added dropwise (~1 mL/min), followed by RuCl(*p*-cymene)[(*S*,*S*)-Ts-DPEN] (0.190 g, 0.30 mmol, 0.01 eq.) as one portion. Nitrogen was bubbled through the reaction mixture over 96 h, at which point the reaction was deemed to be complete by TLC analysis. The reaction mixture was quenched with water (100 mL) and EtOAc (100 mL) was added. The organic layer was separated, and the aqueous phase was extracted with Et_2O (3 × 100 mL). The combined organics were washed with brine (100 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude reaction mixture was purified by flash column chromatography (pentane/EtOAc 20:1) to give the product (4.72 g, 95%, 96:4 e.r.) as an off-white solid.

R_f = 0.17 (pentane/EtOAc 9:1).

$[\alpha]_D^{25}$: –25 (*c* = 2.1, CH_2Cl_2).

NMR Spectroscopy:

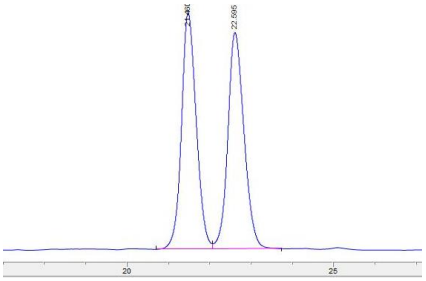
^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.08–7.05 (m, 1H, H_G), 6.96 (dd, $^3J_{HH}$ = 8.3 Hz, $^4J_{HH}$ = 2.4 Hz, 1H, H_D), 6.71 (d, $^3J_{HH}$ = 8.3 Hz, 1H, H_C), 4.98 (q, $^3J_{HH}$ = 6.5 Hz, 1H, H_I), 3.76 (s, 3H, H_A), 2.54 (br s, 1H, H_K), 2.22 (s, 3H, H_F), 1.43 (d, $^3J_{HH}$ = 6.5 Hz, 3H, H_J) ppm;

^{13}C NMR (101 MHz, $CDCl_3$): δ_C 154.5 (C_B), 133.1 (C_H), 130.0 (C_E), 128.4 (C_D), 126.9 (C_G), 110.5 (C_C), 66.7 (C_I), 55.4 (C_A), 23.0 (C_J), 20.6 (C_F) ppm.

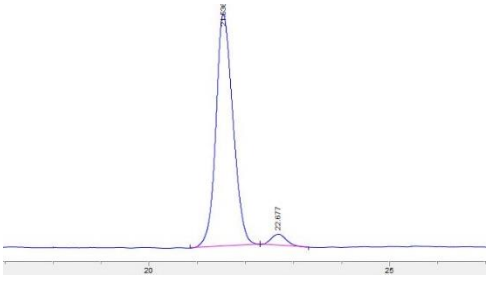
IR (film): ν_{max} 3380 (br), 2969, 2927, 1612, 1501, 1464, 1287, 1244, 1181, 1157, 1140, 1077, 1028 cm^{-1}.

HRMS (APCI): m/z calc'd for $C_{10}H_{13}O$ $[M+H–H_2O]^+$ 149.0961 found 149.0960.

Chiral HPLC (IA column, 98:2 hexane/IPA, 1 mL/min, rt, 254 nm): 21.5 min (major), 22.7 min (minor), 96:4 e.r.

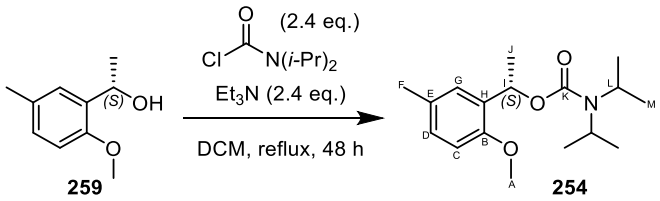


#	Time	Type	Area	Height	Width	Area%	Symmetry
1	21.46	BV	4878.6	196	0.3559	49.957	0.804
2	22.595	VV R	4886.9	179.6	0.4069	50.043	0.77



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	21.536	BV R	5806.1	235	0.3542	95.814	0.756
2	22.677	VV R	253.7	11.4	0.261	4.186	0.818

(*S*)-1-(2-Methoxy-5-methylphenyl)ethyl diisopropylcarbamate (254)



According to a modified literature procedure,[74] alcohol **259** (4.16 g, 25 mmol, 1.0 eq.) was added to a solution of *N*,*N*-diisopropylcarbamoyl chloride (4.91 g, 30 mmol, 1.2 eq.) and triethylamine (4.2 mL, 30 mmol, 1.2 eq.) in anhydrous CH_2Cl_2 (52 mL) and the solution was heated to reflux for 24 h, after which time a further portion of *N*,*N*-diisopropylcarbamoyl chloride (4.91 g, 30 mmol, 1.2 eq.) and triethylamine (4.2 mL, 30 mmol, 1.2 eq.) were added. Following an additional 24 hours at reflux the reaction was deemed complete by TLC analysis and the reaction mixture was cooled to rt. Water (100 mL) was added and the organic layer separated. The aqueous phase was extracted with CH_2Cl_2 (3 x 100 mL). The organic phases were combined, dried over $MgSO_4$ and concentrated *in vacuo*. The crude reaction mixture was purified by flash column chromatography (pentane/EtOAc 9:1) to give the product (6.87 g, 94%) as a colourless, amorphous solid.

R_f = 0.40 (pentane/EtOAc 9:1).

$[\alpha]_D^{25}$: +2 (*c* = 2.1, CH_2Cl_2).

NMR Spectroscopy:

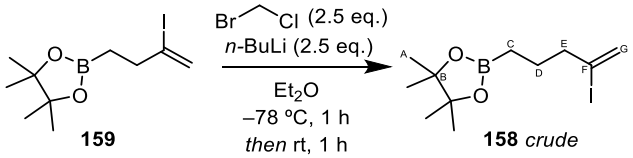
^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.14 (d, $^4J_{HH}$ = 2.3 Hz, 1H, H_G), 7.01 (ddd, $^3J_{HH}$ = 8.3 Hz, $^4J_{HH}$ = 2.3 Hz, *J* = 0.8 Hz, 1H, H_D), 6.75 (d, $^3J_{HH}$ = 8.3 Hz, 1H, H_C), 6.14 (d, $^3J_{HH}$ = 6.4 Hz, 1H, H_I), 4.19–3.62 (br m, 2H, H_L), 3.80 (s, 3H, H_A), 2.28 (s, 3H, H_F), 1.49 (d, $^3J_{HH}$ = 6.4 Hz, 3H, H_J), 1.38–1.06 (br s, 12H, H_M) ppm;

^{13}C NMR (101 MHz, $CDCl_3$): δ_C 155.1 (C_K), 153.9 (C_B), 131.4 (C_H), 129.5 (C_E), 128.4 (C_G), 126.8 (C_D), 110.6 (C_C), 68.0 (C_I), 55.5 (C_A), 21.8 (C_J), 21.1 (br, C_M), 20.7 (C_F) ppm; C_L not observed.

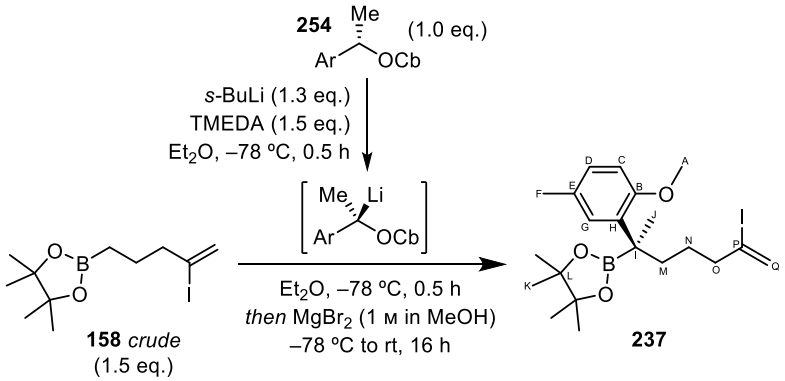
IR (film): ν_{max} 2975, 2934, 1616 (C=O), 1496, 1461, 1370, 1341, 1305, 1236, 1142, 1110 cm^{-1}.

HRMS (ESI): m/z calc'd for $C_{17}H_{27}NNaO_3$ $[M+Na]^+$ 316.1883 found 316.1886.

(*S*)-2-(6-Iodo-2-(2-methoxy-5-methylphenyl)hept-6-en-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (237)



According to a combination of modified literature procedures,[74,75] boronic ester **159** (0.790 g, 2.6 mmol, 1.0 eq.) was dissolved in anhydrous Et_2O (20 mL) and cooled to −78 °C (dry ice/acetone). Bromochloromethane (0.42 mL, 6.4 mmol, 2.5 eq.) was added dropwise (~0.5 mL/min) to the solution, followed by *n*-butyl lithium (1.6 M in hexanes; 4.0 mL, 6.4 mmol, 2.5 eq.) *via* syringe pump (0.08 mL/min). Following the addition, the reaction mixture was stirred at −78 °C for 1 hour and then warmed to rt and stirred at this temperature for 1 hour. The reaction mixture was filtered through a silica plug (eluting Et_2O) and concentrated *in vacuo*. The crude boronic ester was used in subsequent steps without purification.



Diisopropylcarbamate **254** (0.509 g, 1.7 mmol, 1.0 eq.) was dissolved in anhydrous Et_2O (7 mL) and the solution cooled to −78 °C (dry ice/acetone). TMEDA (0.38 mL, 2.6 mmol, 1.5 eq.) was added dropwise (~0.5 mL/min) to the solution, followed by *sec*-butyl lithium (1.3 M in cyclohexane/hexane 92:8; 1.7 mL, 2.3 mmol, 1.3 eq.) dropwise (~0.5 mL/min). The

reaction mixture was stirred at −78 °C for 30 minutes whereupon a solution of the crude boronic ester (1 M in Et_2O; 1.5 eq.) was added dropwise (~0.5 mL/min). Following stirring at −78 °C for 30 minutes, $MgBr_2$ (1 M in MeOH; 2.8 mL, 1.7 eq.) was added at this temperature. The reaction mixture was then warmed to rt and stirred at this temperature for 1 hour. The reaction mixture was quenched with water (35 mL) and the aqueous layer extracted with Et_2O (3 × 35 mL). The combined organics were washed with brine (35 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude reaction mixture was purified by flash column chromatography (pentane/Et_2O 100:1 to 20:1) to give the product (0.722 g, 88%, 96:4 e.r.) as a colourless oil.

The e.r. of boronic ester **237** could not be determined by chiral HPLC/SFC. Instead, the boronic ester was oxidised and the e.r. of alcohol **237'** was determined.

$\mathbf{R_f}$ = 0.31 (pentane/Et_2O 95:5).

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$**:** –19 (*c* = 2.1, CH_2Cl_2).

NMR Spectroscopy:

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 6.98 (d, $^4J_{HH}$ = 2.2 Hz, 1H, H_G), 6.92 (ddd, $^3J_{HH}$ = 8.2 Hz, $^4J_{HH}$ = 2.2 Hz, *J* = 0.8 Hz, 1H, H_D), 6.69 (d, $^3J_{HH}$ = 8.2 Hz, 1H, H_C), 5.93 (apparent q, $^4J_{HH}$ = $^2J_{HH}$ = 1.4 Hz, 1H, H_Q), 5.62 (dd, $^2J_{HH}$ = 1.5 Hz, $^4J_{HH}$ = 0.7 Hz, 1H, $H_{Q'}$), 3.76 (s, 3H, H_A), 2.32–2.25 (m, 5H, $H_{F,\ O,\ O'}$), 1.78 (ddd, J_{HH} = 13.4, 12.3, 4.7 Hz, 1H, H_M), 1.61 (ddd, J_{HH} = 13.4, 12.2, 4.5 Hz, 1H, $H_{M'}$), 1.56–1.43 (m, 2H, $H_{N,\ N'}$), 1.26 (s, 3H, H_J), 1.24 (s, 6H, H_K), 1.23 (s, 6H, $H_{K'}$) ppm;

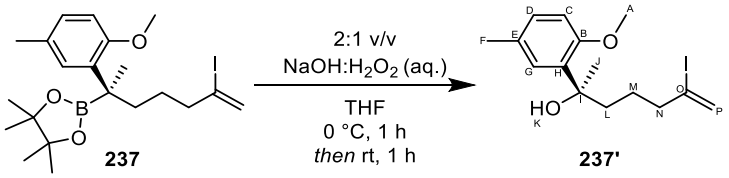
^{13}C NMR (101 MHz, $CDCl_3$): δ_C 154.5 (C_B), 135.5 (C_H), 129.6 (C_E), 127.4 (C_G), 126.6 (C_D), 124.9 (C_Q), 113.0 (C_P), 109.6 (C_C), 82.8 (C_L), 54.9 (C_A), 46.1 (C_O), 35.0 (C_M), 24.9 (C_K), 24.9 ($C_{K'}$), 24.3 (C_N), 21.0 (C_F *or* C_J), 21.0 (C_F *or* C_J) ppm; C_I not observed due to quadrupolar relaxation;

^{11}B NMR (128 MHz, $CDCl_3$): δ_B 33.5 ppm.

IR (film): ν_{max} 2969, 2932, 1690, 1503, 1436, 1368, 1288, 1249, 1217, 1135, 1068, 1048 cm^{-1}.

HRMS (EI): m/z calc'd for $C_{21}H_{32}O_3{}^{11}BI$ $[M]^+$ 470.1584 found 470.1486.

(*R*)-6-Iodo-2-(2-methoxy-5-methylphenyl)hept-6-en-2-ol (237')



According to **General Procedure D**, boronic ester **237** (24 mg, 0.05 mmol, 1.0 eq.) was reacted with a 2 M aqueous solution of NaOH (0.33 mL) and aqueous H_2O_2 (30% w/w; 0.17 mL) at 0 °C in THF (0.33 mL). The crude reaction mixture was purified by flash column chromatography (pentane/EtOAc 10:1) to give the product (14 mg, 76%, 96:4 e.r.) as a colourless oil.

R_f = 0.23 (pentane/EtOAc 10:1).

$[\alpha]_D^{25}$: –3 (*c* = 2.1, CH_2Cl_2).

NMR Spectroscopy:

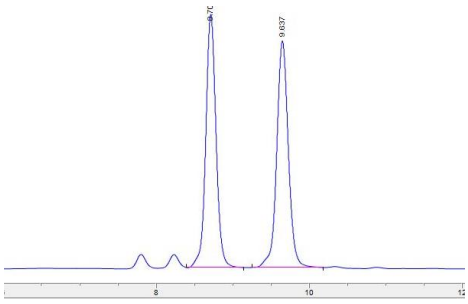
^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.10–7.07 (m, 1H, H_G), 7.05–7.00 (m, 1H, H_D), 6.81 (d, $^3J_{HH}$ = 8.3 Hz, 1H, H_C), 5.98 (apparent q, $^4J_{HH}$ = $^2J_{HH}$ = 1.4 Hz, 1H, H_P), 5.67 (dd, $^2J_{HH}$ = 1.4 Hz, $^4J_{HH}$ = 0.7 Hz, 1H, $H_{P'}$), 4.07 (s, 1H, H_K), 3.87 (s, 3H, H_A), 2.35 (t, $^3J_{HH}$ = 7.1, 2H, $H_{N, N'}$), 2.30 (s, 3H, H_F), 1.92 (ddd, $^2J_{HH}$ = 13.5 Hz, $^3J_{HH}$ = 11.8, 4.8 Hz, 1H, H_L), 1.78 (ddd, $^2J_{HH}$ = 13.5 Hz, $^3J_{HH}$ = 11.5, 5.1 Hz, 1H, $H_{L'}$), 1.57 (s, 3H, H_J), 1.55–1.49 (m, 1H, H_M), 1.49–1.39 (m, 1H, $H_{M'}$) ppm;

^{13}C NMR (101 MHz, $CDCl_3$): δ_C 154.8 (C_B), 134.3 (C_H), 130.1 (C_E), 128.3 (C_D), 127.5 (C_G), 125.4 (C_P), 112.6 (C_O), 111.4 (C_C), 74.9 (C_I), 55.5 (C_A), 45.4 (C_N), 40.5 (C_L), 27.5 (C_J), 23.9 (C_M), 20.8 (C_F) ppm.

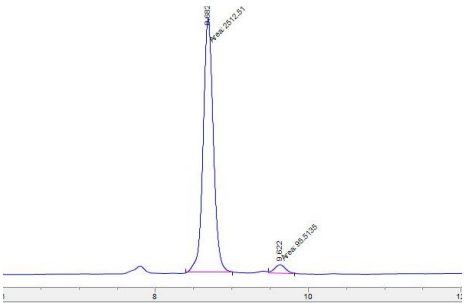
IR (film): ν_{max} 3438 (OH), 2933, 2863, 1619, 1499, 1458, 1364, 1236, 1142, 1033 cm^{-1}.

HRMS (EI): m/z calc'd for $C_{15}H_{21}IO_2$ $[M–H_2O]^+$ 342.0475 found 342.0473.

Chiral HPLC (IC column, 95:5 hexane/IPA, 0.7 mL/min, rt, 254 nm): 8.7 min (major), 9.6 min (minor), 96:4 e.r.

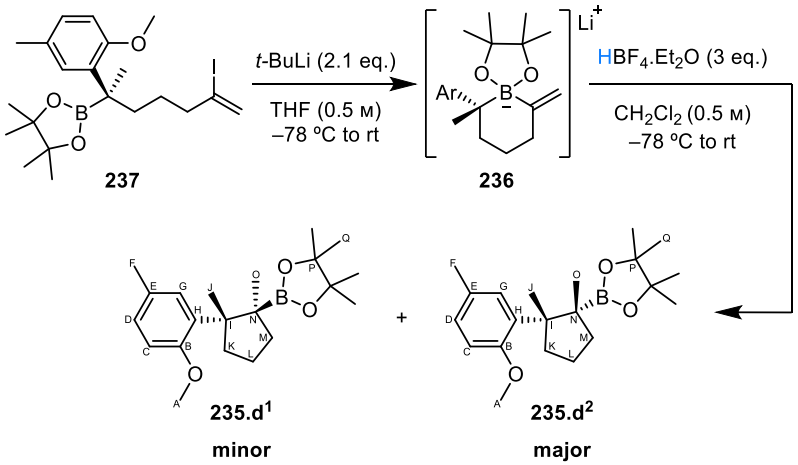


#	Time	Type	Area	Height	Width	Area%	Symmetry
1	8.702	VB	1643.2	176.5	0.1421	49.715	0.931
2	9.637	BB	1662	157.7	0.1645	50.285	0.927



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	8.682	MM	2512.5	267.9	0.1563	96.338	0.93
2	9.622	MM	95.5	9.3	0.1711	3.662	0.884

2-((1S,2S)-2-(2-Methoxy-5-methylphenyl)-1,2-dimethylcyclopentyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (235)



tert-Butyl lithium (1.7 M in pentane; 1.1 mL, 1.9 mmol, 2.1 eq.) was added dropwise (~0.5 }mL/min) to a solution of boronic ester **237** (0.433 g, 0.92 mmol, 1.0 eq.; 96:4 e.r.) in anhydrous THF (1.8 mL, 0.5 M) at −78 °C (dry ice/acetone) and allowed to stir at this temperature for 1 hour. The cooling bath was removed, and the reaction was stirred at rt for a further 1 hour. After this time the solvent was removed *in vacuo* at rt and CH_2Cl_2 (1.8 mL, 0.5 M) was added. The reaction mixture was cooled again to −78 °C (dry ice/acetone) whereupon tetrafluoroboric acid diethyl ether complex (0.38 mL, 2.8 mmol, 3.0 eq.) was added dropwise (~0.5 mL/min). The reaction mixture was stirred at −78 °C for 2 hours and slowly warmed to rt overnight (the replenishment of dry ice in the cooling bath was halted). The reaction mixture was diluted with Et_2O (5 mL) and quenched with saturated aqueous $NaHCO_3$ (5 mL). The aqueous layer was extracted with Et_2O (3 × 5 mL), and the combined organics washed with brine (5 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude residue was analysed by ^1H NMR to determine that the product was formed in 85:15 diastereomeric ratio. The crude reaction mixture was then purified by flash column chromatography

(pentane/CH_2Cl_2 4:1) to afford the product boronic ester (major d^2: 0.126 g, 0.37 mmol, 39%; minor d^1: 0.0212 g, 0.06 mmol, 7%) in 46% combined yield.

