# Novel Transformations on Azetidines

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## Abstract

### Novel Transformations on Azetidines

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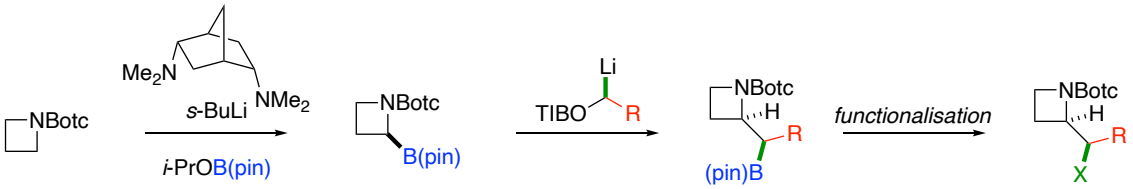
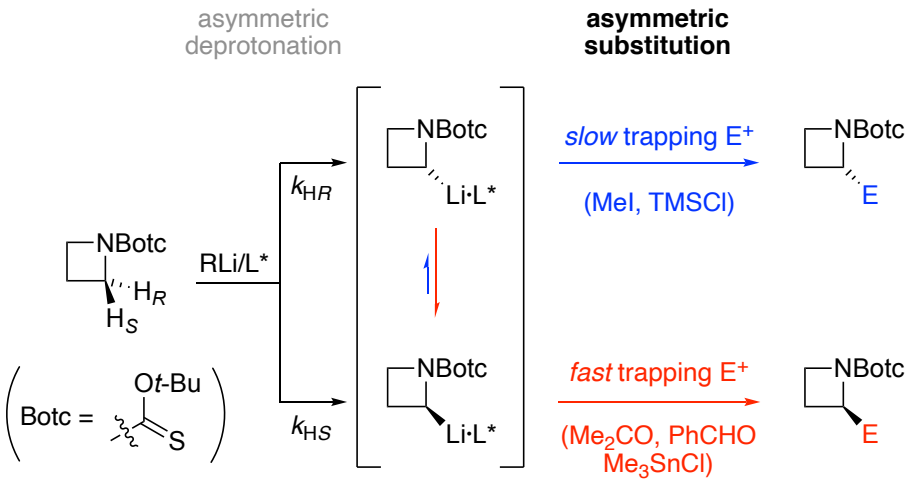
This thesis describes transformations on azetidines, with focus on functionalisation α- to N. Direct asymmetric azetidine functionalisation has been a long-standing challenge, with limited examples in the literature. Recent work within the Hodgson group developed the *N*-*tert*-butoxythiocarbonyl (Botc) directing/activating group as an effective and practical means to effect asymmetric α-lithiation—electrophile trapping on azetidines. This thesis describes significant expansion and mechanistic understanding of this methodology.

The feasibility of accessing enantioenriched 2,4-disubstituted azetidines by α'-lithiation—electrophile trapping is explored, with modifications of the *N*-directing group detailed.

Additionally, examination of an α-boronic ester 'synthetic handle' as a means to functionalise azetidines is detailed. This includes developing a means to synthesise an enantioenriched α-boronic ester azetidine via asymmetric α-lithiation—borylation, with subsequent development of an asymmetric 1,2-metallate rearrangement homologation reaction, to give highly enantioenriched azetidines with control of the two contiguous stereocentres. Derivatisation of the homologated azetidines is described, allowing for access to a range of 2-substituted azetidines previously inaccessible via direct α-lithiation—electrophile trapping.




Finally, studies in the origins of the enantiodetermining mechanisms for the asymmetric α-lithiation—electrophile trapping of *N*-Botc azetidine show an intriguing electrophile dependent mechanism, which can rationalise the origins of the differing sense of asymmetric induction for particular electrophiles



## Acknowledgements

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I would like to acknowledge my friends and family who have supported me throughout my D.Phil, I could not have done this without you. In particular my Hurst Street housemates, who helped make my time away from the lab so enjoyable. My family for all your support, in particular during lockdown. Finally, I would like to send a special thanks to my partner Eva, those love and support made every day a blessing.

## Statement of Authorship

The work described in this thesis is entirely my own, with the following exceptions.

- Asymmetric lithiation—electrophile trapping of *N*-Botc azetidine **101a** in Tables 12 and 17 (Claire Mortimer).

- X-ray crystallography analyses and data (Owen Smith)

- Where reference is given to a published source or thesis.

Signature: Date: 06/10/2020

Name: Pascal Kieran Delany

## Stereochemistry

Throughout this thesis, the schematic nomenclature shown in Figure A is used to differentiate between absolute and relative stereochemistry. Stereoecentres that are enantioenriched, but of *initially* unknown absolute configuration are represented with a hollow wedge or a dashed line.[1]

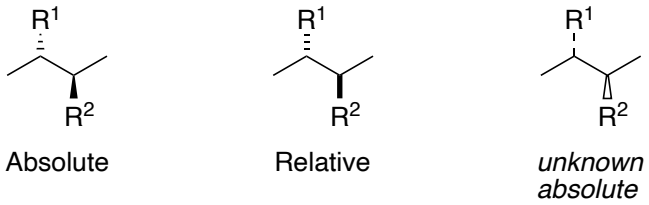



**Figure A.** Stereochemical notation used.

[1] Maehr, H *J. Chem. Inf. Comput. Sci.* **2002**, *42,* 894-902.

## Abbreviations

| | | | |
|---|---|---|---|
| ( )n | number of repeat units | Botc | *tert*-butoxythiocarbonyl |
| Δ | reflux | bpy | 2,2'-bipyridine |
| ° C | degrees Celsius | Bt | benzotriazolyl |
| ~ | approximately | Br | broad |
| % D | percentage deuteration | BRSM | Based on recovered starting material |
| δ | chemical shift | *n*-Bu | butyl |
| µ | micro | *s*-Bu | *sec*-butyl |
| ABB | Azabicyclo[1.1.0]butane | *t*-Bu | *tert*-butyl |
| Ac | acetyl | Bus | *tert*-butyl sulfonyl |
| AIBN | azobisisobutyronitrile | calcd | calculated |
| aq | aqueous | cat. | catalytic |
| Ar | aryl | Cb | *N,N*-diisopropylcarbamate |
| atm | atmosphere | Cbz | carboxybenzoyl |
| BINOL | 1,1'-bi-2-naphthol | $cm^{-1}$ | wavenumber |
| Bn | benzyl | COSY | correlation spectroscopy |
| Boc | *tert*-butyloxycarbonyl | *cf.* | compare |

| | | | |
|---|---|---|---|
| d | day(s), doublet | $E/E^+$ | electrophile |
| dba | dibenzylideneacetone | e.g. | for example |
| DCE | 1,2-dichloroethane | EDC | 1-ethyl-3-(3-dimethylamino)carbodiimide |
| DDQ | 2,3-dichloro-5,6-dicyano- 1,4-benzoquinone | EDG | electron donating group |
| DIAD | diisopropyl azodicarboxylate | epi | epimerisation |
| DIANANE | 2,5-diaminonorbornane | equiv | equivalent(s) |
| DIBAL-H | diisobutylaluminium hydride | er | enantiomeric ratio |
| DIPEA | *N*,*N*-diisopropylethylamine | ESI | electrospray ionisation |
| DKR | dynamic kinetic resolution | Et | ethyl |
| DMAP | 4-dimethylaminopyridine | EWG | electron withdrawing group |
| DMF | dimethylformamide | FI | field ionisation |
| DMSO | dimethyl sulfoxide | g | gram(s) |
| dr | diastereomeric ratio | GC | gas chromatography |
| dtbbpy | di-*tert*-butyl-bipyridine | GCMS | gas chromatography– mass spectrometry |
| DTR | dynamic thermodynamic resolution | h | hour(s) |

| | | | |
|---|---|---|---|
| HAT | hydrogen atom transfer | LDA | lithium diisopropyl amide |
| Hex | hexyl | lit. | literature |
| HPLC | high-performance liquid chromatography | LRMS | low resolution mass spectrometry |
| HRMS | high resolution mass spectrometry | LTMP | lithium 2,2,6,6 tetramethylpiperidide |
| HSQC | heteronuclear single quantum coherence | M | molar, parent mass |
| Hz | hertz | *m* | meta |
| i.e. | That is | m | milli, multiplet, medium |
| IR | infrared | M.S. | molecular sieves |
| *J* | coupling constant | m/z | mass to charge ratio |
| *k* | rate constant | Me | methyl |
| K | kelvin | MHz | megahertz |
| KIE | kinetic isotope effect | min | minute(s) |
| L/L* | generic ligand/generic chiral ligand | mol | mole(s) |
| LCMS | liquid chromatography—mass spectrometry | MOP | 2-(diphenylphosphino)-2'-methoxy-1,1'-binaphthyl |

| | | | |
|---|---|---|---|
| mp | melting point | piv | pivaloyl |
| Ms | mesylate | pKa | acid dissociation constant |
| MTPA-Cl | α-methoxy-α-(trifluoromethyl)phenylacetyl chloride | pKaH | pKa of conjugate acid |
| NBS | *N*-bromosuccinimide | ppm | part(s) per million |
| NMM | *N*-methylmorpholine | ppy | phenyl-pyridine |
| NMR | nuclear magnetic resonance | Pr | propyl |
| NOESY | nuclear Overhauser effect spectroscopy | *i*-Pr | isopropyl |
| Nu | nucleophile | py | pyridine |
| *o* | ortho | q | quartet |
| *p* | para | quant | quantitative |
| p | page number | quin | quintet |
| PCC | pyridinium chlorochromate | R | generic substituent |
| Pd/C | palladium on carbon | rac | racemic |
| PG | protecting group | $R_f$ | retention factor |
| Ph | phenyl | RSM | recovered starting material |
| pin | pinacolato | rt | room temperature |

| | | | |
|---|---|---|---|
| s | singlet, strong | TBME | *tert*-butyl methyl ether |
| sat. | saturated | temp | temperature |
| $S_EAr$ | electrophilic aromatic substitution | Tf | trifluoromethanesulfonyl |
| $S_E2inv$ | bimolecular electrophilic substitution invertive | TFA | trifluoroacetic acid |
| $S_E2ret$ | bimolecular electrophilic substitution retentive | THF | tetrahydrofuran |
| sept | septet | TIB | 2,4,6,-triisopropylbenzoate |
| SET | single electron transfer | TLC | thin layer chromatography |
| SFC | supercritical fluid chromatography | TMEDA | *N*,*N*,*N'*,*N'*-tetramethylethylenediamine |
| Si-gel | silica gel | TMS | trimethylsilyl |
| SM | starting material | TMSCl | trimethylsilyl chloride |
| (–/+)-sp | (−/+)-sparteine | TMSI | trimethylsilyl iodide |
| t | triplet | TOF | time of flight |
| $t_{1/2}$ | half life | Tr | triphenylmethyl |
| TBAF | tetrabutylammonium flouride | Ts | *para*-toluenesulfonyl |
| TBDMS | *tert*-butyldimethylsilyl | w | weak |

## Table of Contents

# 1. Introduction

This thesis describes an application of, and mechanistic investigations into, the lithiation—electrophile trapping of *N*-*tert*-(butoxythiocarbonyl) (Botc) azetidine. When the project was initially conceived, the main aims were to access enantioenriched 2,4-disubstituted-azetidines and to overcome some of the limitations associated with classical azetidine synthesis (discussed below). Therefore, background information regarding the importance of azetidines and their classical synthetic approaches is given. As these routes to azetidines are still widely relevant, recent examples of azetidine synthesis by the classical pathways are presented, with discussion of their pros and cons.

An increasing number of methodologies have been published demonstrating other means to directly functionalise the azetidine ring. Since these works are complimentary to ours and often utilise similar concepts to direct α-functionalisation, they will be discussed in this introduction to show the range of azetidine ring functionalisation available.

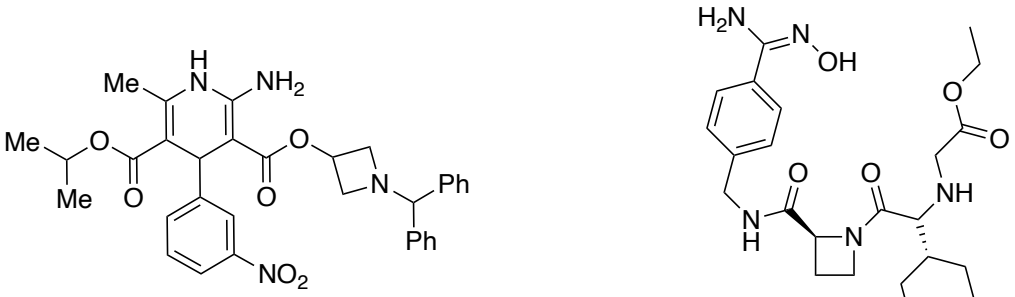
The final part of the introduction will discuss directed α-lithiation, with focus on azetidine synthesis. This will incorporate the most recent work within the group on directed α-lithiation—electrophile trappings on azetidine to show the specific context behind the project(s).

## 1.1 Saturated azacycles

Saturated heterocycles constitute a privileged class of organic compounds. As saturated azacycles are ubiquitous structural motifs in natural products,[1] drug designs,[2] organocatalysts[3] and chiral ligands,[4] they arguably comprise some of the most valuable compounds in organic chemistry. As a result, chemists are constantly developing new and improved methodologies towards their synthesis.

## 1.2 Importance of azetidines

Azetidines make up the four-membered ring category of saturated azacycles. Whilst the strained four-membered ring make azetidines less synthetically available compounds when compared to larger ring analogues (pyrrolidines and piperidines), the conformational rigidity of azetidines gives rise to a range desirable topological and chemical properties.[5] These properties make azetidines useful structural scaffolds in medicinal chemistry, with azetidine compounds often demonstrating high biological activity,[6] or serving as useful bioisoteres.[7] For example, the calcium channel antagonist, azelnidipine **1** (Figure 1) is already in use as a treatment for hypertension,[8] whilst ximelagatran **2** has been an encouraging drug lead reaching the final stages of clinical trials as a thrombin inhibitor.[9]



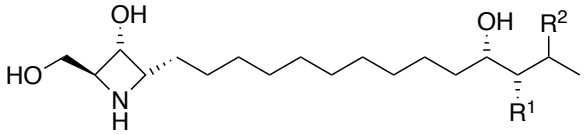

**1** (azelnidipine) **2** (ximelagatran)

**Figure 1.** Azetidine containing drug compounds.

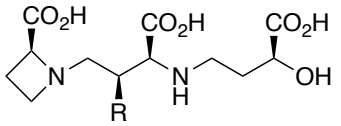
The azetidine structural motif is also found among a few natural products which have been shown to have strong biological activity. Among those are the azetidine alkaloids penaresidins A and B, **3a+3b** (Figure 2) isolated from an Okinawan sponge *Penares* sp.;[10] these are effective at increasing actomyosin ATP-ase activity.[11] Phytosiderophores mugineic acid **4a**, 2'-deoxymugineic acid **4b** and nicotianamine **5** are biosynthesised by plants to aid iron(III) uptake in the synthesis of chlorophyll.[12] This function is essential for

plant growth and consequently these compounds have generated interest in the agrochemical industry as a means for potential biofortification.[13]

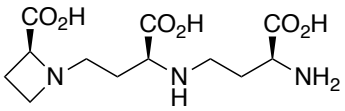
Azetidine non-protein amino acid derivatives, such as, L-azetidine-2-carboxylic acid (**6**) are also of interest to the scientific community.[14] These are found naturally occurring in certain plants, including sugar beets, and are shown to reduce the growth of nearby competing plants.[15] This process works with the uptake of L-azetidine-2-carboxylic acid **6** by the competing plant; resulting in the plant replacing proline amino acids with L-azetidine-2-carboxylic acid **6** in the protein structures, causing diminished protein function. This ability to replace proline in peptide structures also gives azetidine amino acid derivatives potential peptidomimetic properties; due to their rigid four-membered ring system, they are able to effectively alter peptide conformational structure.[16]



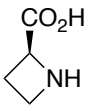
**3a** ($R^1$ = Me, $R^2$ = H, penaresidin A)
**3b** ($R^1$ = H, $R^2$ = Me, penaresidin B)



**4a** (R = OH, mugineic acid)
**4b** (R = H, 2'-deoxymugineic acid)



**5** (nicotianamine)



**6** (L-azetidine-2-carboxylic acid)

**Figure 2**. Naturally occurring azetidine compounds.

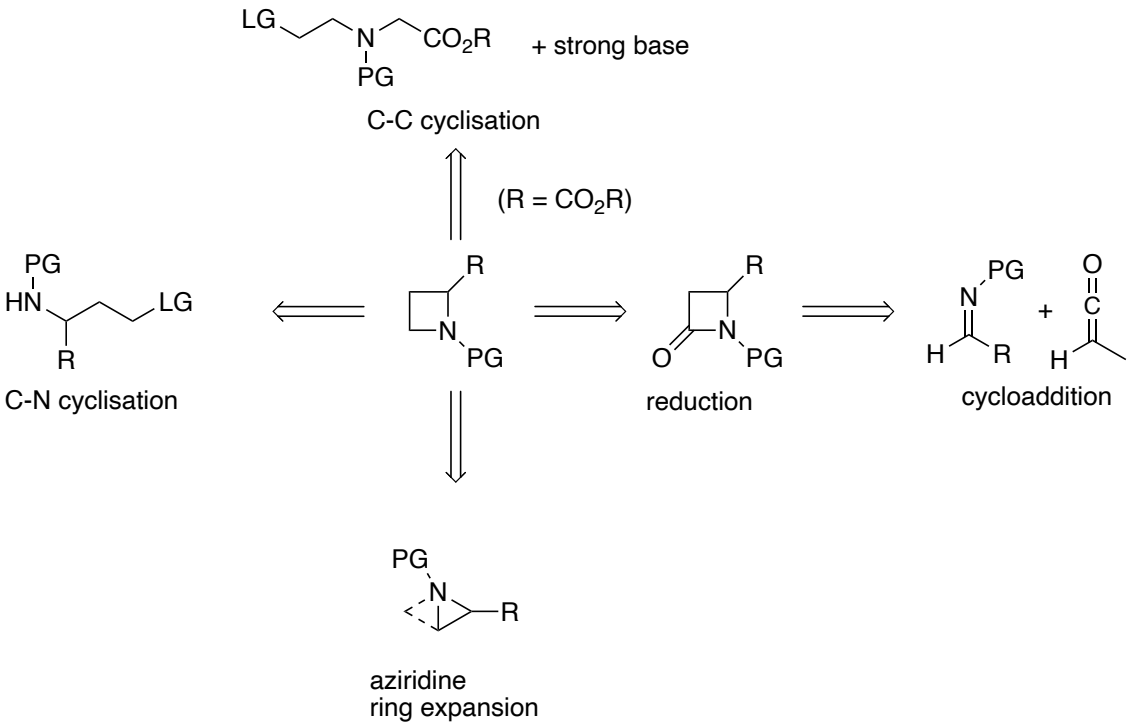
## 1.3 Classical approaches to substituted azetidines

Due to the highly strained nature of azetidines (105.4 kJ mol$^{-1}$, *cf.* aziridine 114.2 kJ mol$^{-1}$),[17] there lacks an effective general approach to synthesising functionalised azetidines (Scheme 1). In a series of cyclisation reactions involving halo-amines, the rate of ring-closing was

found to be slowest for azetidines.[18] This has resulted in a wide variety of substrate specific approaches towards synthesising substituted azetidines.

The majority of approaches depend on synthesising functionalised linear precursors, which often are cyclised via an amine intramolecular nucleophilic attack with an appropriate γ-leaving group (C-N cyclisation). Examples include $S_N2$ displacement of halides,[19] activated alcohols through Mitsunobu-type reactions,[20] activated alkenes,[21] epoxides[22] and activated allyl groups.[23] This approach faces the problem of relying on an energetically challenging cyclisation to form the four-membered ring, which frequently competes with side reactions such as elimination of the leaving group resulting in reduced yields and substrate scope.[11b] It also requires the non-trivial task of synthesising a functionalised linear precursor, which poses additional synthetic challenges, especially for preparing enantioenriched functionalised azetidines.

Similar issues are encountered in C-C cyclisation azetidine formation (Scheme 1). Additionally, anion stabilising functionalities, typically required for C-C cyclisation, reduce anion configurational stability, resulting in poor enantioselectivity. β-Lactam reduction can also provide access to a number of substituted azetidines; however, the lack of general mild reducing conditions limits the synthetic scope. Strain releasing ring expansion of aziridines or azabicyclobutanes (ABB) has gained increased attention; however, examples introducing functionalities at the α-position of the azetidine remain limited.

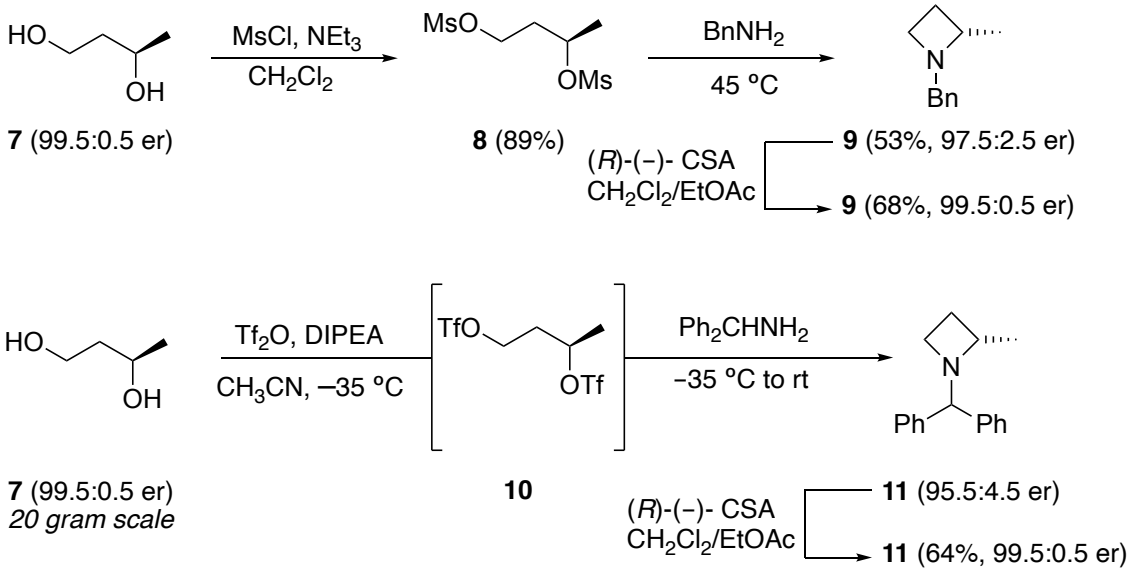



**Scheme 1**. Classical approaches to substituted azetidines.

### 1.3.1 C-N cyclisation

Classical C-N cyclisation generally relies on the preparation of γ-amino alcohols followed by activation of the alcohol group to a suitable leaving group (via halogenation, or sulfonate formation). Another common approach is to synthesise 1,3-dielectrophiles, which can be doubly displaced with a primary amine nucleophile to form azetidines. A recent application of C-N cyclisation in the multi gram synthesis of enantioenriched (*S*)-2-methyl-azetidines **9** and **11** through use of 1,3-dielectrophiles was demonstrated by Smith and co-workers (Scheme 2).[24] Commercially available enantiopure 1,3-diol **7** was initially mesylated to give dimesylate **8**, which, following addition of benzylamine, cyclised to give enantioenriched azetidine **9**. However, this route proved to be inefficient for a multi-gram synthesis due to unwanted dimerisation and polymerisation. To overcome these issues, the authors found that utilising a more reactive ditriflate **10** intermediate, followed by introduction of benzhydrylamine, allowed for efficient 'one-pot' multi-gram 2-methyl-azetidine **11**

formation. However, even under the optimised reaction conditions, a trace amount (~5%) of the elimination product was formed. Additionally, the reaction required a recrystallisation step to recover the enantioenrichment that was eroded in the cyclisation step.

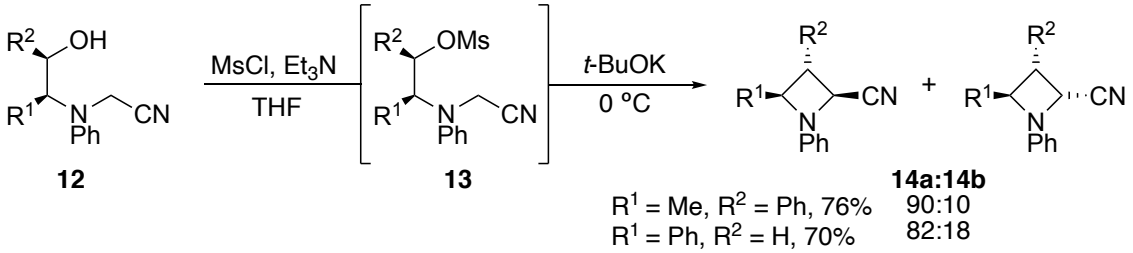



**Scheme 2.** 1,3-dielectrophile synthesis of enantioenriched azetidine via C-N cyclisation.[24]

### 1.3.2 C-C cyclisation

C–C bond forming cyclisation approaches have also provided successful routes to the synthesis of substituted azetidines. These approaches predominantly rely on there being an acidic α-C-H proton stabilised by an appropriate functional group (carboxylic acids,[25] esters[26] and phosphonates[27]) along with a suitable leaving group β- to nitrogen, which is displaced following nucleophilic attack by an anion formed following deprotonation (Scheme 1). These approaches benefit from being able to introduce groups onto the nitrogen that would otherwise be susceptible to nucleophilic attack via the C–N cyclisation approach.[28] However, these methods often suffer from a lack of selectivity in the final cyclisation step, therefore resulting in the final product being either racemic or a mixture of diastereomers.

Extensive work by Couty and co-workers have shown α-amino-nitriles to be versatile α-C-H acidifying groups able to effectively synthesise azetidines via C-C bond formation.[29] This methodology was recently applied to successfully synthesise *N*-aryl-azetidines starting from 'chiral pool' β-amino alcohols (Scheme 3).[30] Interestingly, the cyclisation of *N*-aryl precursors proceeded smoothly despite the greater degree of $sp^2$ hybridisation on the aniline nitrogen, resulting in a higher degree of strain during the *4-exo-tet* cyclisation when compared to the *N*-alkyl analogues. The reaction also tolerated an aryl group attached α- to the nitrile group, to give an azetidine with an α-N quarternary carbon. Although successful for a range of azetidines, the reaction route can suffer from poor diastereoselectivity in the ring closing step, limiting the overall scope of the reaction sequence.



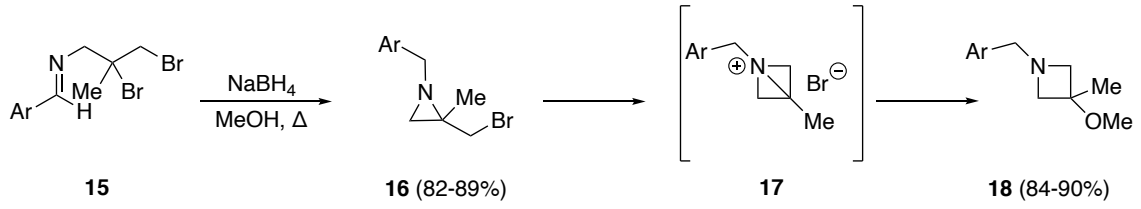

**Scheme 3.** Synthesis of 2,3,4-trisubstituted-azetidines through C-C cyclisation.[30]

Notably, when $R^1$ = Ph, $R^2$ = H, migration of the phenyl group to $R^2$ was achieved when mesylation was performed under reflux. This was believed by the authors to occur via the formation of an intermediate aziridinium species, which would subsequently undergo ring-opening by the chloride anion. Subsequent deprotonation and ring-closing of the resulting β-halo amine successfully gave 2,3-disubstituted-azetidines.

### 1.3.3 Aziridine ring opening

Another method to synthesise azetidines is through ring expansion of aziridines by a ring-opening and a closing mechanism. This potentially allows for larger substrate scope, as aziridine syntheses are well developed.[31] Work by De Kimpe *et al*, provides an effective

approach to 3-methoxy-azetidines from di-brominated imines **15** (Scheme 4).[32] This reaction proceeds by initial formation of aziridine intermediate **16**, which, following displacement of the remaining bromide, forms a reactive azabicyclobutane intermediate **17**. The latter can then undergo nucleophilic attack to open the ring to afford 3-methoxy-azetidines **18**; control of the formation of azetidines or aziridines from the nucleophilic attack was found to be dependent on the solvent used, with MeOH preferentially giving the azetidines. This approach however is yet to be successfully employed in the synthesis of disubstituted azetidines at the 2- or 4- position.

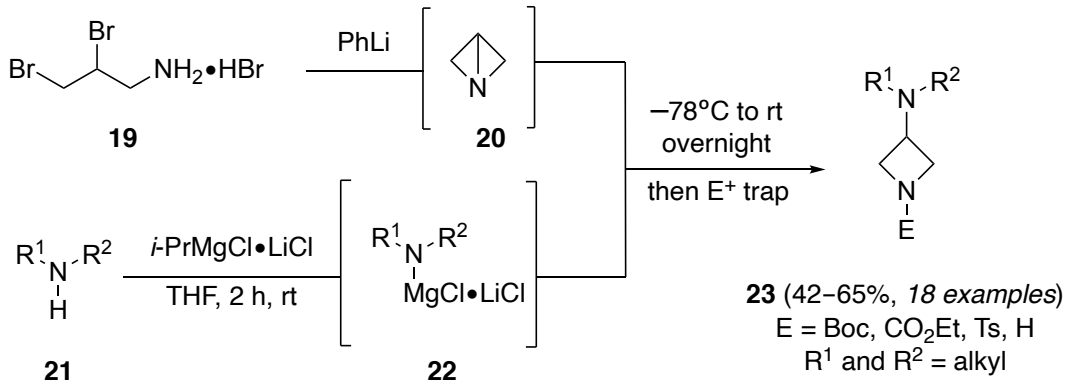



**15** **16** (82-89%) **17** **18** (84-90%)

**Scheme 4**. Azetidine synthesis through an aziridine ring expansion.[32]

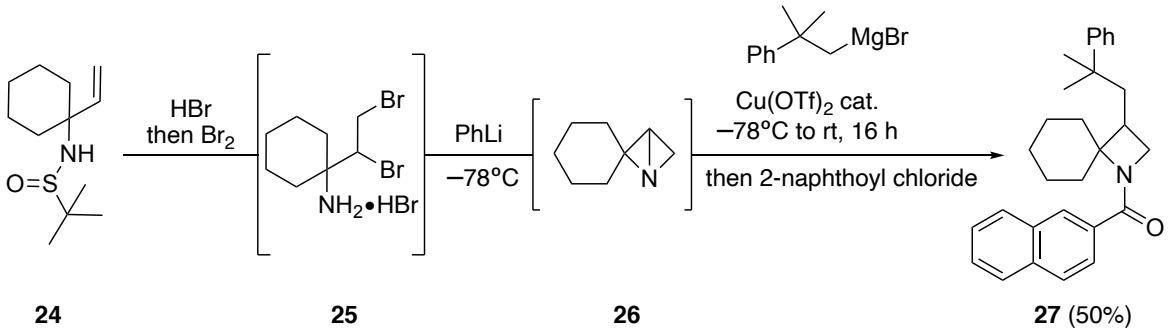
Recent work involving nucleophilic ring-opening of strained ABB **20** has been demonstrated to be an effective means to introduce a nucleophilic group at the 3-position of azetidines.[33] Despite ABB first being synthesised in 1969 with examples of strain-releasing nucleophilic attack,[34] only recently has this methodology become a popularised field for azetidine and other small-ring synthesis. Baran and co-workers have developed a method for direct alkyl amination of an *in situ* formed ABB (Scheme 5).[35] In this approach, ABB **20** is efficiently formed *in situ* by deprotonation of dibromide salt **19** with PhLi following a methodology described by Nagao *et al.* for the nucleophilic thiolation and halogenation of azetidines.[36] It was found that to the *in situ* formed ABB **20**, could be added secondary alkyl "turbo"-amides **22** across the strained central C-N bond. The 3-aminated azetidine could trap at the ring nitrogen atom with a range of electrophiles to give a suitably protected azetidine **23** (free base azetidine could also be isolated). This methodology was also utilised to

"azetidinylate" three late-stage pharmaceuticals, demonstrating potential application in medicinal chemistry.




**Scheme 5.** ABB synthesis and C-N bond addition with turbo amides.[35]

Extension of this methodology to work with simple Grignards catalysed by $Cu(OTf)_2$ (via formation of a reactive Gilman-type nucleophile) has also been demonstrated.[37] The study included the rapid synthesis of structurally complex 2-azaspirocycle **27** as a representative example of the methodology's utility (Scheme 6). However, despite the success of reaction, overall this synthetic approach to α-substituted azetidines suffers from limited examples involving α-substituted ABB's.[38]

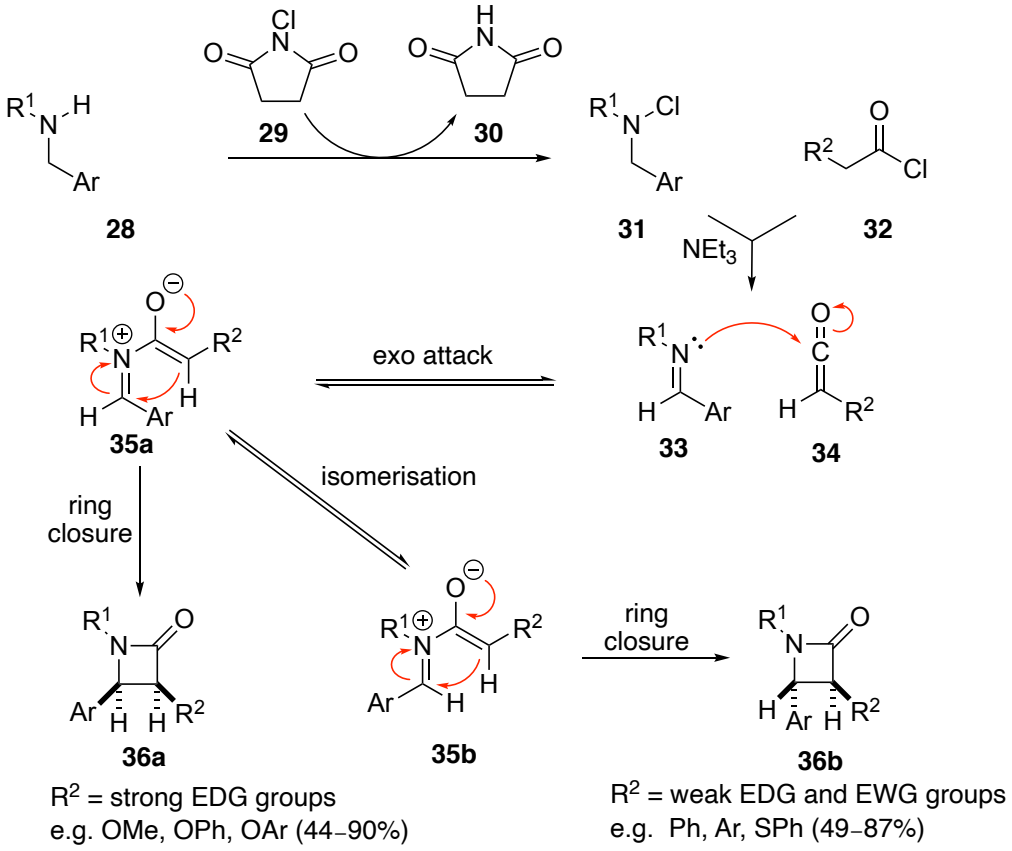



**Scheme 6.** Spirocyclic ABB synthesis and C-N bond addition with Gilman carbon nucleophile.[37]

### 1.3.4 β-lactam (azetidinone) formation and reduction

Azetidines can be accessed from the reduction of 2-azetidinones (β-lactams); the latter being a highly important structural motif in antibiotics[39] and anti-cholesterol drugs.[40] Due to the high number of biologically active compounds containing the β-lactam moiety, there

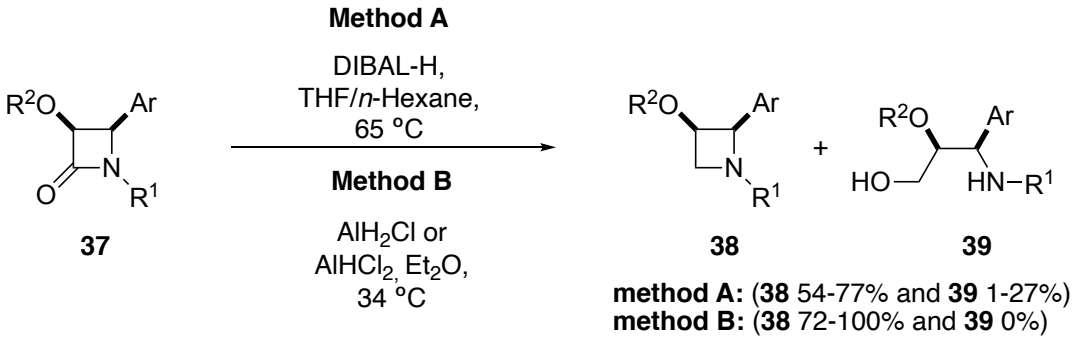
exist many ways to make them.[41] The classical and prevalent route for the synthesis of 2-azetidinones is by Staudinger cycloaddition,[42] a formal [2+2] cycloaddition between an *in situ* formed ketene and an imine. This reaction is generally considered to occur stepwise with initial nucleophilic attack of the ketene from the nitrogen on the imine to give an intermediate zwitterion intermediate, which subsequently undergoes either a ring-closing enolate addition or a 4π electron conrotatory electrocyclic ring closure (Scheme 7).[37-43] This can successfully place a variety of R groups with good diastereoselectivity at the 3- and 4- positions of the β-lactam.[44] A recent example by Porcheddu and co-workers synthesised a range of 3,4-disubstituted-azetidinones from *in situ* formed ketenes (from phenoxyacetyl chloride) and imines (from chloramines), in a one-pot procedure (Scheme 7).[45]




**Scheme 7.** Diastereoselective Staudinger reaction.[45]

It was found in this case that diastereoselectivity could be controlled by the nature of the $R^2$ substituent on ketene **34**. If the $R^2$ substituent is strongly electron donating, then ring closing of the zwitterion **35a** occurs rapidly (favouring formation of *cis* β-lactam **36a**). However, if the $R^2$ substituent is only weakly electron donating or electron withdrawing then isomerisation of zwitterion **35a** to the less sterically hindered zwitterion **35b** occurs with subsequent ring closing, forming the *trans* β-lactam **36b**.