Major diastereomer (d^2):

R_f = 0.33 (pentane/CH_2Cl_2 3:1).

$[\alpha]_D^{25}$**:** –29 (*c* = 2.1, CH_2Cl_2).

NMR Spectroscopy:

^{1}H NMR (500 MHz, $CDCl_3$): δ_H 7.07 (d, $^4J_{HH}$ = 2.2 Hz, 1H, H_G), 6.93 (ddd, $^3J_{HH}$ = 8.2 Hz, $^4J_{HH}$ = 2.2 Hz, *J* = 0.8 Hz, 1H, H_D), 6.75 (d, $^3J_{HH}$ = 8.2 Hz, 1H, H_C), 3.78 (s, 3H, H_A), 2.32–2.24 (m, 5H, $H_{F,\,K,\,K'}$), 1.91–1.84 (m, 1H, H_M), 1.76–1.64 (m, 2H, $H_{L,\,L'}$), 1.61–1.51 (m, 1H, $H_{M'}$), 1.27 (s, 3H, H_O), 1.21 (s, 3H, H_J), 1.14 (s, 6H, H_Q), 1.02 (s, 6H, $H_{Q'}$) ppm;

^{13}C NMR (126 MHz, $CDCl_3$): δ_C 156.2 (C_B), 138.7 (C_H), 128.5 (C_E), 128.4 (C_G), 126.6 (C_D), 111.6 (C_C), 82.3 (C_P), 55.1 (C_A), 50.2 (C_I), 39.5 (C_K), 37.5 (C_M), 24.6 (C_Q), 24.5 ($C_{Q'}$), 21.6 (C_J), 21.0 (C_L), 20.8 (C_F), 20.5 (C_O) ppm; C_N not observed due to quadrupolar relaxation;

^{11}B NMR (128 MHz, $CDCl_3$): δ_B 34.6 ppm.

IR (film): ν_{max} 2975, 2941, 2869, 2831, 1498, 1464, 1378, 1353, 1296, 1286, 1144, 1127 cm^{-1}.

HRMS (EI): m/z calc'd for $C_{21}H_{33}O_3{}^{11}B$ $[M]^+$ 344.2517 found 344.2514.

Minor diastereomer (d^1):

R_f = 0.24 (pentane/CH_2Cl_2 3:1).

$[\alpha]_D^{25}$**:** –6 (*c* = 2.1, CH_2Cl_2).

NMR Spectroscopy:

^{1}H NMR (500 MHz, $CDCl_3$): δ_H 7.10 (d, $^4J_{HH}$ = 2.2 Hz, 1H, H_G), 6.95 (ddd, $^3J_{HH}$ = 8.2 Hz, $^4J_{HH}$ = 2.2 Hz, *J* = 0.8 Hz, 1H, H_D), 6.76 (d, $^3J_{HH}$ = 8.2 Hz, 1H, H_C), 3.81 (s, 3H, H_A), 2.31–2.22 (m, 4H, $H_{F,\,K}$), 2.20–2.11 (m, 1H, H_M), 1.97–1.90 (m, 1H, $H_{K'}$), 1.82–1.73 (m, 2H, $H_{L,\,L'}$), 1.45–1.37 (m, 1H, $H_{M'}$), 1.31 (s, 6H, H_Q), 1.30 (s, 3H, H_J), 1.27 (s, 6H, $H_{Q'}$), 0.71 (s, 3H, H_O) ppm;

^{13}C NMR (126 MHz, $CDCl_3$): δ_C 155.3 (C_B), 137.9 (C_H), 129.7 (C_G), 129.3 (C_E), 126.7 (C_D), 111.6 (C_C), 82.1 (C_P), 55.5 (C_A), 52.9 (C_I), 38.9 (C_K), 37.5 (C_M), 27.5 (C_J), 25.7 (C_Q),

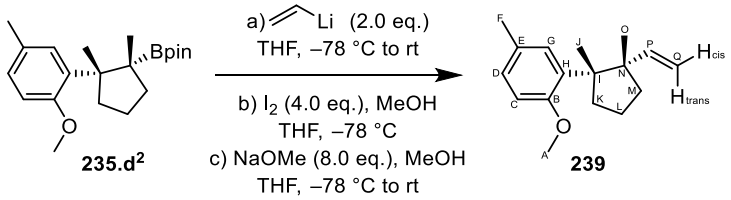
24.5 ($C_{Q'}$), 22.3 (C_O), 21.2 (C_L), 20.8 (C_F) ppm; C_N not observed due to quadrupolar relaxation;

^{11}B NMR (128 MHz, $CDCl_3$): δ_B 34.2 ppm.

IR (film): ν_{max} 2929, 2871, 1499, 1462, 1370, 1350, 1290, 1236, 1146 cm^{-1}.

HRMS (EI): m/z calc'd for $C_{21}H_{33}O_3{}^{11}B$ $[M]^+$ 344.2517 found 344.2511.

2-((1*S*,2*S*)-1,2-Dimethyl-2-vinylcyclopentyl)-1-methoxy-4-methylbenzene (239)



According to a modified literature procedure,[15] boronic ester **235.d²** (123 mg, 0.36 mmol, 1.0 eq.) was dissolved in anhydrous THF (5.8 mL) and cooled to −78 °C (dry ice/acetone). To this solution, a solution of vinyllithium[a] (0.50 M in THF; 1.4 mL, 0.71 mmol, 2.0 eq.) was added dropwise (~0.5 mL/min). The reaction mixture was warmed to rt and stirred at this temperature for 30 minutes. It was then cooled to −78 °C and a solution of iodine (361 mg, 1.4 mmol, 4.0 eq.) in MeOH (1.4 mL) was added dropwise (~0.5 mL/min). The reaction mixture was stirred at −78 °C for 30 minutes whereupon NaOMe (0.5 M in MeOH; 5.7 mL, 2.9 mmol, 8.0 eq.) was added dropwise (~0.5 mL/min). The reaction mixture was warmed to rt and stirred at this temperature for an hour, after which time it was quenched with a saturated aqueous solution of $Na_2S_2O_3$ (5 mL). The aqueous layer was extracted with Et_2O (3 × 5 mL), and the combined organic extracts were washed with brine (5 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude reaction mixture was purified by flash column chromatography (pentane/CH_2Cl_2 50:1 to 33:1) to yield the product (67 mg, 77%) as a colourless oil.

[a] Vinyllithium (in THF) was prepared according to a literature procedure and titrated against *N*-benzylbenzamide before use.[40]

R_f = 0.20 (pentane/CH_2Cl_2 50:1).

$[\alpha]_D^{25}$: –34 (*c* = 2.1, CH_2Cl_2).

NMR Spectroscopy:

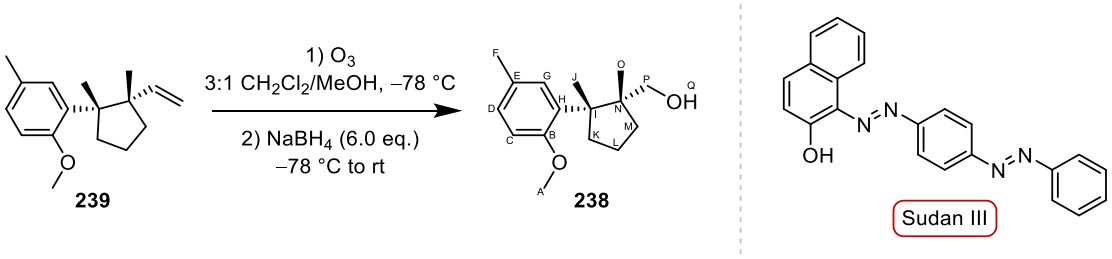
^{1}H NMR (500 MHz, $CDCl_3$): δ_H 7.13 (d, $^4J_{HH}$ = 2.2 Hz, 1H, H_G), 7.00 (dd, $^3J_{HH}$ = 8.2 Hz, $^4J_{HH}$ = 2.2 Hz, 1H, H_D), 6.77 (d, $^3J_{HH}$ = 8.2 Hz, 1H, H_C), 5.73 (dd, $^3J_{HH(trans)}$ = 17.5 Hz, $^3J_{HH(cis)}$ = 10.8 Hz, 1H, H_P), 4.89 (dd, $^3J_{HH(trans)}$ = 17.5 Hz, $^2J_{HH}$ = 1.6 Hz, 1H, H_{Qtrans}), 4.76 (dd, $^3J_{HH(cis)}$ = 10.8 Hz, $^2J_{HH}$ = 1.6 Hz, 1H, H_{Qcis}), 3.76 (s, 3H, H_A), 2.50–2.40 (m, 1H, H_K), 2.31 (s, 3H, H_F), 1.98–1.90 (m, 1H, $H_{K'}$), 1.89–1.68 (m, 4H, $H_{L, L', M, M'}$), 1.42 (s, 3H, H_J), 1.33 (s, 3H, H_O) ppm;

^{13}C NMR (126 MHz, $CDCl_3$): δ_C 156.6 (C_B), 147.6 (C_P), 135.5 (C_H), 129.7 (C_G), 128.6 (C_E), 127.1 (C_D), 111.5 (C_C), 108.8 (C_Q), 54.8 (C_A), 51.3 (C_I), 50.6 (C_N), 39.4 (C_K *or* C_M), 39.3 (C_K *or* C_M), 22.8 (C_J), 22.2 (C_O), 20.9 (C_F), 20.5 (C_L) ppm.

IR (film): ν_{max} 2952, 2875, 1638, 1498, 1465, 1243, 1176, 1063, 1034 cm^{-1}.

HRMS (EI): m/z calc'd for $C_{17}H_{24}O$ $[M]^+$ 244.1822 found 244.1821.

((1*R*,2*S*)-2-(2-Methoxy-5-methylphenyl)-1,2-dimethylcyclopentyl)methanol (238)



According to a modified literature procedure,[203] Sudan III indicator was added to alkene **239** (28 mg, 0.12 mmol, 1.0 eq.) dissolved in 3:1 CH_2Cl_2/MeOH (2.0 mL). The resultant pale red solution was cooled to –78 °C (dry ice/acetone) and ozone was bubbled (at half the maximum output level) through the solution at this temperature until the pale red colour disappeared.

Sudan III is a red diazo compound which reacts with ozone to give a colourless product. Since Sudan III typically reacts with ozone slower than alkenes do, only upon full consumption of ***239*** *did the colour change occur.*

Dry nitrogen was then bubbled through the solution for 1 hour at –78 °C, whereupon $NaBH_4$ (13 mg, 0.35 mmol, 3.0 eq.) was added in one portion and the reaction monitored by TLC. The solution was stirred at –78 °C for 1.5 hours, at which time a further portion of $NaBH_4$ (13 mg, 0.35 mmol, 3.0 eq.) was added. After a further 30 minutes at –78 °C, the reaction mixture was warmed to 0 °C (ice/water) for 1 hour and then to rt for 30 minutes. After this time, the reaction was diluted with EtOAc (5 mL) and quenched with water (5 mL). The aqueous layer was extracted with EtOAc (3 × 5 mL), and the combined organic extracts were washed with brine

(5 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude reaction mixture was purified by flash column chromatography (pentane/EtOAc 10:1) to yield the product (12 mg, 41%, 96:4 e.r.) as a colourless oil.

$\mathbf{R_f}$ = 0.12 (pentane/EtOAc 10:1).

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$**:** –12 (*c* = 1.8, CH_2Cl_2).

NMR Spectroscopy:

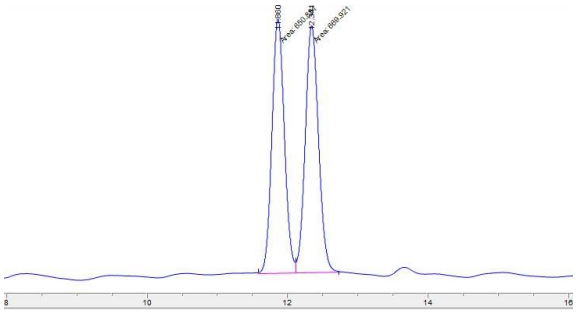
^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.09 (d, $^4J_{HH}$ = 2.2 Hz, 1H, H_G), 7.01 (ddd, $^3J_{HH}$ = 8.2 Hz, $^4J_{HH}$ = 2.2 Hz, *J* = 0.7 Hz, 1H, H_D), 6.80 (d, $^3J_{HH}$ = 8.2 Hz, 1H, H_C), 3.80 (s, 3H, H_A), 3.12 (s, 2H, H_P), 2.50–2.39 (m, 1H, H_K), 2.28 (s, 3H, H_F), 1.95–1.56 (m, 5H, $H_{K', L, L', M}$), 1.41 (s, 3H, H_J), 1.40–1.33 (m, 1H, $H_{M'}$), 1.20 (s, 3H, H_O) ppm; H_Q not observed;

^{13}C NMR (101 MHz, $CDCl_3$): δ_C 156.3 (C_B), 135.3 (C_H), 129.9 (C_E), 129.4 (C_G), 127.8 (C_D), 112.1 (C_C), 70.6 (C_P), 55.3 (C_A), 50.4 (C_I), 49.0 (C_N), 42.0 (C_K), 37.2 (C_M), 24.1 (C_J), 21.3 (C_L), 21.0 (C_F *or* C_O), 20.9 (C_F *or* C_O) ppm.

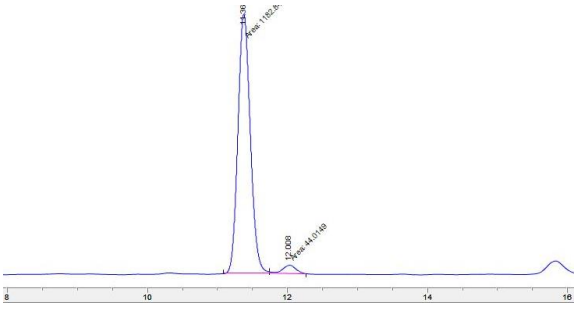
IR (film): ν_{max} 3439 (br), 2945, 2877, 1498, 1465, 1245, 1175, 1068, 1030 cm^{-1}.

HRMS (ESI): m/z calc'd for $C_{16}H_{24}O_2$ $[M+H]^+$ 249.1849 found 249.1847.

Chiral HPLC (IC column, 97:3 hexane/IPA, 0.7 mL/min, rt, 254 nm): 11.4 min (major), 12.0 min (minor), 96:4 e.r.

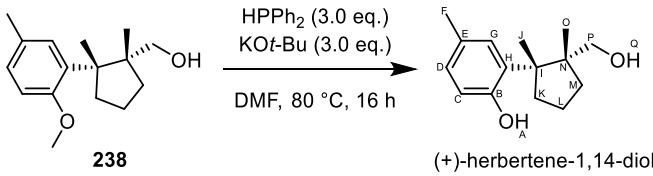


#	Time	Type	Area	Height	Width	Area%	Symmetry
1	11.86	MF	650.9	52.7	0.2058	49.279	0
2	12.341	FM	669.9	51.1	0.2183	50.721	0.909



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	11.36	MF	1182.8	96.2	0.2048	96.412	0.87
2	12.008	FM	44	3.2	0.2292	3.588	1.059

(+)-Herbertene-1,14-diol



238 (+)-herbertene-1,14-diol

According to a modified literature procedure,[204] anhydrous potassium *tert*-butoxide (16 mg, 0.14 mmol, 3.0 eq.) was dissolved in anhydrous DMF (50 µL) at rt and diphenylphosphine (25 µL, 0.14 mmol, 3.0 eq.) was added dropwise. Upon addition of diphenylphosphine the colourless solution turned bright red. The mixture was stirred at rt for 10 minutes, after which time methyl ether **238** (12 mg, 0.05 mmol, 1.0 eq.) was added as a solution in DMF (50 µL) and the reaction mixture was heated to 80 ºC for 16 hours. The reaction mixture was then diluted with CH_2Cl_2 (1 mL) and brine (5 mL) was added. By adding aqueous 2 M HCl, the aqueous layer was adjusted to pH 1–2 and then extracted with CH_2Cl_2 (3 × 5 mL) and the combined organic extracts were washed with brine (5 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude reaction mixture was purified by flash column chromatography (pentane/EtOAc 9:1 to 4:1) to yield the natural product (6.5 mg, 58%, 96:4 e.r.) as a white solid.

R_f = 0.13 (pentane/EtOAc 9:1).

$[\alpha]_D^{25}$: +9.6 (*c* = 1.00, $CHCl_3$).

Literature values: $[\alpha]_D^{21}$*: +33.5 (c = 0.19, CHCl₃);*[5] $[\alpha]_D^{27}$*: +15.5 (c = 1.14, CHCl₃);*[110] $[\alpha]_D^{25}$*: +11.8 (c = 1.00, CHCl₃).*[112]

NMR Spectroscopy:

^{1}H NMR (500 MHz, $CDCl_3$): δ_H 6.96 (d, $^4J_{HH}$ = 2.1 Hz, 1H, H_G), 6.91 (ddd, $^3J_{HH}$ = 8.0 Hz, $^4J_{HH}$ = 2.1 Hz, *J* = 0.8 Hz, 1H, H_D), 6.73 (d, $^3J_{HH}$ = 8.0 Hz, 1H, H_C), 3.36 (d, $^2J_{HH}$ = 11.0 Hz, 1H, H_P), 3.28 (d, $^2J_{HH}$ = 11.0 Hz, 1H, $H_{P'}$), 2.52–2.38 (m, 1H, H_K), 2.27 (s, 3H, H_F), 1.98–1.77 (m, 3H, $H_{K', L, L'}$), 1.56 (s, 3H, H_J), 1.50–1.41 (m, 1H, H_M), 1.32–1.25 (m, 1H, $H_{M'}$), 1.23 (s, 3H, H_O) ppm; H_Q not observed;

^{13}C NMR (125 MHz, $CDCl_3$): δ_C 153.2 (C_B), 132.9 (C_H), 129.8 (C_G), 129.3 (C_E), 128.1 (C_D), 118.2 (C_C), 70.8 (C_P), 50.9 (C_I), 48.9 (C_N), 42.4 (C_K), 36.0 (C_M), 24.0 (C_J), 21.2 (C_L), 21.0 (C_F), 20.4 (C_O) ppm.

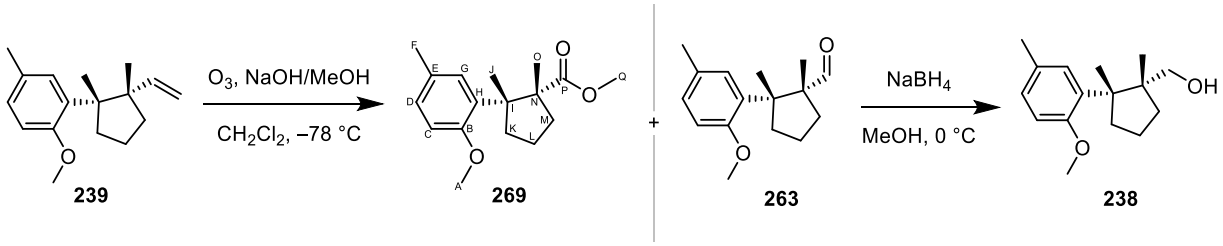
IR (film): ν_{max} 3205 (br), 2956, 2927, 2878, 1463, 1411, 1276, 1260, 1023 cm^{-1}.

HRMS (Negative ion nanospray): m/z calc'd for $C_{15}H_{21}O_2$ $[M–H]^-$ 233.1542 found 233.1546.

All recorded spectroscopic data matched those previously reported in the literature.[112]

6.3.2. Formal total synthesis of (+)-herbertene-1,14-diol

Methyl (1*R*,2*R*)-2-(2-methoxy-5-methylphenyl)-1,2-dimethylcyclopentane-1-carboxylate (269)



According to a modified literature procedure,[205] alkene **239** (24 mg, 0.10 mmol, 1.0 eq.) was dissolved in anhydrous CH_2Cl_2 (2.5 mL) and 2.5 M NaOH in MeOH (0.63 mL) was added dropwise (~0.5 mL/min) at rt. The solution was cooled to −78 °C (dry ice/acetone) and ozone was bubbled through the solution for 3 hours. It was important to have a low output level of ozone to limit decomposition. The reaction progress was monitored by TLC, with the reaction stopped and any excess ozone purged with a flow of oxygen once all starting material had been consumed. The reaction mixture was then diluted with EtOAc (5 mL) and water (5 mL) at −78 °C and then warmed to rt. The aqueous layer was extracted with EtOAc (3 × 5 mL), and the combined organic extracts were washed with brine (5 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude reaction mixture was purified by flash column chromatography (pentane/EtOAc 20:1) to yield methyl ester **269** as a mixture with aldehyde **263** (2:1 **269**/**263**). The mixture was dissolved in anhydrous MeOH (0.20 mL), cooled to 0 °C (ice/water) and $NaBH_4$ (3 mg) was added, selectively reducing aldehyde **263** to yield alcohol **238**, separable from **269** by flash column chromatography (pentane/EtOAc 9:1). Methyl ester **269** (9 mg, 32%, 96:4 e.r.) was isolated as a colourless oil alongside alcohol **238** (3 mg, 13%, 96:4 e.r.).

$\mathbf{R_f}$ = 0.43 (pentane/EtOAc 95:5).

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$**:** –32 (*c* = 1.2, CH_2Cl_2).

NMR Spectroscopy:

^{1}H NMR (500 MHz, $CDCl_3$): δ_H 7.03 (d, $^4J_{HH}$ = 2.2 Hz, 1H, H_G), 6.93 (ddd, $^3J_{HH}$ = 8.2 Hz, $^4J_{HH}$ = 2.2 Hz, *J* = 0.7 Hz, 1H, H_D), 6.70 (d, $^3J_{HH}$ = 8.2 Hz, 1H, H_C), 3.72 (s, 3H, H_A), 3.19 (s, 3H, H_Q), 2.62 (apparent dt, J_{HH} = 12.0, 9.1 Hz, 1H, H_K), 2.29–2.19 (m, 1H, H_M), 2.25 (s, 3H, H_F), 1.92–1.86 (m, 1H, $H_{K'}$), 1.86–1.75 (m, 2H, $H_{L, L'}$), 1.71–1.62 (m, 1H, $H_{M'}$),

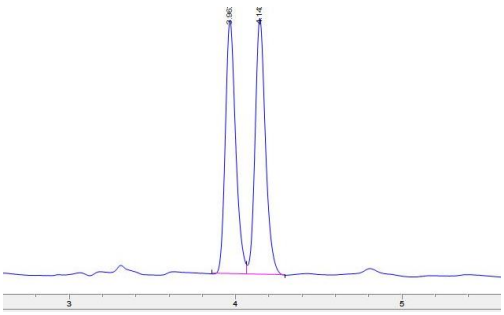
1.45 (s, 3H, H_O), 1.36 (s, 3H, H_J) ppm;

^{13}C NMR (126 MHz, $CDCl_3$): δ_C 178.2 (C_P), 155.8 (C_B), 136.0 (C_H), 128.8 (C_E), 128.2 (C_G), 127.2 (C_D), 111.0 (C_C), 55.8 (C_N), 54.7 (C_A), 52.3 (C_I), 50.8 (C_Q), 40.9 (C_K), 40.1 (C_M), 23.9 (C_J), 22.0 (C_L), 21.6 (C_O), 20.8 (C_F) ppm.

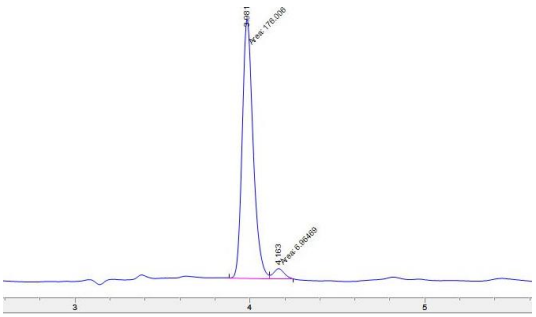
IR (film): ν_{max} 2946, 1728 (C=O), 1500, 1463, 1380, 1249, 1197, 1172, 1138, 1033 cm^{-1}.

HRMS (EI): m/z calc'd for $C_{17}H_{24}O_3$ $[M]^+$ 276.1720 found 276.1717.

Chiral HPLC (AD-H column, 97:3 hexane/IPA, 1 mL/min, rt, 230 nm): 4.0 min (major), 4.2 min (minor), 96:4 e.r.



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	3.962	BV	146.2	33.8	0.0655	49.737	0.769
2	4.142	VB	147.7	34.1	0.066	50.263	0.792



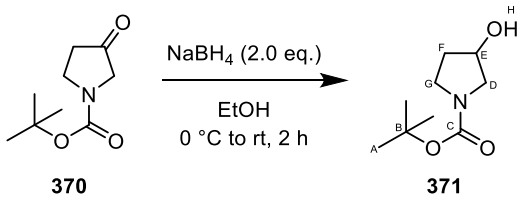
#	Time	Type	Area	Height	Width	Area%	Symmetry
1	3.981	MF	176	40.3	0.0727	96.194	0.773
2	4.163	FM	7	1.6	0.0723	3.806	0.913

All recorded spectroscopic data matched those previously reported in the literature.[108]

6.4. Synthetic procedures – Chapter 4

6.4.1. Synthesis of 1-azabicyclo[2.1.0]pentane (ABP) precursors

***tert*-Butyl 3-hydroxypyrrolidine-1-carboxylate (371)**



Sodium borohydride (1.54 g, 41 mmol, 2.0 eq.) was added portion wise over 5 minutes to a solution of *N*-Boc-3-pyrrolidinone (**370**) (3.77 g, 20 mmol, 1.0 eq.) in anhydrous ethanol (39 mL) at 0 °C (ice/water). The reaction mixture was then warmed to rt and stirred for 2 hours, after which time TLC analysis indicated full conversion. The reaction mixture was diluted with EtOAc (50 mL), and water (50 mL) was added. The aqueous layer was extracted with EtOAc (3 × 50 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude product (3.73 g, 98%) was used in subsequent steps without purification.

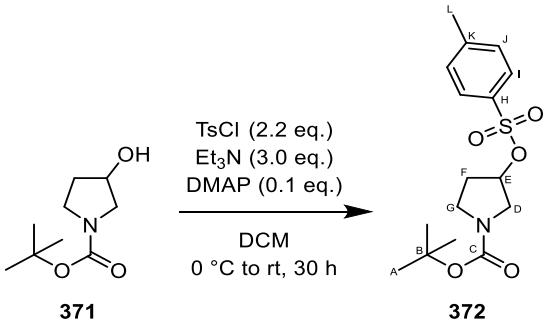
NMR Spectroscopy:

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 4.48–4.36 (m, 1H, H_E), 3.52–3.18 (m, 4H, $H_{D,\,D',\,G,\,G'}$), 2.16 (br s, 1H, H_H), 2.09–1.82 (m, 2H, $H_{F,\,F'}$), 1.45 (s, 9H, H_A) ppm;

^{13}C NMR (101 MHz, $CDCl_3$): δ_C 154.8 (C_C), 79.4 (C_B), 71.2 (C_E), 70.3 (C_E), 54.3 (C_D), 54.2 (C_D), 43.9 (C_G), 43.5 (C_G), 34.1 (C_F), 33.7 (C_F), 28.5 (C_A) ppm; *doubling of peaks due to the presence of rotamers*.

All recorded spectroscopic data matched those previously reported in the literature.[206]

***tert*-Butyl 3-(tosyloxy)pyrrolidine-1-carboxylate (372)**



To a solution of **371** (3.57 g, 19 mmol, 1.0 eq.) in anhydrous CH_2Cl_2 (70 mL) at 0 °C (ice/water), triethylamine (4.0 mL, 29 mmol, 1.5 eq.), DMAP (0.116 g, 0.95 mmol, 0.05 eq.) and then tosyl chloride (4.00 g, 21 mmol, 1.1 eq.) were added sequentially. The reaction was gradually warmed to rt (the ice bath was not replenished) overnight. After this time, TLC analysis indicated incomplete conversion and so triethylamine (4.0 mL, 29 mmol, 1.5 eq.), DMAP (0.116 g, 0.95 mmol, 0.05 eq.) and then tosyl chloride (4.00 g, 21 mmol, 1.1 eq.) were added sequentially at 0 °C and the reaction stirred at rt over a subsequent night. Again, TLC analysis indicated incomplete conversion, however the reaction mixture was diluted with saturated aqueous NaOH (100 mL) and the extracted with EtOAc (3 × 100 mL). The combined organic layers were washed with water (100 mL) and brine (100 mL), then dried over $MgSO_4$ and concentrated *in vacuo*. Crude ^{1}H NMR spectroscopic analysis indicated a 1:7 mixture of starting material/product. The crude reaction mixture was purified by flash column chromatography (3:2 pentane/EtOAc) to give the product (5.14 g, 83%) as an off-white solid.

R_f = 0.44 (pentane/EtOAc 7:3).

NMR Spectroscopy:

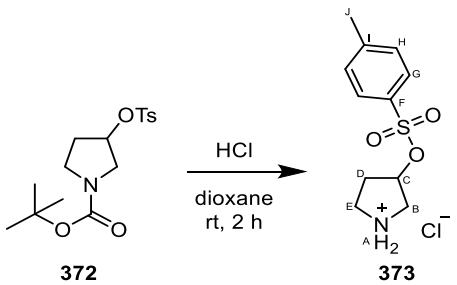
^{1}H NMR (500 MHz, $CDCl_3$): δ_H 7.77 (d, $^3J_{HH}$ = 7.9 Hz, 2H, H_I), 7.34 (d, $^3J_{HH}$ = 7.9 Hz, 2H, H_J), 5.07–4.96 (m, 1H, H_E), 3.53–3.35 (m, 4H, $H_{D, D', G, G'}$), 2.43 (s, 3H, H_L), 2.21–1.86 (m, 2H, $H_{F, F'}$), 1.41 (s, 9H, H_A) ppm;

^{13}C NMR (125 MHz, $CDCl_3$): δ_C 154.1 (C_C), 154.0 (C_C), 145.0 (C_K), 133.9 (C_H), 133.7 (C_H), 130.0 (C_J), 127.7 (C_I), 80.8 (C_B), 80.0 (C_B), 79.7 (C_E), 51.8 (C_D), 51.4 (C_D), 43.6 (C_G), 43.2 (C_G), 32.4 (C_F), 31.3 (C_F), 28.4 (C_A), 21.6 (C_L) ppm; *doubling of peaks due to the presence of rotamers*.

IR (film): ν_{max} 2976, 1693 (C=O), 1403, 1363, 1172, 1115, 895 cm^{-1}.

HRMS (ESI): m/z calc'd for $C_{16}H_{23}NNaO_5S$ $[M+Na]^+$ 364.1189 found 364.1194.

3-(Tosyloxy)pyrrolidine hydrochloride (373)



372 **373**

HCl (4.0 M in dioxane; 24 mL, 95 mmol) was added to a round bottom flask containing **372** (1.30 g, 4.0 mmol) and stirred at rt for 2 hours. After this time, the solvent was removed *in vacuo* and Et_2O (20 mL) was added. The sides of the flask were scratched with a spatula until a pale orange solid precipitated out. The solvent was removed *in vacuo*. Portions of Et_2O (3 × 20 mL) were added to the solid, the suspension sonicated and then the supernatant removed. The resultant pale orange solid was then dried for 2 hours under high vacuum. Pyrrolidine **373** was found to be hygroscopic and thus exposure to air was minimised during its handling. An isolated yield was not determined.

$\mathbf{R_f}$ = 0.26 (CH_2Cl_2/MeOH 9:1).

NMR Spectroscopy:

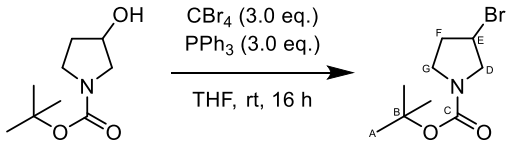
^{1}H NMR (400 MHz, $CDCl_3$): δ_H 9.92 (br s, 2H, H_A), 7.81 (d, $^3J_{HH}$ = 7.8 Hz, 2H, H_G), 7.36 (d, $^3J_{HH}$ = 7.8 Hz, 2H, H_H), 5.21–5.14 (m, 1H, H_C), 3.65–3.47 (m, 3H, $H_{B, B', E}$), 3.44–3.28 (m, 1H, $H_{E'}$), 2.44 (s, 3H, H_J), 2.29–2.09 (m, 2H, $H_{D, D'}$) ppm;

^{13}C NMR (101 MHz, $CDCl_3$): δ_C 145.7 (C_I), 132.8 (C_F), 130.3 (C_H), 128.0 (C_G), 78.6 (C_C), 50.6 (C_B), 43.9 (C_E), 31.8 (C_D), 21.7 (C_J) ppm.

IR (film): ν_{max} 3382 (br), 2979, 2902, 1633, 1361, 1173, 1066 cm^{-1}.

HRMS (ESI): m/z calc'd for $C_{11}H_{15}NO_3S$ $[M+H]^+$ 242.0845 found 242.0847.

***tert*-Butyl 3-bromopyrrolidine-1-carboxylate (374)**



Triphenylphosphine (14.7 g, 56 mmol, 3.0 eq.) and tetrabromomethane (0.62 M in THF; 18.6 g, 56 mmol, 3.0 eq.) were added to a solution of **371** (3.00 g, 19 mmol, 1.0 eq.) dissolved in THF (90 mL) at rt. The reaction mixture was stirred at rt overnight, after which time the solvent was removed and EtOAc (50 mL) was added. The white precipitate (Ph_3P=O) was removed by vacuum filtration and washed with EtOAc. The filtrate was added to a separating funnel containing water (50 mL) and the organic layer was retained, dried over $MgSO_4$ and concentrated *in vacuo*. The crude was purified by flash column chromatography (pentane/EtOAc 4:1) to give the product (3.57 g, 76%) as a lime-coloured oil which then crystalised on standing in the freezer.

$\mathbf{R_f}$ = 0.73 (pentane/EtOAc 1:1).

NMR Spectroscopy:

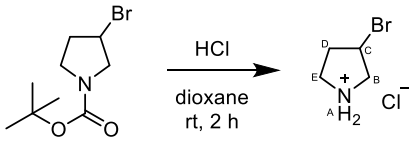
^{1}H NMR (500 MHz, $CDCl_3$): δ_H 4.42 (apparent tt, $^3J_{HH}$ = 7.8, 4.0 Hz, 1H, H_E), 3.80–3.67 (m, 1H, H_D), 3.67–3.60 (m, 1H, $H_{D'}$), 3.62–3.49 (m, 1H, H_G), 3.49–3.30 (m, 1H, $H_{G'}$), 2.34–2.23 (m, 1H, H_F), 2.23–2.10 (m, 1H, $H_{F'}$), 1.41 (s, 9H, H_A) ppm;

^{13}C NMR (125 MHz, $CDCl_3$): δ_C 154.3 (C_C), 154.2 (C_C), 79.6 (C_B), 79.6 (C_B), 55.8 (C_D), 55.4 (C_D), 47.1 (C_E), 46.8 (C_E), 44.1 (C_G), 43.8 (C_G), 36.5 (C_F), 35.7 (C_F), 28.4 (C_A) ppm; *doubling of peaks due to the presence of rotamers*.

IR (film): ν_{max} 2976, 1694 (C=O), 1401, 1366, 1163, 1111 cm^{-1}.

HRMS (ESI): m/z calc'd for $C_5H_9NO_2{}^{79}Br$ $[M–t\text{-Bu}+2H]^+$ 193.9811 found 193.9806.

3-Bromopyrrolidine hydrochloride (375)



374 **375**

HCl (4.0 M in dioxane; 24 mL, 95 mmol) was added to a round bottom flask containing **374** (1.00 g, 4.0 mmol) and stirred at rt for 2 hours. After this time, the solvent was removed *in vacuo* and Et_2O (20 mL) was added. A pale orange solid precipitated out and the supernatant Et_2O was removed. Portions of Et_2O (3 × 20 mL) were then added to the solid, the suspension sonicated and then the supernatant removed. The resultant pale orange solid was then dried for 2 hours under high vacuum. Pyrrolidine **375** was found to be hygroscopic and thus exposure to air was minimised during its handling. An isolated yield was not determined.

$\mathbf{R_f}$ = 0.12 (CH_2Cl_2/MeOH 9:1).

NMR Spectroscopy:

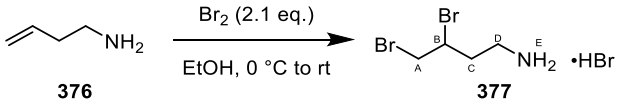
^{1}H NMR (500 MHz, $CDCl_3$): δ_H 10.09 (br s, 2H, H_A), 4.58 (apparent dq, $^3J_{HH}$ = 5.8, 2.8 Hz, 1H, H_C), 3.97–3.78 (m, 1H, H_B), 3.74–3.53 (m, 3H, $H_{B', E, E'}$), 2.53 (dtd, J_{HH} = 14.6, 8.9, 5.7 Hz, 1H, H_D), 2.39 (ddt, J_{HH} = 13.7, 6.5, 3.1 Hz, 1H, $H_{D'}$) ppm;

^{13}C NMR (125 MHz, $CDCl_3$): δ_C 54.0 (C_B), 44.0 (C_E), 43.4 (C_C), 35.9 (C_D) ppm.

IR (film): ν_{max} 3357 (br), 3003, 2759, 1629, 1441, 1236 cm^{-1}.

HRMS (ESI): m/z calc'd for $C_4H_8N^{79}Br$ $[M+H]^+$ 149.9913 found 149.9916.

3,4-Dibromobutan-1-amine hydrobromide (377)



376 **377**

According to a modified literature procedure,[179] bromine (0.11 mL, 2.1 mmol, 2.1 eq.) was added to anhydrous ethanol (0.27 mL) with stirring at 0 °C (ice/water). Homoallylamine (**376**) (92 µL, 1.0 mmol, 1.0 eq.) was then added dropwise at the same temperature. The reaction mixture was warmed to rt overnight (by halting replenishment of the ice bath). The precipitate that formed was washed with cold Et_2O and recrystallised from 20:1 EtOAc/MeOH to give the product (0.224 g, 72% → 1st crop: 117 mg; 2nd crop: 92 mg; 3rd crop: 16 mg) as a fine white powder.

$\mathbf{R_f}$ = 0.12 (CH_2Cl_2/MeOH 9:1).

NMR Spectroscopy:

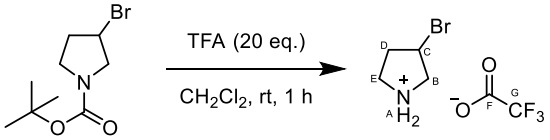
^{1}H NMR (400 MHz, CD_3OD): δ_H 4.40 (dddd, $^3J_{HH}$ = 10.0, 8.6, 4.5, 3.0 Hz, 1H, H_B), 3.97 (dd, $^2J_{HH}$ = 10.6 Hz, $^3J_{HH}$ = 4.5 Hz, 1H, H_A), 3.80 (dd, $^2J_{HH}$ = 10.6 Hz, $^3J_{HH}$ = 8.6 Hz, 1H, $H_{A'}$), 3.22 (ddd, $^2J_{HH}$ = 12.6 Hz, $^3J_{HH}$ = 10.1, 5.1 Hz, 1H, H_D), 3.12 (ddd, $^2J_{HH}$ = 12.6 Hz, $^3J_{HH}$ = 10.0, 5.9 Hz, 1H, $H_{D'}$), 2.55 (dddd, $^2J_{HH}$ = 14.7 Hz, $^3J_{HH}$ = 10.1, 5.9, 3.0 Hz, 1H, H_C), 2.17 (apparent dtd, $^2J_{HH}$ = 14.7 Hz, $^3J_{HH}$ = 10.0, 5.1 Hz, 1H, $H_{C'}$) ppm;

^{13}C NMR (101 MHz, CD_3OD): δ_C 49.8 (C_B), 39.2 (C_D), 37.1 (C_A), 35.2 (C_C) ppm.