β-Lactams have significant ketone character, due to the strained nature of the 4-membered ring preventing facile N lone pair delocalisation into the carbonyl group. As a result, harsh reducing agents, such as diborane, Raney Ni, $LiAlH_4$ (which can induce ring-opening),[46] can be avoided when reducing azetidinones to azetidines. Chloroalanes and DIBAL reduce azetidinones to azetidines efficiently with minimal undesired ring-opening (Scheme 8).[47]




**Scheme 8.** β-lactam reduction with DIBAL and chloroalanes.[47]

A recent example of a Staudinger/chloroalane approach gave a series of β-lactams and azetidines, which showed promising monoacylglycerol lipase inhibition.[48] However, the requirement for carbonyl reduction can be a limiting factor, as it can result in functional group incompatibilities/chemoselectivity problems. Recently, a protocol for reduction of

β-lactams to azetidines using the milder reducing agent sodium borohydride has been reported, which may help overcome these issues.[49]

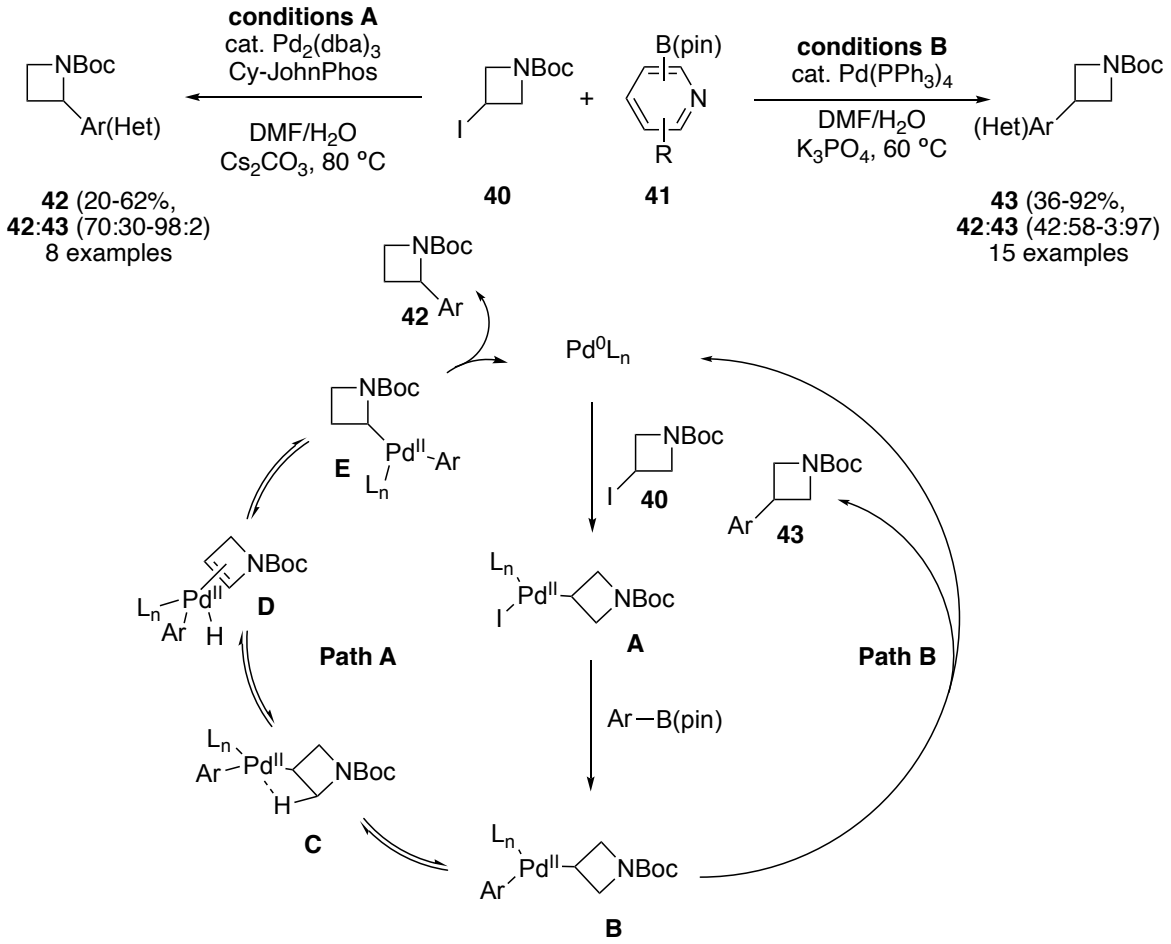
## 1.4 Modern approaches towards the synthesis of functionalised azetidines

Despite the various approaches developed for the synthesis of substituted azetidines through classical methods, a suitable general procedure for their synthesis is still lacking. As unsubstituted (or 3-substituted) azetidines are readily available,[50] a recent focus has been on direct azetidine ring functionalisation. This has been achieved through transition metal-catalysed cross-coupling, C-H activation and photoredox approaches, which avoid the need to perform a potentially challenging ring-closing reaction. Alternatively, utilisation of transition metal-catalysed C($sp^3$)-H activation and photochemical energy transfer [2+2] chemistry have been performed to facilitate ring-closing reactions.

### 1.4.1 Transition metal-catalysed cross-coupling

The commercial availability of *N*-Boc-3-iodo-azetidine **40** has prompted many studies into developing a facile and efficient means to replace the halide through cross-coupling. Cross-coupling of *N*-Boc-3-iodo-azetidine **40** with functionalised aryl groups has been achieved by Negishi,[51] Suzuki,[52] Ni-catalysed reductive cross-coupling[53] and Fe- and Co-catalysed Kumada couplings.[54] Interestingly, work by Wu and co-workers demonstrated a Suzuki cross-coupling of *N*-Boc-3-iodo-azetidine **40** with conditions-dependent regioselectivity, allowing functionalisation at either the 3 or 2 position of the azetidine (Scheme 9).[55] Through careful choice of the phosphine ligand, control between initial reductive elimination or competing β-hydride elimination could be achieved. When Cy-JohnPhos was used as the ligand, β-hydride elimination of complex **B** was favoured, forming a

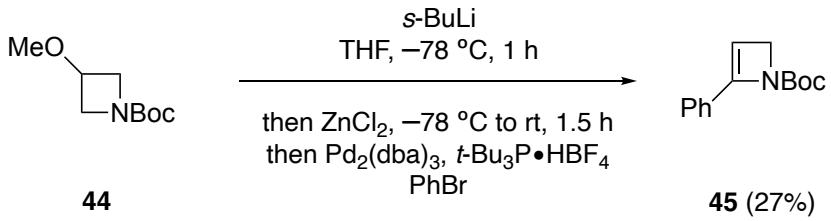
coordinated 2-azetine Pd complex **D** which preferentially underwent migratory insertion and reductive elimination at the 2-position of the azetidine (Path A, Scheme 9). In contrast, when triphenylphosphine was used as the ligand, β-hydride elimination was suppressed and direct reductive elimination of the Pd complex **B** gave preferential cross-coupling at the 3-position of the azetidine (Path B, Scheme 9).




**Scheme 9.** Reagent controlled regioselective transition-metal catalysed cross-coupling.[55]

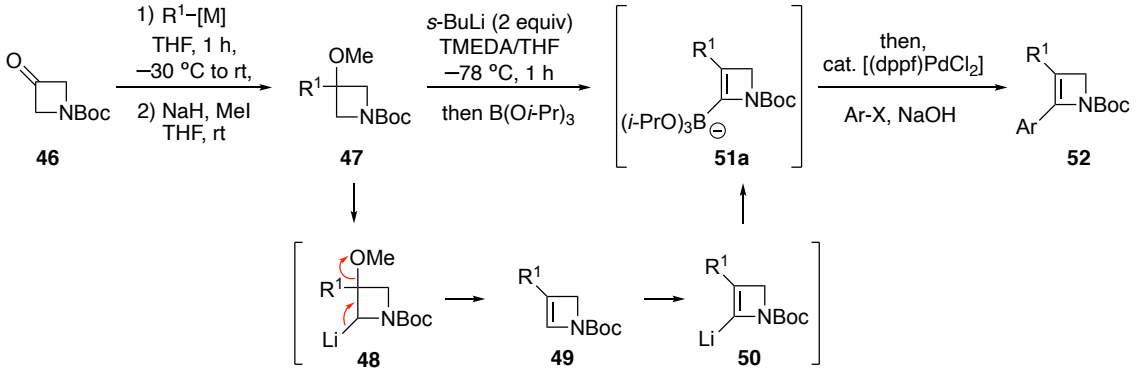
Transition metal-catalysed coupling with an appropriately functionalised azetine has also been demonstrated as a viable route to synthesise 2,3-disubstituted-azetidines. Work within our group, first demonstrated the possibility of performing an $sp^2$-$sp^2$ Pd-catalysed Negishi type cross-coupling on an *in situ* formed lithiated azetine (Scheme 10).[56] Although,

the yield was poor (27%), this demonstrated the feasibility of this approach. Hydrogenation could then be successfully performed on azetines to give substituted azetidines.




**Scheme 10.** Lithiated azetine Negishi cross-coupling.[56]

By changing the coupling reagent to an *in situ* formed boronate **51a**, Didier and co-workers synthesised 2,3-disubstituted azetidines, starting from commercially available *N*-Boc-3-azetidinone **46** (Scheme 11).[57] The reaction was considered to proceed through an initial addition, elimination, lithiation—borylation protocol to give boronate **51a**, which underwent Pd-catalysed Suzuki cross-coupling (Scheme 11). This chemistry was effective for introducing both aromatic and heteroaromatic groups at the 2-position of the azetine. The azetines **52** were subsequently shown to undergo hydrogenation to give a variety of *cis*-2,3-disubstituted-azetidines.

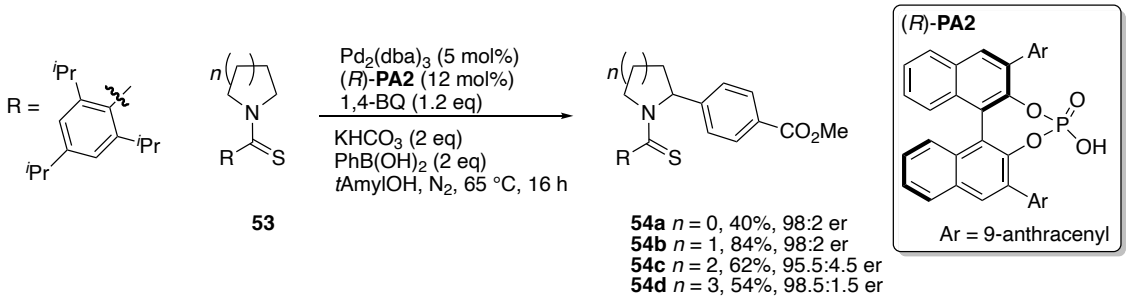



**Scheme 11.** Suzuki cross-coupling of an intermediate boronate azetine.[57]

### 1.4.2 Transition metal-catalysed C($sp^3$)-H activation

Transition metal-catalysed C($sp^3$)-H activation chemistry has gained significant popularity in recent years.[58] Despite this, there remain limited studies on C($sp^3$)-H activation of *N*-azacycles; in particular, regarding α-methylene C($sp^3$)-H activation adjacent to N and especially with azetidines. Work on C($sp^3$)-H activation on azacycles has mainly focused on pyrrolidines.[59] The few examples that have been demonstrated on azetidines will be discussed here.

Enantioselective C($sp^3$)-H activation adjacent to the nitrogen on azetidine has been reported by Yu *et al*.[60] By using a thioamide directing/protecting group on the nitrogen of the *N*-heterocycles, a direct α-C($sp^3$)-H activation for a Pd(II)/Pd(0)-catalysed cross-coupling with an aryl boronic acid could be achieved. Similarly to what was previously found by the Hodgson group,[61] the thioamide functionality was vital for successfully directing the cross-coupling to the adjacent C-H bond; this was speculated to be a result of the larger size of the sulfur atom and different electronic properties compared with amide directing groups. When this reaction was combined with a chiral phosphoric acid acting as an anionic ligand for the Pd species, it was found to give α-arylated *N*-heterocycles in good overall yields and high enantiomeric ratios (Scheme 12).

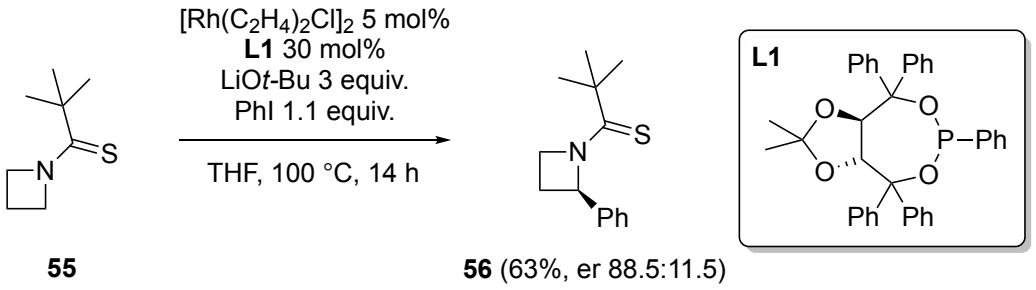



**Scheme 12.** Enantioselective palladium catalysed α-C($sp^3$)-H activation of *N*-heterocycles.[60]

For the single reaction involving an azetidine substrate, a high enantioselectivity could be achieved for the monoarylated-azetidine **54a** (40%, 98:2 er). Interestingly, there was also a small quantity of the 2,4-diarylated compound formed (13%, 98:2 er, >20:1 dr (*trans*:*cis*)), showing the potential for the synthesis of 2,4-diarylsubstituted-azetidines with both high diastereo- and enantio-selectivity.

The same authors have recently described using an oxime directing group to allow Ir(I)-catalysed C($sp^3$)-H activation α-alkylation of numerous azacyclic systems, however, reaction with azetidine substrates failed.[62]

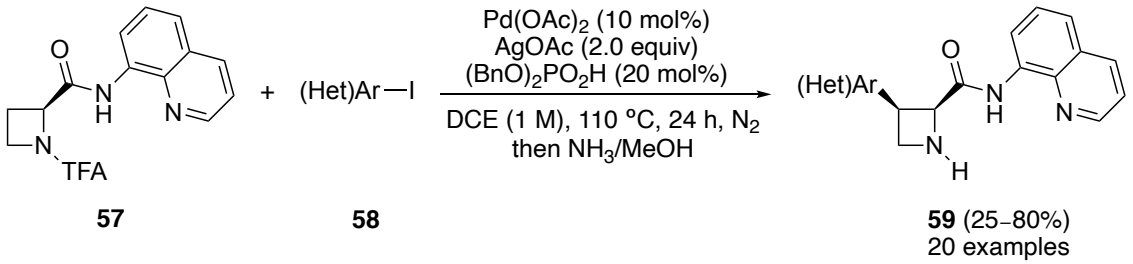
In 2018, Glorius *et al*.[63] reported enantioselective Rh(I)-catalysed α-C($sp^3$)-H activation on a variety of azacyclic compounds. This could be achieved through the use of an *N*-thiopivaloyl directing group (the same directing group previously shown in our lab to effectively direct α-lithiation on azetidine).[61] With the use of a Taddol-derived phosphonite chiral ligand, iodobenzene was successfully coupled to *N*-thiopivaloyl-azetidine **55** in good yield (63%) and high enantioselectivity (88.5:11.5 er) (Scheme 13).




**55** **56** (63%, er 88.5:11.5)

**Scheme 13.** Enantioselective Rh(I)-catalysed C-H activation.[63]

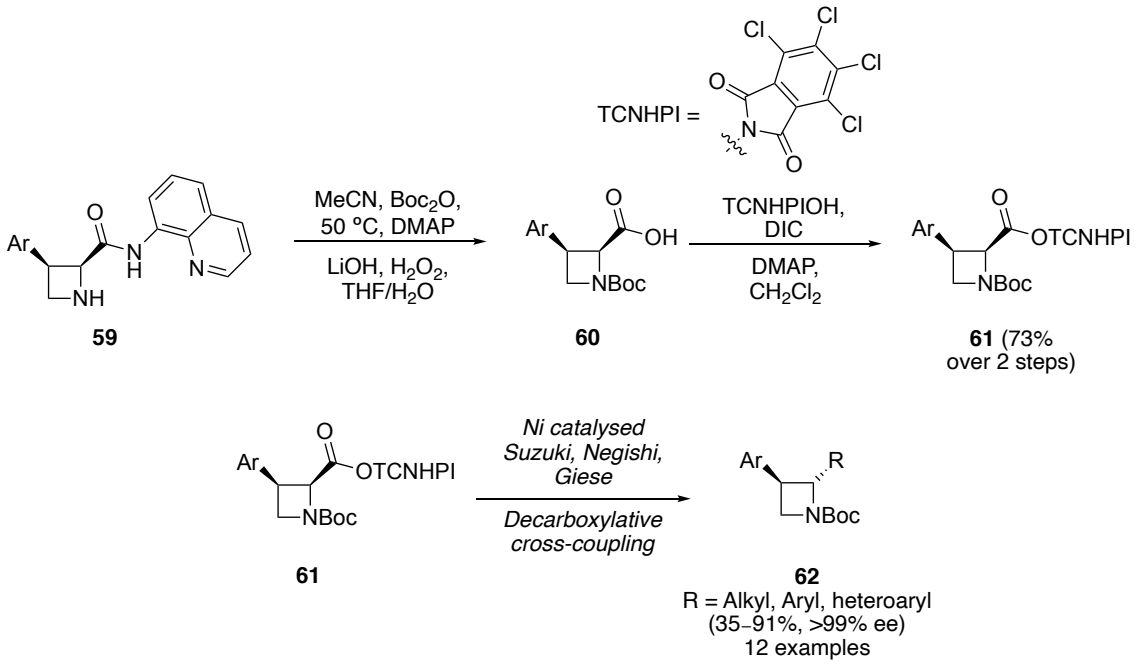
Pd-catalysed C($sp^3$)-H activation at the 3-position of azetidine was demonstrated in the synthesis of highly biologically active antimalarial bicyclic azetidines (up to $EC_{50}$ = 15 nM) and derivatives.[64] The original route to the bicyclic azetidines was achieved through a C-C ring-closing reaction, following a method developed by Couty *et al*.[29a] However, a more efficient synthesis was designed following the amide coupling of an 8-aminoquinoline directing group onto azetidine 2-carboxylic acid, allowing effective C($sp^3$)-H activation and arylation at the 3-position of the azetidine ring (Scheme 14). The reaction proceeded with complete diastereoselectivity giving *cis*-2,3-disubstituted-azetidines **59**. Directing group hydrolysis could be performed under kinetic or thermodynamic conditions to allow for selective formation of *cis* and *trans* 2,3-disubstituted diastereomers.




**Scheme 14.** Pd-catalysed C($sp^3$)-H activation at the 3-position of azetidine.[64]

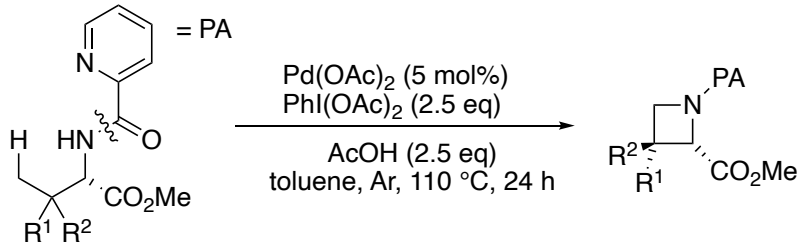
This methodology was further amenable to decarboxylative cross-coupling following removal of the 8-aminoquinoline directing group and formation of a redox-active ester **61** using *N*-hydroxy-tetrachlorophthalimide (TCNHPIOH) (Scheme 15).[65] Ester **61** could undergo decarboxylative cross-coupling under a range of Ni-catalysed cross-coupling conditions (Suzuki, Negishi, Giese), to give enantiopure *trans*-2,3-disubstituted-azetidines **62**. This modular approach allowed for the rapid synthesis of a range of enantiopure 2,3-disubstituted analogues of a potent anti-malarial azetidine previously discovered in a

diversity-orientated synthesis study.[66] This approach was not limited to azetidines and was shown to be effective on a number of saturated heterocyclic and linear carboxylic acids.




**Scheme 15.** Decarboxylative cross-coupling to give enantiopure 2,3-disubstituted azetidines.[65]

Synthesis of a range of 2,3-disubstituted-azetidines has also been achieved through a ring-closing C($sp^3$)-H activation at the γ-position of a series of acyclic amides.[67] With picolinamide as the directing group, γ-C($sp^3$)-H activation could be achieved using a Pd(II)/Pd(IV) catalytic cycle. The intermediate palladacycle could undergo C-N reductive elimination to form the four-membered azacycle (Scheme 16). A requirement for efficient reaction was the need for there to be a substituent located at the β-position of the starting amide. This is due to competing C-O reductive elimination otherwise dominating, as a result of reduced steric constraints on the palladacycle intermediate. Extension of this work showed that it was possible to synthesise configurationally strained bicyclic azetidines[68] and benzazetidines.[69] However, despite these promising results, the authors report 'challenges' involving the removal of the picolinamide directing group under 'mild conditions' which could serve to reduce the synthetic unity of the methodology.



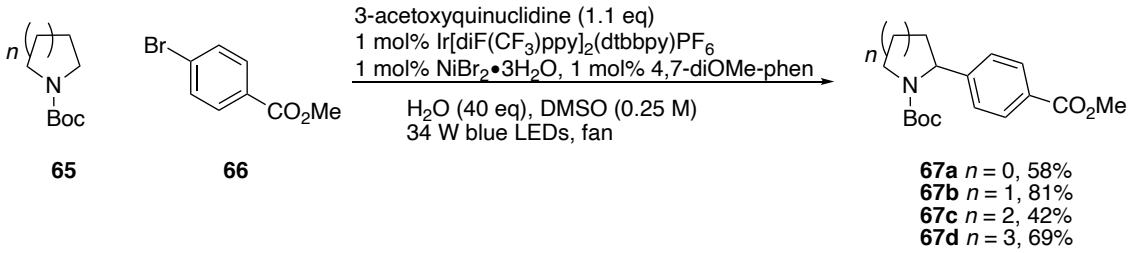

**63a** ($R^1$ = Me, $R^2$ = H) **64a** ($R^1$ = Me, $R^2$ = H, 88%, 6:1 (*cis*:*trans) d.r.*)
**63b** ($R^1$ = Me, $R^2$ = Me) **64b** ($R^1$ = Me, $R^2$ = Me, 91%)
**63c** ($R^1$ = O$^t$Bu, $R^2$ = H) **64c** ($R^1$ = O$^t$Bu, $R^2$ = H, 79%)

**Scheme 16.** 2,3-Disubstituted azetidine **64** synthesis via C(sp$^3$)-H activation and C-N reductive amination.[67]

### 1.4.3 Photoredox C(sp$^3$)-H activation

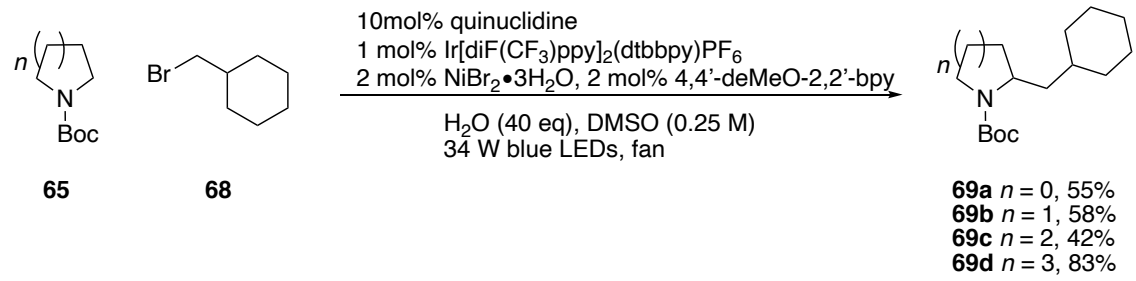
Photoredox C(sp$^3$)-H activation on azacycles, but with limited examples on azetidine systems, has been tried with varying success. MacMillan *et al*.[70] showed that regioselective formation of a radical at the most electron rich C-H bond of the *N*-heterocycle (adjacent to the nitrogen) could lead to Ni-catalysed cross-coupling with an aryl halide (Scheme 17). To synthesise the radical, a UV active Ir(II) species was irradiated to the $^*$Ir(III) excited state which could then oxidise a tertiary amine hydrogen atom transfer (HAT) catalyst via single electron transfer (SET) process. This process forms a radical cation which regioselectively abstracts a hydrogen from the *N*-heterocycle at the most hydridic C(sp$^3$)-H bond. The radical formed can then react with an electrophilic Ni(II) species which has been arylated through oxidative addition. This species then undergoes reductive elimination to form the desired α-arylated *N*-Boc azacycles **67**.

This approach lead to a broad range of α-arylated-pyrrolidines **67b**, with a variety of electronically different aryl groups. It was also successfully applied to a variety of *N*-Boc azacycle ring sizes, including azetidine albeit with slightly reduced yields (Scheme 17).




**Scheme 17.** Photoredox-mediated HAT and nickel catalysis of *N*-heterocycles.[70]

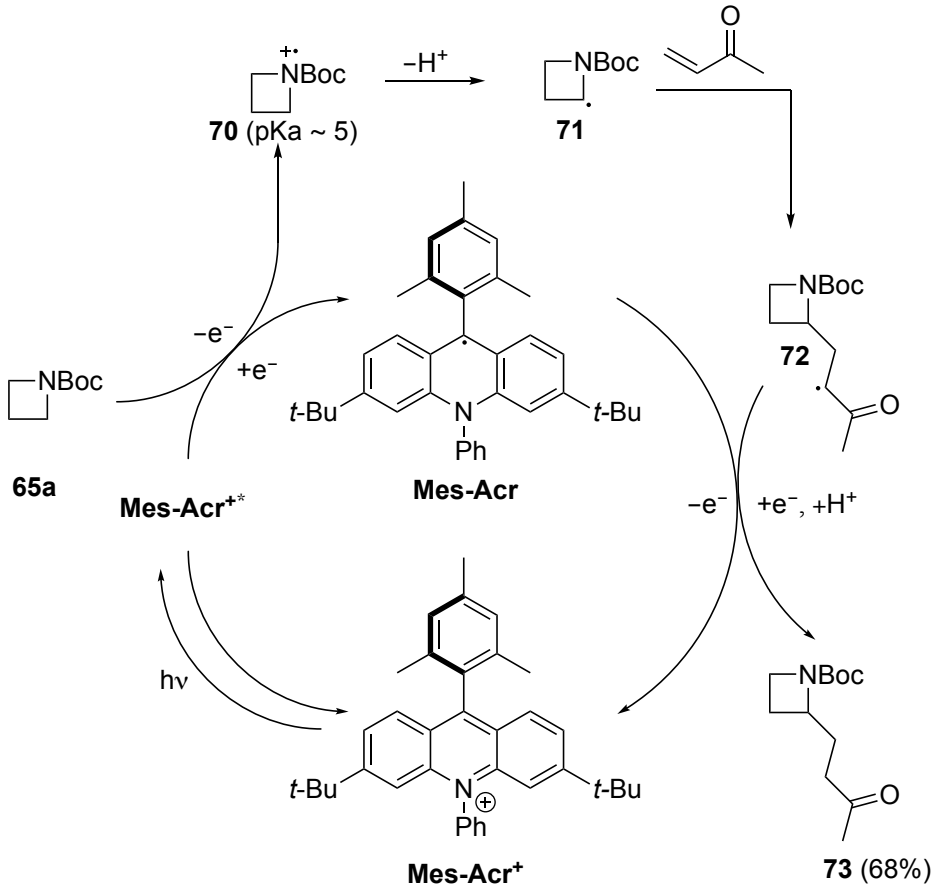
Successful regioselective C($sp^3$)-C($sp^3$) nickel-catalysed cross-couplings have recently been achieved α- to N using a similar photoredox HAT process (Scheme 18).[71] Respectable yields (42-83%) were obtained for a series of saturated azacycles **69** (including azetidine); for pyrrolidines a broad scope of electrophilic alkylating agents were well tolerated. The scope of reaction also extended to both oxacyclic and thiacyclic compounds, as well as acyclic aliphatic amides.




**Scheme 18.** Photoredox-mediated HAT and nickel-catalysed alkylation of azacycles.[71]

Work by the Nicewicz group,[72] has shown that photoredox C($sp^3$)-H activation can be achieved using an acridinium-based organic photocatalyst. The acridinium photocatalyst, once excited into its singlet state, is able to act as a potent oxidising agent (+2.15 Vs SCE, $E_{red}$) and oxidise *N*-Boc carbamate (via SET) to generate the carbamyl radical cation. The pKa of the carbamyl radical cation protons α to N is greatly reduced (≈35 to 5 pKa) which allows facile deprotonation of the radical cation to give the α-carbamyl radical. The radical is then subsequently trapped by a radical acceptor (Michael acceptor) to give the coupled product. This could be performed on a variety of cyclic and acyclic carbamate protected

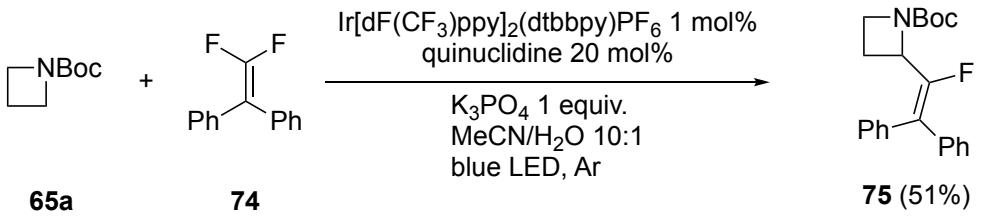
amines in excellent to moderate yields. In the case of *N*-Boc-azetidine **65a**, methyl vinyl ketone (MVK) successfully trapped intermediate α-carbamyl radical **71**, to give the coupled azetidine product **73** in good yield (68%) (Scheme 19).




**Scheme 19.** Proposed mechanism for organic photocatalysed C-H activation.[72]

A similar approach to accessing α-amino radicals was employed by Wang *et al*.;[73] however, instead of directly oxidising the *N*-Boc amino substrate to a radical cation, the excited state iridium photocatalyst oxidised a quinuclidine HAT catalyst to form a radical cation. In methodology similar to Macmillan,[70-71] this newly formed radical cation could undergo HAT with the protected amino compound to form an α-carbamyl radical. The α-carbamyl radical could then be trapped by an *in situ* formed fluoroalkenyl radical to give α-substituted fluoroalkenyl products. This methodology was not limited to amino heterocycles and was successfully applied to ethers and thioethers. *N*-Boc-azetidine **65a** was successfully

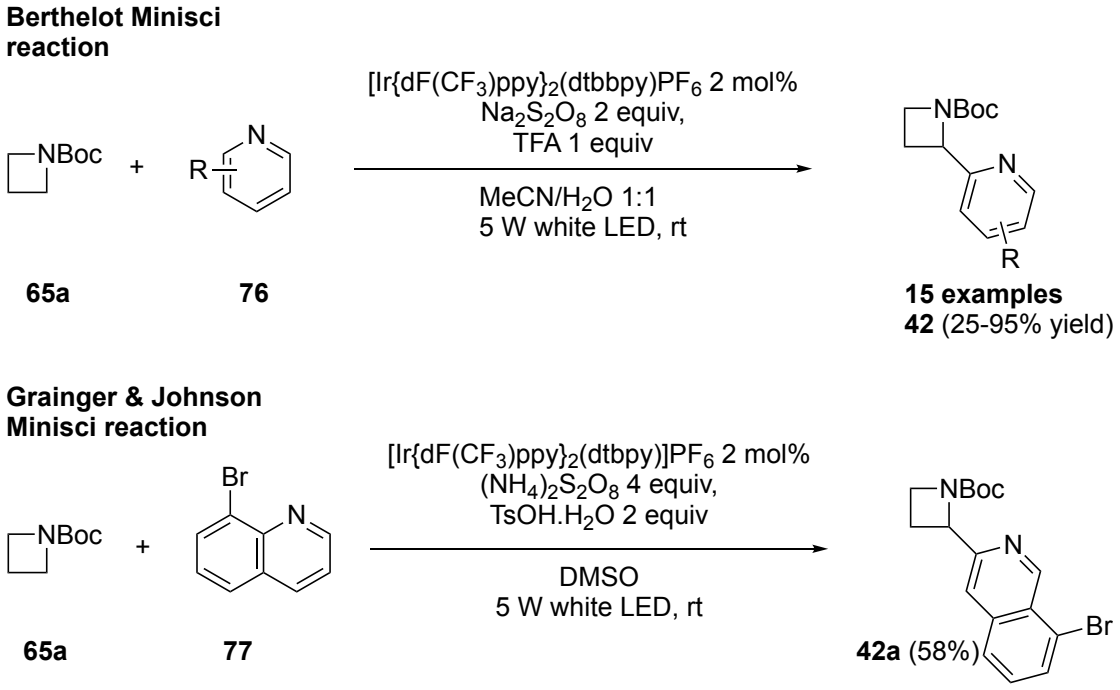
coupled with the diphenylfluoroalkenyl radical to give the coupled product **75** in moderate yield (51%) (Scheme 20).