IR (film): ν_{max} 3668, 3320 (br), 2983, 2901, 1394, 1251, 1066 cm^{-1}.

HRMS (ESI): m/z calc'd for $C_4H_9N^{79}Br_2$ $[M+H]^+$ 229.9175 found 229.9172.

3-Bromopyrrolidine trifluoroacetate (406)



374 **406**

Pyrrolidine **374** (0.500 g, 2.0 mmol, 1.0 eq.) was dissolved in anhydrous CH_2Cl_2 (22 mL) and trifluoroacetic acid (3.0 mL, 40 mmol, 20 eq.) was added dropwise (~1 mL/min) at rt. The resultant solution was stirred at rt for 1 hour, after which time the solvent was removed *in*

vacuo. A minimum amount of Et_2O was added to the amorphous solid to enable its dissolution. Pentane (10 mL) was then added, and a pale orange solid precipitated out. The suspension was sonicated and then the supernatant removed. Portions of pentane/Et_2O 9:1 (3 × 10 mL) were then added to the solid, the suspension sonicated and then the supernatant removed. The resultant pale orange solid was then dried for 2 hours under high vacuum. Pyrrolidine **406** was found to be hygroscopic and thus exposure to air was minimised during its handling. An isolated yield was not determined.

$\mathbf{R_f}$ = 0.29 (CH_2Cl_2/MeOH 9:1).

NMR Spectroscopy:

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 10.24 (br s, 2H, H_A), 4.58 (apparent tt, $^3J_{HH}$ = 5.5, 3.0 Hz, 1H, H_C), 3.78 (dd, J_{HH} = 13.1, 5.5 Hz, 1H, H_B), 3.67–3.56 (m, 2H, $H_{B', E}$), 3.56–3.46 (m, 1H, $H_{E'}$), 2.58–2.46 (m, 1H, H_D), 2.46–2.35 (m, 1H, $H_{D'}$) ppm;

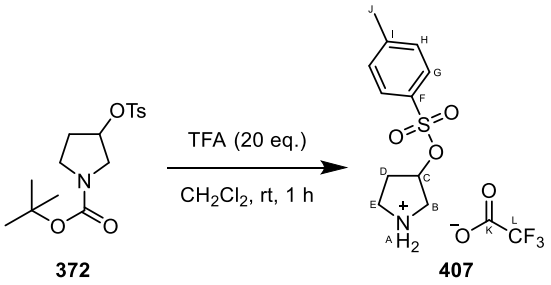
^{13}C NMR (125 MHz, $CDCl_3$): δ_C 162.8 (q, $^2J_{CF}$ = 35.3 Hz, C_F), 116.5 (q, $^1J_{CF}$ = 293.1 Hz, C_G), 54.0 (C_B), 43.9 (C_E), 43.5 (C_C), 35.9 (C_D) ppm;

^{19}F NMR (377 MHz, $CDCl_3$): δ_F −75.6 ppm.

IR (film): ν_{max} 2989 (br), 2585, 2432, 1668, 1617, 1422, 1237, 1175, 1124 cm^{-1}.

HRMS (ESI): m/z calc'd for $C_4H_8N^{79}Br$ $[M+H]^+$ 149.9913 found 149.9909.

3-(Tosyloxy)pyrrolidine trifluoroacetate (407)



372 **407**

Pyrrolidine **372** (0.325 g, 1.0 mmol, 1.0 eq.) was dissolved in anhydrous CH_2Cl_2 (22 mL) and trifluoroacetic acid (1.5 mL, 20 mmol, 20 eq.) was added dropwise (~1 mL/min) at rt. The resultant solution was stirred at rt for 1 hour, after which time the solvent was removed *in vacuo*. A minimum amount of Et_2O was added to the amorphous solid to enable its dissolution. Pentane (5 mL) was then added, and a pale orange solid precipitated out. The suspension was sonicated and then the supernatant removed. Portions of pentane/Et_2O 9:1 (3 × 5 mL) were then added to the solid, the suspension sonicated and then the supernatant removed. The

resultant pale orange solid was then dried for 2 hours under high vacuum. Pyrrolidine **407** was found to be hygroscopic and thus exposure to air was minimised during its handling. An isolated yield was not determined.

$\mathbf{R_f}$ = 0.25 (CH_2Cl_2/MeOH 9:1).

NMR Spectroscopy:

^{1}H NMR (400 MHz, CD_3OD): δ_H 7.90–7.79 (m, 2H, H_G), 7.55–7.41 (m, 2H, H_H), 5.30–5.19 (m, 1H, H_C), 3.56–3.33 (m, 4H, $H_{B, B', E, E'}$), 2.47 (s, 3H, H_J), 2.25–2.17 (m, 2H, $H_{D, D'}$) ppm; H_A not observed;

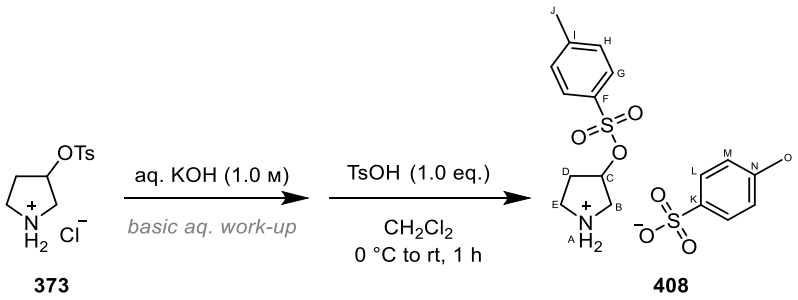
^{13}C NMR (125 MHz, CD_3OD): δ_C 161.6 (q, $^2J_{CF}$ = 37.2 Hz, C_K), 147.3 (C_I), 134.5 (C_F), 131.4 (C_H), 129.1 (C_G), 117.5 (q, $^1J_{CF}$ = 289.7 Hz, C_L), 80.7 (C_C), 52.4 (C_B), 45.0 (C_E), 32.3 (C_D), 21.6 (C_J) ppm;

^{19}F NMR (377 MHz, CD_3OD): δ_F −77.1 ppm.

IR (film): ν_{max} 3675, 2988, 1672, 1599, 1367, 1175, 1050 cm^{-1}.

HRMS (ESI): m/z calc'd for $C_{11}H_{15}NO_3S$ $[M+H]^+$ 242.0845 found 242.0837.

3-(Tosyloxy)pyrrolidine tosylate (408)



373 408

HCl salt **373** (0.278 g, 1.0 mmol, 1.0 eq.) was dissolved in aqueous KOH (1.0 M; 5 mL) and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*.

The free amine was dissolved in anhydrous CH_2Cl_2 (10 mL) and cooled to 0 °C (ice/water). *p*-Toluenesulfonic acid monohydrate (0.190 g, 1.0 mmol, 1.0 eq.) was added portion wise and the resultant solution warmed to rt and stirred at rt for 1 hour. A minimum amount of Et_2O was added to the amorphous solid to enable its dissolution. Pentane (5 mL) was then added, and a pale orange solid precipitated out. The suspension was sonicated and then the supernatant removed. Portions of pentane/Et_2O 9:1 (3 × 5 mL) were then added to the solid, the suspension

sonicated and then the supernatant removed. The resultant pale orange solid was then dried for 2 hours under high vacuum. Pyrrolidine **408** was found to be hygroscopic and thus exposure to air was minimised during its handling. An isolated yield was not determined.

$\mathbf{R_f}$ = 0.54 (CH_2Cl_2/MeOH 9:1).

NMR Spectroscopy:

^{1}H NMR (400 MHz, CD_2Cl_2): δ_H 9.60 (br s, 1H, H_A), 9.42 (br s, 1H, H_A), 8.13–8.05 (m, 2H, H_G *or* H_L), 8.05–7.95 (m, 2H, H_G *or* H_L), 7.65 (d, $^3J_{HH}$ = 8.1 Hz, 2H, H_H *or* H_M), 7.53 (d, $^3J_{HH}$ = 7.9 Hz, 2H, H_H *or* H_M), 5.47–5.38 (m, 1H, H_C), 3.98–3.75 (m, 3H, $H_{B,\,B',\,E}$), 3.75–3.61 (m, 1H, $H_{E'}$), 2.77 (s, 3H, H_J *or* H_O), 2.73 (s, 3H, H_J *or* H_O), 2.53–2.35 (m, 2H, $H_{D,\,D'}$) ppm;

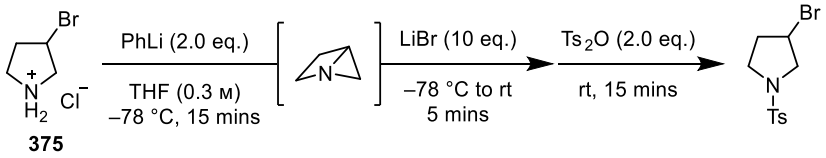
^{13}C NMR (101 MHz, CD_2Cl_2): δ_C 146.2 (C_I *or* C_N), 142.0 (C_F *or* C_K), 141.4 (C_I *or* C_N), 133.4 (C_F *or* C_K), 130.7 (C_H *or* C_M), 129.6 (C_H *or* C_M), 128.4 (C_G *or* C_L), 126.3 (C_G *or* C_L), 79.6 (C_C), 51.4 (C_B), 44.7 (C_E), 32.1 (C_D), 21.9 (C_J *or* C_O), 21.6 (C_J *or* C_O) ppm;

IR (film): ν_{max} 3675, 2987, 2777, 1598, 1364, 1172, 1121, 1096, 1012 cm^{-1}.

HRMS (ESI): m/z calc'd for $C_{11}H_{15}NO_3S$ $[M+H]^+$ 242.0845 found 242.0837.

6.4.2. Ring-opening reactions of 1-azabicyclo[2.1.0]pentane (ABP)

6.4.2.1. General procedure K: formation and ring-opening of ABP with LiBr/Ts_2O

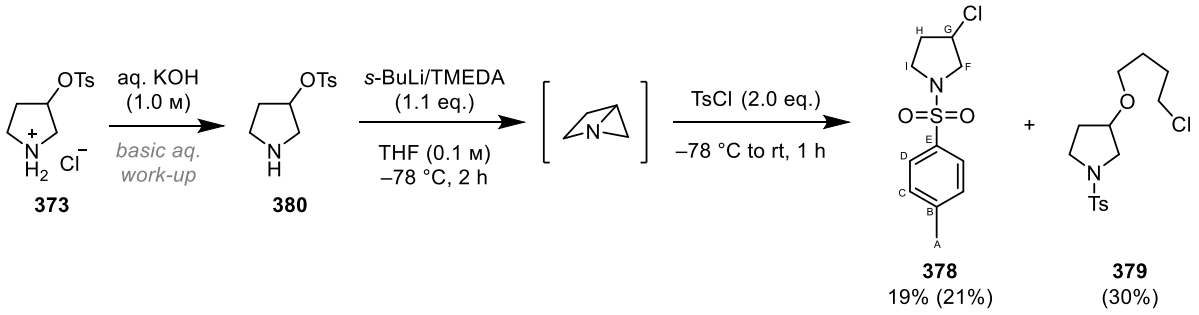


Anhydrous THF (0.74 mL) was added to 3-bromopyrrolidine hydrochloride **375** (37 mg, 0.20 mmol, 1.0 eq.) to give a suspension and cooled to −78 °C (dry ice/acetone). To this suspension, phenyl lithium (in Bu_2O; 0.40 mmol, 2.0 eq.) was added dropwise (~0.5 mL/min) and the reaction mixture stirred at this temperature for 15 minutes, after which time the reaction mixture was homogeneous and pale brown. Lithium bromide (dried with a heat gun under vacuum and left to cool; 174 mg, 2.0 mmol, 10 eq.) was then added to the reaction mixture at −78 °C and the resultant suspension warmed to rt, at which point the lithium bromide dissolved. Tosyl anhydride (131 mg, 0.40 mmol, 2.0 eq.) was added to the solution as a solid at rt and the reaction mixture was stirred at this temperature for 15 minutes. After this time, water (5 mL) and CH_2Cl_2 (5 mL) were added to the reaction vessel. The aqueous layer was extracted with

CH_2Cl_2 (3 × 5 mL) and the combined organic layers dried over $MgSO_4$ and concentrated *in vacuo*. The crude residue was analysed by quantitative ^1H NMR spectroscopy using CH_2Br_2 (0.20 mmol) as an internal standard, and then purified by flash column chromatography.

6.4.2.2. Characterisation of 3-substituted pyrrolidines

3-Chloro-1-tosylpyrrolidine (378)



3-(Tosyloxy)pyrrolidine hydrochloride **373** (0.651 g, 2.0 mmol, 1.0 eq.) was dissolved in aqueous KOH (1.0 M; 5 mL) and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo* to give amine **380**. A portion of this amine was used for the subsequent reaction.

3-(Tosyloxy)pyrrolidine **380** (37 mg, 0.15 mmol, 1.0 eq.) was dissolved in anhydrous THF (1.5 mL) and cooled to −78 °C (dry ice/acetone). TMEDA (0.03 mL, 0.17 mmol, 1.1 eq.) was added dropwise (~0.5 mL/min), followed by *sec*-butyl lithium (1.3 M in cyclohexane/hexane 92:8; 0.13 mL, 0.17 mmol, 1.1 eq.) dropwise (~0.5 mL/min). The reaction mixture stirred at this temperature for 2 hours. Tosyl chloride (58 mg, 0.31 mmol, 2.0 eq.) was added to the reaction mixture at −78 °C. The reaction mixture was warmed to 0 °C (ice/water) and stirred at this temperature for 30 minutes, followed by 30 minutes at rt. After this time, water (5 mL) and CH_2Cl_2 (5 mL) were added to the reaction vessel. The aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL) and the combined organic layers dried over $MgSO_4$ and concentrated *in vacuo*. The crude residue (21% **378** and 30% **379** by quantitative ^1H NMR spectroscopic analysis) was purified by flash column chromatography (10:1 to 9:1 to 4:1 pentane/EtOAc) to afford the pyrrolidine (8 mg, 19%) as a colourless oil.

$\mathbf{R_f}$ = 0.48 (pentane/EtOAc 3:1).

NMR Spectroscopy:

^1H NMR (500 MHz, $CDCl_3$): δ_H 7.76–7.70 (m, 2H, H_D), 7.35–7.28 (m, 2H, H_C), 4.39–4.29

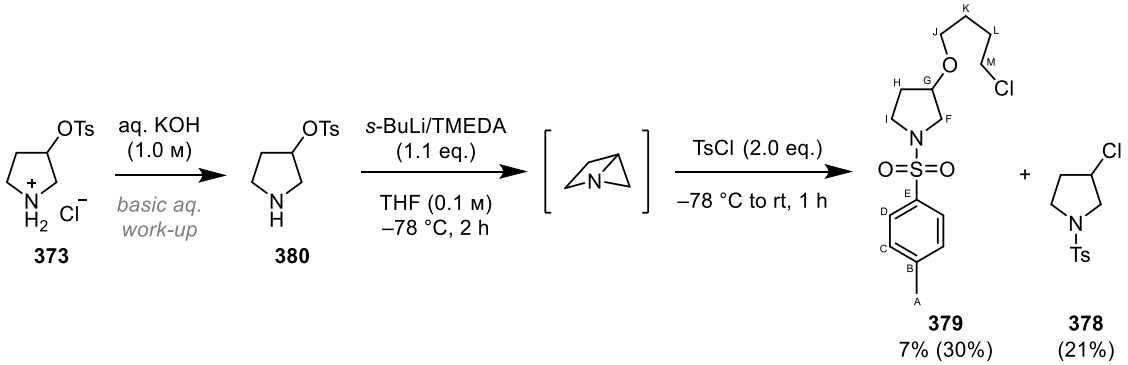
(m, 1H, H_G), 3.73 (dd, J_{HH} = 11.9, 5.0 Hz, 1H, H_F), 3.58–3.37 (m, 3H, $H_{F', I, I'}$), 2.43 (s, 3H, H_A), 2.28–2.14 (m, 1H, H_H), 2.12–1.99 (m, 1H, $H_{H'}$) ppm;

^{13}C NMR (125 MHz, $CDCl_3$): δ_C 143.7 (C_B), 133.7 (C_E), 129.7 (C_C), 127.6 (C_D), 56.8 (C_F), 56.5 (C_G), 45.8 (C_I), 35.7 (C_H), 21.5 (C_A) ppm.

IR (film): ν_{max} 3668, 2979, 2901, 1597, 1394, 1343, 1239, 1160, 1066 cm^{-1}.

HRMS (APCI): m/z calc'd for $C_{11}H_{14}O_2NS^{35}Cl$ $[M+H]^+$ 260.0507 found 260.0510.

3-(4-Chlorobutoxy)-1-tosylpyrrolidine (379)



3-(Tosyloxy)pyrrolidine hydrochloride **373** (0.651 g, 2.0 mmol, 1.0 eq.) was dissolved in aqueous KOH (1.0 M; 5 mL) and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo* to give amine **380**. A portion of this amine was used for the subsequent reaction.

3-(Tosyloxy)pyrrolidine **380** (37 mg, 0.15 mmol, 1.0 eq.) was dissolved in anhydrous THF (1.5 mL) and cooled to −78 °C (dry ice/acetone). TMEDA (0.03 mL, 0.17 mmol, 1.1 eq.) was added dropwise (~0.5 mL/min), followed by *sec*-butyl lithium (1.3 M in cyclohexane/hexane 92:8; 0.13 mL, 0.17 mmol, 1.1 eq.) dropwise (~0.5 mL/min). The reaction mixture stirred at this temperature for 2 hours. Tosyl chloride (58 mg, 0.31 mmol, 2.0 eq.) was added to the reaction mixture at −78 °C. The reaction mixture was warmed to 0 °C (ice/water) and stirred at this temperature for 30 minutes, followed by 30 minutes at rt. After this time, water (5 mL) and CH_2Cl_2 (5 mL) were added to the reaction vessel. The aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL) and the combined organic layers dried over $MgSO_4$ and concentrated *in vacuo*. The crude residue (21% **378** and 30% **379** by quantitative ^{1}H NMR spectroscopic analysis) was purified by flash column chromatography (10:1 to 9:1 to 4:1 pentane/EtOAc) to afford the pyrrolidine (2 mg, 7%) as a colourless oil.

R_f = 0.38 (pentane/EtOAc 3:1).

NMR Spectroscopy:

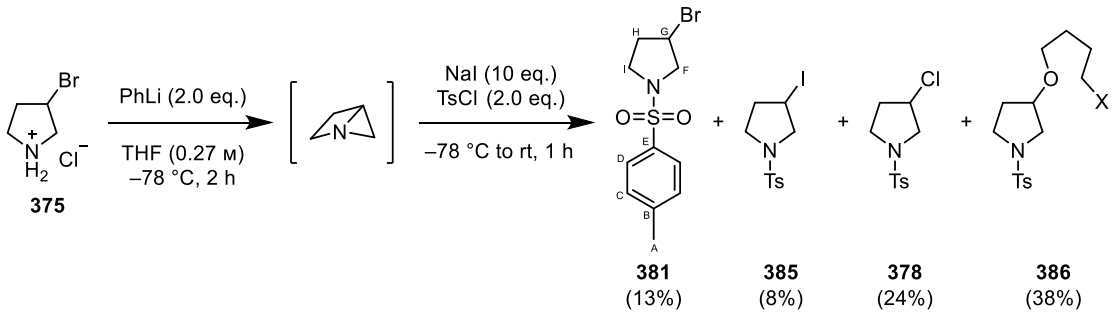
^{1}H NMR (500 MHz, $CDCl_3$): δ_H 7.75–7.66 (m, 2H, H_D), 7.34–7.29 (m, 2H, H_C), 3.92 (apparent dtd, $^{3}J_{HH}$ = 6.1, 4.2, 2.4 Hz, 1H, H_G), 3.47–3.44 (t, $^{3}J_{HH}$ = 6.8 Hz, 2H, $H_{M, M'}$), 3.44–3.38 (m, 2H, $H_{F, I}$), 3.31–3.17 (m, 4H, $H_{F', I', J, J'}$), 2.43 (s, 3H, H_A), 1.95–1.82 (m, 2H, $H_{H, H'}$), 1.74–1.60 (m, 2H, $H_{L, L'}$), 1.53–1.45 (m, 2H, $H_{K, K'}$) ppm;

^{13}C NMR (125 MHz, $CDCl_3$): δ_C 143.4 (C_B), 133.8 (C_E), 129.6 (C_C), 127.7 (C_D), 77.9 (C_G), 67.9 (C_J), 52.9 (C_F), 46.2 (C_I), 44.8 (C_M), 31.5 (C_H), 29.4 (C_L), 27.0 (C_K), 21.5 (C_A) ppm.