**65a** **74** **75** (51%)

**Scheme 20.** α-monofluoroalkenylation via photoredox and HAT catalysis.[73]

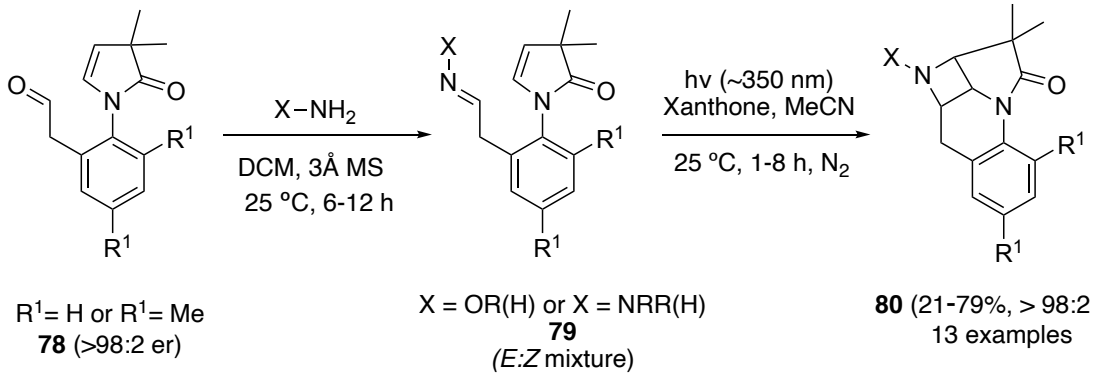
Two similar iridium-catalysed Minisci-type radical cross-dehydrogenative coupling reactions have been independently developed by Johnson and Grainger[74] and by Berthelot[75] (Scheme 21). Under conditions developed by the Berthelot group, the reaction was found to be highly efficient at functionalising *N*-Boc-azetidine **65a**. The increased reactivity (relative to other azacycles) was speculated to be a consequence of the rigid geometry of the 4-membered ring, allowing for optimal alignment of the α-C-H bond with the N-lone pair. This allowed access to a variety of α-heteroarene substituted azetidines in moderate to excellent yields, although a large excess (8-15 equiv) of azetidine **65a** was required (Scheme 21). Grainger and Johnson, despite very similar reaction conditions, showed functionalisation of a broader range of azacycles, as well as adaptation to flow conditions, to afford gram quantities of α-functionalised-pyrrolidine.




**Scheme 21.** Iridium photocatalysed Minisci reactions.[74-75]

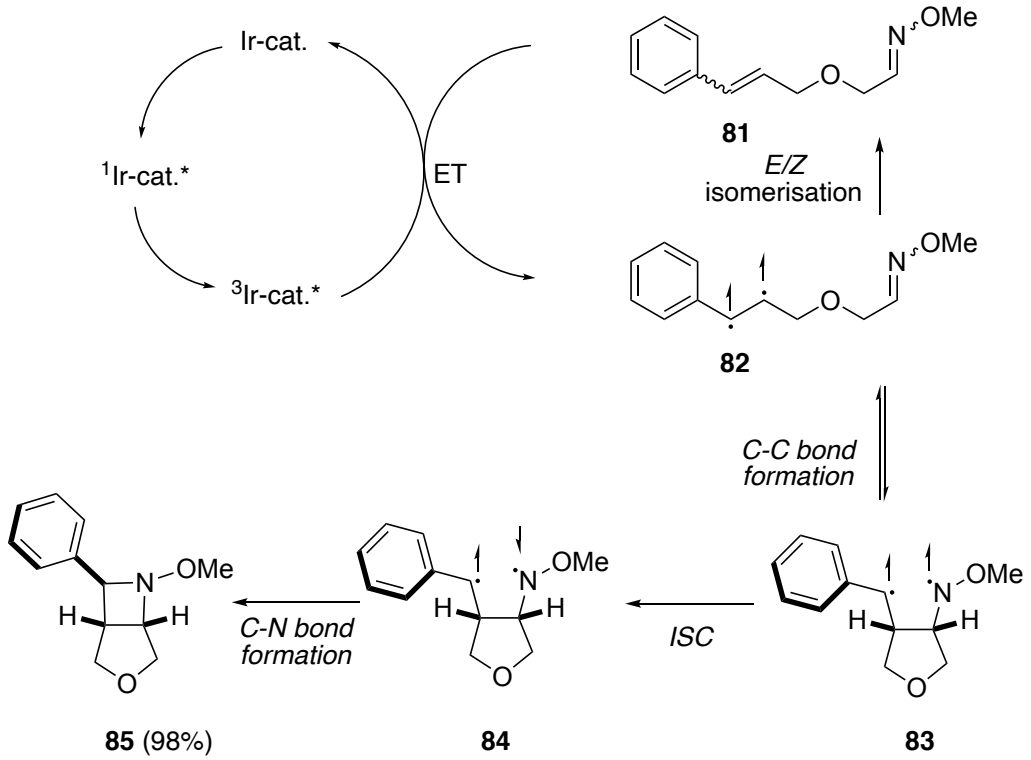
### 1.4.4 [2+2] Photocycloadditions by Triplet Energy-Transfer

An intramolecular atropselective photochemical energy transfer-promoted aza Paternò-Büchi [2+2] between imine and enamides functionalities has been demonstrated by Sivaguru and co-workers.[76] In the presence of excited photosensitiser xanthone with 350 nm light source, efficient energy transfer to the atropisomeric enamide functional group allows for [2+2] photocycloaddition to occur with complete axial-to-point chirality transfer, giving azetidines **80** as a single diastereomer (Scheme 22).




**Scheme 22.** Intramolecular aza Paternò-Büchi [2+2] photocycloaddition.[76]

Similar work by Schindler and co-workers showed that bicyclic azetidines could be synthesised from a linear precursor containing either an oxime or hydrazone functional group and a styrene moiety (Scheme 23).[77] In this variant of the aza Paternò-Büchi [2+2] photocycloaddition, an iridium photocatalyst is able to effect triplet energy transfer with the styrene moiety to give photoexcited biradical intermediate **82**. Biradical intermediate **82** can reversibly add to the oxime functional group to form a tetrahydrofuran triplet biradical intermediate **83**. Intersystem crossing of biradical intermediate **84** allows for ring-closing azetidine formation, with high diastereoselectivity independent of the stereochemistry of the starting material. Overall, this approach provided bicyclic azetidines in high yield and diastereoselectivity. However, the reaction is limited in scope by the need for there to be a suitable styrene or conjugated diene functional group to allow for triplet energy transfer. The Schindler group has recently reported an impressive intermolecular variant of this reaction between a cyclic oxime and alkene coupling partner.[78]



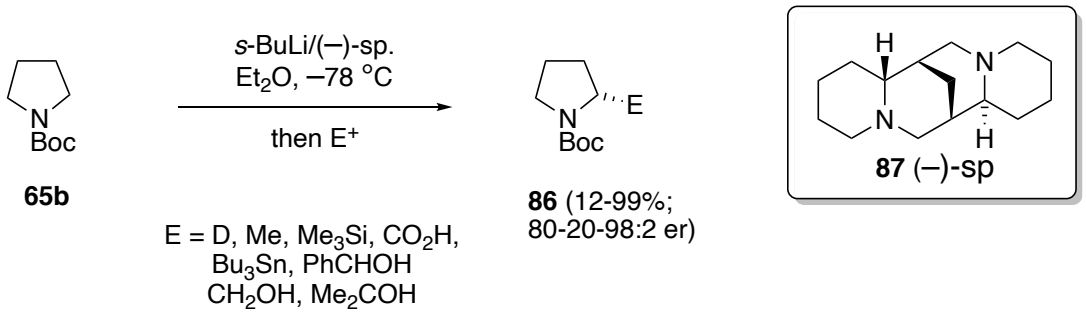

**Scheme 23.** Iridium catalysed oxime [2+2] photocycloaddition.[77]

Despite the emergence of many new methods for azetidine synthesis/functionalisation, many still suffer from a lack of enantioselectivity. The few examples which are able to directly functionalise the α-position of azetidine enantioselectively are currently limited to aryl coupling partners. Fortunately, a complimentary range of enantioenriched azetidines can be synthesised following asymmetric α-lithiation—electrophile trapping.

## 1.5 Directed α-heteroatom lithiation

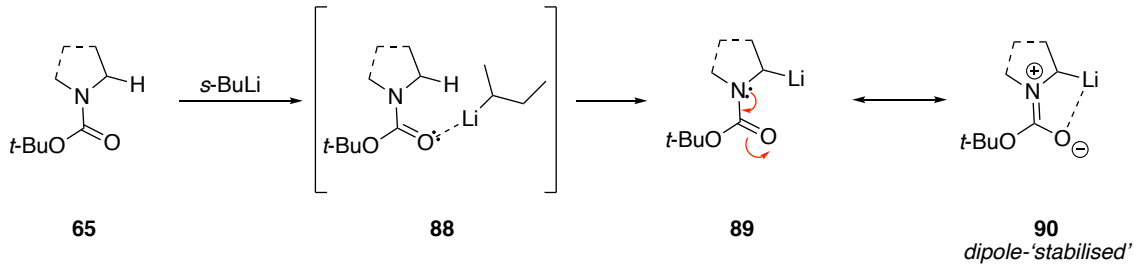
α-Heteroatom (N, O, S, Se) directed α-lithiation—electrophile trapping has long been an effective method to achieve functionalisation of adjacent C($sp^3$) centres.[79] The discovery that combining the organolithium base with chiral ligand (–)-sparteine ((–)-sp **87**, also available as (+)-sp **87**)[80] could induce asymmetric induction in α-lithiation—electrophile trapping (albeit small, ~30% optical purity) demonstrated the potential such sequences could have. However, it was not until Hoppe and co-workers developed a highly enantioselective (>97.5:2.5 er) α-lithiation—electrophile trapping of *O*-alkyl carbamates in the presence of (–)-sp **87** was the potential of this methodology fully realised.[81] Since then, there has been an emergence of methodologies to effect enantioselective α-heteroatom C($sp^3$) lithiation on a wide variety of substrates.

Seminal work by Beak and co-workers demonstrated that enantioselective (–)-sp **87** mediated deprotonation of *N*-Boc-pyrrolidine **65b** could give a configurationally stable carbanion which could then stereoselectively trap electrophiles, to give highly enantioenriched 2-substituted-pyrrolidines (up to 98:2 er, Scheme 24).[82] Since then, advances in enantioselective α-lithiations on a variety of saturated azacycles have shown it to be a highly effective means to perform direct α-C($sp^3$)-H ring functionalisation.[83]




**Scheme 24.** Asymmetric lithiation electrophile trapping of *N*-Boc-pyrrolidine **65b**.[82]

A key factor facilitating α-azacycle lithiation is the use of an *N*-activating functional group which can conjugate with the N atom lone pair of electrons (e.g. Boc). This allows formation of a dipole-'stabilised' organolithium species **90** which is potentially chemically stable and configurationally stable at low reaction temperatures (Scheme 25). Furthermore, *N*-activating functional groups are often able to facilitate and direct α-deprotonation by chelating to the lithium atom of the base (**88**, Scheme 25). This is known as the complex-induced proximity effect (Scheme 25).[84]

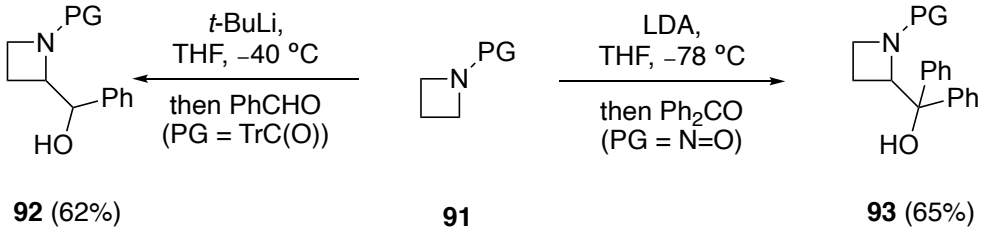



**Scheme 25.** Complex-induced proximity effect to produce dipole- 'stabilised' carbanion.

Further key requirements for such *N*-activating/directing groups, are that they prevent competing direct nucleophilic addition and can be easily installed/removed. This explains the popularity of the *N*-Boc group, as it is ideally suited for such transformations.

### 1.5.1 α-Lithiation—electrophile trapping on azetidines and work within the Hodgson group

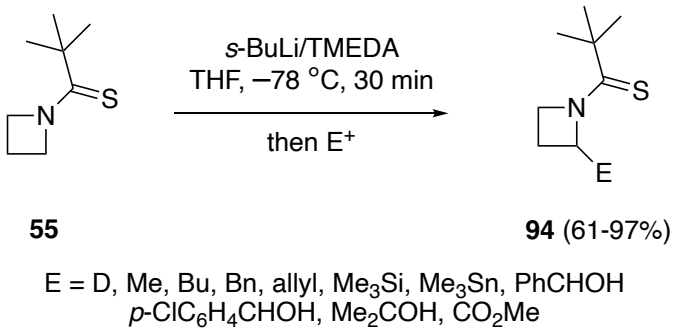
Despite the success of Boc as a directing group in the asymmetric lithiation of pyrrolidine[79] and piperidine,[85] attempted lithiation of *N*-Boc-azetidine **65a** has so far failed to result in efficient α-lithiation.[58] Both triphenylacetyl[86] and nitrosyl[87] directing groups have been shown to facilitate α-lithiation—electrophile trapping on azetidine; however, for toxicity and atom economy reasons use of these directing groups are undesirable and have not been further elaborated (Scheme 26).




**92** (62%) **91** **93** (65%)

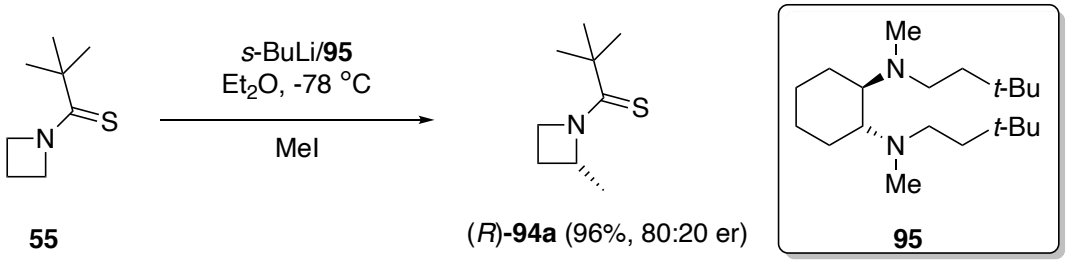
**Scheme 26.** Preliminary α-lithiation—electrophile trapping on azetidines examples.[86-87]

The Hodgson group found that efficient α-lithiation—electrophile trapping on azetidines can be achieved with an *N*-thiopivaloyl group.[61] The success of the thiopivaloyl group was unexpected, as previous work by Seebach had demonstrated thiopivalamide to only effect α-lithiation on a single substrate derived from dimethylamine.[88] Complete α-lithiation of *N*-thiopivaloyl-azetidine **55** was observed in THF in the presence of TMEDA after 30 min at –78 °C following the addition of *s*-BuLi, with subsequent trapping with MeOD (97%, 100% D, Scheme 27). These conditions allowed successful trapping with a range of other electrophiles in high yield, including alkyl/allyl/benzyl halides, aromatic aldehydes, silyl/stannyl chlorides, $CO_2$ and acetone (Scheme 27).




**Scheme 27.** α-lithiation electrophile trapping of *N*-thiopivaloyl-azetidines **55**.[61]

Furthermore, by replacing TMEDA with chiral diamine ligands, asymmetric induction in methylation was achieved. Interestingly, reactions with chiral diamine ligand (–)-sp **87** resulted in 2-methyl-azetidine (*R*)-**94a** with the opposite sense of asymmetric induction to that previously observed in asymmetric α-lithiation—methylation of *N*-Boc-pyrrolidine **65b** (see p 26) and *N*-Boc-piperidine **65c**.[82,85] The highest levels of asymmetric induction were found with Alexakis and co-workers' *trans*-cyclohexane-1,2-diamine-derived ligand **95**,[89] which gave methylated azetidine (*R*)-**94a** in 80:20 er (94% yield, Scheme 28).

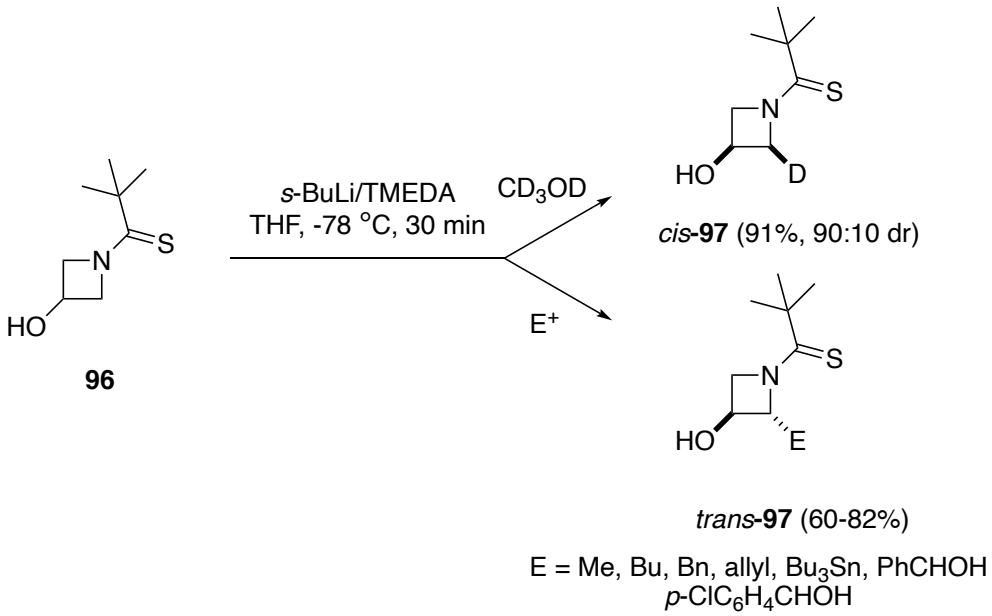



**Scheme 28.** Asymmetric α-lithiation—methylation of *N*-thiopivaloyl-azetidine **55**.[61]

Despite these encouraging results, there were a few drawbacks to this chemistry. Firstly, the *N*-thiopivaloyl directing/activating group required harsh conditions for its removal (5 equiv MeLi in THF 0 °C for 5 h), thus limiting the scope of azetidines available for further derivatisation.[58] Another disadvantage was the reaction only tolerated a limited selection of electrophiles. Electron-rich aromatic aldehydes, such as furfural and

4-methoxybenzaldehyde, gave complex mixtures of trapped azetidine products, and benzophenone, cinnamaldehyde and ethyl chloroformate resulted in only trace product. Enolisable aldehydes and ketones (except acetone) failed to trap through addition, while Mander's reagent and tosyl chloride also failed to give the substituted azetidines.[90]

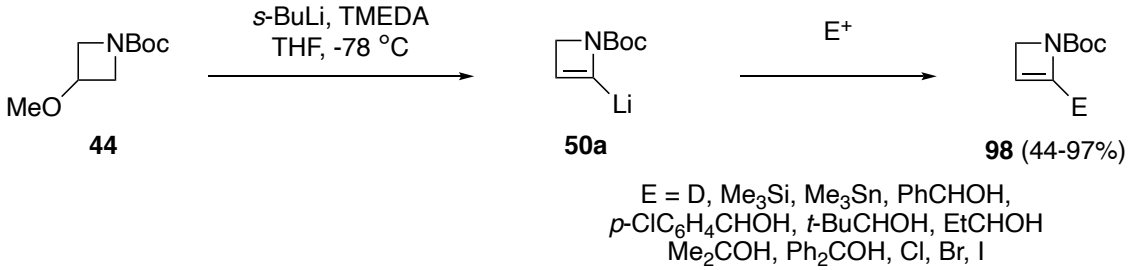
The *N*-thiopivaloyl group was also successfully used in the α-lithiation—electrophile trapping of *N*-thiopivaloylazetidin-3-ol **96** (Scheme 29).[91] Interestingly, it was found that α-lithiation—electrophile trapping worked most effectively with the free hydroxyl present (requiring excess *s*-BuLi). All electrophiles, apart from $CD_3OD$, were shown to trap with a high preference for the *trans* 2,3-disubstituted-azetidine *trans*-**97**. In the case of $CD_3OD$, high preference was observed for the *cis*-2,3-disubstituted-azetidine *cis*-**97** (which was presumed to be due to a directing effect of the OLi group) (see chapter 4, p 151-152).




**Scheme 29.** α-lithiation—electrophile of *N*-thiopivaloyl-azetidin-3-ol **96**.[91]

Attempts at lithiation of *N*-thiopivaloyl-3-silyloxy azetidine resulted in β-elimination of the silyloxy group and the formation of *N*-thiopivaloyl azetine.[92] This result was exploited in

the generation and α-lithiation—electrophile trapping of 2-azetines from *N*-Boc-3-methoxy-azetidine **44** (Scheme 30).[56] Following β-elimination of the methoxy group, *in situ* formed azetine could undergo facile directed deprotonation to give *N*-Boc-2-lithio-azetine **50a** species which could readily trap a large range of electrophiles (including electrophiles which failed with *N*-thiopivaloyl-azetidine **55**).

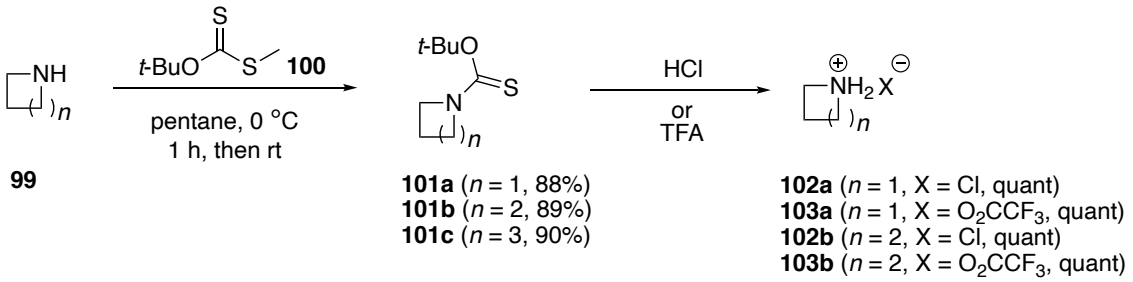



**Scheme 30.** *N*-Boc-azetine formation and α-lithiation—electrophile trapping.[56]

Additionally, the lithiated azetine **50a** intermediate could undergo copper-mediated transmetallation to trap allyl/propargyl bromides to further extend the range of 2-azetine-substituted products previously inaccessible from direct lithiation.[56] Hydrogenation of 2-substituted-azetine **98** allowed access to the 2-substituted-azetidines.

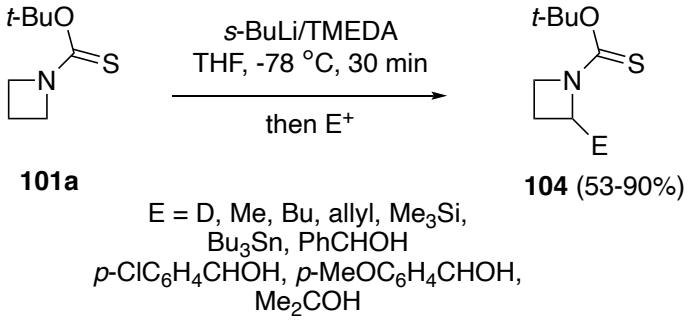
To overcome the concerns surrounding the removal of the *N*-thiopivaloyl directing/activating group, work to develop an alternative directing group was undertaken. It was postulated that a *tert*-butoxythiocarbonyl (Botc) group would be able to effectively direct lithiation at the α-position of azetidine, whilst simultaneously allowing for facile acid deprotection. Introduction of the Botc group could be achieved through addition of azetidine to xanthate **100** in pentane (Scheme 31).[93] Pleasingly, *N*-Botc-azetidine **101a**

could be quantitatively deprotected under acidic conditions (TFA or HCl in $Et_2O$, Scheme 31) or under thermolysis conditions (Δ, EtOH).[94]




**Scheme 31.** *N*-Botc protection and deprotection.[93]

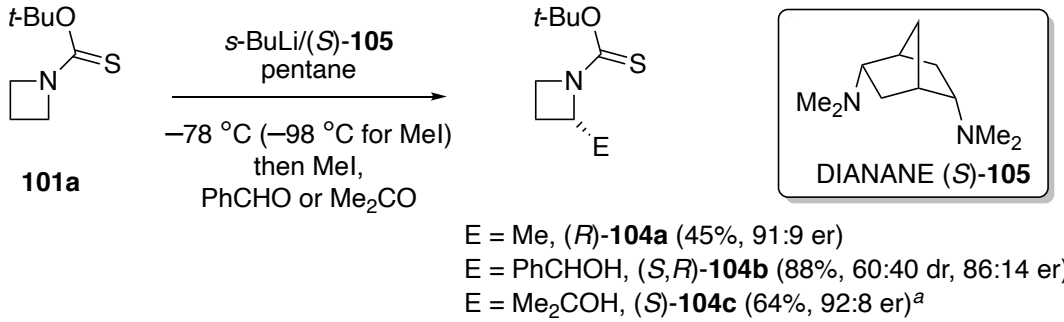
Importantly, the *N*-Botc directing/activating group was found to facilitate complete α-lithiation of azetidine **101a** at –78 °C in THF and TMEDA after 30 min following addition of *s*-BuLi (Scheme 32).[90] Alkylation, allylation, silylation, stannylation as well as trapping with acetone and aromatic aldehydes gave 2-substituted-azetidines **104** in good yields (53-90%).




**Scheme 32.** α-lithiation electrophile trapping of *N*-Botc-azetidines **101a**.[93]

After extensive optimisation it was found that *N*-Botc-azetidine **101a** was amenable to asymmetric α-lithiation—electrophile trapping. Use of Alexakis's chiral diamine ligand DIANANE **105**[95] in pentane enabled trapping in good yields and high enantioselectivity (up to 92:8 er).[93] Notably, the degree of enantioselectivity was found to be dependent on the electrophile, with MeI requiring a lower reaction temperature (–98 °C) to achieve optimal levels of enantioselectivity, compared with the trapping reactions with acetone and

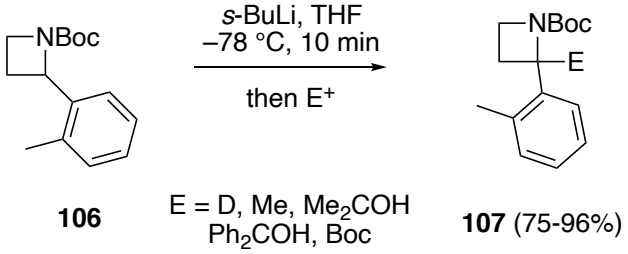
benzaldehyde (–78 °C). Studies at the time to determine origins of enantioselectivity through Sn–Li exchange studies proved to be inconclusive (see chapter 4).[94]




*a)* Stereochemistry (α position) was assigned by analogy to (*R*)-**104a** (see chapter 4 for absolute determination).
*b)* Major diastereomer assigned (*S*,*R*)-**104b** (er shown), minor diastereomer assigned (*S*,*S*)-**104b** (85:15 er).
**Scheme 33.** Asymmetric α-lithiation methylation of *N*-Botc-azetidine **101a**.[93]

Despite the success of this transformation, in particular the high enantioselectivity, there still remained a few issues which reduced the overall synthetic utility. Incompatible electrophiles included enolisable aldehydes and ketones (except acetone and cyclopentanone), Mander's reagent, ethyl chloroformate, DMF, $CO_2$ as well as benzyl bromide. The reaction sequence also did not tolerate attempted transmetallation with $ZnCl_2$ followed by cross-coupling (Scheme 70, p 67) .[94]

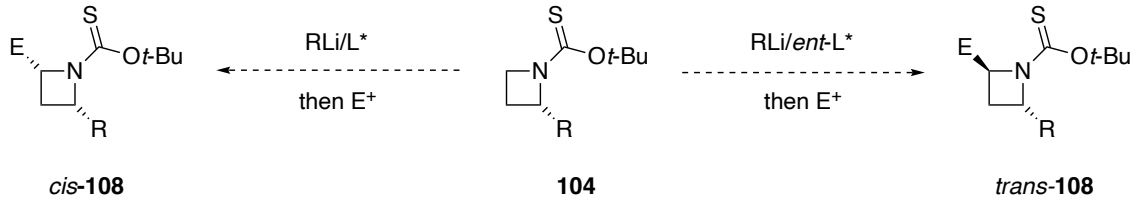
Although methodologies by other authors have demonstrated directed α-lithiation—electrophile trapping of azetidines, they are often achieved through activation of the α-position by incorporation of an acidifying phenyl substituent; this limits their overall utility and occasionally results in competing *ortho*-lithiation (Scheme 34).[16a]




**Scheme 34.** Aryl assisted lithiation of *N*-Boc-azetidine **106.**[16a]

## 1.6 Proposed work

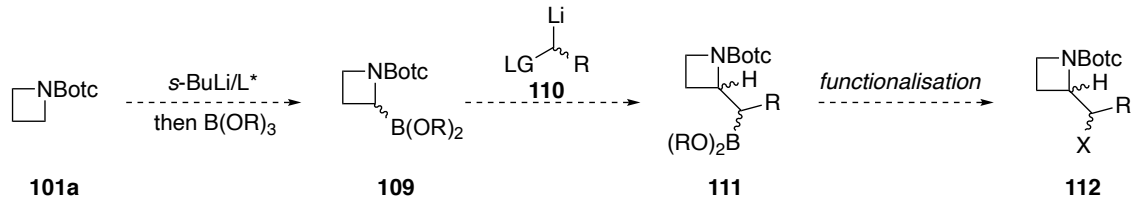
Synthesis of 2,4-disubstituted-azetidines can be accessed through an α'-lithiation—electrophile trapping (discussed further at the start of chapter 2). Importantly, this occurs with no diastereoselectivity, indicating minimal steric influence from the existing 2-substituent. Since it is possible to introduce a 2-substituent through asymmetric α-lithiation—electrophile trapping to form enantioenriched azetidines (Scheme 35), extension of this methodology with enantioenriched 2-substituted-azetidines could provide access to 2,4-disubstituted-azetidines potentially with high levels of enantioenrichment and diastereocontrol (see chapter 2).




*cis*-**108** **104** *trans*-**108**

**Scheme 35**. Potential synthesis of enantioenriched 2,4-disubstituted azetidines

Additionally, to expand the range of enantioenriched 2-substituted-azetidines accessible from the direct α-lithiation—electrophile trapping methodology, it would be appealing to introduce a functional 'handle' amenable to further stereospecific reactions. As boronic esters are versatile functional groups and undergo a broad range of transformations in a stereospecific manner, they offer great potential to be used as a synthetic 'building block.' Access to the boronic ester synthetic 'handle' could conceivably be achieved by an asymmetric α-lithiation—electrophile trapping sequence. Therefore, a further aim of this project was to synthesise an enantioenriched 2-boryl-azetidine, to explore functionalisation of the boronic ester and to develop a broad scope of enantioenriched 2-substituted-azetidines (see chapter 3).



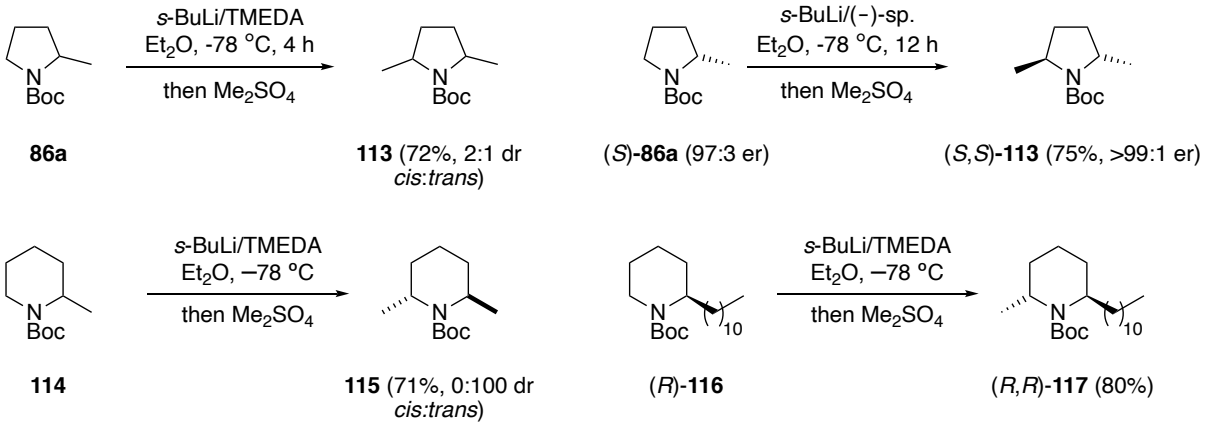

**Scheme 36.** Proposed azetidine borylation and functionalisation.

The third aim was to establish the enantiodetermining mechanism in the asymmetric α-lithiation—electrophile trapping of *N*-Botc azetidine **101a**. Since previous work showed peculiar results regarding temperature and electrophile variations in asymmetric induction,[94] we predicted a complex mechanism with possible competing pathways. With previous mechanistic studies performed on *N*-thiopivaloyl-azetidine showing an interesting electrophile dependence of the sense of asymmetric induction,[96] work to determine the absolute configuration of 2-substituted-*N*-Botc-azetidines **104** previously trapped by our asymmetric α-lithiation—electrophile trapping needed to be undertaken. The overall aim of this part of the project was to explain previous results obtained within the group and to set a foundation of knowledge for future works involving the asymmetric α-lithiation—electrophile trapping of *N*-Botc-azetidine **101a** (chapter 4)

## 2. Synthesis of enantioenriched 2,4-dimethyl-azetidines by asymmetric α'-lithiation—electrophile trapping

### 2.1 Introduction: Previous examples of α'-lithiation—electrophile trapping on 2-substituted azacycles

Existing examples of α'-lithiation—methylation on 2-methyl-*N*-Boc-pyrrolidine **86a** and 2-methyl-*N*-Boc-piperidine **114** gave 2,5-dimethyl-*N*-Boc-pyrrolidine **113** in 72% yield (2:1 *cis*:*trans*, Scheme 37)[97] and exclusively *trans*-2,6-dimethyl-*N*-Boc-piperidine **115** in 76% yield, respectively.[98] Access to enantioenriched 2,5-disubstituted-*N*-Boc-pyrrolidine by sequential asymmetric α-lithiation—electrophile trappings gives both *cis* and *trans* 2,5-disubstituted-pyrrolidines essentially enantiopure as a result of chiral amplification.[99] Due to the highly diastereoselective nature of α'-lithiation—electrophile trapping of 2-alkyl-*N*-Boc-piperidines, there is no need to perform an asymmetric lithiation to access highly enantioenriched *trans*-2,6-disubstituted-*N*-Boc-piperidines, as demonstrated in the total synthesis of (–)-epidihydropinidine[100] and (–)-solenopsin (Scheme 37).[101]




**86a** **113** (72%, 2:1 dr *cis*:*trans*) (*S*)-**86a** (97:3 er) (*S*,*S*)-**113** (75%, >99:1 er)

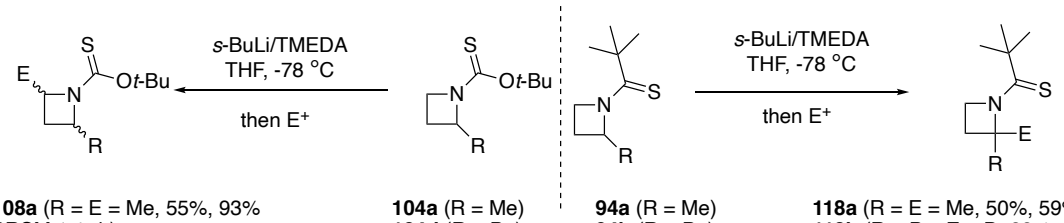
**114** **115** (71%, 0:100 dr *cis*:*trans*) (*R*)-**116** (*R*,*R*)-**117** (80%)

**Scheme 37.** Synthesis of 2,5 disubstituted pyrrolidines and 2,6-disubstituted piperidines by α'-lithiation—electrophile trapping.[97-101]

Previous work in the group on α'-lithiation—electrophile trapping sequence, performed on 2-alkyl-*N*-Botc-azetidines **104a** and **104d**, were able to give 2,4-disubstituted-azetidines

**108**, albeit in reduced yields (methylation shown in Scheme 38).[102] The high regioselectivity for the second lithiation—electrophile trapping sequence was complimentary to that obtained with 2-alkyl-*N*-thiopivaloyl-azetidines **94**, which were found to preferentially give 2,2-disubstituted-azetidines **118**.[102]

Computational and NMR studies revealed that the origin of the regioselectivity is a result of rotamer stability, with 2-methyl-*N*-thiopivaloyl-azetidine **94a** favouring the *cis* rotamer with the bulky *t*-Butyl group facing away from the 2-substituent on the azetidine. With 2-methyl-*N*-Botc-azetidine **104a**, rotamer preference was less pronounced; however, the oxygen 'spacer' between the thiocarbonyl and the *t*-butyl group resulted in reduced steric interactions between the 2-methyl group and the *t*-butyl group. In this latter case, the favoured rotamer was *trans*, with the thiocarbonyl group facing away from the 2-substituent on azetidine, enabling α'-lithiation of 2-alkyl-*N*-Botc-azetidines. NMR studies revealed that at the reaction temperatures (–78 °C or –98 °C) rotamer interconversion does not occur ($\Delta G^{\ddagger}$ = 74.4-76.1 kJ $mol^{-1}$), which results in incomplete α'-lithiation. Undesired lithiation at the substituted site does not occur for 2-alkyl-*N*-Botc-azetidines **104a** and **104d**, presumably due to the decreased acidity of the tertiary C-H bond or an unfavourable directing group conformation for the minor *cis* rotamer. In the case of 2-alkyl-*N*-thiopivaloyl-azetidine **94** deprotonation at the substituted site occurs, likely due to the greater electron withdrawing nature of the thiopivaloyl group, allowing for effective lithiation.[102]




**108a** (R = E = Me, 55%, 93% BRSM;1:1 dr)
**108b** (R = Me, E = D, 94%, 59% D)
**108c** (R = Bu, E = Me, 46%, 68% BRSM;1:1 dr)
**108d** (R = Bu, E = D, 96%, 59% D)

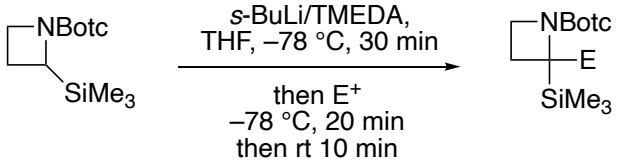
**104a** (R = Me)
**104d** (R = Bu)

**94a** (R = Me)
**94b** (R = Bu)

**118a** (R = E = Me, 50%, 59% BRSM)
**118b** (R = Bu, E = D, 88%, 59% D)
**118c** (R = Bu, E = Me, 41%, 69% BRSM)

**Scheme 38.** Regioselective α'-lithiation—electrophile trapping of thiocarbonyl protected azetidines.[94,102]

Regioselectivity could also be controlled with the addition of α-anion stabilising groups such as $SiMe_3$, which for 2-trimethylsilyl-*N*-Botc-azetidine **104e** gave 2,2-disubstituted-azetidines **119** (Scheme 39).[94]

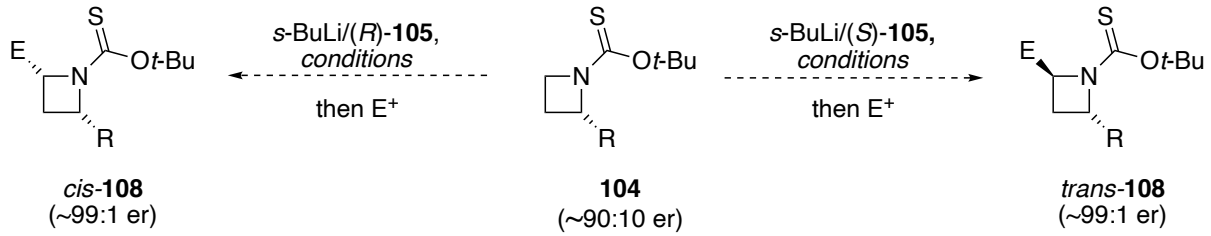



**104e**

**119a** E = $SiMe_3$ (16%)
**119b** E = $CH_2SiMe_3$ (22%)

**Scheme 39.** Regioselective α-lithiation electrophile trapping of 2-silyl-*N*-Botc-azetidine **104e.**[94]

In the racemic α'-lithiation—methylation of 2-alkyl-*N*-Botc-azetidines **104a** and **104d** there was no diastereoselectivity in the formation of 2,4-dialkyl-*N*-Botc-azetidines **108a** and **108c** (1:1 dr, Scheme 38). The lack of diastereoselectivity was actually encouraging for my initial work on this project, as it suggested no steric/stereoelectronic bias in the α'-lithiation—electrophile trapping (unlike 2-alkyl-*N*-Boc-piperidines, Scheme 37, p 36), implying that the asymmetric variant should allow access to both diastereomers in high diastereo/enantioselectivity under reagent (ligand) control (Scheme 40).




*cis*-**108**
(~99:1 er)

**104**
(~90:10 er)

*trans*-**108**
(~99:1 er)

**Scheme 40.** Proposed access to highly enantioenriched 2,4-disubstituted-azetidines.

By performing sequential asymmetric α-lithiation—electrophile trappings on *N*-Botc-azetidine **101a**, it was envisioned that access to highly enantioenriched 2,4-disubstituted-azetidines (with enantioenhancement)[103] could be achieved (Scheme 40). This is desirable, as 2,4-disubstituted-azetidines possess a variety of uses, including as a chiral auxiliary,[104] as chiral ligands for a number of transformations,[105] as a chiral resolving reagent for phosphorus ligands[106] and as a configurationally rigid *N*,*N*-dialkyl bioisotere.[107]

## 2.2. Results and discussion

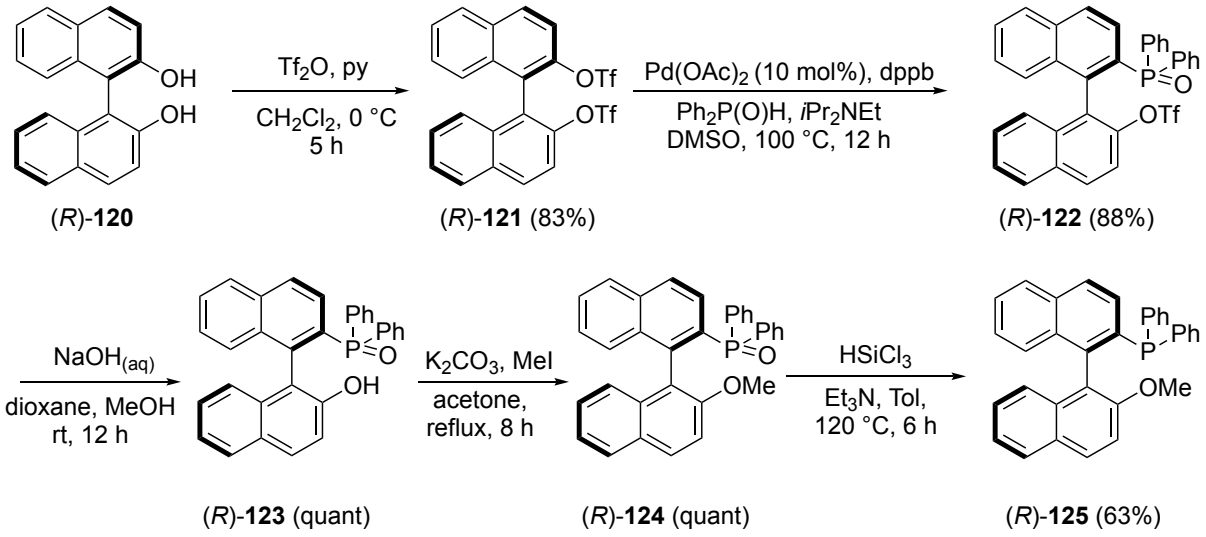
### 2.2.1 Synthesis of MOP and DIANANE ligands

Before investigating asymmetric α'-lithiation—electrophile trapping on monosubstituted enantioenriched *N*-Botc-azetidines, synthesis of enantiopure DIANANE **105** ligands was required, since it had been found to be the optimal ligand.[93] It was hoped that by following a synthetic route described by Berkessel and co-workers,[95,108] synthesis of enantiopure DIANANE **105** could be achieved in 4 steps, starting from commercially available norbornadiene. This sequence required the preparation of an enantiopure binaphthyl MeO-MOP ligand **125**, which was crucial for asymmetric hydrosilylation of norbornadiene in the first step of DIANANE **105** synthesis.

The initial route chosen for the MeO-MOP ligand synthesis was first described by Zeng *et al.*[109] This route was favoured compared to older routes, due to the shorter time required

whilst maintaining an overall high yield. However, it proved unsuitable as an intermediate triflate was unable to undergo palladium-catalysed C-P cross-coupling, therefore preventing further elaboration.

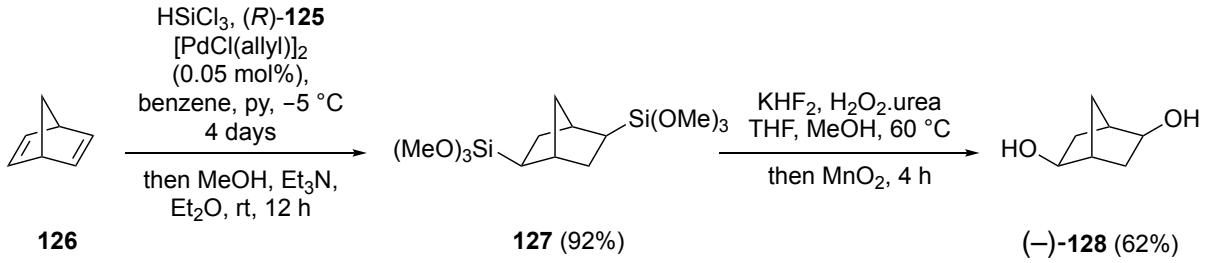
After determining the unfeasibility (in my hands) of the shorter route, it was decided to synthesise the MeO-MOP ligand using the more established route developed by Hayashi *et al.* (Scheme 41).[110] The route is very similar to the one originally attempted, however, for the key Pd-catalysed C-P cross-coupling step, a ditriflate **121** is utilised, in a reaction first described by Morgans *et al*.[111] Following this sequence generated over a gram of the desired (*R*)-MeO-MOP (*R*)-**125** ligand in overall 47% yield, when starting with (*R*)-BINOL (*R*)-**120** (Scheme 41). The same sequence starting with (*S*)-BINOL (S)-**120** gave (*S*)-MeO-MOP ligand (*S*)-**125** in 53% overall yield, thereby enabling access to both enantiomers of chiral diamine ligand DIANANE **105**.




**Scheme 41.** MeO-MOP **125** synthesis.

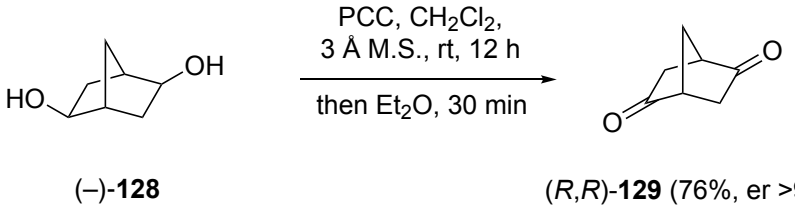
Hydrosilylation using the 'in-house' prepared MeO-MOP (*R*)-**125** ligand generated disilylated norbornane **127** in good yields (92%, Scheme 42). Importantly the reaction time

was extended by 1 day to what was previously described, so as to minimise any trace monosilylated compound remaining. Tamao-Fleming oxidation then gave diol (–)-**128** in good yields (62%, Scheme 42).



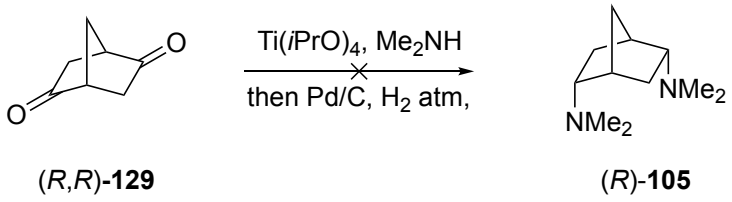

**Scheme 42.** Enantioselective hydrosilylation of norbornadiene and Tamao-Fleming oxidation.

PCC oxidation of diol (–)-**128** gave dione (*R*,*R*)-**129** in 76% yield (Scheme 43), with HPLC analysis showing a single enantiomer (>99:1 er). PCC oxidation was found to be preferable to Swern oxidation, the latter giving dione **129** in inconsistent yields (25-93%) .



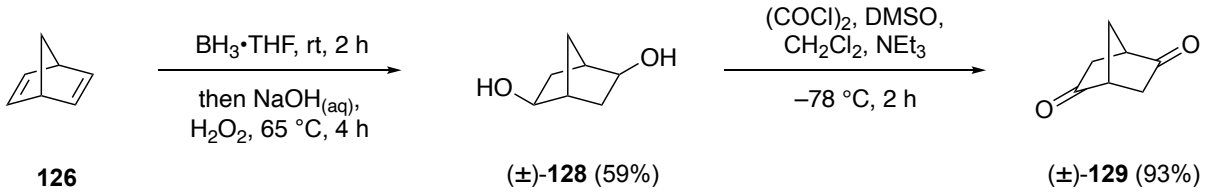

**Scheme 43.** PCC oxidation of diol **128.**

Initial attempts at reductive amination of dione **129** on a 200 mg scale, however, proved unsuccessful (Scheme 44). This was considered to be caused by partially hydrolysed titanium isopropoxide; however, the reaction still failed on changing the source of the Lewis acid to a new bottle.




**Scheme 44.** Attempted reductive amination of dione **129.**

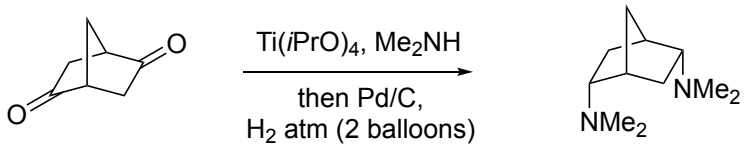
Test reductive aminations on racemic dione (±)-**129** were performed in an attempt to troubleshoot the reaction. Racemic dione **129** was prepared by hydroboration-oxidation of norbornadiene **126** to give the racemic diol (±)-**128** (59%), which was oxidised to dione (±)-**129** in 93% yield (Scheme 45).[112]




**126** (±)-**128** (59%) (±)-**129** (93%)

**Scheme 45.** Hydroboration-oxidation of norbornadiene and Swern oxidation.

Racemic dione (±)-**129** was then reacted with dimethylamine under reductive amination conditions to give DIANANE (±)-**105** in moderate yield (53%). It was found that the quality of the balloon used for the hydrogenation was critical for reaction success, with new double-wrapped balloons providing sufficient $H_2$ pressure to allow successful reduction. When these conditions were applied on enantiopure dione (*R*,*R*)-**129**, the reaction worked well, giving the desired DIANANE (*R*)-**105** in 82% yield (optical purity 99%, $[\alpha]^D$:40.2, lit.[95] $[\alpha]^D$: 40.6, Scheme 46). The overall reaction sequence could be performed on a multi-gram scale to give both enantiomers of DIANANE (*R*)-**105** & (*S*)-**105** in overall 36 and 27% yield respectively, starting from norbornadiene.

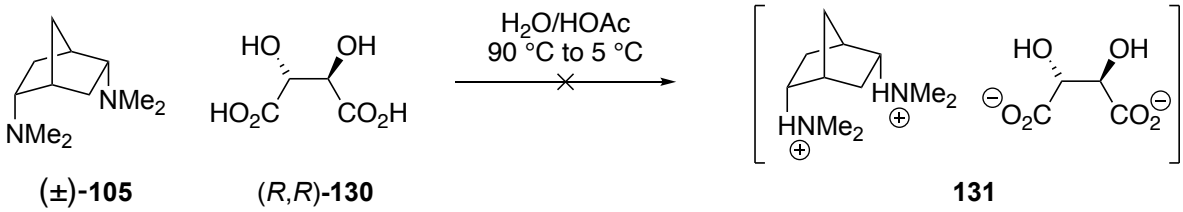



(*R*,*R*)-**129** (*R*)-**105** (82%)

**Scheme 46.** Synthesis of DIANANE (*R*)-**105** via reductive amination.

It was hoped that a quicker more efficient method to obtain enantioenriched DIANANE ligands could be achieved through chiral resolution. Resolution of racemic diamines is well established in the literature, with the chiral resolution of *trans*-1,2-diaminocyclohexane by

Jacobsen *et al.*[113] demonstrating high synthetic utility. Following the same conditions for the resolution of *trans*-1,2-diaminocyclohexane with (*R*,*R*)-tartaric acid **130** on racemic DIANANE (±)-**105**, however, failed to produce any crystalline solid and instead returned an unresolved oily residue (Scheme 47). This could be a consequence of the tertiary amine groups preventing strong electrostatic/hydrogen bonding interactions, therefore, hindering crystallisation

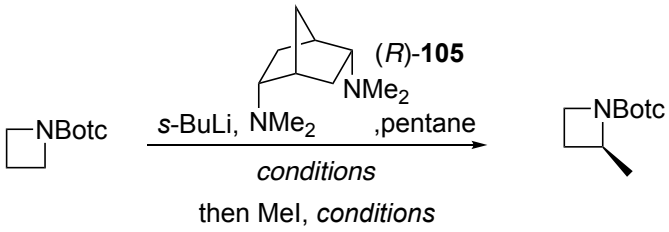



(±)-**105** (*R*,*R*)-**130** **131**

**Scheme 47.** Attempted chiral resolution of DIANANE **105** with tartaric acid.

### 2.2.2 Asymmetric lithiations and trappings of *N*-Botc-azetidines

Work towards replicating previous results on the asymmetric α-lithiation—methylation of *N*-Botc-azetidine **101a** was initially undertaken. Pleasingly, chiral HPLC conditions for 2-methyl-azetidine **104a** were found, allowing for 'in-house' enantiomeric analysis. Following the procedure previously reported in the group, azetidine **104a** was synthesised in similar yield, albeit with reduced enantioselectivity (46%, 60% BRSM, 83:17 er; lit.[93] 45%, 83% BRSM, 91:9 er) (Table 1, entry 1). The reduced enantioselectivity may have been a consequence of the reaction being performed by different experimentalists. The reaction was repeated on a 1 gram scale (Table 1, entry 2), however, this failed to give a high yield or enantiomeric induction (20%, 32% BRSM, 80:20 er). These variable results for the asymmetric α-lithiation—methylation of *N*-Botc-azetidine **101a** were a concern, so ensuring reproducible results for this reaction became a priority before focusing on α'-lithiation—electrophile trapping.




**101a** (*S*)-**104a**

| Entry | Scale (mmol, 101a) | Lithiation temp (time) | Methylation temp (time) | Pre-complex formation? | % Yield (BRSM) | er (*S*:*R*)[a] |
|---|---|---|---|---|---|---|
| 1 | 1.54 | –98 °C (1 h) | –98 °C (1 h) | Yes | 46 (60) | 83:17 |
| 2 | 5.60 | –98 °C (1 h) | –98 °C (1 h) | Yes | 20 (32) | 80:20 |
| 3[b] | 0.43 | –98 °C (1 h) | –98 °C (1 h) | Yes | 23 (92) | 67:33 |
| 4[b,c] | 0.47 | –98 °C (1 h) | –98 °C (1 h) | Yes | 25 (n/a) | 82:18 |
| 5[b,d] | 0.45 | –98 °C (1 h) | –98 °C (1 h) | Yes | 24 (52) | 75:15 |
| 6[b] | 0.45 | –98 °C (1 h) –78 °C (10 min) | –98 °C (1 h) | No | 46 (67) | 85:15 |
| 7[b] | 0.45 | then –98 °C( 50 min) | –98 °C (1 h) | No | 37 (57) | 85:15 |
| 8[b] | 0.45 | –78 °C (1 h) | –78 °C (1 h) | No | 57 (65) | 79:21 |

[a)] (*S*)-**104a** stereochemistry determined by comparison with authentic sample of (*R*)-**104b**.[94] [b)] *s*-BuLi from Acros Organics. [c)] MeI distilled before use. [d)] internal thermometer used.

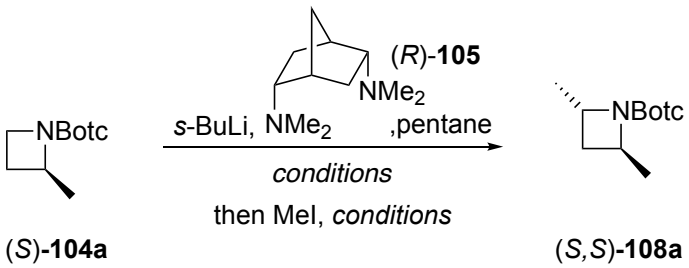
**Table 1.** Asymmetric methylation of *N*-Botc-azetidine **101a.**

Changing the source of *s*-BuLi, distillation of electrophile MeI, or using an internal thermometer all failed to give enantioenriched 2-methyl-azetidine (*S*)-**104a** in similar levels to that previously described in the group. The methodology involved a pre-complexation of *s*-BuLi with DIANANE ligand **105** prior to addition to *N*-Botc-azetidine **101a**. However, it was found that improved yields and enantioselectivities were obtained when performing

the reaction without pre-complexation (Table 1, entries 6-8). An attempt at improving yields by lithiation at –78 °C for 10 mins before cooling to –98 °C gave 2-methyl-azetidine (*S*)-**104a** in slightly reduced yield 37%; however, the level of enantioselectivity (85:15 er) was the same as when the reaction was performed entirely at –98 °C (entries 6 & 7). The latter suggests that enantioselectivity might not be induced by an asymmetric deprotonation (see Chapter 4). Performing the reaction at –78 °C with no pre-complex formation gave similar yields and enantioselectivities to those previously obtained in the group at that temperature.[94]

### 2.2.3 Attempted synthesis of enantioenriched 2,4-disubstituted-azetidines

Attempts were made at performing an α'-lithiation—electrophile trapping on enantioenriched 2-methyl-*N*-Botc-azetidine (*S*)-**104a** (Table 2).




| Entry (er (*S*)-104a) | Lithiation temp (time) | Methylation temp (time) | Pre-lithiation Complex formation | Yield (BRSM) | er (dr) |
|---|---|---|---|---|---|
| 1 | –98 °C | –98 °C | Yes | 31% | 95:5 |
| (85:15) | (1 h) | (1 h) | | (54%) | (86:14) |
| 2 | –78 °C | –78 °C | Yes | 21% | 90:10 |
| (83:17) | (1 h) | (1 h) | | (36%) | (70:30) |
| 3 | –78 °C | –78 °C | No | 21% | 94:6 |
| (80:20) | (2 h) | (2 h) | | (32%) | (76:24) |

**Table 2.** Asymmetric methylation of *N*-Botc-2-methylazetidine (*S*)-**104a.**

The results demonstrate that highly enantioenriched *trans*-2,4-dimethyl-azetidine (*S*,*S*)-**108a** could be accessed via this approach; however, the overall yield for the transformation was disappointingly low. Interestingly, it appears that the enantioenhancement, whilst occurring, is not as prominent as expected (*cf.* Table 2, entry 1, expected 97:3 er) whilst the diastereoselectivity is higher than expected (*cf.* Table 2, entry 1, expected 77:23 dr), assuming the rate of formation of *meso*-2,4-dimethyl-azetidine *meso*-**108a** is to be approximately the same as for *trans*-2,4-dimethyl-azetidine *trans*-**108a** (with the same selectivity for methyl azetidine (*S*)-**104a** formation ~85:15). This suggests that there are subtle influences by the methyl substituent in the asymmetric α'-lithiation—methylation, which slightly favour formation of *trans*-2,4-dimethyl-azetidine *trans*-**108a** over *meso*-2,4-dimethyl-azetidine *meso*-**108a**. Running the reaction at –78 °C failed to improve the reaction yield (Table 2, entries 2-3).

One of the major issues for α'-lithiation—electrophile trapping of 2-methyl *N*-Botc-azetidine **104a** is that it exists in a rotameric ratio of 2.5:1. This is significant, since previous studies show that only the major rotamer, where the thiocarbonyl group is facing towards the unsubstituted α'-position, could effectively undergo α'-lithiation—electrophile trapping (Figure 3).[102] Unfortunately, rotameric conversion did not occur at a significant rate compared to the reaction timescale at –78 °C ($t_{1/2}$ = 168.2 days for minor rotamer). Additionally when the reaction was run at –40 °C to increase the rate of rotamer interconversion,[114] decomposition of the lithiated intermediate was observed.[102]

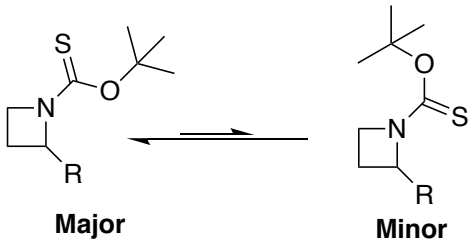
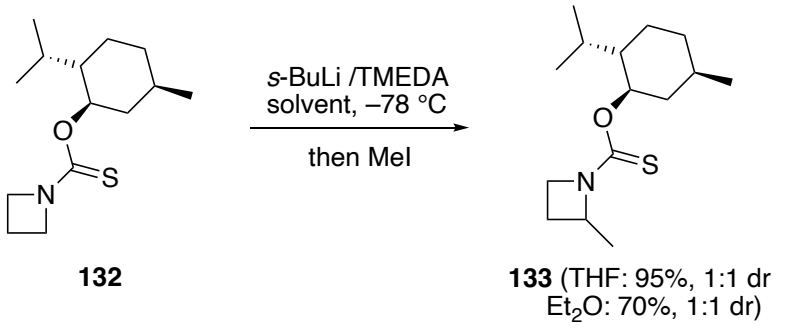



**Figure 3.** Rotamers of 2-substituted *N*-Botc-azetidine **104.**

### 2.2.4 Modifications to the thiocarbonyl protecting/directing group

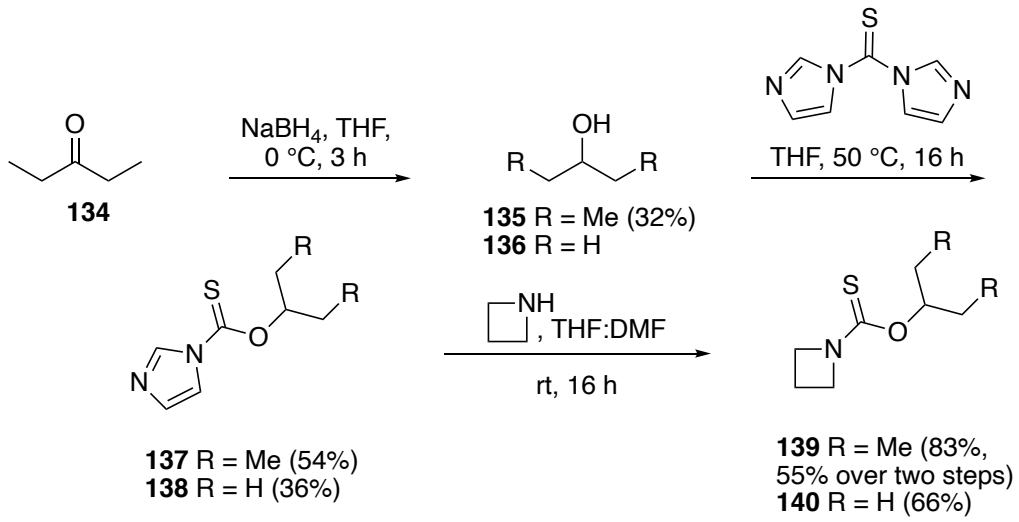
To improve the rotameric ratio and/or to increase the rate of rotameric interconversion, synthesis of less sterically-hindered thiocarbonyl protected/activated azetidines was undertaken. The initial reasonings for using the *tert*-butoxy thiocarbonyl group were that the bulky *tert*-butoxy group would prevent nucleophilic attack at the thiocarbonyl functional group, that it could direct lithiation and that it could be easily removed; it was therefore imperative that less sterically hindered protecting groups met these three criteria.

Previous studies by the group, in which the *tert*-butoxy group was replaced by (L)-menthoxy derivative **132**, to be used as a chiral auxiliary, showed that the secondary alcohol derivative remained highly effective at undergoing α-lithiation—electrophilic trapping sequence (Scheme 48).




**Scheme 208.** Methylation of (L)-menthol-derived azetidine **132.**[94]

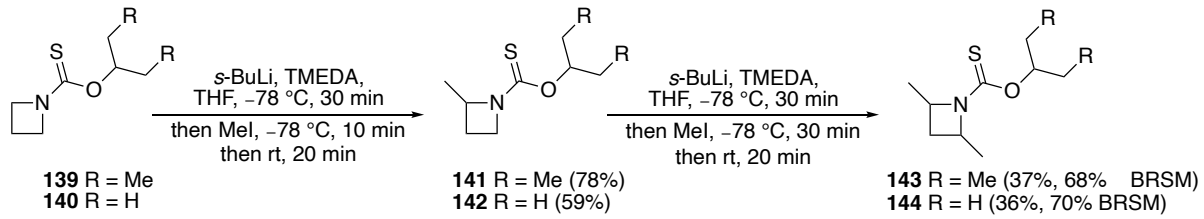
Despite the lack of diastereoselectivity, the exceptionally high yield found for the methylation in THF suggested that the use of a secondary alcohol derivative could be advantageous. This was further supported by results described by the Yu group, which used a 3-pentanol-derived thiocarbonyl directing group for α'-C($sp^3$)-H activation of 2-substituted pyrrolidines.[115] Synthesis of the 3-pentanol and *i*-propanol azetidine carbothioates **139** and **140** was achieved following the route described by Yu (Scheme 49).




**Scheme 49.** Synthesis of O-alkyl-azetidine-1-carbothioates **139** and **140.**

Reduction of pentan-3-one **134** using $NaBH_4$ afforded the desired 3-pentanol **135** which was then reacted with 1,1'-thiocarbonyldiimidazole to give carbothioate **137**, in 54% yield. Carbothioate **137** was then reacted with azetidine to give the desired protected azetidine **139** in good yield (83%). Pleasingly, a second synthesis performed without purification of carbothioate **137** gave azetidine **139** in 55% yield starting from 3-pentanol. Formation of the isopropanol derived azetidine was also performed, as it would allow access to the smallest secondary alcohol derivative; this gave the desired protected azetidine **140** (Scheme 49).

With the two new protected/activated azetidines at hand, lithiation—electrophile trapping with MeI under racemic conditions was performed (Scheme 50).




**Scheme 50.** α-Lithiation—electrophilic trapping of carbothioates **139** and **140** derivatives.

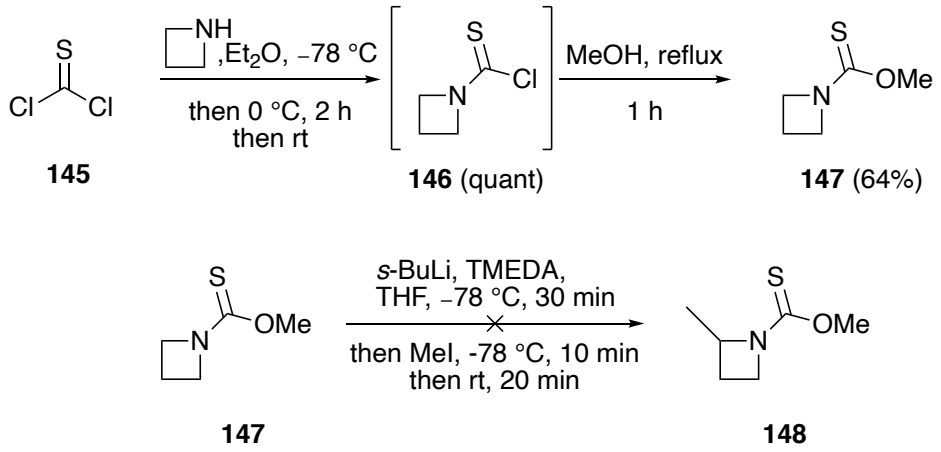
Lithiation—methylation of azetidines **139** and **140** proceeded smoothly, giving 2-methyl-azetidines **141** and **142** in 78% and 59% yield, respectively. However, both compounds **141** and **142** were found to have rotameric ratios of (2.5:1) by NMR spectroscopy, identical to 2-methyl-*N*-Botc-azetidine **104a**. Azetidines **141** and **142** would therefore face similar issues of limited lithiation, unless there was a significant lowering of rotation barrier. However, the low yields obtained for disubstituted-azetidines **143** and **144** in the second lithiation—electrophile trapping sequence indicated rotamer rotation did not occur at an appreciable rate at –78 °C (Scheme 50).

Attempts at deprotection of both azetidines **139** and **140** with neat TFA in $CH_2Cl_2$ at rt also failed to cleanly give the deprotected azetidine trifluoroacetate salt,[115] giving a mixture of the salt, starting material and multiple unidentifiable peaks by $^1$H NMR spectroscopy.

### 2.2.5 Sterically unhindered azetidines

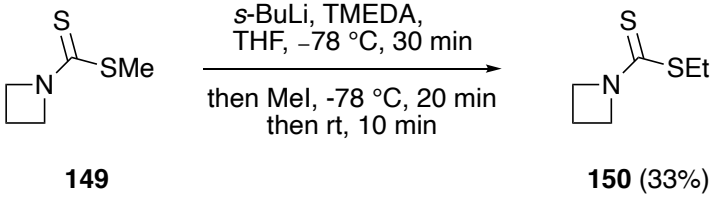
With no improved synthesis of 2,4-disubstituted-azetidines from secondary alcohol *N*-alkoxythiocarbonyl-azetidines, focus moved towards the synthesis of the methanol derivative, azetidine thiocarbonyl **147** (Scheme 51), possessing the least sterically hindering alkoxy substituent. A successful synthesis via azetidine thionyl chloride **146**[90] gave the methoxythiocarbonyl-azetidine **147** in 64% yield over two steps requiring only a

single purification. Unfortunately, attempts at lithiation—electrophile trapping failed to give the desired methylated product and returned only starting material (54% RSM).




**Scheme 51.** Synthesis of methoxy carbothioate **147** and attempted lithiation—electrophile trapping.

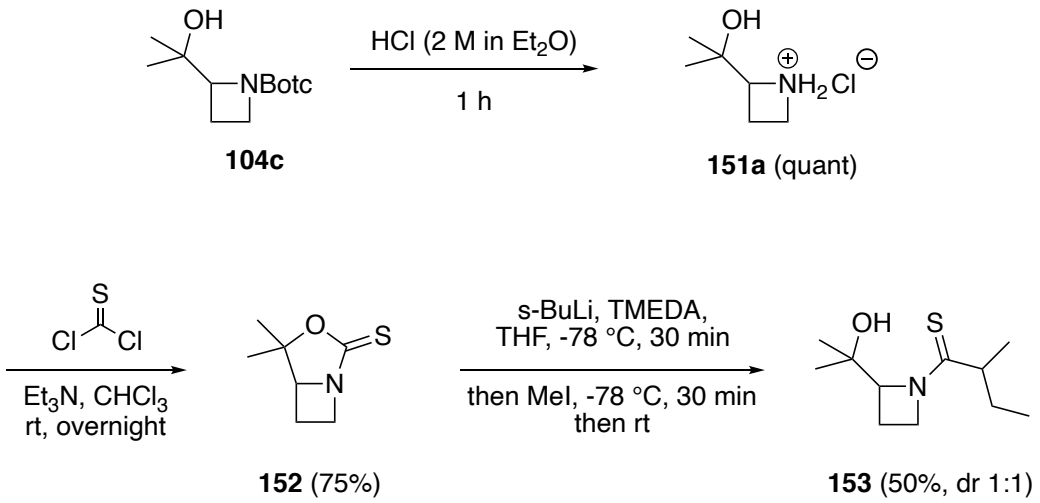
Attempts at a lithiation and electrophile trapping sequence on azetidine dithiocarbamate **149** (a side-product in *N*-Botc-azetidine **101a** formation)[94] using MeI as the electrophile, resulted in methylation at the carbon α- to the sulfur to give the ethyl compound **150,** albeit in low yield (33%) (Scheme 52). There was no apparent deprotonation α- to nitrogen on the ring however, probably due to the increased acidity of α-sulfur protons.[116]




**Scheme 52.** α- to S Lithiation—electrophile trapping of dithiocarbamate **149.**

### 2.2.6 Conformationally locked azabicyclic carbothioate

Beak and Bertini Gross found that α-lithiation—electrophile trappings of pyrrolidine-derived oxazolidinones occurred far more efficiently than *N*-Boc pyrrolidine **101b**.[117] It was considered that effective access to 2,4-disubstituted-azetidines might be achieved with the corresponding azabicyclic carbothioate systems (Scheme 53).