IR (film): ν_{max} 3668, 2978, 2901, 1406, 1342, 1253, 1066 cm^{-1}.

HRMS (ESI): m/z calc'd for $C_{15}H_{22}O_3NS^{35}Cl$ $[M+H]^+$ 332.1082 found 332.1084.

3-Bromo-1-tosylpyrrolidine (381)



Anhydrous THF (0.74 mL) was added to 3-bromopyrrolidine hydrochloride **375** (37 mg, 0.20 mmol, 1.0 eq.) to give a suspension and cooled to −78 °C (dry ice/acetone). To this suspension, phenyl lithium (1.9 M in Bu_2O; 0.21 mL, 0.40 mmol, 2.0 eq.) was added dropwise (~0.5 mL/min) and the reaction mixture stirred at this temperature for 2 hours. Sodium iodide (300 mg, 2.0 mmol, 10 eq.) was added to the reaction mixture at −78 °C followed by tosyl chloride (76 mg, 0.40 mmol, 2.0 eq.). The reaction mixture was warmed to 0 °C (ice/water) and stirred at this temperature for 30 minutes, followed by 30 minutes at rt. After this time, water (5 mL) and CH_2Cl_2 (5 mL) were added to the reaction vessel. The aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL) and the combined organic layers dried over $MgSO_4$ and concentrated *in vacuo*. The crude residue (8% **385**, 13% **381**, 24% **378** and 38% **386** by quantitative ^{1}H NMR spectroscopic analysis) was purified by flash column chromatography (10:1 pentane/EtOAc) to give an analytically pure sample of **381** (14 mg).

$\mathbf{R_f}$ = 0.48 (pentane/EtOAc 3:1).

NMR Spectroscopy:

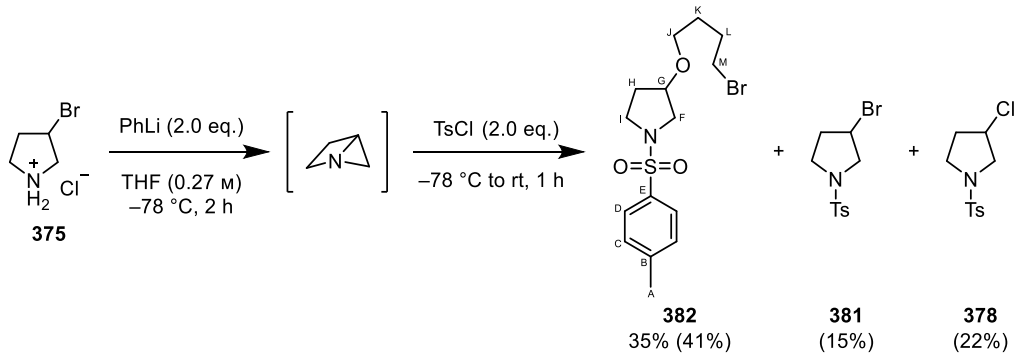
^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.78–7.67 (m, 2H, H_D), 7.37–7.30 (m, 2H, H_C), 4.33 (apparent tt, $^3J_{HH}$ = 5.3, 3.1 Hz, 1H, H_G), 3.86 (dd, J_{HH} = 12.1, 5.3 Hz, 1H, H_F), 3.62–3.40 (m, 3H, $H_{F', I, I'}$), 2.43 (s, 3H, H_A), 2.36–2.24 (m, 1H, H_H), 2.20–2.07 (m, 1H, $H_{H'}$) ppm;

^{13}C NMR (101 MHz, $CDCl_3$): δ_C 143.8 (C_B), 133.8 (C_E), 129.8 (C_C), 127.6 (C_D), 57.2 (C_F), 46.2 (C_I), 45.5 (C_G), 36.4 (C_H), 21.6 (C_A) ppm.

IR (film): ν_{max} 3668, 2982, 2901, 1406, 1394, 1251, 1066 cm^{-1}.

HRMS (APCI): m/z calc'd for $C_{11}H_{14}O_2NS^{79}Br$ $[M+H]^+$ 304.0001 found 304.0012.

3-(4-Bromobutoxy)-1-tosylpyrrolidine (382)



Anhydrous THF (0.74 mL) was added to 3-bromopyrrolidine hydrochloride **375** (37 mg, 0.20 mmol, 1.0 eq.) to give a suspension and cooled to −78 °C (dry ice/acetone). To this suspension, phenyl lithium (1.9 M in Bu_2O; 0.21 mL, 0.40 mmol, 2.0 eq.) was added dropwise (~0.5 mL/min) and the reaction mixture stirred at this temperature for 2 hours. Tosyl chloride (76 mg, 0.40 mmol, 2.0 eq.) was added to the reaction mixture at −78 °C. The reaction mixture was warmed to 0 °C (ice/water) and stirred at this temperature for 30 minutes, followed by 30 minutes at rt. After this time, water (5 mL) and CH_2Cl_2 (5 mL) were added to the reaction vessel. The aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL) and the combined organic layers dried over $MgSO_4$ and concentrated *in vacuo*. The crude residue (41% **382**, 15% **381** and 22% **378** by quantitative ^{1}H NMR spectroscopic analysis) was purified by flash column chromatography (10:1 to 9:1 to 8:1 pentane/EtOAc) to afford the pyrrolidine (26 mg, 35%) as a colourless oil.

$\mathbf{R_f}$ = 0.40 (pentane/EtOAc 3:1).

NMR Spectroscopy:

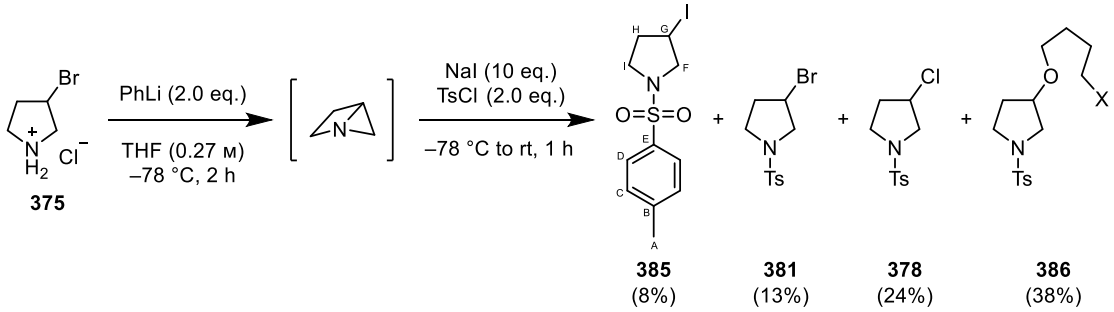
^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.76–7.68 (m, 2H, H_D), 7.36–7.27 (m, 2H, H_C), 3.91 (apparent dtd, $^3J_{HH}$ = 6.2, 4.2, 2.3 Hz, 1H, H_G), 3.47–3.36 (m, 2H, $H_{F,\,I}$), 3.32 (t, $^3J_{HH}$ = 6.7 Hz, 2H, $H_{M,\,M'}$), 3.30–3.16 (m, 4H, $H_{F',\,I',\,J,\,J'}$), 2.43 (s, 3H, H_A), 1.90–1.83 (m, 2H, $H_{H,\,H'}$), 1.79–1.69 (m, 2H, $H_{L,\,L'}$), 1.55–1.45 (m, 2H, $H_{K,\,K'}$) ppm;

^{13}C NMR (101 MHz, $CDCl_3$): δ_C 143.4 (C_B), 133.8 (C_E), 129.6 (C_C), 127.7 (C_D), 77.9 (C_G), 67.8 (C_J), 52.9 (C_F), 46.2 (C_I), 33.6 (C_M), 31.5 (C_H), 29.5 (C_L), 28.3 (C_K), 21.6 (C_A) ppm.

IR (film): ν_{max} 3668, 2980, 2901, 1406, 1248, 1066 cm^{-1}.

HRMS (ESI): m/z calc'd for $C_{15}H_{22}O_3NS^{79}Br$ $[M+H]^+$ 376.0577 found 376.0580.

3-Iodo-1-tosylpyrrolidine (385)



Anhydrous THF (0.74 mL) was added to 3-bromopyrrolidine hydrochloride **375** (37 mg, 0.20 mmol, 1.0 eq.) to give a suspension and cooled to −78 °C (dry ice/acetone). To this suspension, phenyl lithium (1.9 M in Bu_2O; 0.21 mL, 0.40 mmol, 2.0 eq.) was added dropwise (~0.5 mL/min) and the reaction mixture stirred at this temperature for 2 hours. Sodium iodide (300 mg, 2.0 mmol, 10 eq.) was added to the reaction mixture at −78 °C followed by tosyl chloride (76 mg, 0.40 mmol, 2.0 eq.). The reaction mixture was warmed to 0 °C (ice/water) and stirred at this temperature for 30 minutes, followed by 30 minutes at rt. After this time, water (5 mL) and CH_2Cl_2 (5 mL) were added to the reaction vessel. The aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL) and the combined organic layers dried over $MgSO_4$ and concentrated *in vacuo*. The crude residue (8% **385**, 13% **381** and 24% **378** and 38% **386** by quantitative ^{1}H NMR spectroscopic analysis) was purified by flash column chromatography (10:1 pentane/EtOAc) to give an analytically pure sample of **385** (4 mg).

$\mathbf{R_f}$ = 0.57 (pentane/EtOAc 3:1).

NMR Spectroscopy:

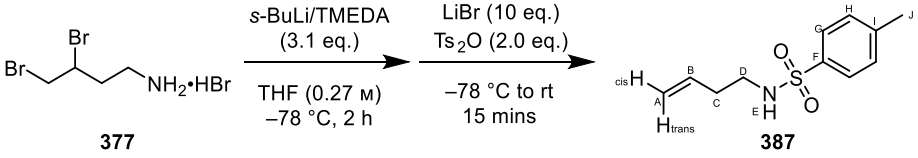
^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.78–7.68 (m, 2H, H_D), 7.38–7.31 (m, 2H, H_C), 4.21–4.12 (m, 1H, H_G), 3.91 (dd, J_{HH} = 11.6, 5.9 Hz, 1H, H_F), 3.59–3.53 (m, 1H, $H_{F'}$), 3.44 (dd, J_{HH} = 7.4, 6.0 Hz, 2H, $H_{I, I'}$), 2.44 (s, 3H, H_A), 2.32–2.21 (m, 1H, H_H), 2.18–2.07 (m, 1H, $H_{H'}$) ppm;

^{13}C NMR (125 MHz, $CDCl_3$): δ_C 143.8 (C_B), 133.9 (C_E), 129.8 (C_C), 127.6 (C_D), 58.6 (C_F), 47.0 (C_I), 38.1 (C_H), 21.6 (C_A), 17.2 (C_G) ppm.

IR (film): ν_{max} 3668, 2981, 2901, 1394, 1250, 1230, 1066 cm^{-1}.

HRMS (APCI): m/z calc'd for $C_{11}H_{14}O_2NSI$ $[M+H]^+$ 351.9863 found 351.9878.

***N*-(but-3-en-1-yl)-4-methylbenzenesulfonamide (387)**



Anhydrous THF (0.26 mL) was added to 3,4-dibromobutan-1-amine hydrobromide **377** (22 mg, 0.07 mmol, 1.0 eq.) to give a suspension and cooled to −78 °C (dry ice/acetone). To this suspension, TMEDA (32 µL, 0.22 mmol, 3.1 eq.) was added followed by *sec*-butyl lithium (1.3 M in cyclohexane/hexane; 0.17 mL, 0.22 mmol, 3.1 eq.) dropwise (~0.5 mL/min) and the reaction mixture stirred at this temperature for 2 hours. Lithium bromide (dried with a heat gun under vacuum and left to cool; 60 mg, 0.69 mmol, 10 eq.) was then added to the reaction mixture at −78 °C and the resultant suspension warmed to rt, at which point the lithium bromide dissolved. Tosyl anhydride (45 mg, 0.14 mmol, 2.0 eq.) was added to the solution as a solid at rt and the reaction mixture was stirred at this temperature for 15 minutes. After this time, water (4 mL) and CH_2Cl_2 (4 mL) were added to the reaction vessel. The aqueous layer was extracted with CH_2Cl_2 (3 × 4 mL) and the combined organic layers dried over $MgSO_4$ and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (3:1 pentane/EtOAc) to give the product (4 mg, 26%) as a colourless oil.

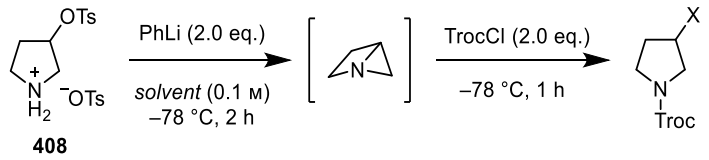
NMR Spectroscopy:

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.79–7.70 (m, 2H, H_G), 7.37–7.27 (m, 2H, H_H), 5.62 (ddt, $^3J_{HH(trans)}$ = 17.1 Hz, $^3J_{HH(cis)}$ = 10.3 Hz, $^3J_{HH}$ = 6.9 Hz, 1H, H_B), 5.11–4.99 (m, 2H, H_A), 4.37 (br s, 1H, H_E), 3.02 (apparent q, $^3J_{HH}$ = 6.6 Hz, 2H, H_D), 2.43 (s, 3H, H_J), 2.20 (apparent qt, $^3J_{HH}$ = 6.6 Hz, $^4J_{HH}$ = 1.3 Hz, 2H, H_C) ppm;

^{13}C NMR (101 MHz, $CDCl_3$): δ_C 143.5 (C_I), 137.0 (C_F), 134.2 (C_B), 129.7 (C_H), 127.1 (C_G), 118.3 (C_A), 42.0 (C_D), 33.6 (C_C), 21.5 (C_J) ppm.

All recorded spectroscopic data matched those previously reported in the literature.[207]

6.4.2.3. General procedure L: formation and ring-opening of ABP with TrocCl

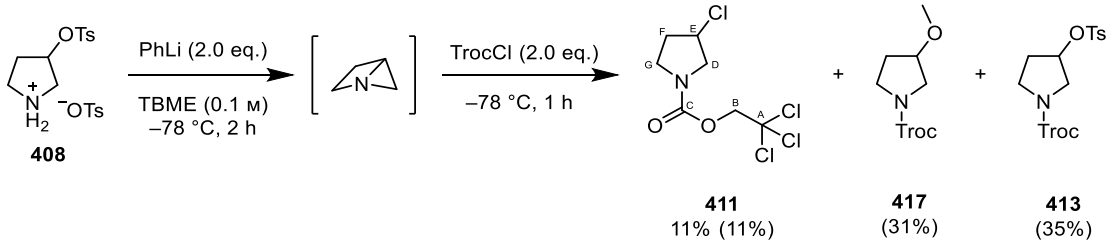


3-(Tosyloxy)pyrrolidine tosylate **408** was stored as a stock solution in CD_2Cl_2 over 3 Å molecular sieves. The concentration of this stock solution was determined by quantitative ^{1}H NMR spectroscopic analysis (0.10 mL of stock solution, 0.10 mmol CH_2Br_2 internal standard and 0.40 mL CD_2Cl_2).

3-(Tosyloxy)pyrrolidine tosylate **408** (in CD_2Cl_2; 0.10 mmol, 1.0 eq.) was added to a Schlenk flask and the solvent removed *in vacuo* to give a pale orange solid. Anhydrous solvent (1.00 mL) was then added to the flask to give a suspension and cooled to −78 °C (dry ice/acetone). To this suspension, phenyl lithium (in Bu_2O; 0.20 mmol, 2.0 eq.) was added dropwise (~0.5 mL/min) and the reaction mixture stirred at this temperature for 2 hours. 2,2,2-Trichloroethyl chloroformate (0.03 mL, 0.20 mmol, 2.0 eq.) was added to the reaction mixture at −78 °C and the reaction mixture was stirred at this temperature for a further 1 hour. After this time, water (5 mL) and CH_2Cl_2 (5 mL) were added to the reaction vessel. The aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL) and the combined organic layers dried over $MgSO_4$ and concentrated *in vacuo*. The crude residue was purified by flash column chromatography to give the product.

6.4.2.4. Solvent screen: characterisation of 3-substituted pyrrolidines

2,2,2-Trichloroethyl 3-chloropyrrolidine-1-carboxylate (411)



According to **General Procedure L**, 3-(tosyloxy)pyrrolidine tosylate **408** (0.24 M in CD_2Cl_2; 0.42 mL, 0.10 mmol, 1.0 eq.) suspended in anhydrous *tert*-butyl methyl ether (1.00 mL) was allowed to react with phenyl lithium (1.85 M in Bu_2O; 0.11 mL, 0.20 mmol, 2.0 eq.) and 2,2,2-trichloroethyl chloroformate (0.03 mL, 0.20 mmol, 2.0 eq.) to give a crude residue (11% **411**, 31% **417** and 35% **413** by quantitative ^{1}H NMR spectroscopic analysis) which was purified by flash column chromatography (9:1 to 7:1 pentane/EtOAc) to afford the pyrrolidine (3 mg, 11%) as a colourless oil.

$\mathbf{R_f}$ = 0.17 (pentane/EtOAc 4:1).

NMR Spectroscopy:

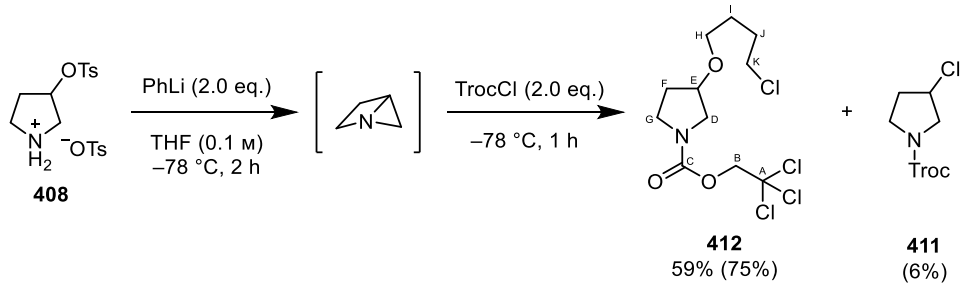
^{1}H NMR (400 MHz, $CDCl_3$): δ_H 4.87–4.67 (m, 2H, H_B), 4.59–4.45 (m, 1H, H_E), 3.87–3.58 (m, 4H, $H_{D, D', G, G'}$), 2.41–2.15 (m, 2H, $H_{F, F'}$) ppm;

^{13}C NMR (125 MHz, $CDCl_3$): δ_C 153.0 (C_C), 152.8 (C_C), 95.6 (C_A), 95.6 (C_A), 75.0 (C_B), 75.0 (C_B), 57.1 (C_E), 56.6 (C_E), 55.7 (C_D), 55.3 (C_D), 44.3 (C_G), 43.8 (C_G), 35.7 (C_F), 35.0 (C_F) ppm; *doubling of peaks due to the presence of rotamers*.

IR (film): ν_{max} 3675, 2988, 2901, 1721 (C=O), 1416, 1344, 1251, 1123, 1066 cm^{-1}.

HRMS (EI): m/z calc'd for $C_7H_9O_2N^{35}Cl_4$ $[M]^+$ 278.9382 found 278.9386.