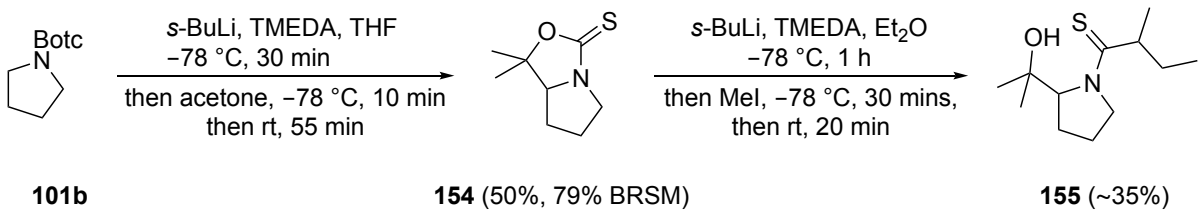



**Scheme 53.** Synthesis and attempted lithiation—electrophile trapping of azabicyclic thione **152.**

Treatment of alcohol **104c**, derived from lithiation—acetone trapping, with NaH followed by heating failed to give the desired bicyclic product **152**. A two-step procedure to **152** was therefore examined. Removal of the Botc protecting group from the tertiary alcohol with HCl (2 M in $Et_2O$) gave the desired chloride salt **151** in quantitative yield, without any unwanted dehydration product(s) (Scheme 53). The chloride salt was then treated with $Et_3N$ and thiophosgene to give the desired azabicyclic compound **152** in good yield (75%).

Lithiation—electrophile trapping with azabicyclic thione **152**, however, failed to give the desired trapped product, but instead returned starting material (18%) and the ring-opened alcohol **153** (50%) derived from nucleophilic attack of the *s*-BuLi at the thiocarbonyl group (Scheme 53). A repeat of the reaction with a quench at –78 °C instead, also gave the ring-opened thioamide **153** in 37% yield. To avoid nucleophilic addition, LTMP was examined as a sterically hindered base, however this only returned starting material **152** (70%).

The corresponding oxazolidine-2-thione **154** was also synthesised using a route previously described within the Hodgson group (Scheme 54).[94] Attempts at lithiation—electrophile trapping on azabicycle **154** using *s*-BuLi most likely resulted in ring-opening, caused by nucleophilic attack of *s*-BuLi at the thiocarbonyl. The ring-opened compound **155** could not be fully purified from unknown side-products; however, the appearance of a $^{13}C$ NMR peak at 212 ppm indicated the formation of a thioamide. Whilst IR spectra showed a broad OH peak suggesting that ring-opening had indeed occurred. Attempts at lithiation using LTMP failed to deprotonate bicyclic compound **154** and instead returned starting material (62%).



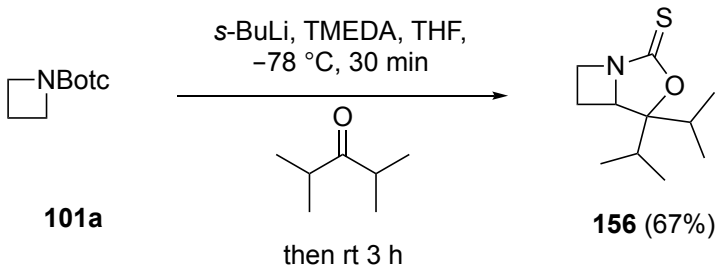

**101b** **154** (50%, 79% BRSM) **155** (~35%)

**Scheme 54.** Synthesis and attempted lithiation—electrophile trapping of azabicyclic thione **154.**

Bicyclic azetidine thione **152** was chosen as a substrate due to the fact that the precursor for thione synthesis, alcohol **104c** was readily available in our lab. Dimethyl thione **152**, however, is not a 'true' analogue of the work performed by Beak and Bertini Gross, who use diisopropyl and ditertbutyl alkyl groups on their bicyclic pyrrolidine system.[117] The reason for using the bulky alkyl groups was to prevent nucleophilic attack of *s*-BuLi at the carbonyl carbon. It was therefore decided to synthesise diisopropyl thione **156**, in order to fully establish whether a directed α-lithiation could take place.

Synthesis of thione **156**, was performed following a lithiation—electrophile trapping sequence on *N*-Botc-azetidine **101a** with 2,4-dimethylpentanone as the electrophile. Following the addition of the electrophile, the mixture was allowed to stir at rt for 3 h to

allow the intermediate alkoxide to attack the thiocarbonyl functional group. This gave the desired thione **156** in 67% yield (Scheme 55).

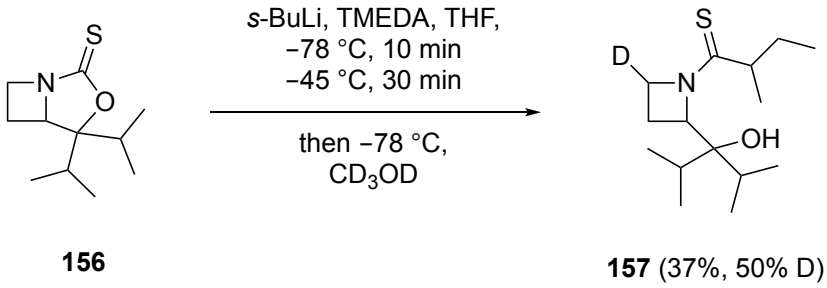



**101a** **156** (67%)

**Scheme 55.** α-Lithiation—electrophile trapping to give bicyclic thione **156.**

Attempts to lithiate **156** at –78 °C for 1 h using *s*-BuLi, followed by trapping with MeI, only resulted in 86% recovered starting material. Interestingly, the reaction mixture underwent a dramatic colour change to bright yellow on addition of *s*-BuLi at –78 °C, possibly indicating deprotonation. MeI is not a fast-trapping electrophile[118] and therefore the reaction was performed again using $CD_3OD$ as the electrophile; however, this also returned recovered starting material (93%).

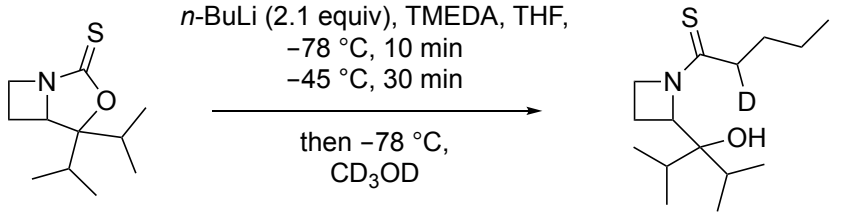
Raising the temperature to –45 °C for 30 min in order to promote lithiation resulted in the addition of *s*-BuLi to the thiocarbonyl, to give thioamide **157** (37%) and recovered starting material (44%) (Scheme 56). Despite addition and ring-opening occurring, $^1$H NMR analysis of the protons α- to N integrated only to 1.5 H. HRMS analysis showed the base peak for the suspected compound at [M+H+1]; these two results suggested that significant α-lithiation had occurred. Despite potential α-lithiation occurring, the fact that it only occurred on the ring opened thioamide **157** and was not seen at all on the recovered starting material **156** suggested that the directed lithiation most likely occurred following ring-opening.




**156** **157** (37%, 50% D)

**Scheme 56.** Attempted lithiation of thione **156.**

The same reaction was also performed with *n*-BuLi (Scheme 57); again, ring-opening due to nucleophilic attack by *n*-BuLi at thiocarbonyl carbon occurred to give deuterated thioamide **158** (36%) and recovered starting material (40%). This time, the excess *n*-BuLi was able to deprotonate at the α-position of the thioamide to form an enolate intermediate, which was then able to trap the electrophile to give deuterium incorporation. There was no evidence of deuterium incorporation in the recovered starting material **156**.




**156** **158** (36%, >90% D)

**Scheme 57.** Attempted lithiation of thione **156** using *n*-BuLi.

Bicyclic thione **156** was suitably crystalline to allow for x-ray crystallographic analysis (Figure 3). The latter showed the atomic distance between the sulfur atom and the closest proton, $NCH_{cis}$. The interatomic distance from this crystal structure was calculated at approximately 3.1 Å. This interatomic distance is comparable to the x-ray crystal structure of a 2-methyl-*N*-thiopivaloyl-azetidine **94a** which was measured at 3.0 Å (Figure 3). However, the closest proton is the $NCH_{cis}$ endocyclic proton and therefore it is most likely that sterics prevent effective lithiation. We would predict a strong diastereoselective bias

towards the formation of *cis* lithiated species, as exclusive *cis* diastereoselectivity was seen by Beak and Bertini Gross.[117]

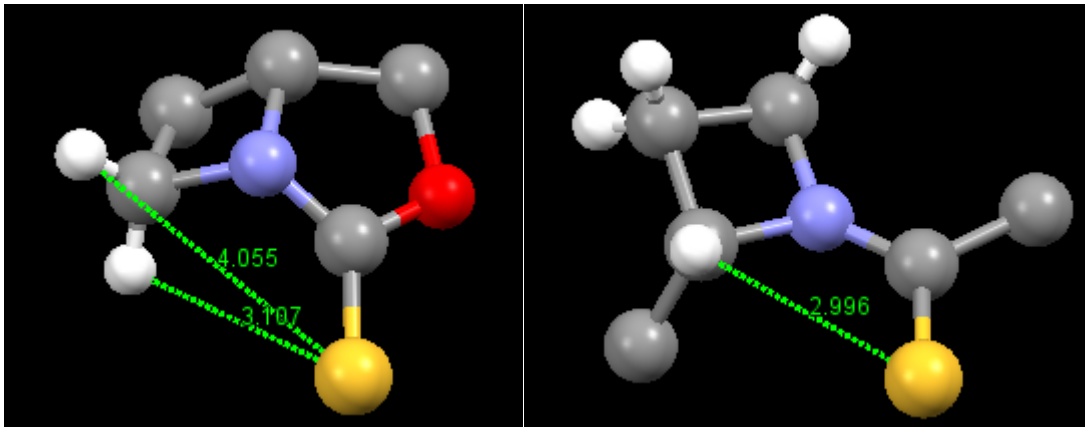



**Figure 3.** Crystal structure of bicyclic thione **156** (left) and 2-methyl-*N*-thiopivaloyl azetidine **94a** (ring). Bond distances between sulfur and α-hydrogens shown. Atoms hidden in diagram for clarity.

## 2.3 Summary

Synthesis of highly enantioenriched *trans*-2,4-dimethyl-azetidine (*S,S*)-**108a** was achieved via α'-lithiation—electrophile trapping. This demonstrated proof of principle, however, the transformation was not synthetically viable, giving *trans*-2,4-dimethyl-azetidine (*S,S*)-**108a** in low yield. This was partly due to MeI being a poor electrophile (asymmetric synthesis of methyl azetidine **104a**, 46% yield at –98 °C); however, the most probable cause for the low yields was likely incomplete lithiation as a result of *N*-Botc rotamers. Attempts to alter the rotamer ratio/interconversion rate of the thiocarbamate directing group were performed and demonstrated that secondary alkoxy groups were suitable at directing lithiation. However, secondary alkoxy thiocarbamates failed to improve yields for α'-lithiation—electrophile trapping, whilst additionally proving difficult to remove. Methoxy thiocarbamate **147** failed to promote α-lithiation, whilst methyl dithiocarbamate **149** promoted α-S lithiation.

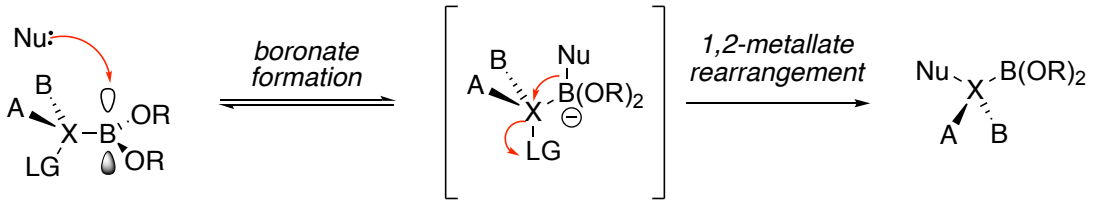
Synthesis of novel thiocarbamate azabicyclic systems were achieved; importantly, tertiary alcohol **104c** could undergo *N*-Botc deprotection under acidic conditions without competing elimination. However, configurationally locked azabicyclic compounds failed to undergo directed α-lithiation—electrophile trapping and instead preferentially underwent nucleophilic addition/ring-opening.

Having failed to access disubstituted azetidines and pyrrolidines via conformationally rigid azabicycles, work looked towards developing and expanding the current α-lithiation—electrophile trapping chemistry through the synthesis of potentially useful synthetic 'handles'. Boronic ester functionalities were shown to be useful synthetic 'handles', accessible via lithiation—borylation chemistry,[119] and therefore focus turned to the synthesis of 2-substituted boronic esters.

# 3. Synthesis and homologation of an azetidin-2-yl boronic Ester

## 3.1 Introduction to boronic ester homologation

Boron-containing functional groups have long been established as useful synthetic handles for further compound functionalisation.[120] One of the key properties of many boron functional groups is the availability of the empty p(AO) on boron. This enables boron functional groups to be very useful electron acceptors, forming a reactive coordinatively saturated 8 electron tetrahedral boronate complex (e.g. **160**, Scheme 58). The build-up of negative charge on the boronate increases the nucleophilicity of the substituents co-ordinated to boron. If there is an appropriately located leaving group (LG, generally α- to the boron atom), migration of a boronate substituent (into the anti-periplanar X-LG σ* orbital, Scheme 58) with displacement of the leaving group can occur.[121] This can result in a concerted 1,2-shift, which occurs stereospecifically with retention of configuration of the migrating group and inversion at the migrating terminus. These features of boronic ester homologations render such reactions extremely powerful in synthesis.



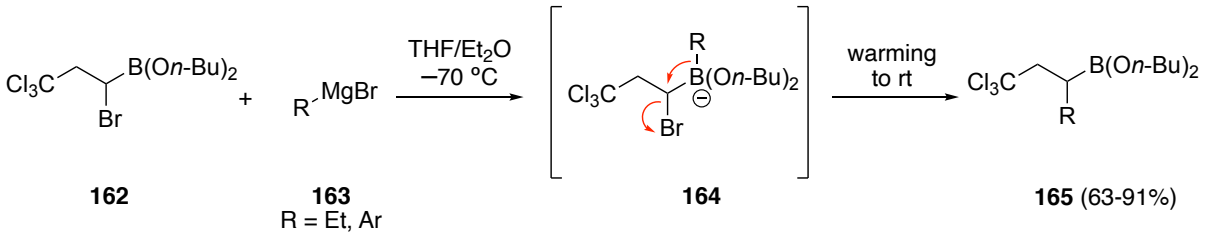

**159** **160** **161**

**Scheme 58.** Generic boronate formation and 1,2-metallate rearrangement mechanism.

As this chapter will focus around the functionalisation of azetidines through boronic ester homologation, a brief discussion of the development of boronic ester homologation/1,2-metallate rearrangement is presented here — with emphasis on α-amino boronic esters and azetidine boronic esters.

### 3.1.1 Matteson homologation

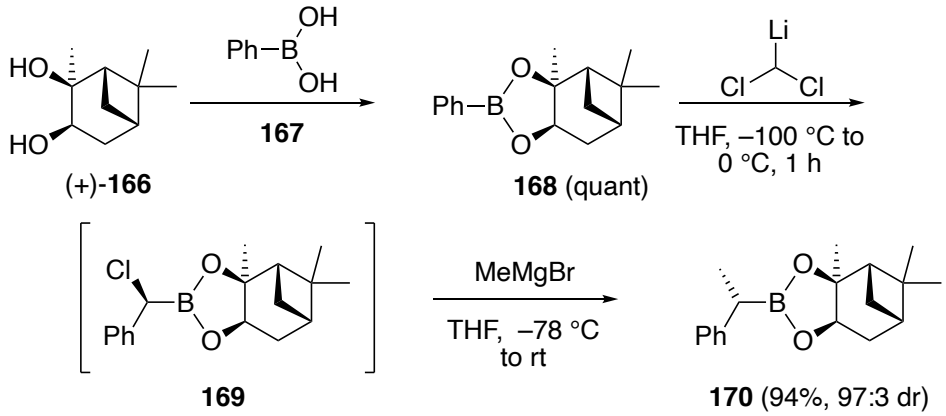
The seminal work on $C(sp^3)$-$C(sp^3)$ bond-forming boronic ester assisted nucleophilic displacement was reported by Matteson and co-workers (Scheme 59).[122] In that work, nucleophilic displacement of a bromide positioned α- in boronic ester **162** was shown to be possible with a variety of nucleophiles. Interestingly, the presence of the neighbouring boronic ester greatly facilitated the bromide displacement, compared to non-boronic ester analogues of **162** which underwent competing dehydrobrominative elimination.




**162** **163** R = Et, Ar **164** **165** (63-91%)

**Scheme 59.** α-bromo 1,2-metallate boronate rearrangement.[122]

The synthetic potential of this transformation was greatly enhanced when work from the same group developed an efficient means to synthesise α-chloro boronic esters from *in situ* prepared $LiCHCl_2$ which underwent 1,2-metallate rearrangement following introduction of an appropriate nucleophile.[123] Furthermore, condensation of enantioenriched diol ligands such as (+)-pinanediol onto the boronic ester functional group allowed for the synthesis and homologations of α-chloro boronic esters to occur with high levels of diastereoselectivity (~95:5 dr, Scheme 60).[124]




**Scheme 60.** Example of diastereoselective Matteson homologation using (+)-pinanediol.[124]

Dramatic increases in diastereoselectivity (>99:1 dr) were achieved by the introduction of $ZnCl_2$ to the reaction mixture, which allowed enantiopure synthesis of a number of natural products including insect pheromones (3*S*, 4*S*)-4-methyl-3-heptanol and *exo*-brevicomin.[125] The origins of the increased diastereoselectivity were found to be a result of complexation of $ZnCl_2$ to the boronate complex, with transition state **171a** being favoured over transition **171b** for both steric and electronic reasons (Figure 4).[126] This leads to differentiation between the diastereotopic chlorine atoms in which only the chlorine anti-periplanar to $R^1$ in TS **171** is displaced.

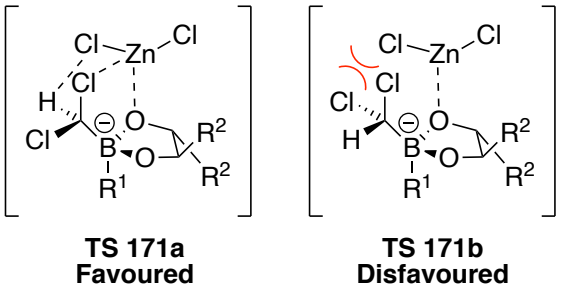
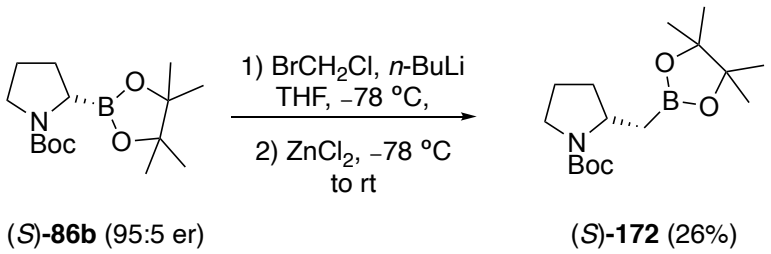



**Figure 4.** Stereoelectronic origins of improved diastereoselectivity with $ZnCl_2$

This results in highly diastereoenriched α-chloro boronic esters, which can be further elaborated stereospecifically. The utility in this methodology is a consequence of a number of features: the high diastereoselectivity it can impart, the availability of starting materials

(including enantioenriched diols) and the ability to perform several successive/iterative homologations.[127]

Despite the success of this methodology, there are still a few major drawbacks. Firstly, selectivity is substrate controlled; that is if the incorrect enantiomer of the diol ligand is attached to the boronic ester, a three-step reaction sequence is required to form the boronic ester with the "correct" stereochemistry.[127] Occasionally, diastereomeric boronate complexes have different reaction pathways (C-migration versus O-migration) as a result of altered sterics around the migrating terminus.[128] Finally, functional group intolerance was seen in reactions with leaving groups at the β-position to the boron atom, resulting in competing β-elimination.[129] Functional groups such as α-amido boronic esters have also proven to be challenging substrates to undergo Matteson homologation.[130] For example, an attempted synthesis of kainic acid failed due to difficulties encountered during homologation of a pyrrolidine-2-boronic ester precursor.[131] Similarly, Whiting and co-workers could only achieve low yields (26%) in the one-carbon homologation of pyrrolidine boronic ester (*S*)-**86b** (Scheme 61).[132] The latter was conveniently prepared by an asymmetric α-lithiation—electrophile trapping on *N*-Boc-pyrrolidine **101b** using (–)-sp **87** as the chiral diamine ligand (see p 27).[119]

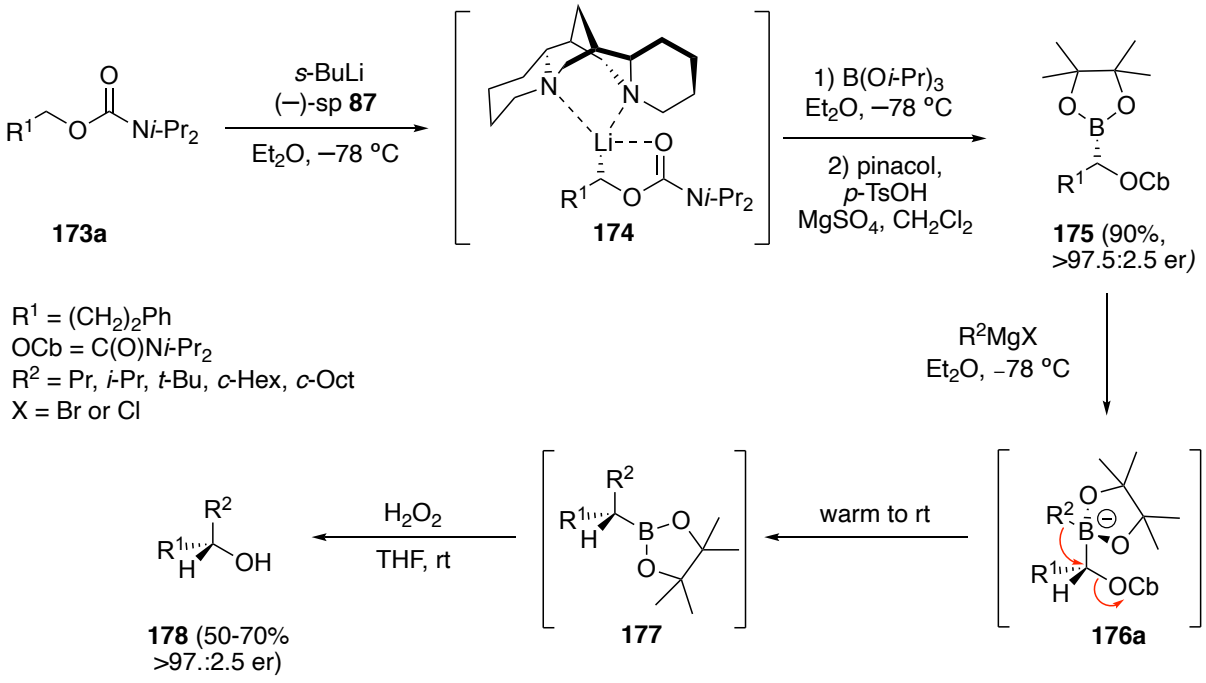



(*S*)-**86b** (95:5 er) (*S*)-**172** (26%)

**Scheme 61.** Matteson homologation of 2-B(pin)-*N*-Boc-pyrrolidine (*S*)-**86b.**[132]

### 3.1.2 Reagent controlled homologation

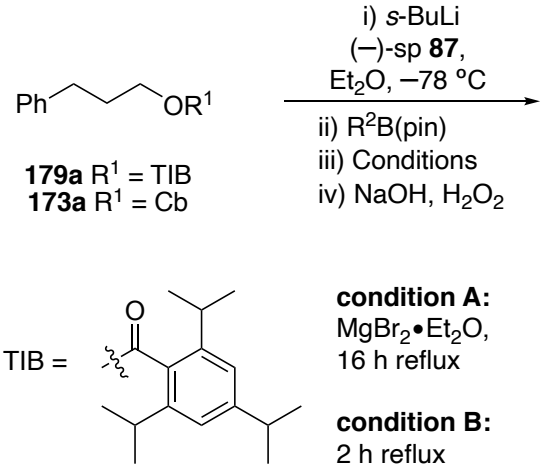
The preparation of an enantioenriched LiCHRCl equivalent (chiral carbenoid) would allow for the development of reagent-controlled homologation. Such species would be able to form an 'ate' complex with a boronic ester and undergo stereospecific homologation to give enantioenriched products. Hoppe and co-workers realised this sequence, through (–)-sp **87** mediated asymmetric α-lithiation—borylation of *O*-alkyl carbamate **173a** with B(*i*-OPr)$_3$ followed by subsequent transesterification to pinacol boronic ester **175** (Scheme 62).[133] Addition of an alkyl Grignard to form a boronate, with warming to allow 1,2-metallate rearrangement and hydroperoxide oxidation, gave highly enantioenriched secondary alcohols **178** in good yields (50-70% yields, >97.5:2.5 er).




**Scheme 62.** Hoppe's stepwise asymmetric 1,2-metallate rearrangement.[133]

Despite the success of this approach, performing this transformation over a number of steps reduced the overall appeal of this approach. Streamlined approaches utilising different chiral carbenoid equivalents such as α-chloro sulfoxides[134] and sulfonium ylides[135] have also proven viable alternatives. However, Aggarwal and co-workers' modification of

Hoppe's methodology, incorporating α-lithiation—borylation—oxidation of *O*-alkyl carbamates in a "one-pot system" to synthesise enantioenriched secondary alcohols, has proved to be the most effective/direct route.[136] Importantly, these reactions were unaffected by substrate stereochemistry allowing several iterative homologations to be performed with very high diastereo- and enantiocontrol (opposite enantiomer of organolithium accessible with O'Brien's (+)-sparteine surrogate).[137] Additionally, replacement of the carbamate group by a more electron-withdrawing triisopropyl benzoyl (TIB) directing group, able to undergo (–)-sp **87** mediated asymmetric α-lithiation to give a configurationally stable anion, allowed for the successful 1,2-metallate rearrangement to occur with challenging migrating substrates (Scheme 63).[138]



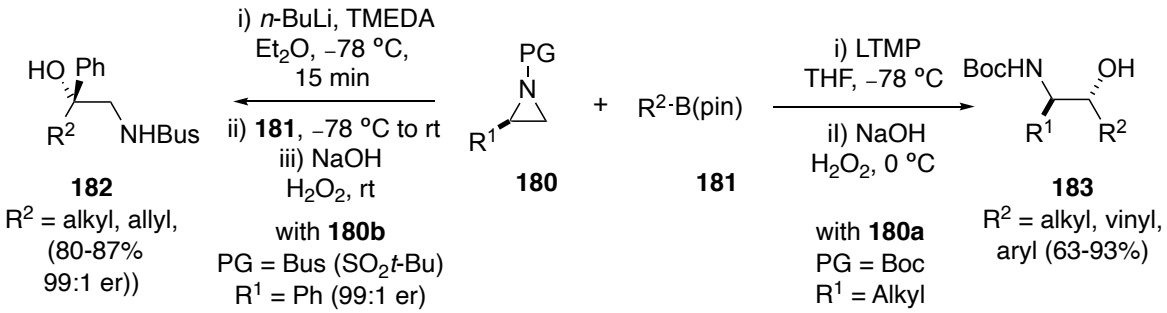

| $R^1$ | $R^2$ | Cond. | Yield (%) | e.r. |
|---|---|---|---|---|
| Cb | Me | A | 50 | 95:5 |
| TIB | Me | B | 76 | 96:4 |
| Cb | $(CH_2)_2COO$*t*-Bu | A | 35 | 93:7 |
| TIB | $(CH_2)_2COO$*t*-Bu | B | 63 | 96:4 |
| Cb | $(CH_2)_2CN$ | A | 0 | n.d |
| TIB | $(CH_2)_2CN$ | B | 46 | 97:3 |

**Scheme 63.** Improved boronate 1,2-metallate rearrangement with TIB esters.[138]

### 3.1.3 Saturated azacycle boronate homologation

Synthesis of enantioenriched β-amino alcohols was achieved by Aggarwal *et al.* through directed α-lithiation—borylation and 1,2-metallate rearrangement of aziridines (Scheme 64).[139] Using α-lithiation conditions developed within the Hodgson group,[140] monosubstituted *N*-Boc aziridines **180a** could be deprotonated and trapped

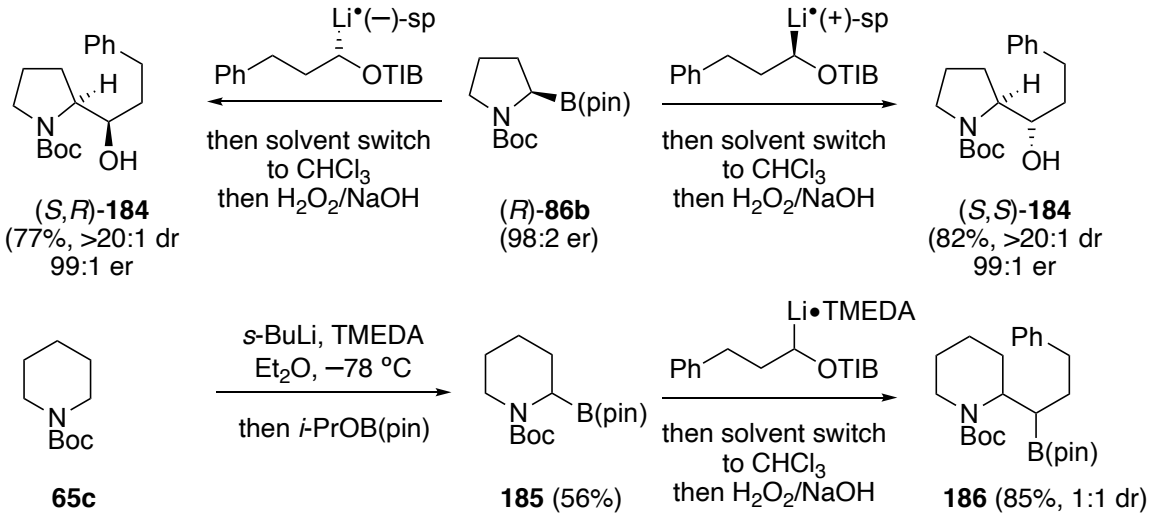
diastereoselectively to form a *trans in situ* boronate intermediate. On warming, the boronate underwent strain-releasing stereospecific 1,2-metallate rearrangement and ring-opening of the aziridine, which upon oxidation gave β-amino alcohols **183** in high diastereoselectivity. Regioselective lithiation (at the more acidic α-N position) and ring-opening of aziridine to create a quaternary stereocentre was also achieved when using enantioenriched *N*-Bus phenyl aziridine **180b** (Scheme 64).




**Scheme 64.** Aziridine lithiation—borylation ring-opening 1,2-metallate rearrangement.[139]

Enantio- and diastereoselective homologation of 2-B(pin)-*N*-Boc-pyrrolidine **86b** was demonstrated in a total synthesis of (–)-stemaphylline.[141] In order to succeed in the total synthesis, Aggarwal *et al.* had to overcome the difficulties associated with homologation/1,2-metallate rearrangement on α-amido boronic esters situated on a unstrained ring system (see p 60). This was achieved by utilising triisopropylbenzoyloxy organolithium as the chiral carbenoid equivalent (see above) and also by employing a solvent switch from $Et_2O$ to $CHCl_3$ following boronate complex formation. The solvent switch dramatically lowered the calculated enthalpy of activation for the 1,2-migration (28.7 ($CHCl_3$) vs 34.2 (TBME) kcal $mol^{-1}$), which the authors speculated being a consequence of increased Lewis acidity of the $Li^+$ cations in $CHCl_3$. Through choice of chiral diamine ligand (–)-sp **87** or (+)-sp **87**, both *syn* and *anti* diastereomers (*S,R*)-**184** and (*S,S*)-**184** could be accessed with high diastereo- and enantio-selectivity (Scheme 65). Additionally, employing

the same solvent switch conditions to 2-B(pin)-*N*-Boc-piperidine **185** also resulted in successful homologation (Scheme 65).

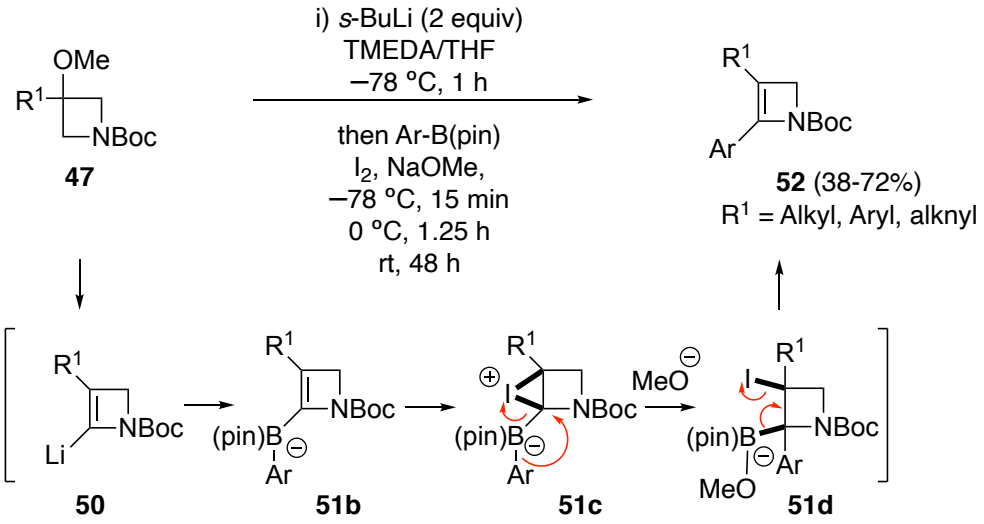



**Scheme 65.** α-azacyclic boronic ester synthesis and homologation.[141]

The authors also demonstrated Matteson homologation and Zweifel olefination[142] as further means to functionalise both pyrrolidine α-amido boronic ester **86** and homologated pyrrolidine β-amido boronic ester **184**, illustrating the diverse synthetic potential of α-amido boronic esters.

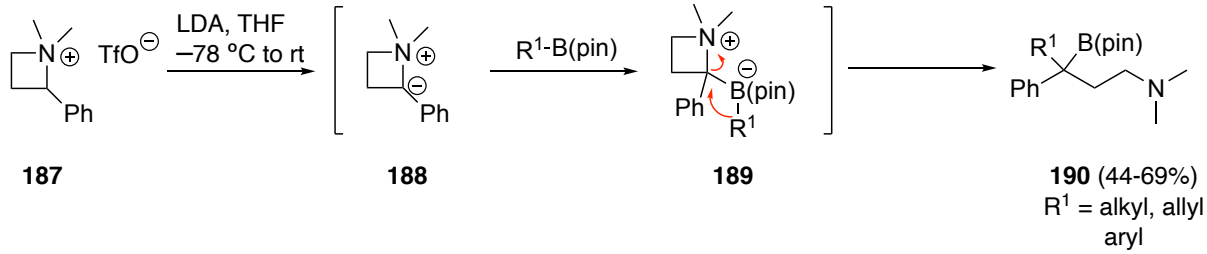
### 3.1.4 Azetidine/azetine boronate transformations

Didier and co-workers described a transition metal-free Zweifel arylation approach towards synthesising 2,3-disubstituted-azetines (Scheme 66).[57] Introduction of iodine to the *in situ* formed unsaturated boronate complex **51b** results in the activation of the alkene forming an iodonium species **51c** which promotes 1,2-metallate rearrangement. The formed β-halide boronic ester **51d** can then undergo β-elimination to 'reform' the now 2,3-disubstituted-azetines **52**.



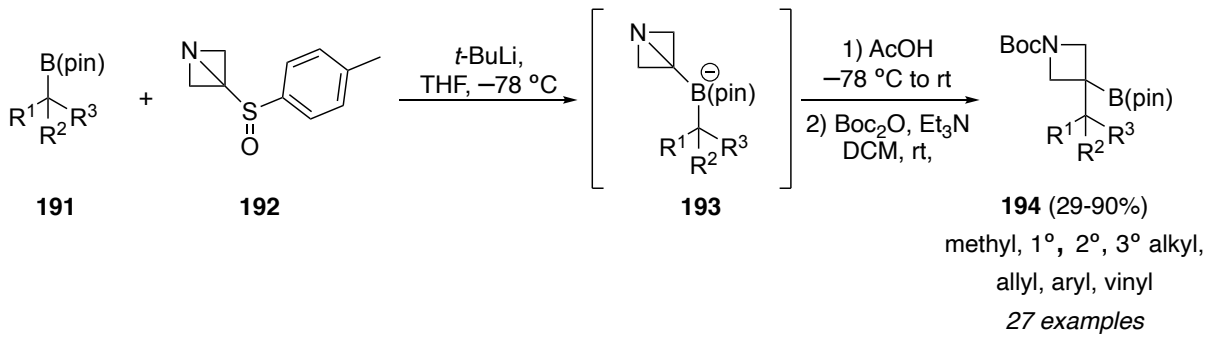

**Scheme 66.** *in situ* boronate Zweifel azetine functionalisation.[57]

Ring-opening of an *in situ* α-azetidinium boronic ester **189**, to synthesise 3-aryl amino propane tertiary boronic ester derivatives, has been demonstrated by Aggarwal, Myers and Casoni (Scheme 67).[143] To facilitate this transformation, the authors used 2-phenyl-azetidinium triflate **187**, which allowed for ylide **188** formation through regioselective lithiation at the benzylic position. Azetidinium ylide **188** could subsequently be trapped by an alkyl or aryl boronic ester to form a boronate complex **189** which could then undergo ring-opening 1,2-metallate rearrangement to give a number of 3-aryl amino propane boronic esters. Interestingly, the analogous pyrrolidinium ion failed to undergo the same transformation, suggesting that the release of ring-strain is an important factor for this reaction. Unfortunately, there was low configurational stability of the azetidinium ylide **188**, which resulted in rapid loss of stereochemical information during this transformation precluding enantioselective synthesis.




**Scheme 67.** Azetidinium ring-opening via 1,2-metallate rearrangement.[143]

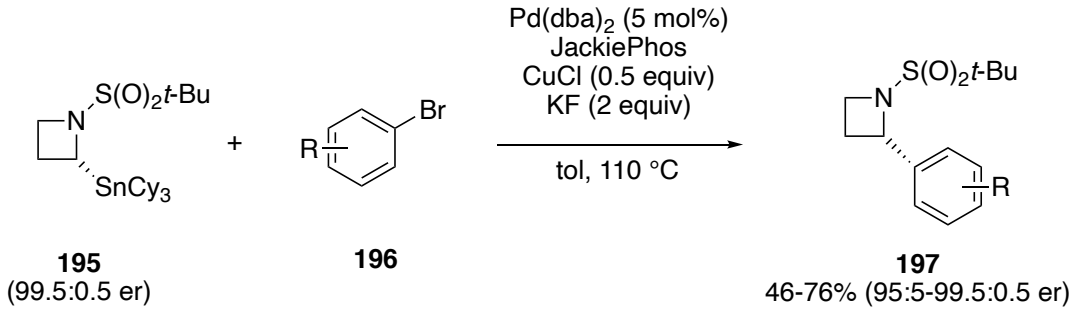
An example of ring-strain release driven boronic ester homologation for the synthesis and functionalisation of azetidines at the 3-position has also been realised by Aggarwal and co-workers (Scheme 68).[144] This was enabled by lithiation of [1.1.0] ABB either by direct deprotonation or by lithium–sulfoxide exchange of the corresponding ABB sulfoxide **192**. Lithiation at the bridgehead position of ABB was believed to occur due to the increased s-character of the C-H bond at the strained position. Lithiated ABB could then trap a boronic ester, forming a boronate complex **193** which could then undergo strain-releasing ring-opening 1,2-metallate rearrangement, following addition of acetic acid. The reaction tolerated primary, secondary and tertiary boronic esters, and both enantiopure and diastereomerically pure boronic esters underwent migration with complete enantio- and diastereospecificity indicating a stereospecific 1,2-migration. The 3,3-disubstituted boronic esters **194** could be further functionalised under a range of possible boronic ester transformations to give a range of 3,3-disubstituted-azetidines.




**Scheme 68.** ABB borylation and 1,2-metallate rearrangement.[144]

## 3.2 Results and discussion

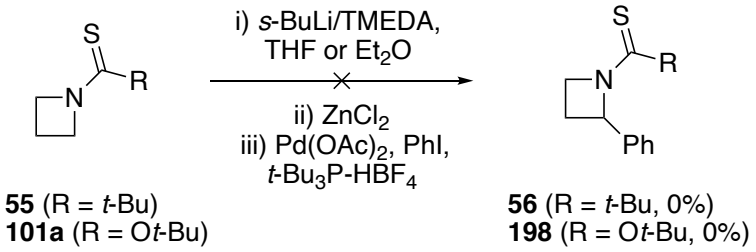
It was considered that significant expansion of the range of substituents at the 2-positions of *N*-Botc-azetidines, accessible from the previously developed lithiation—electrophile trapping methodology, could be achieved following access to a synthetic 'handle' at the 2-position which would allow further elaboration, particularly in an asymmetric manner. Which synthetic 'handle' to target was non-trivial, however. For example, 2-stannyl azacycles offer opportunities for further elaboration through cross-couplings,[145] oxidative *N*-acyliminium formation[146] and photochemical radical cross-coupling.[147] Moreover, recent work has demonstrated that 2-stannyl-azetidines are capable of undergoing stereoretentive Pd-catalysed C($sp^3$)-C($sp^2$) Stille cross-couplings, enabling access to enantioenriched 2-aryl-azetidines **197** (Scheme 69).[148]




**Scheme 69.** Stereospecific Stille azetidine cross-coupling.[148]

However, despite access to *N*-Botc stannane **104f**, it was not considered as a potential 'handle' for a number of reasons. Firstly, asymmetric lithiation—electrophile trapping with $Me_3SnCl$ had only managed to give moderately enantioenriched stannane **104f** (up to 67:33 er, see p 32).[94] This is problematic for stereospecific transformations, such as Stille couplings (Scheme 69). Secondly, previous attempts at Negishi cross-coupling following transmetallation of lithiated *N*-Botc-azetidine **101a**, using conditions developed by Campos[99b,149] and also Coldham and Leonori,[150] failed to produce any of the desired

arylated product (Scheme 70).[94] Similar results were observed with *N*-thiopivaloyl-azetidine **55**,[90] which could suggest an incompatibility of transition metal catalysed cross-coupling reactions with the thiocarbonyl group. 2-Halo-azetidines were not considered due to perceived stability issues and a general lack of synthetic precedent. α-Aminoalkanesulfinates are accessible through lithiation—electrophile trapping, however, only radical based derivatisations have been demonstrated,[151] which in our case would pose a considerable synthetic challenge for asymmetric functionalisation. Similarly, α-aziridine sulfones have been successfully synthesised through lithiation—electrophile trapping,[140] however, only a limited range of functionalisation has been demonstrated on saturated α-azacyclic systems.[152]




**Scheme 70.** Previous attempts at transmetallation Negishi cross-coupling.[90,94]

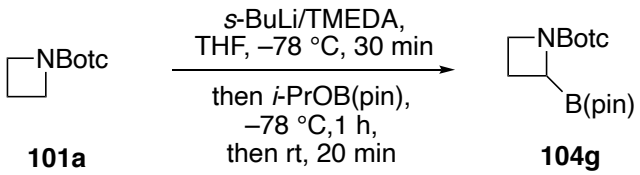
As boronic esters are amenable to both transition metal-free (Matteson homologation, and Zweifel)[153] and transition metal-catalysed (Suzuki) transformations,[154] they were considered the most suitable group for azetidine derivatisation. Additionally, asymmetric synthesis of α-boryl-pyrrolidines (98:2 er) by lithiation—borylation had proven to be a synthetically viable approach (see p 64). [141]

### 3.2.1 Synthesis and purification of 2-boryl *N*-Botc-azetidines

The first attempt at lithiation—borylation of *N*-Botc-azetidine **101a** with *i*-PrOB(pin) as the electrophile revealed, following $^{1}$H NMR analysis of the crude reaction, that most of the

starting material had been consumed to form the desired product. However, despite this initial success, isolation of pure 2-B(pin)-azetidine **104g** proved to be very challenging. Column chromatography of the crude reaction mixture resulted in the isolation of impure 2-B(pin)-azetidine **104g** in 33% yield. The appearance of pinacol and *N*-Botc-azetidine **101a** impurity peaks in the $^{1}$H NMR spectrum of the isolated boronic ester **104g** was cause for concern, as it suggested boronic ester **104g** was susceptible to hydrolysis and protodeborylation during chromatography.

For the corresponding 2-B(pin)-*N*-Boc-pyrrolidine **86b**, there are conflicting reports regarding the compound's suitability for purification by column chromatography. In the original isolation paper, the authors report column chromatography as a suitable means for purification.[119] The authors were working on large scale (4.66 mmol *N*-Boc-pyrrolidine **65b**) compared to our initial test reaction (0.23 mmol of **101a**) and therefore it was considered that the issues of purification in our case could be a result of scale. Re-running lithiation—borylation on a 1.2 mmol scale did result in an improved yield of boronic ester **104g** (47%) following column chromatography. However, there were still issues in obtaining pure product **104g** (trace SM and pinacol seen in product NMR). In Aggarwal's synthesis of 2-B(pin)-*N*-Boc-pyrrolidine **86b**,[141] the purification method states "fast column chromatography" although no specifications were given. Interpreting "fast column chromatography" to mean plug of silica, a lithiation—borylation of *N*-Botc-azetidine **101a** (1.2 mmol) gave boronic ester **104g** in slightly improved yield (51%) (Scheme 71), despite issues of partial product decomposition on silica. Further increasing the reaction scale to 5.6 mmol of starting *N*-Botc-azetidine **101a** gave boronic ester **104g** in 53% yield.



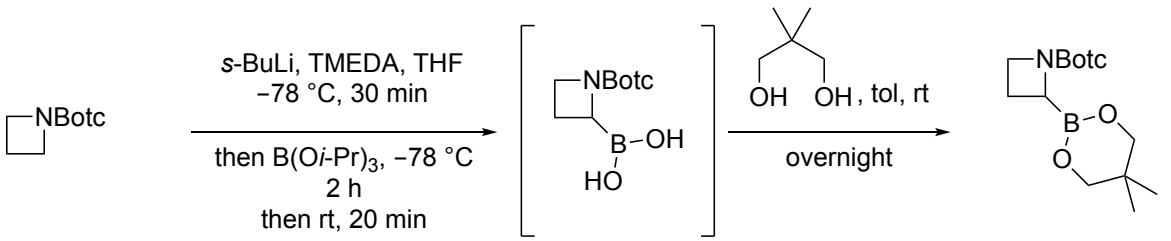

**101a** **104g**

| scale (mmol 101a) | yield |
|---|---|
| 0.23 | 33% |
| 1.20 | 47% |
| 1.20[a] | 51% |
| 5.6[a] | 53% |

**Scheme 71.** Initial lithiation—borylation work-up optimisation. [a)]Purification by a short plug of silica.

Work involving lithiation—borylation to form α-amino boronic esters by Ley and co-workers avoided the use of an aqueous acidic work-up and instead made use of an acetyl chloride quench to induce collapse of the boronate complex.[155] The authors also employed phosphate-buffered saline (PBS) solution during work-up and oven-dried silica for column chromatography. Replication of these conditions for the lithiation—borylation of *N*-Botc-azetidine **101a** (0.23 mmol) gave moderate yields of the desired boronic ester **104g** (43%).

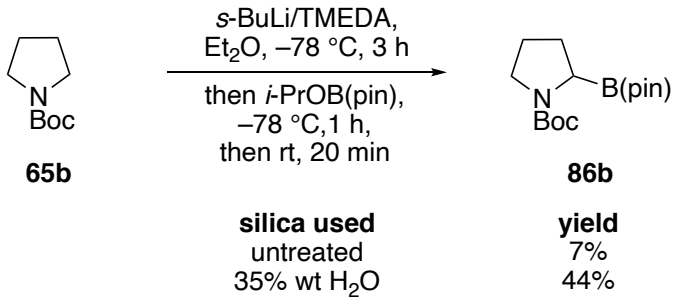
In an effort to avoid the issues surrounding the purification of boronic ester **104g**, a chromatography-free method described by Vedsø *et al.* was followed,[156] which gave neopentyl boronic ester **104i** in low yield 16% (Scheme 72). Attempts at isolating the intermediate boronic acid **104h** via recrystallization also failed to give the acid as an isolable pure compound.




**101a** **104h** **104i** (~16%)

**Scheme 72.** Synthesis of 2-neopentyl boronic ester **104i.**

In the purification of 2-B(pin)-*N*-Boc-pyrrolidine **86b**, Baran and co-workers reported the need to use 35% wt $H_2O$-deactivated silica to facilitate purification.[157] With the conflicting reports on the purification of 2-B(pin)-*N*-Boc-pyrrolidine **86b**, an authentic sample was prepared following lithiation—borylation of *N*-Boc-pyrrolidine **65b** (44% yield, Scheme 73). In my hands, it was found that the utilisation of 35% wt $H_2O$-deactivated silica was essential in order to reduce product streaking during purification, with untreated silica resulting in product streaking/poor resolution and reduced yields (7%, Scheme 73).




**Scheme 73.** Lithiation—borylation of *N*-Boc-pyrrolidine **65b** with purification with untreated and 35% wt $H_2O$-deactivated silica.

Lithiation—borylation was performed on *N*-Botc-azetidine **101a** with purification using a plug of 35% wt $H_2O$-deactivated silica. However, despite reducing the amount of impurities seen in the isolated boronic ester **104g**, the yield remained unsatisfactory at 53%. A series of different column conditions were tested in order to develop the most effective work-up procedure, but all except 35% wt $H_2O$-deactivated silica gave product decomposition. Florisil, neutral alumina, basic alumina and C-18 reverse phase silica failed to return any boronic ester following a column of crude (~80 mol%) boronic ester **104g** (by $^1$H NMR analysis).

Although 35% wt $H_2O$-deactivated silica did not noticeably decompose boronic ester **104g**, it could only moderately resolve the reaction crude resulting in time consuming and

inefficient work-up. An attempt at purification of crude boronic ester **104g** by Kugelrohr distillation under reduced pressure (30 mmHg) resulted in decomposition of the product at temperatures approaching 100 °C. Attempts to crystallise the crude boronic ester directly after work-up proved difficult, resulting in isolation of side-product diazetidine boronic ester **199** 7% yield, which most likely formed before complete electrophile trapping of the carbanion had occurred (Figure 5).

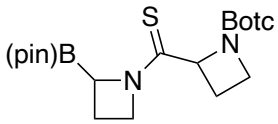
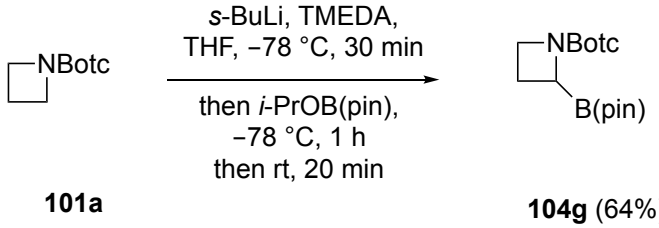



**Figure 5.** Side product **199**, isolated during crystallisation.

To aid crystallisation, pinacol was azetropically removed by addition of a mixture of MeOH: $H_2O$ (1:1) and rotary evaporation.[158] This helped the crude solidify, allowing recrystallisation which, when performed with activated charcoal in hexane, gave analytically pure boronic ester **104g** (64%) (Scheme 74). However, this process was unsatisfactory as it failed to be consistently reproducible (27-41% yields) and therefore further work into optimising the work-up procedure was examined.




**101a** **104g** (64%)

**Scheme 74.** Synthesis of 2-B(pin)-azetidine **104g** with purification recrystallisation purification.

Boric acid-impregnated silica has been shown to be effective in aiding chromatographic purification for a number of boronic esters, as a result of boric acid "capping" the free silanol groups and therefore minimising over absorption of the boronic ester.[159] So as to determine whether or not boric acid-impregnated silica was beneficial for the purification

of boronic ester **104g**, column chromatography experiments were run. Three columns were loaded with 100 mg of pure boronic ester **104g**, and the amount of recovered pure boronic ester **104g** was recorded (Table 3).

| Entry | Silica | Mass of silica | % recovered boronic ester 104g |
|---|---|---|---|
| 1 | Boric acid silica | 5 g | 91 |
| 2 | Boric acid silica | 10 g | 85 |
| 3 | 35% wt $H_2O$ silica | 10 g | 69 |

**Table 3.** Comparison of boric acid-impregnated silica versus 35% wt $H_2O$-silica.

Table 3 shows that boric acid-impregnated silica shows reduced tendency to absorb boronic ester **104g** compared with 35% wt $H_2O$ silica (entries 2 and 3). With these results it was hoped that boric acid-impregnated silica would improve the reaction yields and purification process for boronic ester **104g**. However, attempted lithiation—borylation on *N*-Botc-azetidine **101a** with purification through a plug of boric acid-impregnated silica gave boronic ester **104g** in only 43% yield.

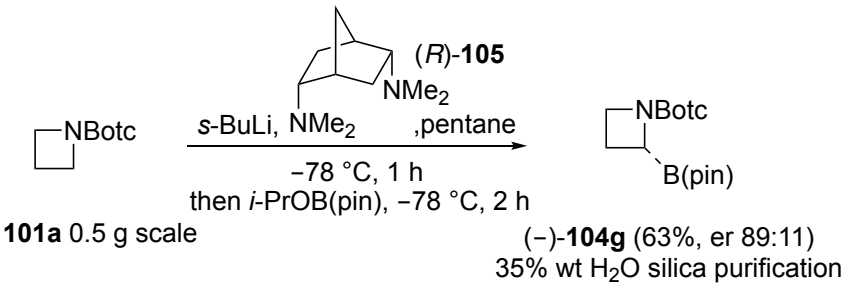
Despite the concerns regarding the isolation of pure boronic ester **104g**, it was decided to examine the asymmetric synthesis of boronic ester **104g**. This was because it was considered important to access boronic ester **104g** in high levels of enantioenrichment for the project to be of significant value and worthwhile pursuing.

### 3.2.2 Asymmetric lithiation and electrophile trapping

While optimisation of reaction conditions and work-up procedure for the synthesis of boronic ester (±)-**104g** were ongoing, attempts at the enantioselective synthesis of boronic

ester **104g** through asymmetric lithiation—borylation were performed. Initial asymmetric lithiation—borylation was carried out following the previously described *N*-Botc-azetidine **101a** asymmetric lithiation—electrophile trapping procedure, with both lithiation and trapping temperature at –78 °C.[93] High levels of enantioenriched trapped products have been achieved at –78 °C or –98 °C, with carbonyl electrophiles working efficiently at –78 °C (acetone and aromatic aldehydes) and MeI working best at –98 °C (see p 32).[93]

The reaction was first performed on a 50 mg scale so as not to use up excessive and precious enantiopure DIANANE ligand (*R*)-**105**. This scale however was problematic for work-up, since unreacted starting material **101a** was mixed with boronic ester **104g** in the reaction crude. It was therefore decided to increase the scale 10-fold in order to allow for easier purification. Under these conditions the reaction worked far more effectively, providing enantioenriched boronic ester (–)-**104g** in good yield (63%) and high er (89:11) (Scheme 75).

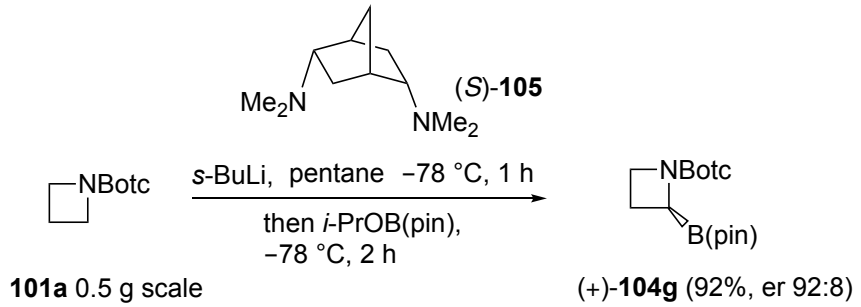



**Scheme 75.** Asymmetric lithiation—borylation.

The level of enantioenrichment of boronic ester **104g** was similar to those previously reached with carbonyl based electrophiles (~90:10 er), suggesting that *i*-PrOB(pin) traps in a similar manner. Indeed both electrophiles are assumed to coordinate with the $Li^+$ cation prior to trapping.[160] There were however still issues surrounding the easy isolation of boronic ester (–)-**104g**. In this case 35% wt $H_2O$-silica was utilised for column

chromatography, resulting in suspected reduction in the overall yield as analysis of the reaction crude by $^1$H NMR spectroscopy showed only traces of pinacol.

Attempts at asymmetric lithiation—borylation with DIANANE (*S*)-**105** to access the opposite enantiomer, boronic ester (+)-**104g**, were performed (Scheme 76).



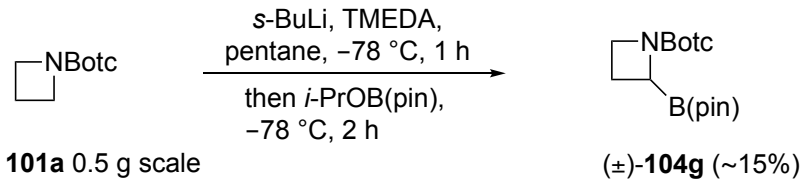

**Scheme 76.** Asymmetric lithiation/borylation using (*S*)-DIANANE (*S*)-**105**.

The reaction proceeded very cleanly to give boronic ester (+)-**104g** in a high yield (92%) and er (92:8). HPLC data as well as specific rotation data proved that the desired opposite enantiomer of boronic ester **104g** had been successfully synthesised. The reaction proceeded so cleanly that chromatographic purification of the crude was deemed unnecessary with ~5% *N*-Botc-azetidine **101a** as the only discernible contaminant, especially seeing as purification of boronic ester **104g** had been proven to be difficult and inefficient. Instead, the trace *N*-Botc-azetidine **101a**, could be removed under high-vac which enabled the solidification and isolation of pure enantioenriched boronic ester **104g**. The increased purity of the reaction when run in pentane compared with THF could be a result of the difference in partition coefficients of the solvents. Reactions run in THF are often contaminated with pinacol and other unknown polar impurities; these impurities are not seen when run in pentane. Presumably, extraction of the reaction mixture when the reaction is run in THF would enable higher concentrations of polar impurities in the organic

layer. This would not be the case when performed in pentane, where impurities such as pinacol would not be soluble and would remain in the aqueous layer and thus easily removed. This theory was supported following analysis of two reaction extracts, the first using petrol as the solvent and the second using $Et_2O$. The petrol extract gave mostly product with minimal trace unknown impurities as observed by $^1H$ NMR spectroscopy analysis; however, for the $Et_2O$ extract, a far larger amount of unknown impurities was observed in the $^1H$ NMR spectra.

### 3.2.3 Synthesis of racemic 2-B(pin)-*N*-Botc-azetidine 104g in pentane

The high yield that arose from the asymmetric lithiation—borylation in pentane suggested that using a non-coordinating hydrocarbon solvent allowed for clean boronic ester **104g** formation. This is somewhat surprising, as studies into solvent effects on the rate of borylation have demonstrated that non-polar solvents such as PhMe dramatically decrease the rate of borylation.[161] Our earlier racemic lithiation—borylation reactions on *N*-Botc-azetidine **101a** were performed in THF which had been shown to be the best solvent for racemic α-lithiation—electrophile trapping of *N*-Botc-azetidine **101a** within the group.[93] This would suggest that the borylation step in the racemic lithiation—borylation reaction sequence is problematic. However, studies on the effect of solvents on the rate of α-lithiation—borylations of carbamates and benzoates have shown that even sub-stoichiometric amounts of THF in the reaction could dramatically increase the rate of borylation.[161] To establish whether or not the use of THF in the racemic lithiation—borylation of *N*-Botc-azetidine **101a** was problematic, and also hoping to achieve similarly high yields obtained for the asymmetric reaction, a racemic lithiation—borylation reaction using TMEDA as the diamine ligand in pentane was performed (Scheme 77).




**101a** 0.5 g scale

(±)-**104g** (~15%)

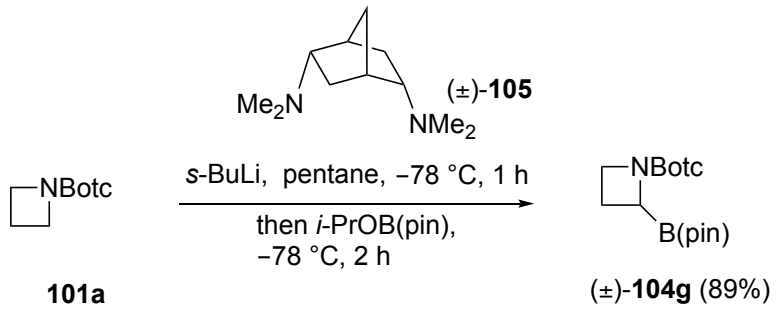
**Scheme 77.** Lithiation—borylation in pentane with TMEDA as ligand.

Analysis of the reaction crude by $^{1}$H NMR spectroscopy showed a significant number of unknown impurities which could not be separated from the product. The messy nature of the reaction using TMEDA in contrast to the reaction using (*S*)-DIANANE (*S*)-**105** shows that the nature of the diamine ligand is highly important for the effectiveness of the reaction. Indeed, lithiation using TMEDA in pentane resulted in the formation of a precipitate in the reaction mixture, potentially due to the insolubility of the *s*-BuLi/TMEDA aggregates formed. The DIANANE **105** ligand therefore appears to work well due to its ability to effectively create a soluble and reactive lithium/DIANANE complex in pentane. This would also explain the large difference in yields obtained for the racemic reaction in THF (64%) and in pentane (~15%), as THF would also effectively solvate/help form the reactive lithium/diamine aggregates.

A test lithiation—electrophile trapping of *N*-Botc-azetidine **101a** with MeI in pentane and TMEDA was performed to determine whether issues with lithiation in pentane and TMEDA was problematic. The reaction gave 2-methyl-*N*-Botc-azetidine **104a** in 23% yield (7% RSM), suggesting that lithiation—electrophile trapping in pentane/TMEDA is less effective than with pentane/DIANANE **105**. Additionally, during reaction work-up there was a noticeable foul odour suggesting the formation of volatile thiol/sulfide side products had occurred.

Having found that the yields for the asymmetric lithiation—borylation reaction using enantiopure DIANANE **105** in pentane with *N*-Botc-azetidine **101a** (Scheme 76) were significantly higher (92%) compared to the reaction under racemic conditions (TMEDA in THF) (64%), it was envisioned to attempt the synthesis of racemic boronic ester **104g** using racemic DIANANE (±)-**105** as the diamine ligand to aid lithiation.

Following the procedure earlier reported (p 42), DIANANE (±)-**105** was synthesised in a four step sequence starting from norbornadiene. With DIANANE (±)-**105**, an attempt to synthesise racemic boronic ester **104g** following the conditions developed for the asymmetric synthesis was performed. Pleasingly, the reaction proceeded in high yield (89%) on a 0.63 g scale (Scheme 78). Additionally, following an acid/base extraction of the aqueous washes, 88% of DIANANE (±)-**105** was recovered.



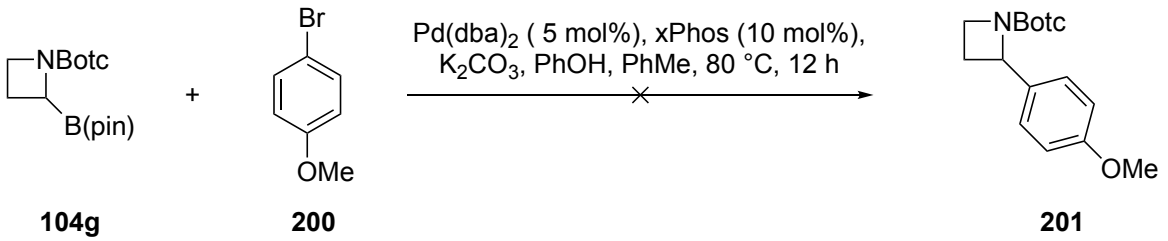

**Scheme 78.** DIANANE **105** promoted synthesis of racemic boronic ester **104g.**

### 3.2.4 α-Boronic ester 104g functionalisation

With an efficient synthesis of boronic ester **104g** established, work on assessing its utility as a synthetic 'building block' was carried out.

Suzuki-Miyaura cross-coupling reactions on α-amino boronic acids and boronic ester derivatives have remained fairly limited. Ohmura and co-workers have successfully cross-coupled benzylic α-amino boronic esters to a variety of aryl halides.[162] Despite being only

successful on benzylic boronic esters, an attempt at performing a reaction using their conditions on 2-B(pin)-azetidine **104g** was undertaken (Scheme 79).




**104g** **200** **201**

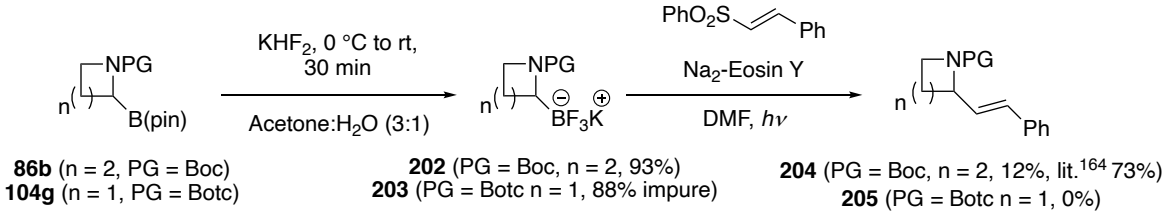
**Scheme 79.** Attempted Suzuki-Miyuara cross-coupling.

The reaction unfortunately only returned aryl bromide **200** (98% RSM) and none of the boronic ester **104g**. It is possible that under the high temperatures the thiocarbamate protecting group was removed, given it has previously been shown to thermally deprotect in ethanol at reflux over 12 h.[93] The same authors more recently reported a Pd-catalysed cross-coupling of non-benzylic α-amino boronic esters,[163] however, the reported conditions required an even higher reaction temperature (145 °C), which was deemed unsuitable for boronic ester **104g**. Given previous failed attempts at transition metal-catalysed cross-couplings on thiocarbonyl protected azetidines in the group,[90,94] no further attempts to develop Suzuki-Miyuara cross-coupling conditions were considered. Instead, attempts at functionalising boronic ester **104g** under transition metal-free conditions were explored.

Molander and co-workers have demonstrated eosin-Y-catalysed visible light-mediated photoredox alkenylation of secondary potassium trifluoroborate salts, including several examples on an α-amino pyrrolidine potassium trifluoroborate salt **202** (Scheme 80).[164] Conversion of azetidine boronic ester **104g** to potassium trifluorobororate salt **203** was attempted to evaluate the possibility of performing a photoredox alkenylation on an

azetidine equivalent. Reacting boronic ester **104g** with $KHF_2$ gave a white solid, potentially azetidine trifluoroborate salt **203** (88%); however, $^1H$ NMR analysis indicated multiple unknown impurity peaks which could not be removed on further washing of the salt. The same procedure was performed on 2-B(pin)-*N*-Boc-pyrrolidine **86b**, giving clean trifluoroborate salt **202** (93%, Scheme 80).

A test photoredox alkenylation was performed on pyrrolidine trifluoroborate salt **202** with styrene sulfone, which after 72 h gave 12% of the desired alkenylated pyrrolidine **204**. The reduced yield compared to the lit.[164] (73%) was attributed to a weak visible light source used in the reaction set-up. However, with formation of desired alkenylated product **204**, the reaction was attempted with the impure azetidine trifluoroborate salt **203**. Disappointingly, after 1 week of reaction mixture stirring under visible green light, no desired alkenylated product **205** was observed.

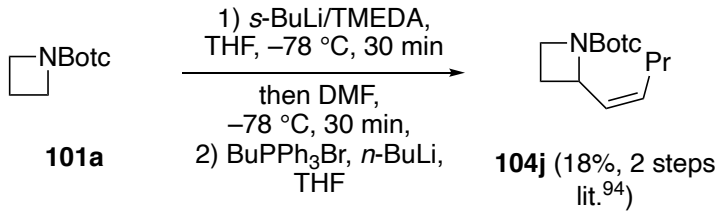



**Scheme 80.** Attempted organocatalysed photoredox alkenylation.

Reactions of azetidine trifluoroborate **203** were not investigated any further due to a number of reasons. Firstly, the additional step in the synthesis of borate salt **203** renders the reaction sequence inefficient, especially when considering that equivalent α-azetidinyl radicals can be accessed from decarboxylation of commercially available *N*-Boc-azetidine-2-carboxylic acid.[165] Secondly, there were issues surrounding the purity of trifluoroborate salt **203**. Finally, formation of an α-amino radical would most likely result in the loss of any stereoinformation and therefore would render the asymmetric synthesis

a greater challenge. This would be undesirable since synthesis of enantioenriched boronic ester **104g** can be achieved and therefore it would be more appropriate to exploit stereospecific transformations.

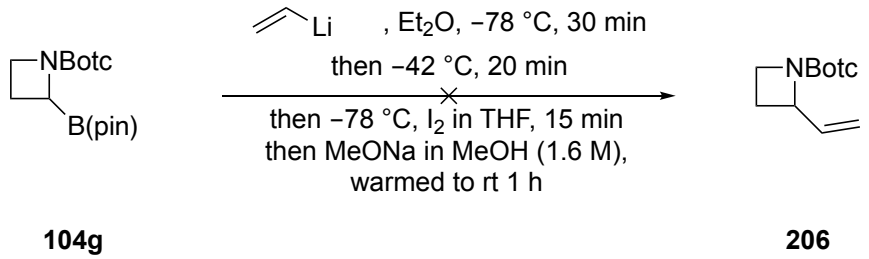
Attempts to functionalise α-boronic ester **104g** through Zweifel olefination were next investigated. This would be synthetically useful, as forming an $sp^3$-$sp^2$ carbon-carbon bond at the α-position of azetidine has been shown to be synthetically challenging via lithiation—electrophile trapping chemistry.[94] Previous work within the group had partial success at forming an $sp^3$-$sp^2$ carbon-carbon bond following α-lithiation—DMF trapping, followed by immediate Wittig reaction giving alkenylated azetidine **104j** in 18% yield (Scheme 81). The Zweifel olefination was therefore an attractive transformation to perform especially as it is enantiospecific and highly stereoselective, allowing formation of both *E*- and *Z*- isomers depending on the reaction conditions.[142]




**Scheme 81.** *N*-Botc-azetidine formylation and Wittig reaction.[94]

An attempt at applying the Zweifel conditions using tetravinyl tin reported by Aggarwal *et al.*[141] on boronic ester **104g** resulted in a messy mixture of unidentifiable compounds (Scheme 82). It was speculated that the tetravinyl tin was insufficiently pure and therefore preventing effective Sn–Li exchange, resulting in poor boronate formation. The starting boronic ester **104g** would then have been subjected to iodine which could react with the thiocarbonyl group and result in decomposition of the azetidine. It is well-known that iodine interacts with thioamides and thioureas.[166] A test reaction to evaluate the stability

of *N*-Botc-azetidine **101a** with iodine in THF at –78 °C for just 15 min resulted in only 15% recovered starting material.