2,2,2-Trichloroethyl 3-(4-chlorobutoxy)pyrrolidine-1-carboxylate (412)



According to **General Procedure L**, 3-(tosyloxy)pyrrolidine tosylate **408** (0.44 M in CD_2Cl_2; 0.23 mL, 0.10 mmol, 1.0 eq.) suspended in anhydrous THF (1.00 mL) was allowed to react with phenyl lithium (1.85 M in Bu_2O; 0.11 mL, 0.20 mmol, 2.0 eq.) and 2,2,2-trichloroethyl chloroformate (0.03 mL, 0.20 mmol, 2.0 eq.) to give a crude residue (75% **412** and 6% **411** by quantitative ^{1}H NMR spectroscopic analysis) which was purified by flash column chromatography (4:1 pentane/EtOAc) to afford the pyrrolidine (21 mg, 59%) as a colourless oil.

$\mathbf{R_f}$ = 0.23 (pentane/EtOAc 4:1).

NMR Spectroscopy:

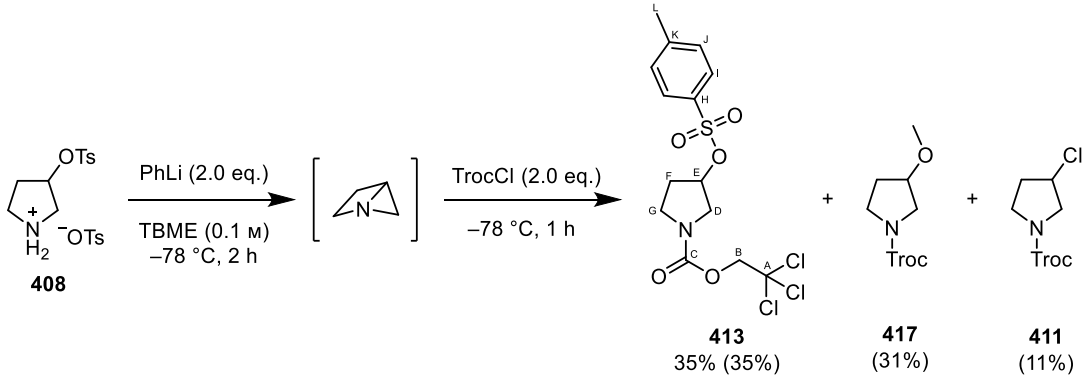
^{1}H NMR (400 MHz, $CDCl_3$): δ_H 4.83–4.64 (m, 2H, H_B), 4.11–4.00 (m, 1H, H_E), 3.64–3.38 (m, 8H, $H_{D, D', G, G', H, H', K, K'}$), 2.10–1.90 (m, 2H, $H_{F, F'}$), 1.89–1.79 (m, 2H, $H_{J, J'}$), 1.75–1.66 (m, 2H, $H_{I, I'}$) ppm; *doubling of peaks due to the presence of rotamers*;

^{13}C NMR (101 MHz, $CDCl_3$): δ_C 153.2 (C_C), 95.9 (C_A), 78.1 (C_E), 75.0 (C_B), 68.2 (C_H), 51.7 (C_D), 51.4 (C_D), 45.0 (C_K), 44.6 (C_G), 44.2 (C_G), 31.4 (C_F), 30.6 (C_F), 29.6 (C_J), 27.2 (C_I) ppm; *doubling of peaks due to the presence of rotamers*.

IR (film): ν_{max} 3675, 2971, 2901, 1716 (C=O), 1414, 1345, 1198, 1111 cm^{-1}.

HRMS (ESI): m/z calc'd for $C_{11}H_{18}O_3N^{35}Cl_4$ $[M+H]^+$ 352.0035 found 352.0039.

2,2,2-Trichloroethyl 3-(tosyloxy)pyrrolidine-1-carboxylate (413)



According to **General Procedure L**, 3-(tosyloxy)pyrrolidine tosylate **408** (0.24 M in CD_2Cl_2; 0.42 mL, 0.10 mmol, 1.0 eq.) suspended in anhydrous *tert*-butyl methyl ether (1.00 mL) was allowed to react with phenyl lithium (1.85 M in Bu_2O; 0.11 mL, 0.20 mmol, 2.0 eq.) and 2,2,2-trichloroethyl chloroformate (0.03 mL, 0.20 mmol, 2.0 eq.) to give a crude residue (35% **413**, 31% **417** and 11% **411** by quantitative ^{1}H NMR spectroscopic analysis) which was purified by flash column chromatography (9:1 to 7:1 pentane/EtOAc) to afford the pyrrolidine (15 mg, 35%) as a colourless oil.

$\mathbf{R_f}$ = 0.30 (pentane/EtOAc 2:1).

NMR Spectroscopy:

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.85–7.70 (m, 2H, H_I), 7.42–7.31 (m, 2H, H_J), 5.11 (apparent tt, $^3J_{HH}$ = 4.2, 1.9 Hz, 0.5H, H_E), 5.08 (apparent tt, $^3J_{HH}$ = 4.2, 1.8 Hz, 0.5H, H_E),

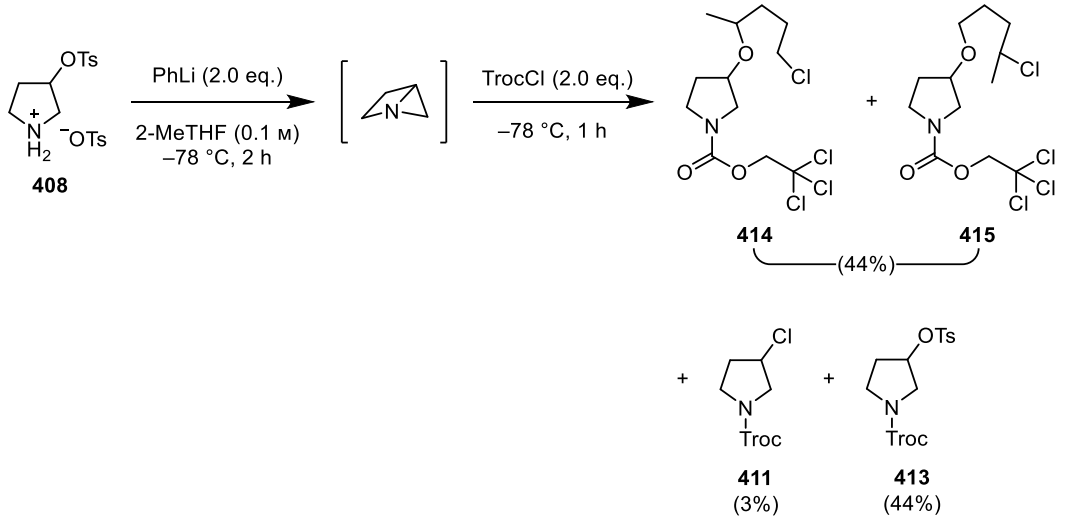
4.81–4.61 (m, 2H, H_B), 3.72–3.46 (m, 4H, $H_{D, D', G, G'}$), 2.46 (s, 3H, H_L), 2.32–1.96 (m, 2H, $H_{F, F'}$) ppm; *doubling of peaks due to the presence of rotamers*;

^{13}C NMR (125 MHz, $CDCl_3$): δ_C 152.8 (C_C), 152.7 (C_C), 145.4 (C_K), 133.7 (C_H), 133.7 (C_H), 130.2 (C_J), 127.8 (C_I), 95.6 (C_A), 80.2 (C_E), 79.5 (C_E), 75.0 (C_B), 75.0 (C_B), 52.3 (C_D *or* C_G), 51.9 (C_D *or* C_G), 44.2 (C_D *or* C_G), 43.8 (C_D *or* C_G), 32.4 (C_F), 31.5 (C_F), 21.8 (C_L) ppm; *doubling of peaks due to the presence of rotamers*.

IR (film): ν_{max} 3675, 2988, 2901, 1720 (C=O), 1598, 1416, 1363, 1174, 1124, 1057 cm^{-1}.

HRMS (ESI): m/z calc'd for $C_{14}H_{16}O_5NNaS^{35}Cl_3$ $[M+Na]^+$ 437.9707 found 437.9698.

2,2,2-Trichloroethyl 3-((5-chloropentan-2-yl)oxy)pyrrolidine-1-carboxylate (414) and 2,2,2-Trichloroethyl 3-((4-chloropentyl)oxy)pyrrolidine-1-carboxylate (415)



According to **General Procedure L**, 3-(tosyloxy)pyrrolidine tosylate **408** (0.44 M in CD_2Cl_2; 0.23 mL, 0.10 mmol, 1.0 eq.) suspended in anhydrous 2-MeTHF (1.00 mL) was allowed to react with phenyl lithium (1.85 M in Bu_2O; 0.11 mL, 0.20 mmol, 2.0 eq.) and 2,2,2-trichloroethyl chloroformate (0.03 mL, 0.20 mmol, 2.0 eq.) to give a crude residue (44% **414**/**415**, 3% **411** and 44% **413** by quantitative ^{1}H NMR spectroscopic analysis) which was purified by flash column chromatography (95:5 to 4:1 pentane/EtOAc) to afford a mixture of pyrrolidines (18 mg), each as a mixture of two diastereomers, as a colourless oil.

$\mathbf{R_f}$ = 0.43 (pentane/EtOAc 4:1).

NMR Spectroscopy: *Peaks reported for a mixture of regioisomers, each as a mixture of two diastereomers, with doubling of peaks due to the presence of rotamers.*

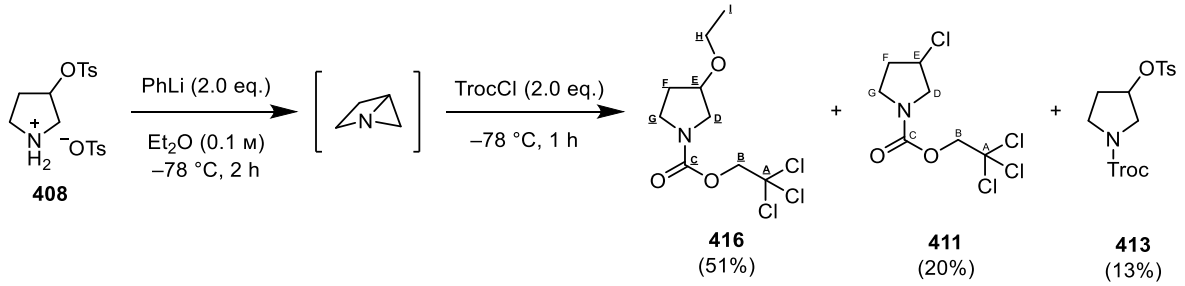
^{1}H NMR (400 MHz, $CDCl_3$): δ_H 4.83–4.65 (m, 4.9H), 4.21–4.10 (m, 1.0H), 4.10–3.97 (m, 1.8H), 3.63–3.38 (m, 11.4H), 2.10–1.55 (m, 8.7H), 1.54–1.47 (m, 2.9H), 1.19–1.12 (m, 3.0H) ppm;

^{13}C NMR (101 MHz, $CDCl_3$): δ_C 153.1, 153.1, 153.1, 153.0, 95.8, 95.8, 78.0, 75.4, 75.3, 75.0, 74.9, 74.9, 74.9, 74.8, 74.8, 74.5, 73.3, 73.1, 73.0, 73.0, 68.4, 68.4, 68.4, 68.4, 68.3, 58.6, 58.6, 58.6, 57.1, 56.6, 55.7, 55.3, 52.7, 52.3, 51.8, 51.7, 51.5, 51.3, 45.2, 45.2, 44.7, 44.5, 44.23, 44.2, 44.1, 44.1, 43.8, 40.1, 39.3, 37.1, 37.1, 37.0, 35.7, 35.0, 34.3, 34.2, 34.1, 32.4, 31.7, 31.5, 31.3, 30.7, 30.6, 30.0, 28.8, 28.7, 27.0, 27.0, 25.4, 25.4, 22.6, 20.2, 20.1, 20.1, 20.0 ppm.

IR (film): ν_{max} 3674, 2952, 1717 (C=O), 1415, 1343, 1241, 1196, 1121 cm^{-1}.

HRMS (ESI): m/z calc'd for $C_{12}H_{19}O_3N^{35}Cl_4$ $[M+H]^+$ 366.0192 found 366.0203.

2,2,2-Trichloroethyl 3-ethoxypyrrolidine-1-carboxylate (416)



According to **General Procedure L**, 3-(tosyloxy)pyrrolidine tosylate **408** (0.44 M in CD_2Cl_2; 0.23 mL, 0.10 mmol, 1.0 eq.) suspended in anhydrous Et_2O (1.00 mL) was allowed to react with phenyl lithium (1.85 M in Bu_2O; 0.11 mL, 0.20 mmol, 2.0 eq.) and 2,2,2-trichloroethyl chloroformate (0.03 mL, 0.20 mmol, 2.0 eq.) to give a crude residue (51% **416**, 20% **411** and 13% **413** by quantitative ^{1}H NMR spectroscopic analysis) which was purified by flash column chromatography (9:1 to 7:1 to 3:1 pentane/EtOAc) to afford a mixture of pyrrolidines (18 mg, 3:1 **416**/**411**) as a colourless oil.

*Characterisation given for a 3:1 mixture of **416**/**413**.*

$\mathbf{R_f}$ = 0.34 (pentane/EtOAc 4:1).

NMR Spectroscopy: *Assignments (underlined) made for the major product **416**.*

^{1}H NMR (500 MHz, $CDCl_3$): δ_H 4.83–4.65 (m, 2.6H, $\underline{H_B}$), 4.57–4.50 (m, 0.3H, H_E), 4.11–4.02 (m, 1H, $\underline{H_E}$), 3.86–3.61 (m, 1.2H, $H_{D,\ D',\ G,\ G'}$), 3.61–3.44 (m, 6H,

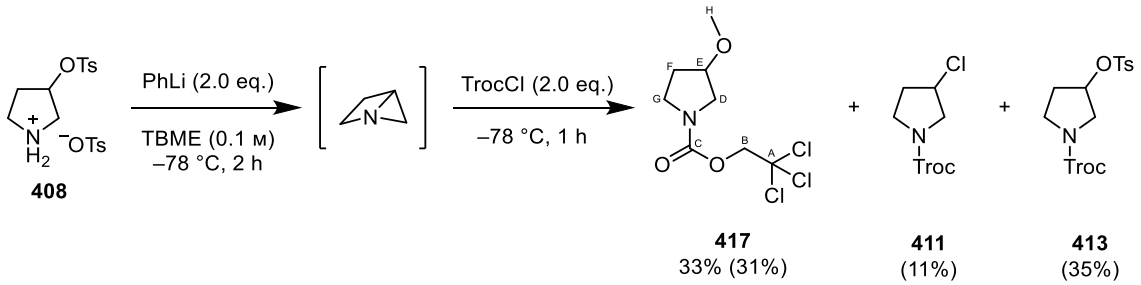
$H_{D, D', G, G', H, H'}$), 2.37–2.18 (m, 0.6H, $H_{F, F'}$), 2.10–1.89 (m, 2H, $H_{F, F'}$), 1.20 (t, $^3J_{HH}$ = 7.0 Hz, 1.5H, H_I), 1.20 (t, $^3J_{HH}$ = 7.0 Hz, 1.5H, H_I) ppm; *doubling of peaks due to the presence of rotamers*;

^{13}C NMR (125 MHz, $CDCl_3$): δ_C 153.1 (C_C), 153.0 (C_C), 153.0 (C_C), 152.8 (C_C), 95.8 (C_A), 95.6 (C_A), 95.6 (C_A), 77.8 (C_E), 75.0 (C_B), 74.9 (C_B), 74.9 (C_B), 74.9 (C_B), 64.5 (C_H), 64.4 (C_H), 57.1 (C_E), 56.6 (C_E), 55.7 (C_D), 55.3 (C_D), 51.7 (C_D), 51.4 (C_D), 44.5 (C_G), 44.3 (C_G), 44.1 (C_G), 43.8 (C_G), 35.7 (C_F), 35.0 (C_F), 31.4 (C_F), 30.6 (C_F), 15.4 (C_I), 15.4 (C_I) ppm; *doubling of peaks due to the presence of rotamers*.

IR (film): ν_{max} 3675, 2974, 2901, 1715 (C=O), 1414, 1344, 1200, 1107, 1066 cm^{-1}.

HRMS (ESI): m/z calc'd for $C_9H_{15}O_3N^{35}Cl_3$ $[M+H]^+$ 290.0112 found 290.0117.

2,2,2-Trichloroethyl 3-methoxypyrrolidine-1-carboxylate (417)



According to **General Procedure L**, 3-(tosyloxy)pyrrolidine tosylate **408** (0.24 M in CD_2Cl_2; 0.42 mL, 0.10 mmol, 1.0 eq.) suspended in anhydrous *tert*-butyl methyl ether (1.00 mL) was allowed to react with phenyl lithium (1.85 M in Bu_2O; 0.11 mL, 0.20 mmol, 2.0 eq.) and 2,2,2-trichloroethyl chloroformate (0.03 mL, 0.20 mmol, 2.0 eq.) to give a crude residue (31% **317**, 11% **411** and 35% **413** by quantitative ^{1}H NMR spectroscopic analysis) which was purified by flash column chromatography (9:1 to 7:1 pentane/EtOAc) to afford the pyrrolidine (9 mg, 33%) as a colourless oil.

$\mathbf{R_f}$ = 0.21 (pentane/EtOAc 4:1).

NMR Spectroscopy:

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 4.86–4.60 (m, 2H, H_B), 4.04–3.89 (m, 1H, H_E), 3.67–3.42 (m, 4H, $H_{D, D', G, G'}$), 3.34 (s, 1.5H, H_H), 3.34 (s, 1.5H, H_H), 2.14–1.88 (m, 2H, $H_{F, F'}$) ppm; *doubling of peaks due to the presence of rotamers*;

^{13}C NMR (125 MHz, $CDCl_3$): δ_C 153.1 (C_C), 153.0 (C_C), 95.8 (C_A), 95.8 (C_A), 79.6 (C_E),

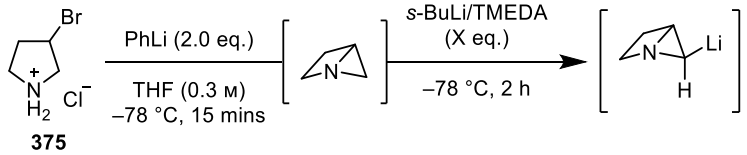
78.9 (C_E), 74.9 (C_B), 74.9 (C_B), 56.6 (C_H), 56.6 (C_H), 51.2 (C_D *or* C_G), 51.0 (C_D *or* C_G), 44.5 (C_D *or* C_G), 44.1 (C_D *or* C_G), 31.0 (C_F), 30.2 (C_F) ppm; *doubling of peaks due to the presence of rotamers.*

IR (film): ν_{max} 3675, 2987, 2901, 1718 (C=O), 1416, 1352, 1241, 1122, 1056 cm^{-1}.

HRMS (ESI): m/z calc'd for $C_8H_{12}O_3N^{35}Cl_3$ $[M+H]^+$ 275.9956 found 275.9958.

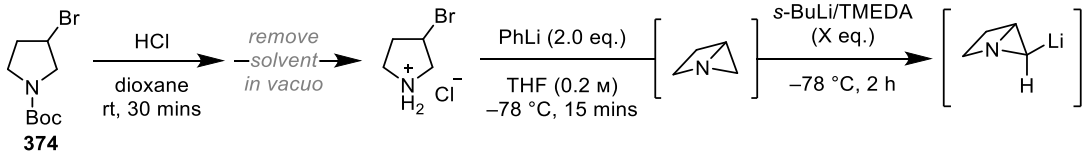
6.4.3. Lithiation, functionalisation and ring-opening reactions of 1-azabicyclo[2.1.0]pentane (ABP)

6.4.3.1. General procedure M: formation of ABP-Li with PhLi and *s*-BuLi/TMEDA from 375



Anhydrous THF (0.74 mL) was added to 3-bromopyrrolidine hydrochloride **375** (37 mg, 0.20 mmol, 1.0 eq.) to give a suspension and cooled to −78 °C (dry ice/acetone). To this suspension, phenyl lithium (in Bu_2O; 0.40 mmol, 2.0 eq.) was added dropwise (~0.5 mL/min) and the reaction mixture stirred at this temperature for 15 minutes, after which time the reaction mixture was homogeneous and pale brown. At −78 °C, TMEDA (X eq.) was added, followed by *sec*-butyl lithium (in cyclohexane/hexane; X eq.) dropwise (~0.5 mL/min). The red/brown reaction mixture was stirred at −78 °C for 2 hours. The solution of ABP-Li was used immediately (according to **General Procedures Q**–**S**).