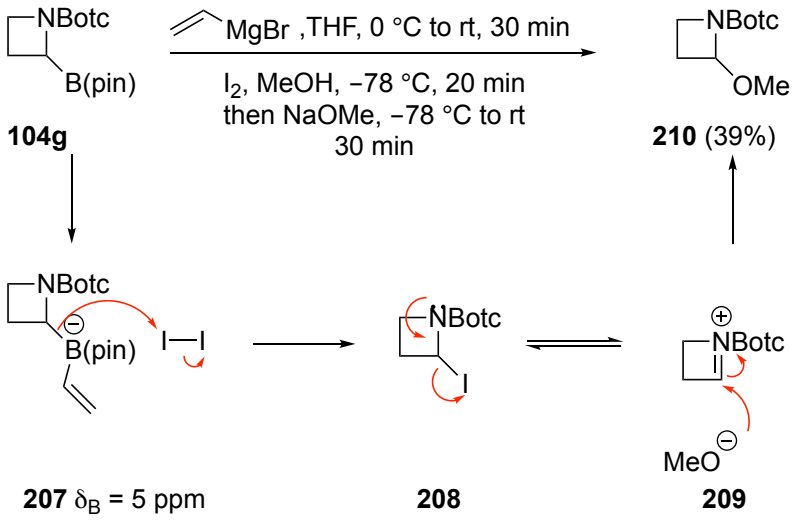



**104g** **206**

**Scheme 82.** Attempted Zweifel olefination.

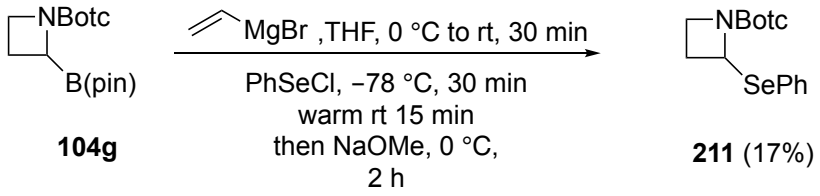
Zweifel conditions involving the addition of vinyl Grignard instead of vinyl lithium was attempted (Scheme 83).[167] Taking an aliquot of the reaction mixture after addition of the Grignard and running a $^{11}$B NMR spectrum showed complete consumption of the starting boronic ester **104g** and the appearance of a single peak at $\delta_B$ = 5 ppm, suggesting complete boronate formation. However, under these conditions none of the desired alkene product was observed, instead, there was the believed formation of *N*,*O*-acetal **210** in 39% yield. *N*,*O*-acetal **210** mass ion could not be seen in HRMS; however, $^1$H and $^{13}$C NMR did indicate the formation of *N,O*-acetal **210**. Indicative $^1$H NMR peaks are the highly downfield NCH dd peak at $\delta_H$ = 5.24 ppm and OMe peak at $\delta_H$ = 3.49 ppm. A 2D HSQC experiment showed the NCH proton correlating with a carbon at $\delta_c$ = 91.7 ppm; this corresponds to a large downfield shift for the α-carbon which is usually found in the 50-60 ppm region of the $^{13}$C spectrum for other *N*-Botc azetidines. It also corresponds to a similar chemical shift found in other azetidine *N,O*-acetals in the lit.[168] Moreover, the 2D COSY spectrum revealed that the NCH proton was only coupling with the protons on the adjacent carbon within the ring which further suggests that a heteroatom is bonded at the α-position of the ring. All other peaks in the $^1$H and $^{13}$C NMR match for *N,O*-acetal **210**.

The formation of the *N,O*-acetal **210** can be rationalised by a nucleophilic attack of boronate intermediate **207** on iodine to give the α-iodo-azetidine intermediate **208**. This is subsequently eliminated with the aid of the nitrogen lone pair to form an transient iminium species **209** which sodium methoxide nucleophilically attacks to give the *N,O*-acetal **210** (Scheme 83). Increasing the equivalents of iodine had a detrimental effect on the amount of *N,O*-acetal **210** formed, with one equivalent giving 39% yield, 1.2 equivalents giving **210** in 30% and 2 equivalents giving 18% yield. This is most likely due to increasing decomposition of the thiocarbonyl protecting group.




**Scheme 83.** Attempted Zweifel olefination and mechanism for suspected product.

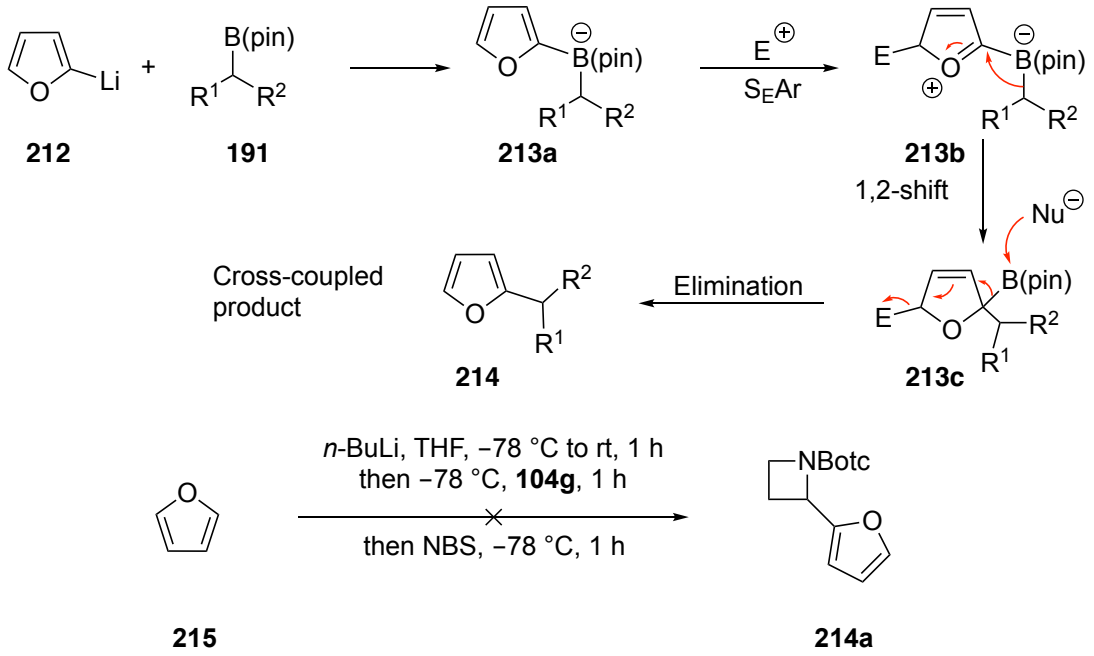
In an attempt to avoid formation of the undesired *N,O*-acetal **210**, Zweifel conditions in which the alkene activating electrophile is PhSeCl instead of iodine were examined with boronic ester **104g** (Scheme 84).[169] However, this resulted in formation of suspected α-selenide azetidine **211**. Again, HRMS failed to show mass ion peaks; however, $^{1}$H NMR spectroscopy indicated an α-heteroatom substituted azetidine with an aromatic phenyl group. $^{13}$C NMR analysis failed to aid in characterisation due to compound decomposition in the NMR tube.




**Scheme 84.** Attempted Zweifel olefination with PhSeCl.

An $sp^3$-$sp^2$ transition metal-free coupling reaction was also examined with 2-B(pin)-azetidine **104g** (Scheme 85). This reaction is envisioned to proceed through an initial lithiation of an electron rich aryl group, then boronate formation followed by the introduction of an electrophile which preferentially reacts in an $S_EAr$ fashion. This activates the intermediate boronate towards a nucleophilic 1,2-shift, which is then followed by an elimination (Scheme 85).[170]

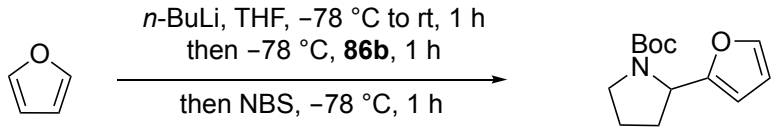
**Proposed mechanism**




**Scheme 85.** Proposed mechanism[170] and attempted transition metal free cross-coupling.

Unfortunately, with 2-B(pin)-azetidine **104g** the reaction did not give the desired furyl product **214a**, most likely a consequence of decomposition of the thiocarbonyl group by NBS. Verification of the literature procedure was performed and gave desired furan

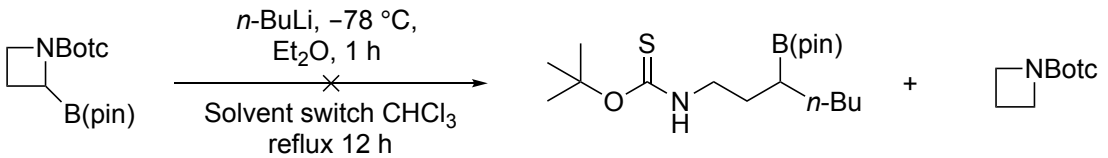
pyrrolidine **214b** in 47% yield (Scheme 86), a slightly lower yield to that reported (lit. 74%).[170]




**215** **214b** (47%)

**Scheme 86.** Transition metal free cross-coupling of 2-B(pin)-*N*-Boc-pyrrolidine **86b.**

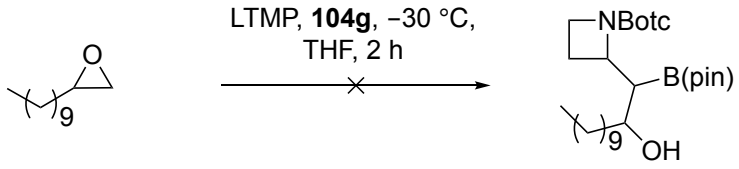
Attempts at azetidine boronate 1,2-rearrangement/ring-opening were briefly investigated. Using a solvent switch to $CHCl_3$ to allow for favourable migrating conditions (see p 64) under reflux resulted in the formation of the protodeboronated *N*-Botc-azetidine **101a** (17%) (Scheme 87). The same reaction performed without solvent switch and stirring overnight at rt resulted in only RSM (26%). These results are not entirely unexpected as nucleophilic ring-opening of azetidines is synthetically challenging, with examples often involving 2-aryl-azetidines (see p 65) and the use of Lewis acids to facilitate nucleophilic attack.[171] It may be possible that successful rearrangement ring-opening of azetidine **104g** could be promoted with a suitable Lewis acid; however, this was not investigated as successful access to linear γ-amino boronic esters via Ir catalysed hydroboration has previously been demonstrated.[172]




**104g** **216** **101a** (17%)

**Scheme 87.** Attempted ring-opening via 1,2-metallate rearrangement.

Epoxide lithiation and ring-opening 1,2-metallate rearrangement has also been described by Aggarwal *et al.*[173] and was attempted on boronic ester **104g**. However, this resulted in no formation of the desired product **218**, recovering only starting epoxide **217** (72%) and boronic ester **104g** (95%). The reaction most likely failed to efficiently form the boronate complex: boronic ester **104g** electrophile must trap the lithiated epoxide rapidly as decomposition of lithiated epoxides is well known.[174] A test lithiation of epoxide **217** and trapping with TMSCl gave 53% yield (lit.[174] 61%), suggesting that boronate formation was probably not efficient.




**217** **218**

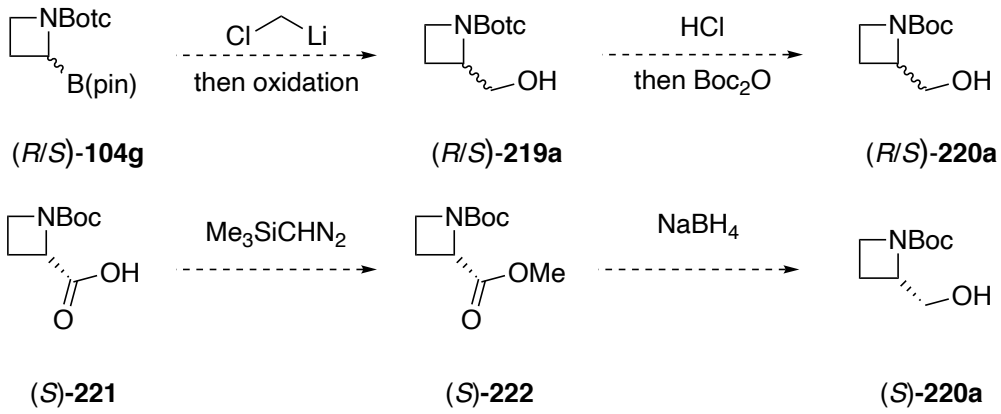
**Scheme 88.** Attempted epoxide lithiation/ring-opening.

Having failed to functionalise azetidine boronic ester **104g** under a range of different reaction conditions, work focused on performing arguably the most important non-transition metal-catalysed transformation of boronic esters: C-C bonding forming Matteson homologation. This would potentially enable determination of absolute configuration, through derivatisation to compounds with known stereochemistry.

### 3.2.5 Attempted Matteson homologations on 2-B(pin)-*N*-Botc-azetidine 104g

With enantioenriched boronic ester (–)-**104g** and (+)-**104g** being successfully synthesised, the absolute stereochemistry needed to be determined for any potential future asymmetric/natural product synthesis projects. Work on *N*-thiopivaloyl-azetidine **55** had shown that the sense of asymmetric induction for lithiation—electrophile trapping is

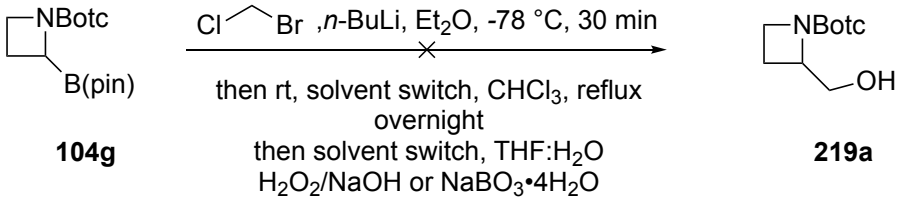
electrophile dependent.[96] We therefore could not assign the absolute stereochemistry of boronic ester (–)-**104g** and (+)-**104g** by analogy with previously trapped enantioenriched *N*-Botc-azetidines **104**.[93] As a suitable crystal structure could not be obtained, derivatisation of enantioenriched boronic ester (–)-**104g** or (+)-**104g** to a compound of known absolute configuration was attempted. (*S*)-2-Hydroxymethyl-azetidine (*S*)-**220**, derived from (*S*)-azetidine-2-carboxylic acid (*S*)-**221** was considered a suitable target compound. This could be accessed through a Matteson homologation, followed by protecting group interconversion from boronic ester (–)/(+)-**104g** and by methylation and reduction from carboxylic acid (*S*)-**221** (Scheme 89).




**Scheme 89.** Proposed route to azetidine (*S*)-**220a** with known absolute configuration.

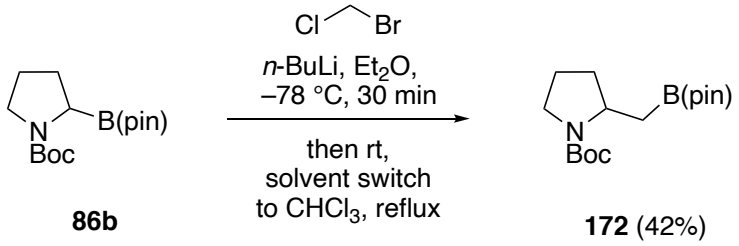
An initial attempt at the Matteson homologation of boronic ester **104g** using chloroiodomethane failed to give the desired alcohol product. Examples in the lit.[141] with *N*-Boc-pyrrolidine boronic ester **86b** had been with bromochloromethane as the carbenoid source. A second attempt using bromochloromethane, however, also failed to give the desired alcohol **219a** (Scheme 90). These reactions used basic hydrogen peroxide for the oxidation step which was considered potentially unsuitable for the thiocarbamate protecting group. Studies on similar dimethylthiocarbamates as an alcohol protecting group utilised basic hydrogen peroxide as a means to cleave the thiocarbamate group.[175]

Therefore, another attempt was performed using the milder oxidant $NaBO_3.4H_2O$, but again no alcohol **219a** was observed and instead the reaction returned only pinacol.



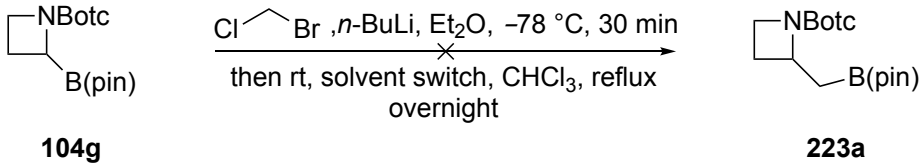

**Scheme 90.** Attempted Matteson homologation and oxidation.

To verify that I could perform the Matteson homologation following Aggarwal's procedure, a homologation of pyrrolidine boronic ester **86b** was carried out giving desired homologated boronic ester **172** in 42% yield (lit.[141] 79% following oxidation to alcohol, Scheme 91). The reduced yield most likely arose during isolation of boronic ester **172**, which the original authors avoided by *in situ* oxidation.




**Scheme 91.** Matteson homologation of 2-B(pin)-*N*-Boc-pyrrolidine **86b.**

A test reaction on *N*-Botc-azetidine **101a** with basic hydrogen peroxide resulted in complete loss of the starting material (after 2 h at 0 °C), suggesting that the thiocarbonyl protecting group is unstable under harsh oxidation conditions (a similar reaction with $NaBO_3.4H_2O$ 1 h at rt gave 56% RSM **101a**). To determine whether the 1,2-metallate step was proceeding, an attempt to isolate the intermediate homologated boronic ester **223a** without oxidation was performed (Scheme 92).

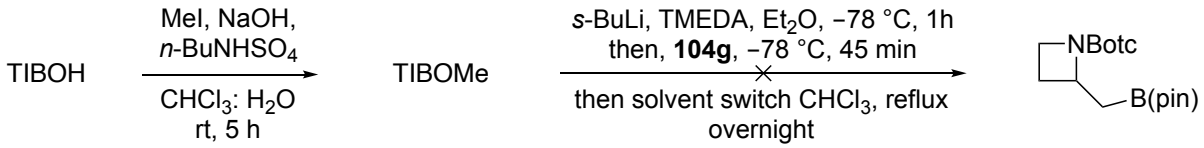



**104g** **223a**

**Scheme 92.** Attempted Matteson homologation

The reaction, however, only gave trace *N*-Botc-azetidine **101a** (via protodeboronation) and pinacol. Matteson has previously described the use of a metal salt, $ZnCl_2$ (0.5-0.65 equiv) as an additive to increase yields and diastereoselectivity of the homologation reaction.[125] The homologation was therefore attempted in the presence of sub-stoichiometric amounts of $ZnCl_2$ (0.6 equiv), but this also failed to provide any homologated boronic ester **223a**.

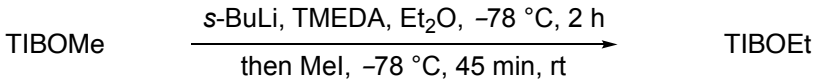
Beak's α-lithiated benzoate ester as a carbenoid reactive intermediate capable of performing 1,2-metallate shifts has been extensively studied by Aggarwal *et al*.[138,176-177] Triisopropylbenzoate as a directing/leaving group has enabled access to sterically hindered tertiary boronic esters and alcohols which previously could not be obtained using alternative carbenoids. Therefore, it was hoped that methyl triisopropyl benzoate **179b** could potentially give access to the desired homologated alcohol **219a** (Scheme 93). Preparation of methyl benzoate ester **179b** proceeded smoothly under phase-transfer conditions (87%, lit.[176] 95%, Scheme 93). However, attempts at homologation failed to give the desired boronic ester **223a** (39% RSM **179b**, Scheme 93). Additionally, an attempt to perform an *in situ* oxidation ($NaBO_3.4H_2O$) of boronic ester **223a** to provide the alcohol directly failed to give desired product **219a** (61% RSM **179b**).




**224** **179b** (87%) **223a**

**Scheme 93.** Attempted homologation using methyl triisopropylbenzoate.

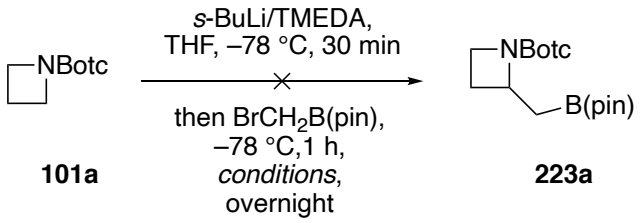
A test lithiation—electrophile trapping reaction was performed on methyl benzoate **179b**, using methyl iodide as the electrophile, which gave ethyl benzoate **179c** in 61% yield, similar to the lit.[178] (84%) (Scheme 94). This suggests that the lithiation is not the problematic step and instead boronate formation and/or migration is preventing product formation.




**179b** **179c** (61%)

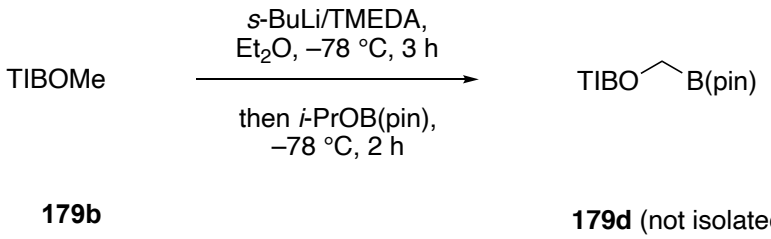
**Scheme 94.** α-Lithation and methylation of methyl benzoate **179b.**

Performing the transformation through lithiation of *N*-Botc-azetidine **101a** followed by using $BrCH_2B(pin)$ as the electrophile was also attempted (Scheme 95). This should allow access to a similar boronate intermediate which may undergo 1,2-rearrangement. The reaction was tried under three different migration conditions: 1) warming to rt in THF overnight, 2) warming to rt in THF overnight with $ZnCl_2$, 3) solvent switch to $CHCl_3$ followed by heating to reflux overnight. $^1$H NMR analysis of the reaction crude for all three reactions showed unreacted starting material **101a**, suggesting that $BrCH_2B(pin)$ is not a suitable electrophile to trap and homologate *N*-Botc-azetidine **101a**.




**Scheme 95.** Attempted Matteson homologation on *N*-Botc-azetidine **101a.**

Formation of the triisopropyl equivalent of $BrCH_2B(pin)$ (i.e., $TiBOCH_2B(pin)$) was attempted via a lithiation—electrophile trapping of methyl triisopropylbenzoate **179b** (Scheme 96). Although it is believed that product was formed following $^1H$ NMR analysis of the reaction crude and mass spectrometry ($[M+Na]^+$ parent ion of 411.2 seen in LRMS), the product could not be purified following column chromatography (trace product observed in multiple column fractions).

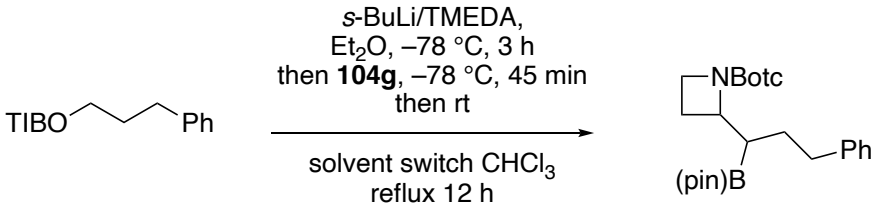



**Scheme 96.** Attempted lithiation borylation of methyl benzoate **179b.**

### 3.2.6 Initial homologation of 2-B(pin)-*N*-Botc-azetidine 104g with lithiated benzoates and comparative routes to synthesise amino alcohols

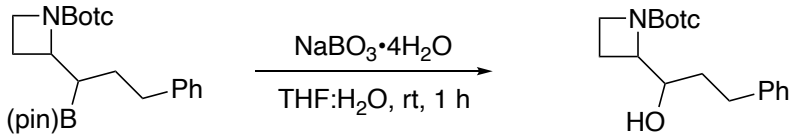
Despite methyl triisopropyl benzoate **179b** being found to be an unsuitable substrate for boronate formation and 1,2-metallate rearrangement, attempts with other benzoate analogues were performed. The failure of the methyl benzoate was not entirely unexpected, as previous studies had demonstrated that methyl boronates were reluctant to undergo migration.[179] 3-Phenylpropyl benzoate **179a** is often the preferred substrate for homologation methodologies which involve challenging migration and therefore, a homologation of boronic ester **104g** using this substrate was performed. A similar

successful transformation with 2-B(pin)-*N*-Boc-pyrrolidine **86b** had been demonstrated with the use of 3-phenylpropyl benzoate ester **179a** (p 64). Benzoate ester **179a** could be conveniently prepared following a Mitsunobu reaction of triisopropyl benzoic acid and the corresponding alcohol (95%, lit.[141] 95%). Performing homologation on boronic ester **104g** with lithiated benzoate **179a**, following the same reaction conditions developed for pyrrolidine **86b**, pleasingly gave the homologated azetidine boronic ester **223b** in 45% yield (Scheme 97).




**Scheme 97.** Boronic ester **104g** homologation under Aggarwal type conditions.

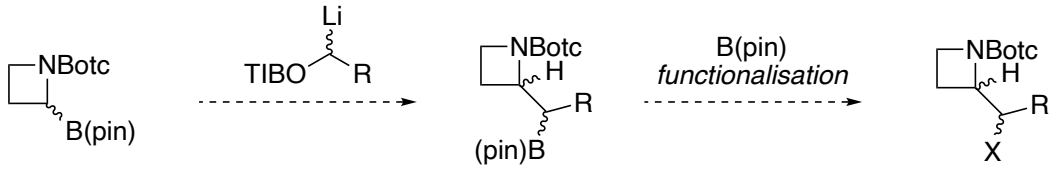
Interestingly, in the current case, boronic ester **223b** was formed with a dr 80:20. This was surprising as almost all previous examples of benzoate homologation occurred non-diastereoselectively (~1:1 dr).[180] Before continuing optimisation of the homologation reaction, a test functionalisation of homologated boronic ester **223b** was performed to ensure further derivatisation to synthetically desirable compounds could be accomplished. Both diastereomers of boronic ester **223b** were separately oxidised using $NaBO_3.4H_2O$ [181] (to avoid potential oxidation of the thiocarbonyl), to give the desired alcohols **219b** in satisfactory yields (66-64%) and with no stereochemical leakage (Scheme 98).




**223b** **219b** (64-66%)

**Scheme 98.** Boronic ester **223b** oxidation to alcohol **219b.**

This transformation is of note as previous *N*-Botc-azetidine **101a** lithiation—electrophile trappings with enolisable aldehydes or ketones failed to give the desired alcohol product.[94] The homologation can also be utilised with enantioselective deprotonation of the benzoate ester which, when combined with enantioenriched boronic ester **104g**, can give two contiguous stereocentres with, in principle, complete stereocontrol as a result of stereospecific 1,2-metallate rearrangement.[141] The diastereomeric homologated boronic esters **223** and **223'** could serve as a handle for further functionalisation, such as arylations, amination, halogenation and carbon-carbon bond forming homologations (Scheme 99).

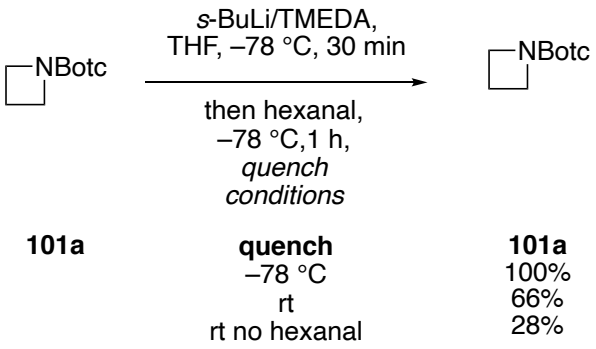



**104g** **223** **112**

**Scheme 99.** Potential further functionalisations.

To ensure the viability of this transformation, it was decided to check other possible synthetic pathways to 1,2-amino alcohols via lithiation—electrophile trapping. Although, as noted above, previous work in the group had shown that enolisable aldehydes failed to trap 2-lithio *N*-Botc-azetidine, it was decided to test the reaction in my hands. When using hexanal as the electrophile, complete recovery of starting *N*-Botc-azetidine **101a** was observed when the reaction was quenched at –78 °C (100% RSM, Scheme 100). To test whether quenching of the organolithium occurred due to enolisation of hexanal, the same

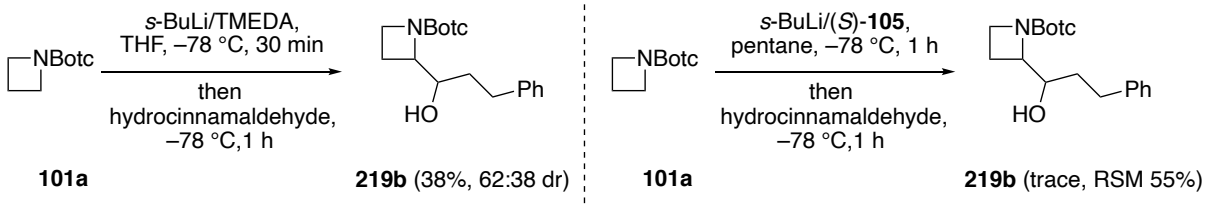
experiment was performed with quenching at rt. If hexanal is quenching the organolithium at –78 °C, we would expect a high recovery of starting *N*-Botc-azetidine **101a**. If hexanal does not quench the organolithium, then we would expect reduced recovery of the starting azetidine **101a**. This is because 2-lithio-*N*-Botc azetidine is chemically unstable at temperatures higher than –40 °C.[102] To demonstrate the latter, *N*-Botc-azetidine **101a** was lithiated at –78 °C for 30 min before being allowed to warm to rt for 1 h before being quenched with aq $NH_4Cl$, which gave only 28% RSM. In contrast, lithiation with hexanal as the electrophile and warming at rt for 1 h before quenching with aq $NH_4Cl$ gave 66% RSM, indicating partial quenching of the organolithium species by hexanal had occurred.




**Scheme 100.** Chemical stability of lithiated *N*-Botc-azetidine **101a.**

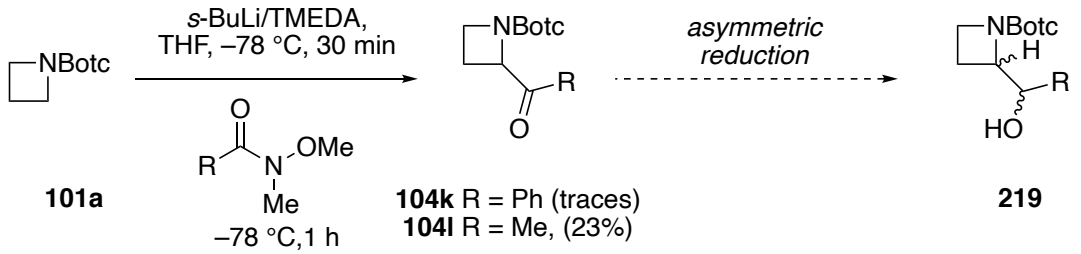
Hydrocinnamaldehyde was also tested to directly compare with previously formed diastereomeric alcohols **219b** and **219b'**. Interestingly, following introduction of the aldehyde to 2-lithio-*N*-Botc-azetidine at –78 °C with quenching at the same temperature, the reaction gave the diastereomeric alcohols **219b** and **219b'** in 38% yield (62:38 dr, RSM 47%, Scheme 101). With hydrocinnamaldehyde, product was observed, indicating that addition is competing with enolisation. It is surprising for this electrophile that an increase rate of carbonyl addition relative to enolisation occurred; this could have been due to the cation co-ordinating properties of the phenyl group, allowing for precomplexation of the electrophile which enables increased carbonyl addition. An asymmetric lithiation—

electrophile trapping was performed in pentane at –78 °C in the presence of DIANANE (*S*)-**105**. However, only trace impure product **219b** was observed (55% RSM) therefore, making this route to enantioenriched 1,2-amino alcohols unfeasible.




**Scheme 101.** Lithiation electrophile trapping of *N*-Botc-azetidine **101a** with hydrocinnamaldehyde.

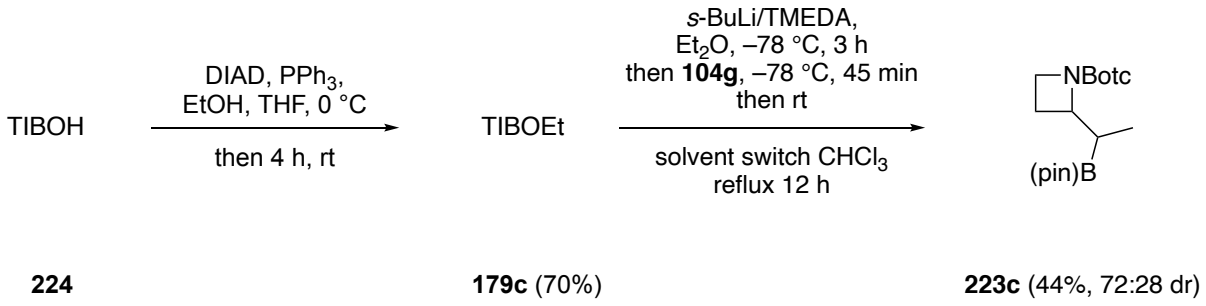
A recent study has shown the possibility of trapping organolithium intermediates with Weinreb amides to give 1,2-amino ketones.[182] If an azetidinyl ketone could be made efficiently, then the possibility of an asymmetric reduction could be a more direct route to enantioenriched azetidine 1,2-amino alcohols. Two lithiation—electrophile trappings of *N*-Botc-azetidine **101a** were performed, using *N*-methoxy-*N*-phenylacetamide and *N*-methoxy-*N*-methylacetamide as electrophiles (Scheme 102). In the case of *N*-methoxy-phenylacetamide only trace product was seen in the crude. With *N*-methoxy-*N*-methylacetamide, the reaction gave 23% yield (31% BRSM) of desired ketone **104l**. As the reaction was low yielding, it was decided that these pathways to amino alcohols **219** would be less efficient compared to homologation 1,2-metallate rearrangement.




**Scheme 102.** Lithiation-electrophile trapping of **101a** with Weinreb amides.

### 3.2.7 Optimisation of homologation 1,2-metallate rearrangement with lithiated benzoates

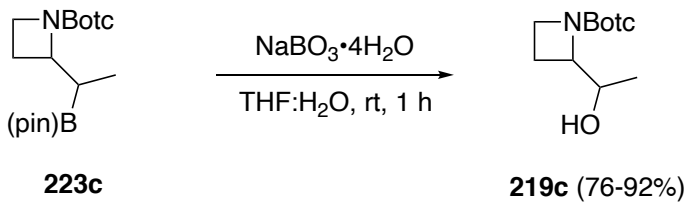
To determine if other alkyl benzoates worked as efficiently as the 3-phenyl propyl benzoate **179a**, ethyl triisopropyl benzoate **179c** was prepared following a Mitsunobu reaction (70%). Subsequent 1,2-boronate rearrangement was performed using azetidine boronic ester **104g** under the same conditions that worked previously (see p 92). This reaction gave the desired product **223c** in 44% yield (72:28 dr), similar to that previously seen for 3-phenylpropyl benzoate ester **223b** (Scheme 103).




**Scheme 103.** Boronate 1,2-rearrangement with ethyl benzoate **179c** and boronic ester **104g.**

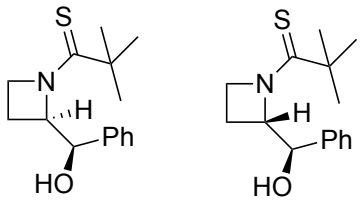
The reaction again proceeded with diastereoselectivity (dr 72:28, *cf.* 80:20 dr, p 92) suggesting the possible existence of a matched-mismatched effect. The slight decrease in diastereoselectivity seen with ethyl benzoate **179c** suggested a possible influence of the benzoate alkyl on the reaction diastereoselectivity.

Pleasingly, boronic esters **223c** and **223c'** were efficiently converted to alcohols **219c** and **219c'** with $NaBO_3.4H_2O$ in 76% and 92% yields, respectively (Scheme 104).