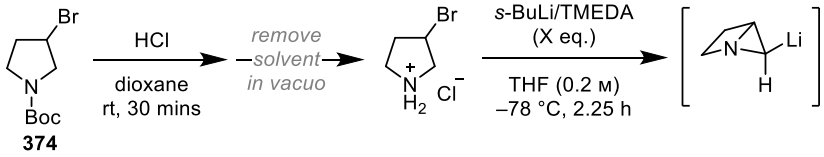
6.4.3.2. General procedure N: formation of ABP-Li with PhLi and *s*-BuLi/TMEDA from 374



N-Boc pyrrolidine **374** (50 mg, 0.20 mmol, 1.0 eq.) was added to a Schlenk flask and HCl (4 M in dioxane; 1.3 mL) was added at rt. The resultant solution was stirred at rt for 30 minutes, after which time the solvent was removed *in vacuo*. A liquid nitrogen-cooled trap was placed between the Schlenk flask and Schlenk line to collect the removed HCl/dioxane and prevent damage to the Schlenk line and vacuum pump. The pale pink solid was then washed with

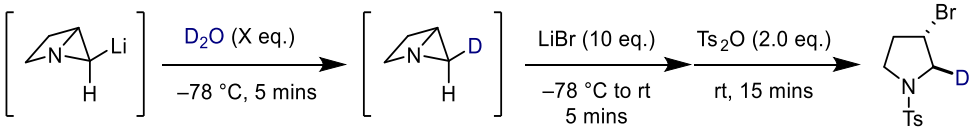
anhydrous THF (3 × 1 mL) under a N_2 atmosphere (THF was added to the dry solid under a N_2 atmosphere to give a fine suspension, the Schlenk flask was sonicated and then the THF was removed *in vacuo*). Anhydrous THF (1.00 mL) was added to the pale pink solid to give a fine suspension and cooled to −78 °C (dry ice/acetone). To this suspension, phenyl lithium (in Bu_2O; 0.40 mmol, 2.0 eq.) was added dropwise (~0.5 mL/min) and the reaction mixture stirred at this temperature for 15 minutes, after which time the reaction mixture was homogeneous and pale brown. At −78 °C, TMEDA (X eq.) was added, followed by *sec*-butyl lithium (in cyclohexane/hexane; X eq.) dropwise (~0.5 mL/min). The red/brown reaction mixture was stirred at −78 °C for 2 hours. The solution of ABP-Li was used immediately (according to **General Procedures Q**–**S**).

6.4.3.3. General procedure O: formation of ABP-Li with *s*-BuLi/TMEDA from 374



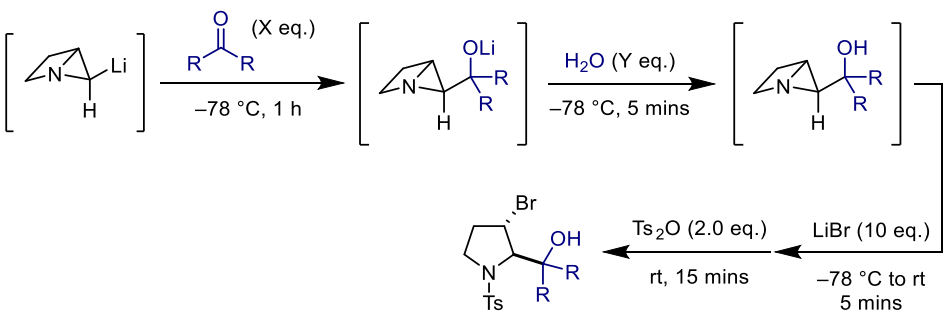
N-Boc pyrrolidine **374** (50 mg, 0.20 mmol, 1.0 eq.) was added to a Schlenk flask and HCl (4 M in dioxane; 1.3 mL) was added at rt. The resultant solution was stirred at rt for 30 minutes, after which time the solvent was removed *in vacuo*. A liquid nitrogen-cooled trap was placed between the Schlenk flask and Schlenk line to collect the removed HCl/dioxane and prevent damage to the Schlenk line and vacuum pump. The pale pink solid was then washed with anhydrous THF (3 × 1 mL) under a N_2 atmosphere (THF was added to the dry solid under a N_2 atmosphere to give a fine suspension, the Schlenk flask was sonicated and then the THF was removed *in vacuo*). Anhydrous THF (1.00 mL) was added to the pale pink solid to give a fine suspension and cooled to −78 °C (dry ice/acetone). To this suspension, TMEDA (X eq.) was added, followed by *sec*-butyl lithium (in cyclohexane/hexane; X eq.) dropwise (~0.5 mL/min). The cream reaction mixture was stirred at −78 °C for 2 hours and 15 minutes. The solution of ABP-Li was used immediately (according to **General Procedures Q**–**S**).

6.4.3.4. General procedure P: deuteration of ABP-Li



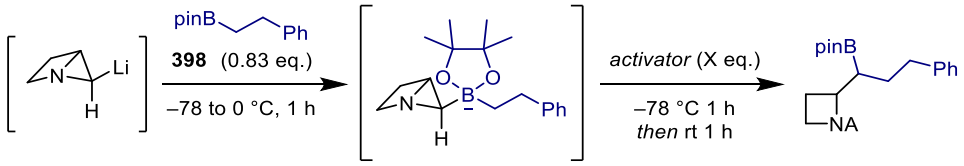
D_2O (2 M in THF; X eq.) was added dropwise (~0.5 mL/min) to a solution of ABP-Li in THF (prepared according to **General Procedures N–P** and used immediately) at −78 °C (dry ice/acetone) and the solution stirred at −78 °C for 5 minutes. Lithium bromide (dried with a heat gun under vacuum and left to cool; 174 mg, 2.0 mmol, 10 eq.) was then added to the reaction mixture at −78 °C and the resultant suspension warmed to rt, at which point the lithium bromide dissolved. Tosyl anhydride (131 mg, 0.40 mmol, 2.0 eq.) was added to the solution as a solid at rt and the reaction mixture was stirred at this temperature for 15 minutes. After this time, water (5 mL) and CH_2Cl_2 (5 mL) were added to the reaction vessel. The aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL) and the combined organic layers dried over $MgSO_4$ and concentrated *in vacuo*. The crude residue was analysed by quantitative ^{1}H NMR spectroscopy using CH_2Br_2 (0.20 mmol) as an internal standard to determine the yield and extent of D incorporation (measured by comparing the integrals of the peak at 4.33 ppm (intact) and 3.86 ppm (depleted)). The crude product was then purified by flash column chromatography.

6.4.3.5. General procedure Q: addition of ketones to ABP-Li



The ketone (2 M in THF; X eq.) was added dropwise (~0.5 mL/min) to a solution of ABP-Li in THF (prepared according to **General Procedures N–P** and used immediately) at −78 °C (dry ice/acetone) and the reaction left to stir at −78 °C for 1 hour. H_2O (2 M in THF; Y eq.) was then added dropwise (~0.5 mL/min) and the solution stirred at −78 °C for 5 minutes. Lithium bromide (dried with a heat gun under vacuum and left to cool; 174 mg, 2.0 mmol, 10 eq.) was then added to the reaction mixture at −78 °C and the resultant suspension warmed to rt, at which point the lithium bromide dissolved. Tosyl anhydride (131 mg, 0.40 mmol, 2.0 eq.) was added to the solution as a solid at rt and the reaction mixture was stirred at this temperature for 15 minutes. After this time, water (5 mL) and CH_2Cl_2 (5 mL) were added to the reaction vessel. The aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL) and the combined organic layers dried over $MgSO_4$ and concentrated *in vacuo*. The crude residue was analysed by quantitative ^{1}H NMR spectroscopy using CH_2Br_2 (0.20 mmol) as an internal standard, and then purified by flash column chromatography.

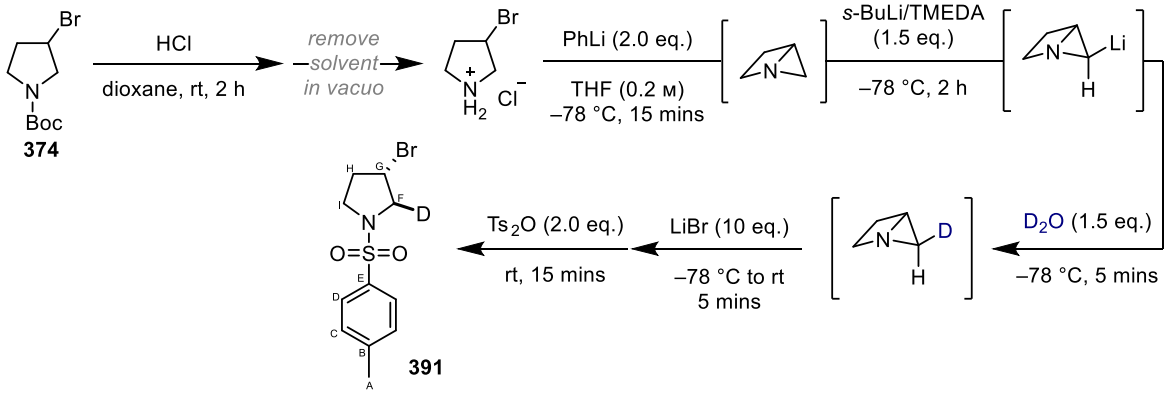
6.4.3.6. General procedure R: addition of boronic esters to ABP-Li



According to a modified literature procedure,[179] boronic ester **398** (1 M in THF; 0.83 eq.) was added dropwise (~0.5 mL/min) to a solution of ABP-Li in THF (prepared according to **General Procedures N**–**P** and used immediately) at −78 °C (dry ice/acetone) and the reaction warmed to 0 °C (ice/water) and left to stir for 1 hour. After this time, the reaction mixture was cooled back to −78 °C the activator (X eq.) was added dropwise (~0.5 mL/min). The reaction mixture was stirred at −78 °C for 1 hour, followed by rt for 1 hour. After this time, an aliquot of the reaction mixture was analysed by ^{11}B NMR. Then water (5 mL) and Et_2O (5 mL) were added to the reaction vessel. The aqueous layer was extracted with Et_2O (3 × 5 mL) and the combined organic layers dried over $MgSO_4$ and concentrated *in vacuo*. The crude residue was analysed by quantitative ^{1}H NMR spectroscopy using CH_2Br_2 as an internal standard.

6.4.3.7. Characterisation of 1,2,3-trisubstituted pyrrolidines

3-Bromo-1-tosylpyrrolidine-2-*d* (391)



According to a combination of **General Procedures N** and **P**, *N*-Boc pyrrolidine **374** (50 mg, 0.20 mmol, 1.0 eq.) was added to a Schlenk flask and HCl (4 M in dioxane; 1.3 mL) was added at rt. The resultant solution was stirred at rt for 30 minutes, after which time the solvent was removed *in vacuo*. A liquid nitrogen-cooled trap was placed between the Schlenk flask and Schlenk line to collect the removed HCl/dioxane and prevent damage to the Schlenk line and vacuum pump. The pale pink solid was then washed with anhydrous THF (3 × 1 mL) under a N_2 atmosphere (THF was added to the dry solid under a N_2 atmosphere to give a fine suspension, the Schlenk flask was sonicated and then the THF was removed *in vacuo*).

Anhydrous THF (1.00 mL) was added to the pale pink solid to give a fine suspension and cooled to −78 °C (dry ice/acetone). To this suspension, phenyl lithium (1.8 M in Bu_2O; 0.23 mL, 0.40 mmol, 2.0 eq.) was added dropwise (~0.5 mL/min) and the reaction mixture stirred at this temperature for 15 minutes, after which time the reaction mixture was homogeneous and pale brown. At −78 °C, TMEDA (50 µL, 0.30 mmol, 1.5 eq.) was added, followed by *sec*-butyl lithium (1.3 M in cyclohexane/hexane; 0.23 mL, 0.30 mmol, 1.5 eq.) dropwise (~0.5 mL/min). The red/brown reaction mixture was stirred at −78 °C for 2 hours. To this solution, D_2O (2 M in THF; 0.15 mL, 0.30 mmol, 1.5 eq.) was then added dropwise (~0.5 mL/min) and the solution stirred at −78 °C for 5 minutes. Lithium bromide (dried with a heat gun under vacuum and left to cool; 174 mg, 2.0 mmol, 10 eq.) was then added to the reaction mixture at −78 °C and the resultant suspension warmed to rt, at which point the lithium bromide dissolved. Tosyl anhydride (0.5 M in THF; 131 mg, 0.40 mmol, 2.0 eq.) was added to the solution at rt and the reaction mixture was stirred at this temperature for 15 minutes. After this time, water (5 mL) and CH_2Cl_2 (5 mL) were added to the reaction vessel. The aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL) and the combined organic layers dried over $MgSO_4$ and concentrated *in vacuo*. The crude residue was analysed by quantitative ^{1}H NMR spectroscopy using CH_2Br_2 (0.20 mmol) as an internal standard and the extent of D incorporation was calculated to be >95%. The crude residue was then purified by flash column chromatography (9:1 pentane/EtOAc) to give the product (43 mg, 71%) as a white solid. A 95:5 D/H ratio was confirmed by quantitative HRMS (ESI).

R_f = 0.46 (pentane/EtOAc 3:1).

NMR Spectroscopy:

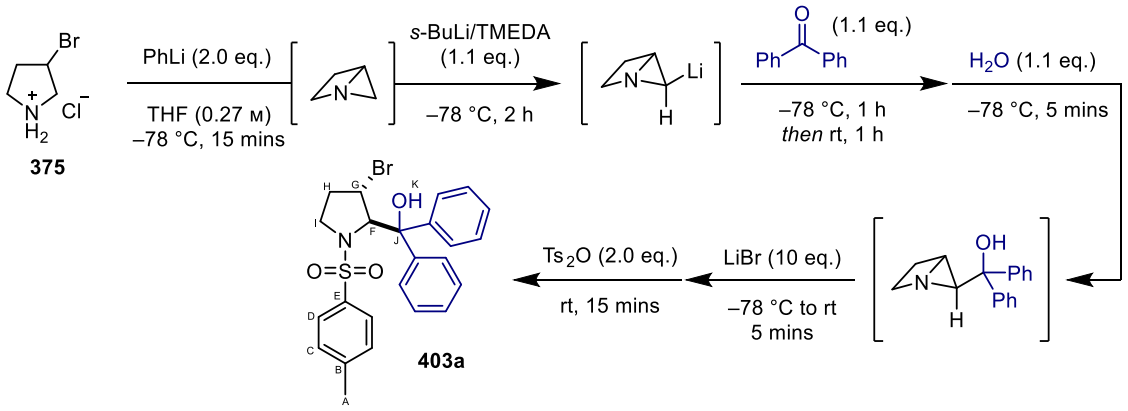
^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.76–7.68 (m, 2H, H_D), 7.37–7.28 (m, 2H, H_C), 4.32 (apparent dt, $^3J_{HH}$ = 5.9, 3.2 Hz, 1H, H_G), 3.58–3.55 (m, 1H, H_F), 3.55–3.40 (m, 2H, $H_{I, I'}$), 2.43 (s, 3H, H_A), 2.34–2.23 (m, 1H, H_H), 2.18–2.08 (m, 1H, $H_{H'}$) ppm;

^{13}C NMR (101 MHz, $CDCl_3$): δ_C 143.8 (C_B), 133.8 (C_E), 129.7 (C_C), 127.6 (C_D), 56.9 (1:1:1 t, $^2J_{CD}$ = 22.2 Hz, C_F), 46.2 (C_I), 45.4 (C_G), 36.4 (C_H), 21.6 (C_A) ppm.

IR (film): ν_{max} 3668, 2901, 1597, 1342, 1158, 1096 cm^{-1}.

HRMS (APCI): m/z calc'd for $C_{11}H_{13}DO_2NS^{79}Br$ $[M+H]^+$ 305.0064 found 305.0066.

(3-Bromo-1-tosylpyrrolidin-2-yl)diphenylmethanol (403a)



According to a combination of **General Procedures M** and **Q**, anhydrous THF (0.74 mL) was added to 3-bromopyrrolidine hydrochloride **375** (37 mg, 0.20 mmol, 1.0 eq.) to give a suspension and cooled to −78 °C (dry ice/acetone). To this suspension, phenyl lithium (1.8 M in Bu_2O; 0.22 mL, 0.40 mmol, 2.0 eq.) was added dropwise (~0.5 mL/min) and the reaction mixture stirred at this temperature for 15 minutes, after which time the reaction mixture was homogeneous and pale brown. At −78 °C, TMEDA (34 µL, 0.22 mmol, 1.1 eq.) was added, followed by *sec*-butyl lithium (1.3 M in cyclohexane/hexane; 0.17 mL, 0.22 mmol, 1.1 eq.) dropwise (~0.5 mL/min). The red/brown reaction mixture was stirred at −78 °C for 2 hours. After this time, benzophenone (1 M in THF; 40 mg, 0.22 mmol, 1.1 eq.) was added dropwise (~0.5 mL/min) and the reaction left to stir at −78 °C for 1 hour. H_2O (2 M in THF; 0.11 mL, 0.22 mmol, 1.1 eq.) was then added dropwise (~0.5 mL/min) and the solution stirred at −78 °C for 5 minutes. Lithium bromide (dried with a heat gun under vacuum and left to cool; 174 mg, 2.0 mmol, 10 eq.) was then added to the reaction mixture at −78 °C and the resultant suspension warmed to rt, at which point the lithium bromide dissolved. Tosyl anhydride (131 mg, 0.40 mmol, 2.0 eq.) was added to the solution as a solid at rt and the reaction mixture was stirred at this temperature for 15 minutes. After this time, water (5 mL) and CH_2Cl_2 (5 mL) were added to the reaction vessel. The aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL) and the combined organic layers dried over $MgSO_4$ and concentrated *in vacuo*. The crude residue (47% **403a** by quantitative ^1H NMR spectroscopic analysis) was purified by flash column chromatography (10:1 pentane/EtOAc) to give the product (35 mg, 36%) as a white crystalline solid.

$\mathbf{R_f}$ = 0.39 (pentane/EtOAc 4:1).

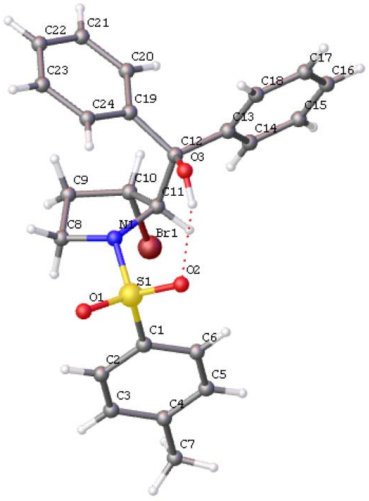
NMR Spectroscopy:

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.78–7.64 (m, 2H, H_D), 7.47–7.38 (m, 2H, H_{Ph}), 7.38–7.13 (m, 10H, H_C + H_{Ph}), 4.90 (s, 1H, H_F), 4.75 (br s, 1H, H_K), 4.23 (d, $^{3}J_{HH}$ = 5.3 Hz, 1H, H_G), 3.44–3.30 (m, 1H, H_I), 3.19 (apparent td, J_{HH} = 9.1, 1.3 Hz, 1H, $H_{I'}$), 2.37 (s, 3H, H_A), 1.57 (dd, $^{2}J_{HH}$ = 14.6 Hz, $^{3}J_{HH}$ = 7.3 Hz, 1H, H_H), 0.72 (dddd, $^{2}J_{HH}$ = 14.6 Hz, $^{3}J_{HH}$ = 10.8, 8.9, 5.3 Hz, 1H, $H_{H'}$) ppm;

^{13}C NMR (101 MHz, $CDCl_3$): δ_C 145.5 (C_{Ph}), 144.4 (C_B), 143.0 (C_{Ph}), 133.0 (C_E), 129.7 (C_D), 128.7 (C_C), 128.4 (CH_{Ph}), 128.3 (CH_{Ph}), 127.9 (2 × CH_{Ph}), 127.9 (CH_{Ph}), 127.4 (CH_{Ph}), 79.9 (C_F), 77.3 (C_J), 51.1 (C_G), 48.0 (C_I), 34.1 (C_H), 21.7 (C_A) ppm.

IR (film): ν_{max} 3675, 3464 (br), 2988, 2901, 1598, 1447, 1338, 1154, 1046 cm^{-1}.

HRMS (ESI): m/z calc'd for $C_{24}H_{24}O_3NNaS^{79}Br$ $[M+Na]^+$ 508.0552 found 508.0551.

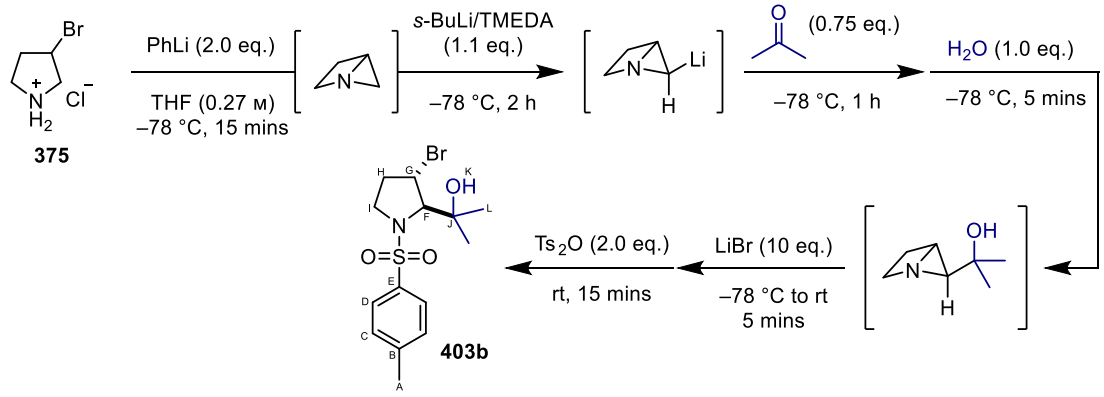


*Supplementary Figure 3. Crystal structure of **403a**.*

*Supplementary Table 1. Crystal data and structure refinement for **403a**.*

Empirical formula	$C_{24}H_{24}BrNO_3S$
Formula weight	486.41
Temperature/K	100(2)
Crystal system	orthorhombic
Space group	$P2_12_12_1$
a/Å	7.6692(2)
b/Å	13.9399(4)
c/Å	19.8126(6)
α/°	90
β/°	90
γ/°	90
Volume/Å^3	2118.12(10)
Z	4
ρ_{calc}g/cm^3	1.525
μ/mm^{-1}	3.782
F(000)	1000.0
Crystal size/mm^3	0.248 × 0.084 × 0.061
Radiation	CuKα (λ = 1.54178)
2θ range for data collection/°	7.754 to 144.506
Index ranges	$-9 \leq h \leq 8$, $-17 \leq k \leq 17$, $-23 \leq l \leq 24$
Reflections collected	28417
Independent reflections	4177 [R_{int} = 0.0825, R_{sigma} = 0.0430]
Data/restraints/parameters	4177/1/277
Goodness-of-fit on F^2	1.059
Final R indexes [I>=2σ (I)]	R_1 = 0.0383, wR_2 = 0.1007
Final R indexes [all data]	R_1 = 0.0400, wR_2 = 0.1019
Largest diff. peak/hole / e Å^{-3}	0.90/-0.68

2-(3-Bromo-1-tosylpyrrolidin-2-yl)propan-2-ol (403b)



According to a combination of **General Procedures M** and **Q**, anhydrous THF (0.74 mL) was added to 3-bromopyrrolidine hydrochloride **375** (37 mg, 0.20 mmol, 1.0 eq.) to give a suspension and cooled to −78 °C (dry ice/acetone). To this suspension, phenyl lithium (1.9 M in Bu_2O; 0.40 mmol, 2.0 eq.) was added dropwise (~0.5 mL/min) and the reaction mixture stirred at this temperature for 15 minutes, after which time the reaction mixture was homogeneous and pale brown. At −78 °C, TMEDA (34 µL, 0.22 mmol, 1.1 eq.) was added, followed by *sec*-butyl lithium (1.3 M in cyclohexane/hexane; 0.18 mL, 0.22 mmol, 1.1 eq.) dropwise (~0.5 mL/min). The red/brown reaction mixture was stirred at −78 °C for 2 hours. After this time, acetone (1 M in THF; 11 µL, 0.15 mmol, 0.75 eq.) was added and the reaction left to stir at −78 °C for 1 hour. H_2O (2 M in THF; 0.10 mL, 0.20 mmol, 1.0 eq.) was then added dropwise (~0.5 mL/min) and the solution stirred at −78 °C for 5 minutes. Lithium bromide (dried with a heat gun under vacuum and left to cool; 174 mg, 2.0 mmol, 10 eq.) was then added to the reaction mixture at −78 °C and the resultant suspension warmed to rt, at which point the lithium bromide dissolved. Tosyl anhydride (131 mg, 0.40 mmol, 2.0 eq.) was added to the solution as a solid at rt and the reaction mixture was stirred at this temperature for 15 minutes. After this time, water (5 mL) and CH_2Cl_2 (5 mL) were added to the reaction vessel. The aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL), and the combined organic layers dried over $MgSO_4$ and concentrated *in vacuo*. The crude residue (34% **403b** by quantitative ^{1}H NMR spectroscopic analysis) was purified by flash column chromatography (10:1 to 2:1 pentane/EtOAc then 9:1 to 4:1 CH_2Cl_2/EtOAc) to give the product (21 mg, 38%) as a white solid.

$\mathbf{R_f}$ = 0.40 (CH_2Cl_2/EtOAc 4:1).

NMR Spectroscopy:

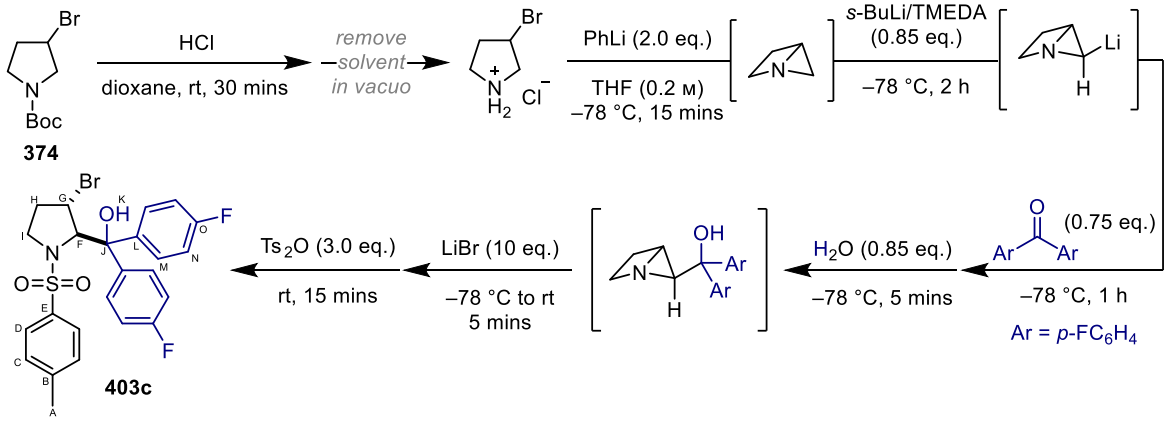
^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.84–7.77 (m, 2H, H_D), 7.38–7.31 (m, 2H, H_C), 4.34 (ddd, $^3J_{HH}$ = 6.1, 4.0, 2.2 Hz, 1H, H_G), 3.97 (d, $^3J_{HH}$ = 2.2 Hz, 1H, H_F), 3.62 (apparent dt, $^2J_{HH}$ = 10.9 Hz, $^3J_{HH}$ = 7.5 Hz, 1H, H_I), 3.50 (ddd, $^2J_{HH}$ = 10.9 Hz, $^3J_{HH}$ = 7.4, 5.4 Hz, 1H, $H_{I'}$), 2.92 (s, 1H, H_K), 2.48–2.34 (m, 1H, H_H), 2.44 (s, 3H, H_A), 1.79 (dddd, J_{HH} = 14.1, 7.5, 5.4, 4.0 Hz, 1H, $H_{H'}$), 1.39 (s, 3H, H_L), 1.26 (s, 3H, $H_{L'}$) ppm;

^{13}C NMR (101 MHz, $CDCl_3$): δ_C 144.3 (C_B), 133.6 (C_E), 129.7 (C_D), 128.5 (C_C), 78.4 (C_F), 73.1 (C_J), 48.9 (C_I), 47.7 (C_G), 36.1 (C_H), 28.3 (C_L), 25.9 ($C_{L'}$), 21.6 (C_A) ppm.

IR (film): ν_{max} 3662, 3510 (br), 2971, 2924, 1598, 1342, 1158, 1091 cm^{-1}.

HRMS (ESI): m/z calc'd for $C_{14}H_{20}O_3NNaS^{79}Br$ $[M+Na]^+$ 384.0239 found 384.0230.

(3-Bromo-1-tosylpyrrolidin-2-yl)bis(4-fluorophenyl)methanol (403c)



According to a combination of **General Procedures N** and **Q**, *N*-Boc pyrrolidine **374** (50 mg, 0.20 mmol, 1.0 eq.) was added to a Schlenk flask and HCl (4 M in dioxane; 1.3 mL) was added at rt. The resultant solution was stirred at rt for 30 minutes, after which time the solvent was removed *in vacuo*. A liquid nitrogen-cooled trap was placed between the Schlenk flask and Schlenk line to collect the removed HCl/dioxane and prevent damage to the Schlenk line and vacuum pump. The pale pink solid was then washed with anhydrous THF (3 × 1 mL) under a N_2 atmosphere (THF was added to the dry solid under a N_2 atmosphere to give a fine suspension, the Schlenk flask was sonicated and then the THF was removed *in vacuo*). Anhydrous THF (1.00 mL) was added to the pale pink solid to give a fine suspension and cooled to −78 °C (dry ice/acetone). To this suspension, phenyl lithium (1.8 M in Bu_2O; 0.23 mL, 0.40 mmol, 2.0 eq.) was added dropwise (~0.5 mL/min) and the reaction mixture stirred at this temperature for 15 minutes, after which time the reaction mixture was homogeneous and pale brown. At −78 °C, TMEDA (25 µL, 0.17 mmol, 0.85 eq.) was added, followed by *sec*-butyl lithium (1.3 M in cyclohexane/hexane; 0.14 mL, 0.17 mmol, 0.85 eq.) dropwise (~0.5 mL/min).

The red/brown reaction mixture was stirred at −78 °C for 2 hours. To this solution 4,4′-difluorobenzophenone (1 M in THF; 33 mg, 0.15 mmol, 0.75 eq.) was added and the reaction left to stir at −78 °C for 1 hour. H_2O (2 M in THF; 0.09 mL, 0.17 mmol, 0.85 eq.) was then added dropwise (~0.5 mL/min) and the solution stirred at −78 °C for 5 minutes. Lithium bromide (dried with a heat gun under vacuum and left to cool; 174 mg, 2.0 mmol, 10 eq.) was then added to the reaction mixture at −78 °C and the resultant suspension warmed to rt, at which point the lithium bromide dissolved. Tosyl anhydride (196 mg, 0.60 mmol, 3.0 eq.) was added to the solution as a solid at rt and the reaction mixture was stirred at this temperature for 15 minutes. After this time, water (5 mL) and CH_2Cl_2 (5 mL) were added to the reaction vessel. The aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL) and the combined organic layers dried over $MgSO_4$ and concentrated *in vacuo*. The crude residue (41% **403c** and 62% **381** by quantitative ^{1}H NMR spectroscopic analysis) was purified by flash column chromatography (20:1, 9:1 to 5:1 pentane/EtOAc) to give a mixture of **403c** and **381**. An analytically pure sample of **403c** (6 mg) was isolated through further flash column chromatography (3:1 toluene/EtOAc).

$\mathbf{R_f}$ = 0.28 (pentane/EtOAc 4:1).

NMR Spectroscopy:

^{1}H NMR (500 MHz, $CDCl_3$): δ_H 7.83–7.73 (m, 2H, H_D), 7.48–7.41 (m, 2H, H_M), 7.39–7.35 (m, 2H, H_C), 7.32–7.27 (m, 2H, $H_{M'}$), 7.12–7.06 (m, 2H, H_N), 7.01–6.95 (m, 2H, $H_{N'}$), 4.94–4.85 (m, 2H, $H_{F,\,K}$), 4.22 (d, $^3J_{HH}$ = 5.2 Hz, 1H, H_G), 3.49–3.38 (m, 1H, H_I), 3.30–3.24 (m, 1H, $H_{I'}$), 2.46 (s, 3H, H_A), 1.73–1.64 (m, 1H, H_H), 0.91–0.77 (m, 1H, $H_{H'}$) ppm;

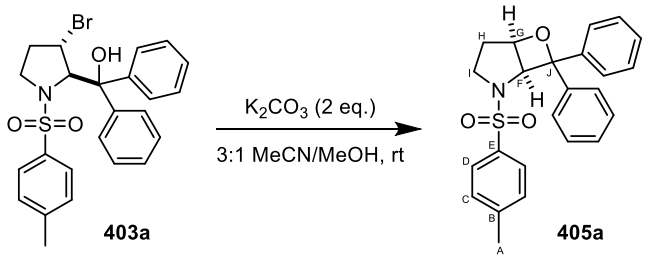
^{13}C NMR (125 MHz, $CDCl_3$): δ_C 162.5 (d, $^1J_{CF}$ = 248.2 Hz, C_O), 162.3 (d, $^1J_{CF}$ = 249.5 Hz, $C_{O'}$), 144.7 (C_B), 141.2 (d, $^4J_{CF}$ = 3.4 Hz, C_L), 138.6 (d, $^4J_{CF}$ = 3.3 Hz, $C_{L'}$), 132.6 (C_E), 130.0 (d, $^3J_{CF}$ = 8.0 Hz, C_M), 129.7 (C_D), 129.2 (d, $^3J_{CF}$ = 8.1 Hz, $C_{M'}$), 128.8 (C_C), 115.3 (d, $^2J_{CF}$ = 21.3 Hz, C_N), 114.9 (d, $^2J_{CF}$ = 21.2 Hz, $C_{N'}$), 79.2 (C_F), 77.2 (C_J), 50.6 (C_G), 48.0 (C_I), 34.1 (C_H), 21.7 (C_A) ppm;

^{19}F NMR (377 MHz, $CDCl_3$): δ_F −113.8 ppm.

IR (film): ν_{max} 3475 (br), 2959, 2922, 2858, 1601, 1507, 1343, 1230, 1158 cm^{-1}.

HRMS (Nanospray w/ NaCl additive): m/z calc'd for $C_{24}H_{22}O_3NNaS^{79}BrF_2$ $[M+Na]^+$ 544.0370 found 544.0352.

7,7-Diphenyl-2-tosyl-6-oxa-2-azabicyclo[3.2.0]heptane (405a)



According to a modified literature procedure,[180] alcohol **403a** (18 mg, 0.04 mmol, 1.0 eq.) was dissolved in 3:1 MeCN/MeOH (anhydrous) (1.08 mL/0.36 mL) at rt. Potassium carbonate (10 mg, 0.07 mmol, 2.0 eq.) was added to the solution and the resultant suspension stirred at rt for 5 hours after which time TLC analysis confirmed full consumption of starting material. Then, water (5 mL) and EtOAc (5 mL) were added to the reaction vessel. The aqueous layer was extracted with EtOAc (3 × 5 mL) and the combined organic layers dried over $MgSO_4$ and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (9:1 pentane/EtOAc) to afford the product (11 mg, 73%) as a colourless oil.

$\mathbf{R_f}$ = 0.56 (pentane/EtOAc 4:1).

NMR Spectroscopy:

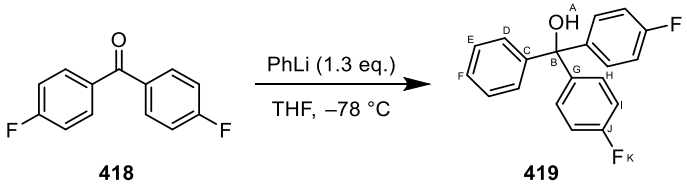
^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.56–7.47 (m, 3H, H_{Ar}), 7.47–7.39 (m, 2H, H_{Ar}), 7.38–7.05 (m, 9H, H_{Ar}), 5.21 (d, $^3J_{HH}$ = 4.6 Hz, 1H, H_F), 5.16 (apparent t, $^3J_{HH}$ = 4.6 Hz, 1H, H_G), 3.57 (dd, $^2J_{HH}$ = 12.4 Hz, $^3J_{HH}$ = 8.4 Hz, 1H, H_I), 3.01 (apparent td, $^2J_{HH}$ = $^3J_{HH}$ = 12.4 Hz, $^3J_{HH}$ = 6.0 Hz, 1H, $H_{I'}$), 2.32 (s, 3H, H_A), 1.83 (dd, $^2J_{HH}$ = 14.1 Hz, $^3J_{HH}$ = 5.9 Hz, 1H, H_H), 0.96 (dddd, $^2J_{HH}$ = 14.1 Hz, $^3J_{HH}$ = 11.7, 8.5, 4.3 Hz, 1H, $H_{H'}$) ppm;

^{13}C NMR (101 MHz, $CDCl_3$): δ_C 145.3 (C_{Ar}), 143.6 (C_B), 141.3 (C_{Ar}), 136.7 (C_{Ar}), 129.9 (C_C), 128.6 (CH_{Ar}), 127.9 (CH_{Ar}), 127.3 (CH_{Ar}), 127.0 (CH_{Ar}), 126.8 (CH_{Ar}), 125.0 (CH_{Ar}), 124.8 (CH_{Ar}), 91.0 (C_J), 82.5 (C_G), 68.7 (C_F), 48.4 (C_I), 32.0 (C_H), 21.5 (C_A) ppm.

IR (film): ν_{max} 3675, 2971, 2901, 1598, 1348, 1160, 1066 cm^{-1}.

HRMS (ESI): m/z calc'd for $C_{24}H_{23}O_3NNaS$ $[M+Na]^+$ 428.1291 found 428.1289.

Bis(4-fluorophenyl)(phenyl)methanol (419)



418 419

Ketone **418** (22 mg, 0.10 mmol, 1.0 eq.) was dissolved in anhydrous THF (0.20 mL) and cooled to −78 °C (dry ice/acetone), at which temperature phenyl lithium (1.84 M in Bu_2O; 0.07 mL, 0.13 mmol, 1.3 eq.) was added. The reaction mixture was stirred at −78 °C for 1.5 hours, after which time aqueous saturated NH_4Cl (2 mL) and EtOAc (2 mL) were added. The aqueous layer was extracted with EtOAc (3 × 2 mL) and the combined organic layers dried over $MgSO_4$ and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (95:5 to 9:1 pentane/EtOAc) to afford the product (20 mg, 68%) as a colourless oil.

$\mathbf{R_f}$ = 0.21 (pentane/EtOAc 95:5).

NMR Spectroscopy:

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.37–7.28 (m, 2H, H_H), 7.28–7.17 (m, 7H, $H_{D, E, F, H}$), 7.07–6.90 (m, 4H, H_I), 2.76 (s, 1H, H_A) ppm;

^{13}C NMR (101 MHz, $CDCl_3$): δ_C 162.1 (d, $^{1}J_{CF}$ = 246.7 Hz, C_J), 146.7 (C_C), 142.6 (d, $^{4}J_{CF}$ = 3.3 Hz, C_G), 129.7 (d, $^{3}J_{CF}$ = 8.1 Hz, C_H), 128.3 (C_D *or* C_E), 127.8 (C_D *or* C_E), 127.7 (C_F), 114.9 (d, $^{2}J_{CF}$ = 21.4 Hz, C_I), 81.4 (C_B) ppm;

^{19}F NMR (377 MHz, $CDCl_3$): δ_F −115.1 ppm.

IR (film): ν_{max} 3471, (br), 2925, 2854, 1602, 1506, 1447, 1227, 1159, 1015 cm^{-1}.

HRMS (EI): m/z calc'd for $C_{19}H_{14}OF_2$ $[M]^+$ 296.1003 found 296.1007.

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