**Scheme 104.** Oxidation of boronic ester **223c**

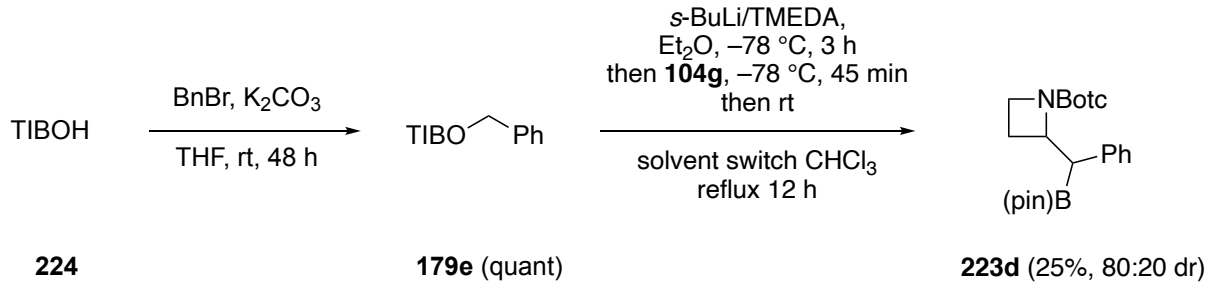
A substrate that would be potentially useful for determining relative (and absolute) configuration of homologated boronic esters was considered to be azetidines **94c** and **94c'**. Work within the group had previously assigned relative stereochemistry for benzaldehyde-trapped *N*-Botc-azetidines **104b** and **104b'**,[94] by conversion to 2-hydroxyphenyl *N*-thiopivaloyl-azetidines **94c** and **94c'** which had been assigned by x-ray crystallography (Figure 6).[90]




**94c** **94c'**

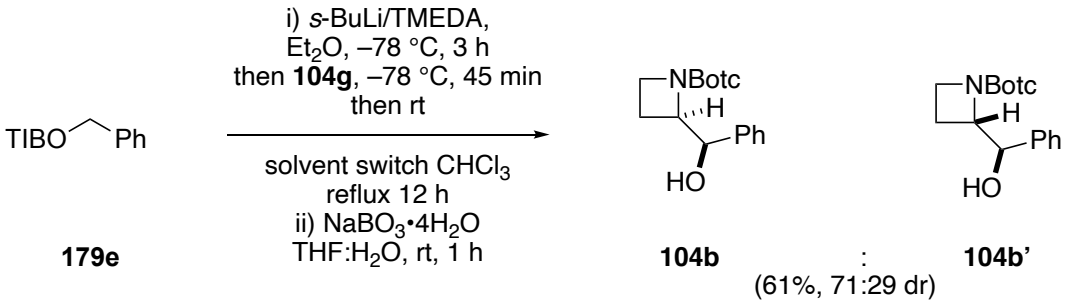
**Figure 6.** Diastereomers with known absolute configuration.

Even though direct lithiation—electrophile trapping with aromatic aldehydes with azetidine **101a** has been successfully achieved, introduction of benzylic groups by homologation could still be useful synthetically, especially since current asymmetric lithiation—electrophile trapping with aromatic aldehydes occurs with only slight diastereoselectivity (dr 60:40 for benzaldehyde). Benzyl benzoate **179e**, was successfully synthesised in quantitative yield following a procedure previously described in the lit.[183] (Scheme 105). Lithiation of benzyl ester **179e**, followed by 1,2-metallate rearrangement with boronic ester **104g**, gave homologated boronic ester **223d** (Scheme 105), however overall yield for the transformation was significantly reduced (25%; 80:20 dr), compared with the earlier non-benzylic examples (Schemes 97 and 103)




**Scheme 105.** 1,2-metallate rearrangement with benzyl benzoate **179e.**

Repeating the reaction with reduced lithiation time and by performing an *in situ* oxidation gave (chromatographically separable) alcohols **104b** and **104b'** in 61% yield (71:29 dr, Scheme 106), with the major diastereomer corresponding to the same major diastereomer observed from lithiation—electrophile trapping.[93]



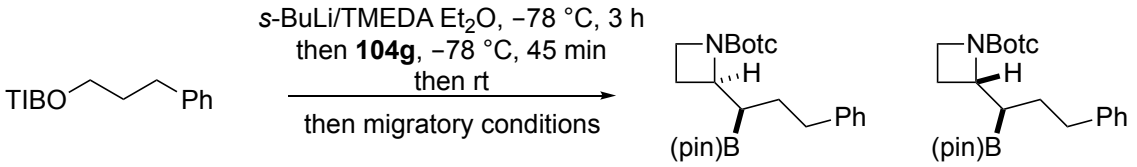

**Scheme 106.** Homologation and oxidation of benzylic benzoate 179e to give alcohols **104b** and **104b'** (correct relative stereochemistry is shown here, see section 4.2.2, chapter 4).

The improved reactivity could be a consequence of the formation of a mesomerically stabilised benzylic partial ion, which could aid the intermediate boronate 1,2-migration.[160a] This allows tentative assignment of relative stereochemistry on previous homologated boronic esters (see section 3.2.10 for conclusive boronic ester **223** determination). However, benzylic boronate complexes have been shown to reversibly dissociate back to the organolithium species.[184] The latter would be problematic for absolute configuration determination via asymmetric homologation, as the benzylic organolithium would be expected to be configurationally unstable under the reaction conditions. Consequently, benzylic benzoates were no longer considered as suitable for reagents for asymmetric 1,2-

metallate rearrangement. Although work by Blakemore and co-workers have developed means to asymmetrically homologate benzylic benzoates/carbamates, in our case this would require separate conditions for optimisation.[184]

### 3.2.8 Optimisation of 1,2-metallate rearrangement racemate via lithiation—borylation

Optimisation of 1,2-metallate rearrangement was performed on the racemic system before work developing the asymmetric reaction commenced. For the optimisation, phenylpropyl triisopropyl benzoate **179a** was used as the coupling partner, owing to potential favourable inductive effects and through-space interactions of the phenyl group[185] and precedent in the lit.[141]




**179a** **223b** **223b'**

| Entry | Solvent switch to $CHCl_3$ | Heating temp (time) | % Yield | d.r (223b:223b') | % recovered 179a |
|---|---|---|---|---|---|
| 1 | No | 35 °C (24 h) | 7 | 0:100 | 36 |
| 2 | Yes | 50 °C (12 h) | 27 | 100:0 | 50 |
| 3 | Yes | 70 °C (12 h) | 45 | 80:20 | 26 |

**Table 4.** Initial optimisation of 1,2-metallate rearrangement. Reaction using 1.3 eq of benzoate ester **179a**, 1 eq of boronic ester **104g.**

Initial optimisation studies focused on 1,2-migration of the boronate intermediate (Table 4), given the well-established lithiation conditions for benzoate **179a**.[138] Variations in 1,2-metallate rearrangement conditions were tested to determine whether or not the

solvent switch to $CHCl_3$ was essential. Keeping the reaction in $Et_2O$ (Table 4, entry 1) did manage to produce a small amount of coupled boronic ester **223b'**. However, when a solvent switch to $CHCl_3$ was performed,[186] an increase in yield was seen (Table 4, entries 2 and 3). Another initial concern was whether the heating temperature would cause decomposition and/or deprotection of the *N*-Botc group. Previous work in the group had shown that deprotection of the *N*-Botc group was possible under reflux in ethanol;[93] it was therefore a concern that deleterious deprotection could be occurring at similar migration temperatures. Leaving the reaction overnight in $CHCl_3$ at 50 °C (Table 4, entry 2), however, resulted in a lower yield than allowing the reaction to reflux in $CHCl_3$ overnight (Table 4, entry 3). Interestingly, the three different migratory conditions resulted in significantly different diastereomeric ratios. The fact that only a single diastereomer was obtained for entry 2, compared with a mixture for entry 3, suggests that one of the diastereomeric boronate complexes migrates more easily. The diastereoselectivity was reversed when the reaction was maintained in $Et_2O$ (Table 4, entry 1).

It has been found that using non-polar solvents for 1,2-metallate rearrangement can influence the rate of migration, speculated to be a consequence of the position of the free $Li^+$ cation allowing favourable reaction conformation formation (Figure 7).[186] There would also be an increased Lewis acidity to the $Li^+$ cation in non-coordinating solvents, therefore increasing the reactivity for migration. [141,187] It is therefore possible that a coordinating solvent such as $Et_2O$ can affect the diastereoselectivity, by altering the preferred reactive conformation as a result of a change in the position of the $Li^+$ cation. This could result in a change in rate for 1,2-migration between the two diastereomeric boronate complexes.

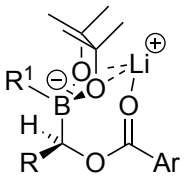
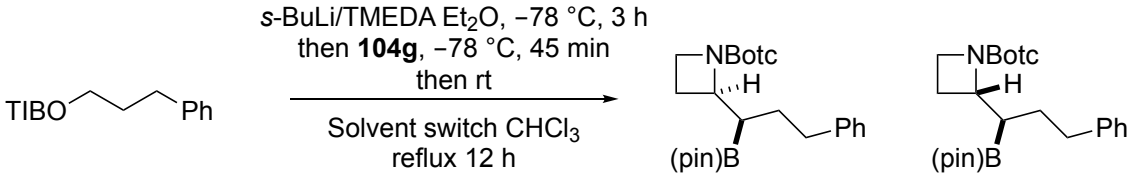



**Figure 7.** Speculated favourable $Li^+$ cation location in non-coordinating solvents.

With initial optimisation performed on the migratory conditions for homologation, variations of the equivalents of boronic ester **104g** and benzoate **179a** were investigated (Table 5). It was hoped that increasing the ratio of benzoate **179a** would aid complete formation of the boronate intermediates and, therefore, give higher yields. It has previously been shown that changing equivalents of the boronic ester and/or the lithiated coupling partner can have a beneficial effect on the overall yield of the transformation.[188]




**179a** **223b** **223b'**

| Entry | Benzoate 179a equiv. | Boronic ester 104g equiv. | % Yield | d.r 223b:223b' | % recovered 179a |
|---|---|---|---|---|---|
| 1 | 1.3 | 1 | 45 | 80:20 | 26 |
| 2 | 2 | 1 | 12 | 59:41 | 50 |
| 3 | 1 | 1 | 37 | 81:19 | 34 |
| 4 | 1 | 1.5 | 71[a] | 83:17 | 13 |

[a] % Yield based on limiting reagent benzoate **179a.**

**Table 5.** Optimisation of conditions through variations in reagent equivalents.

Increasing the amount of benzoate **179a** from the original conditions (Table 5, entry 1) to 2 equivalents (Table 5, entry 2) resulted in a sharp decrease in yield and in diastereoselectivity. This suggests that a large excess of lithiated benzoate **179a** and/or

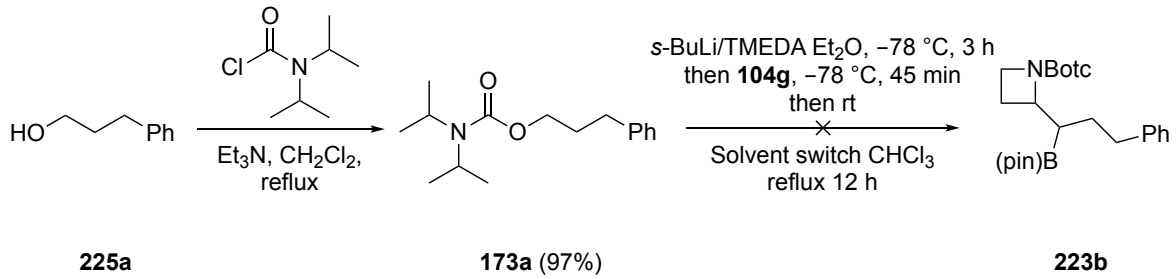
*s*-BuLi is detrimental to the reaction. This could be due to unwanted side-reactions which could cause decomposition of the intermediate boronate. This may also explain the reduction in diastereoselectivity. Using equimolar amounts of benzoate **179a** and boronic ester **104g** gave a moderate yield (Table 5, entry 3), although yields based on recovered benzoate **179a** (56% BRSM) had increased compared with entry 1 (47% BRSM). There was also minimal change in diastereoselectivity. Increasing the equivalents of boronic ester **104g** to 1.5 in the reaction (Table 5, entry 4) gave the greatest improvement in yield 71% (81% BRSM).

This suggests that additional unreacted lithiated benzoate and/or *s*-BuLi could be responsible for decreased yields, as in this case any unreacted lithiated species will react with boronic ester **223** or the boronate intermediate. Having excess boronic ester **104g** would prevent any deleterious reactions occurring during the warming to room temperature. However, the reaction giving higher yields with boronic ester **104g** in excess was not preferable, as in this case boronic ester **104g** was considered the more valuable/precious material. Nonetheless, if boronic ester **104g** is developed as a synthetic 'building block' then there would be future instances where the benzoate is the more precious material and running the reaction with excess boronic ester would be desired.

A few alternative conditions and reagents were also attempted, so as to gain further insight into the reaction, as well as hopefully increasing the overall reaction yield. Firstly, addition of a Lewis acid, such as $MgBr_2$, has in some instances been shown to improve yields, especially for lithiated carbamate carbenoid species.[136] However, homologation using

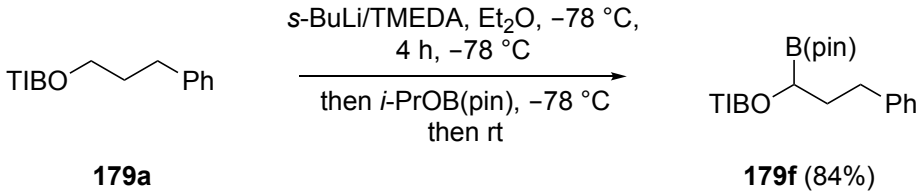
$MgBr_2$ as a Lewis acid to aid the 1,2-metallate rearrangement with benzoate **179a** gave only 6% yield of boronic esters **223b** and **223b'**.

A synthesis of phenylpropyl carbamate **173** was performed in order to test the suitability of a lithiated carbamate in the 1,2-metallate rearrangement reaction. Carbamate **173a** was synthesised following a lit.[189] procedure, in high yield 97% (Scheme 107). Carbamate **173a** was then subjected to lithiation and 1,2-metallate rearrangement conditions previously optimised (Table 5, entry 4). However, this failed to give the desired coupled product **223b**, with the reaction mixture blackening during reflux suggesting decomposition.




**Scheme 107.** Formation of carbamate **173a** and attempted lithiation/1,2-rearrangement.

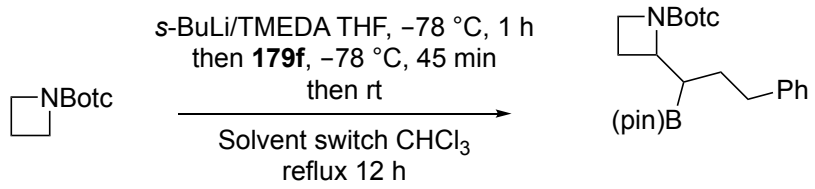
Another variation that could potentially improve the 1,2-metallate rearrangement reaction would be to reverse the partners containing the boronic ester functional group and organolithium species. As the *N*-Botc group allows for efficient α-deprotonation on the azetidine ring, it could be possible to trap such a lithiated species with a boronic ester with a suitable leaving group α- to the boronic ester. Using benzoate boronic ester **179f** would form the same boronate intermediate and therefore would be able to migrate under the same conditions as previously described (Table 5). To test this approach, a synthesis of boronic ester **179f** was undertaken (Scheme 108).




**179a** **179f** (84%)

**Scheme 108.** Lithiation/borylation of benzoate ester **179f.**

Following conditions in the lit.[190] which describe a synthesis of the analogous carbamate, benzoate boronic ester **179f** was efficiently synthesised in good yield following an α-lithiation—borylation sequence. Benzoate boronic ester **179f** was then subjected to 1,2-metallate rearrangement conditions following addition to α-deprotonated *N*-Botc-azetidine **101a** (Scheme 109).




**101a** **223b** (37%, dr 65:35)

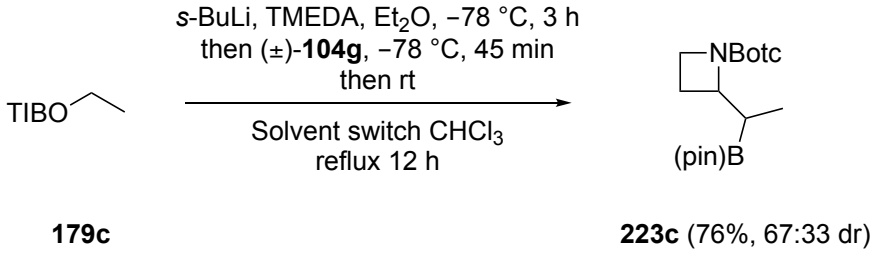
**Scheme 109.** Direct lithiation of *N*-Botc-azetidine **101a** and 1,2-metallate rearrangement.

Although the reaction gave boronic ester **223b**, the yield was low (37%, 65:35 dr). This could be due to the change in solvent from $Et_2O$ to THF, required for efficient lithiation of azetidine **101a**;[94] however, this would contradict studies by Aggarwal *et al*.[161] which showed THF increases the rate of borylation.

The fact that the reaction had a reduced level of diastereoselectivity (*cf.* Table 5, entry 4, p 101) does help indicate whether the origin of selectivity is a result of preferable formation of one boronate intermediate over the other, or from difference in 1,2-metallate rearrangement energies. If there was no diastereoselectivity during the boronate formation step and diastereoselectivity occurred only during 1,2-migration, then we would expect to see similar levels of diastereoselectivity (as both reactions are performed with

identical migration conditions). The difference in diastereoselectivity therefore suggests that the two different approaches to reach the same boronate intermediates occur with different levels of diastereoselectivity.

With improved conditions for the 1,2-metallate established (1.5 equiv of boronic ester, p 101), a reaction with ethyl triisopropyl benzoate **179c** was performed (Scheme 110), since this would be the preferred substrate for determination of absolute configuration following the asymmetric variant of the reaction (Scheme 110).




**179c** **223c** (76%, 67:33 dr)

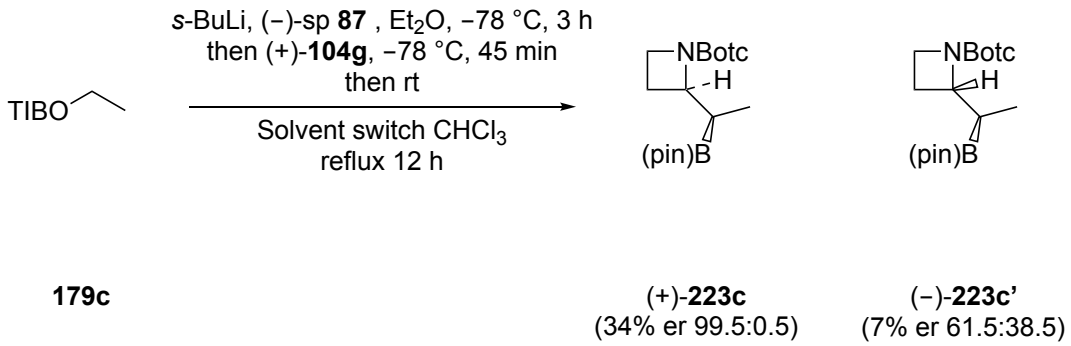
**Scheme 110.** Optimised conditions for 1,2-metallate rearrangement on benzoate **179c.**

Pleasingly, the optimised conditions developed provided boronic esters **223c** and **223c'** in improved yield (76%, 67:33 dr) compared with previous conditions (*cf.* 44%, 72:28 dr, p 95).

### 3.2.9 Asymmetric 1,2-metallate rearrangement via asymmetric lithiation

Having optimised reaction conditions for the racemic 1,2-metallate rearrangement reaction, work on performing the asymmetric reaction began. This could be achieved by combining enantioenriched boronic ester **104g** with asymmetrically lithiated benzoate esters. Asymmetric lithiation of benzoate esters **179** with (–)-sp **87** is well known and highly enantioselective (er ~ 95:5).[138] It therefore should be possible to synthesise 2-substituted-azetidines with two contiguous stereocentres with high enantioselectivity via this approach.

To test this, ethyl triisopropyl benzoate **179c** was initially chosen (Scheme 111), as this would allow for easier determination of absolute configuration via derivatisation (See section 3.2.10).

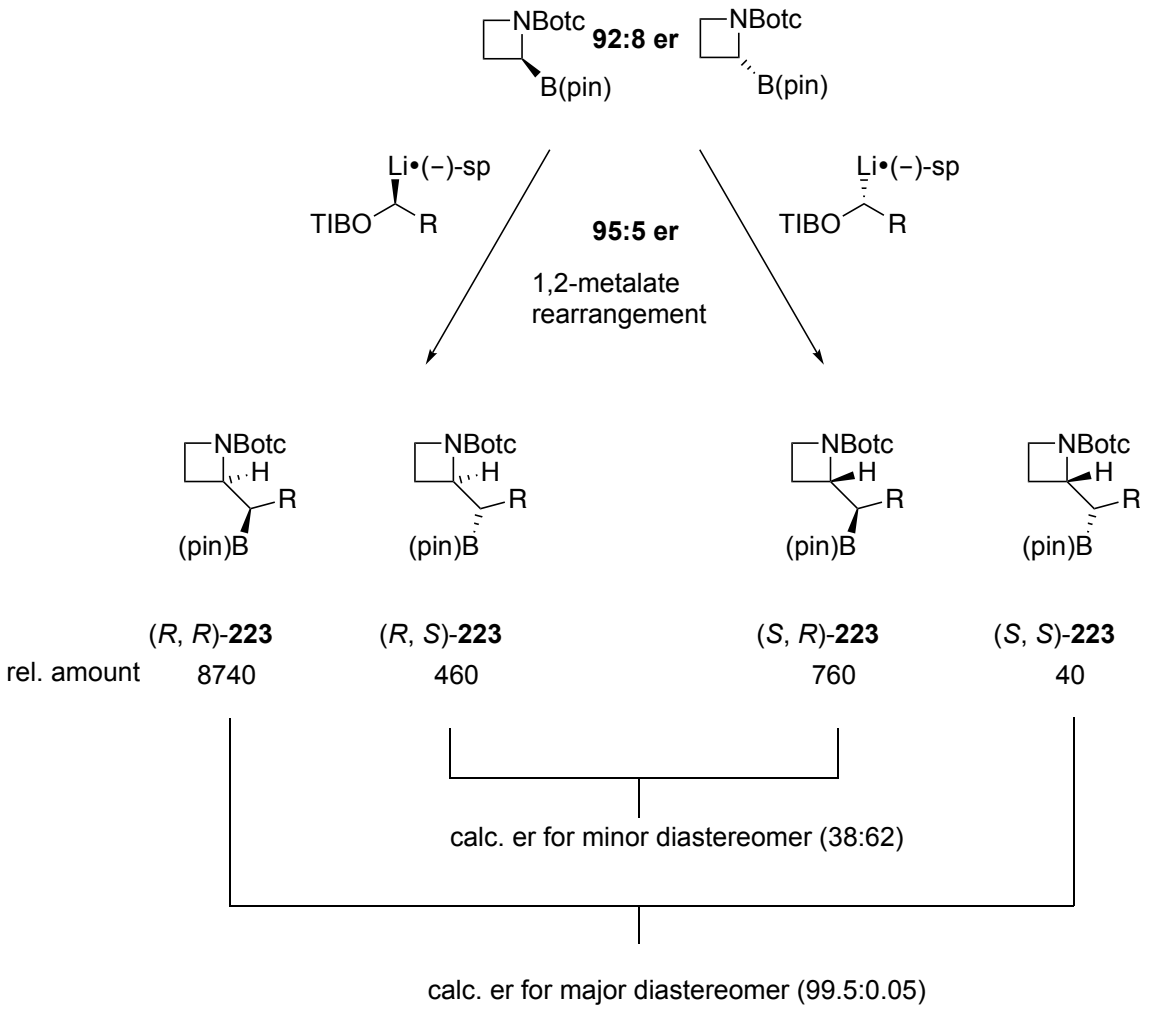



**179c** (+)-**223c** (34% er 99.5:0.5) (−)-**223c'** (7% er 61.5:38.5)

**Scheme 111.** Asymmetric lithiation and 1,2-metallate rearrangement.

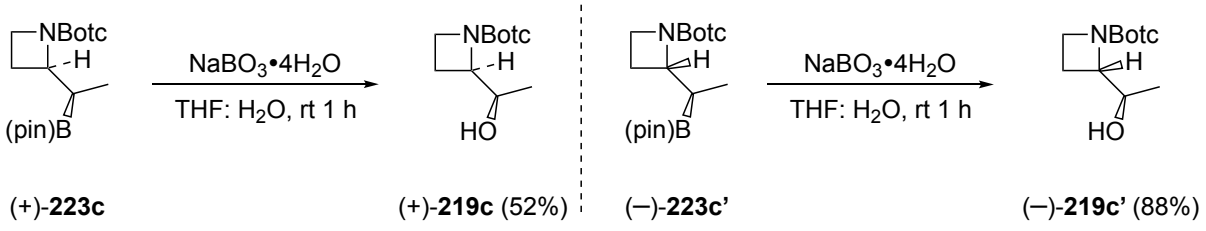
The reaction gave the desired boronic ester (+)-**223c** highly enantioenriched (er 99.5:0.5) albeit in low yield (34%). The chromatographically separable diastereomeric boronic ester (–)-**223c'** was also formed in 7% yield with moderate enantioenrichment (er 61.5:38.5).

The formation of diastereomer (+)-**223c** essentially enantiopure and diastereomer (–)-**223c'** with moderate enantioenrichment indicates the presence of chiral amplification as described by the Horeau principle.[191] This is in good agreement with the predicted enantioselectivities (Scheme 112), assuming that asymmetric benzoate lithiation proceeds with same degree of enantioselectivity (~95:5 er) as previously reported in the lit.[138]




**Scheme 112.** Calc. er's and chiral amplication for the asymmetric 1,2-metallate rearrangement.

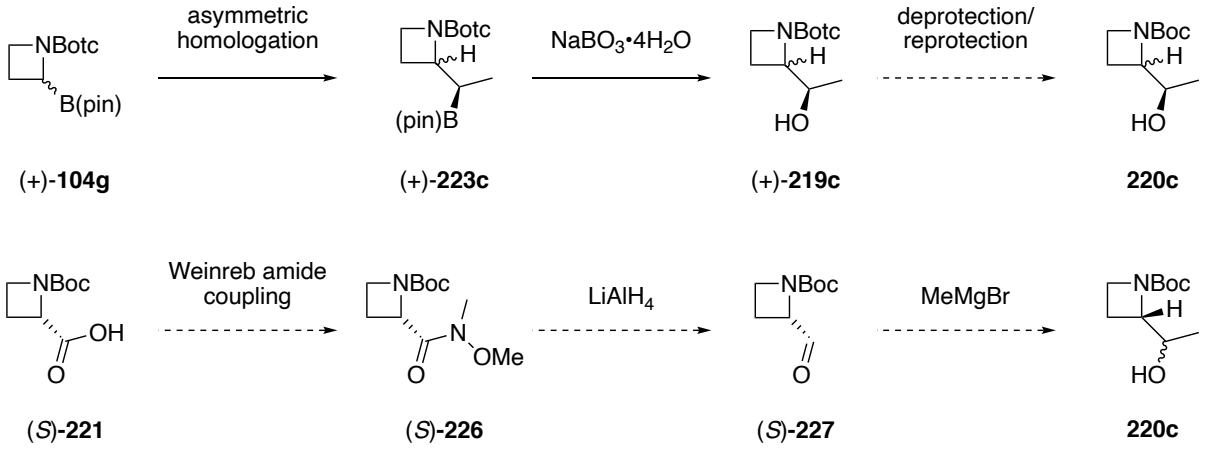
Determination of enantiomeric ratios was achieved following oxidation of the boronic esters (+)-**219c** and (–)-**219c** to their respective alcohols (Scheme 113). This transformation would enable determination of both absolute and relative stereochemistry.




**Scheme 113.** Oxidation of enantioenriched boronic esters (+)-**223c** and (–)-**223c'**

### 3.2.10 Determination of absolute configuration studies

To determine the absolute/relative configuration of the enantioenriched boronic esters (+)-**104g**, (+)-**223c** and (–)-**223c'**, a derivatisation to compounds with known absolute configuration was performed (Scheme 114).

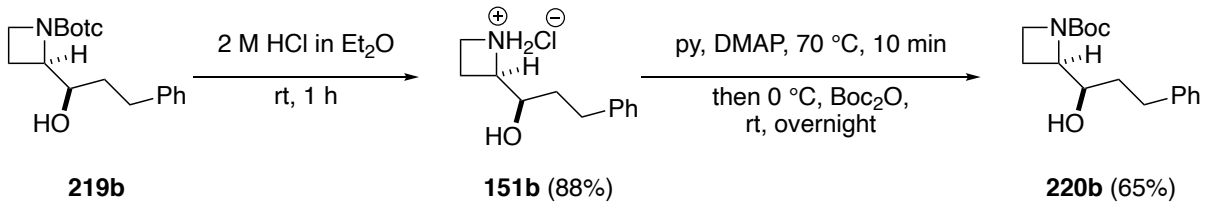



**Scheme 114.** Proposed route for absolute configuration determination.

This required a few test reactions to determine the feasibility of the planned reaction sequence. This would involve performing a deprotection/protection sequence to convert alcohol *N*-Botc-azetidines **219** to alcohol *N*-Boc-azetidines **220**, ideally giving separable products.

Alcohol **219b** was deprotected under acidic conditions to give azetidinium chloride **151b** (Scheme 115). It was decided to perform the deprotection on alcohol **219b** and not boronic ester **223b**, having previously established that tertiary alcohol **104c** (Scheme 53) could undergo an identical deprotection without unwanted decomposition (see p 50). This showed that the secondary alcohols were stable with respect to acidic deprotection and further demonstrated the ease of removal of the *tert*-butoxythiocarbonyl protecting group.

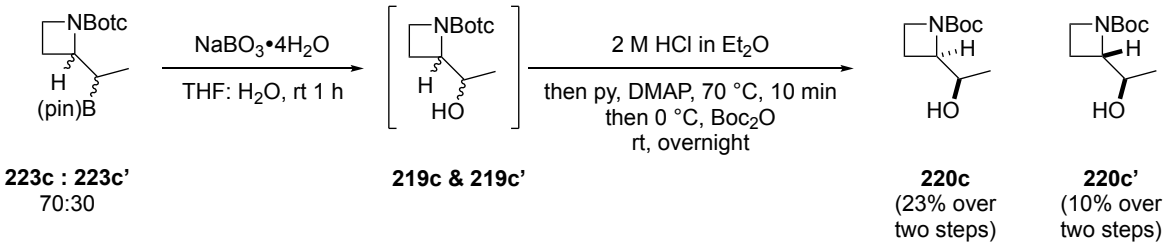
Having formed chloride salt **151b**, a Boc protection was performed to give the desired *N*-Boc protected alcohol **220b** in moderate yield (65%, Scheme 115).




**219b** **151b** (88%) **220b** (65%)

**Scheme 115.** Botc deprotection and Boc protection of alcohol **219b.**

The same sequence was performed on a racemic mixture of diastereomers of boronic esters **223c** and **223c'**. This was performed as a single sequence without purification of the intermediate alcohols, giving *N*-Boc alcohols **220c** and **220c'** in 23% and 10% respectively (Scheme 116).



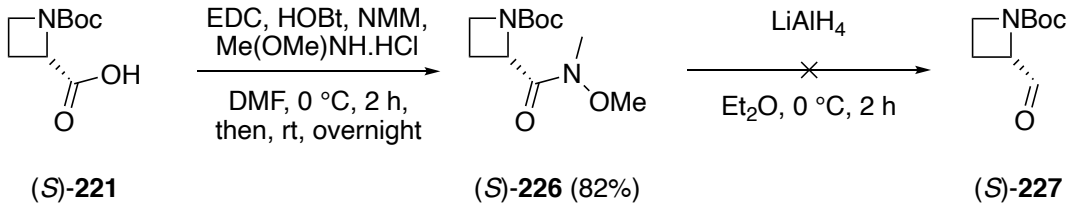

**223c : 223c'** 70:30 **219c & 219c'** **220c** (23% over two steps) **220c'** (10% over two steps)

**Scheme 116.** Preparation of alcohols **220c** and **220c'** in a single sequence requiring a single purification step.

Importantly, diastereomers **220c** and **220c'** could be easily separated by column chromatography. This meant that enantiopure derivatives synthesised from enantiopure (*S*)-carboxylic acid **221**, would be separable and allow for accurate specific rotation values to be determined, which was important for determination of absolute stereochemistry (Schemes 118 and 119).

Having shown that diastereomers **220c** and **220c'** could be synthesised and purified from boronic esters **223c** and **223c'**, synthesis of alcohols from enantiopure (*S*)-carboxylic acid **221** was undertaken. Precedent in the lit.[192] suggested that enantiopure azetidine

α-aldehyde **227** could be synthesised from a reduction of a Weinreb amide **226**, which could be synthesised from enantiopure carboxylic acid (*S*)-**221** (Scheme 117).

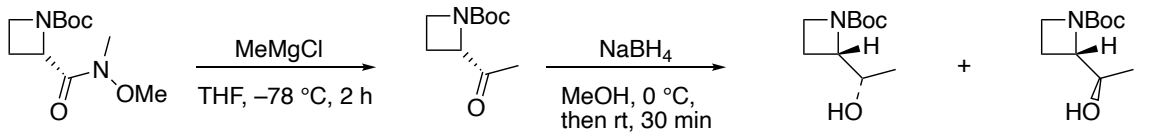



(*S*)-**221** (*S*)-**226** (82%) (*S*)-**227**

**Scheme 117.** Formation of Weinreb amide and attempted reduction.

Formation of the Weinreb amide (*S*)-**226** from carboxylic acid (*S*)-**221** proceeded smoothly (82%), however, in my hands reduction of the Weinreb amide (*S*)-**226** to aldehyde (*S*)-**227** managed to only produce traces of aldehyde (*S*)-**227**, as seen in by analysis of the crude $^{1}$H NMR (peak at ~9 ppm), and which could not be isolated following column chromatography (Scheme 117).

Instead, synthesis was achieved through a slight modification of the original route, via methylation of Weinreb amide (*S*)-**226** to ketone (*S*)-**228** (86%), followed by reduction with $NaBH_4$ to diastereomeric alcohols (–)-**220c** and (–)-**220c'** in 32% and 30%, respectively (Scheme 118). Specific rotation of diastereomers derived from (*S*)-carboxylic acid (*S*)-**221** both gave negative $[\alpha]_D^{25}$ values.



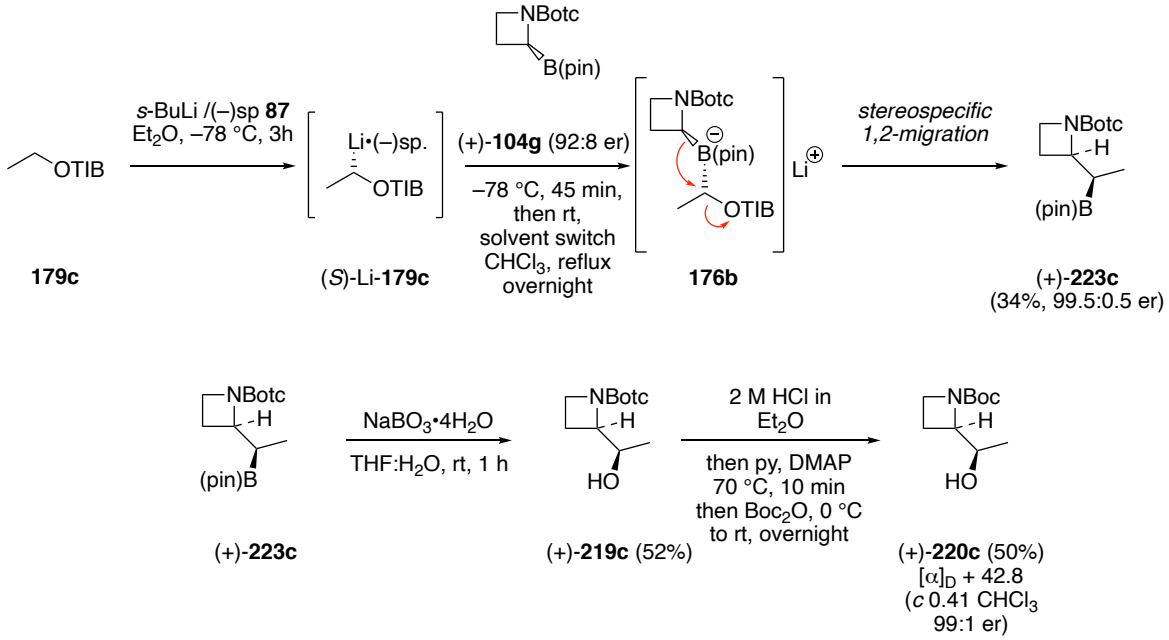

(*S*)-**226** (*S*)-**228** (86%)

(–)-**220c** (32%)
$[\alpha]_D$ – 47.4
(*c* 0.82 $CHCl_3$)
94:6 er)

(–)-**220c** (30%)
$[\alpha]_D$ – 40.1
(*c* 0.87 $CHCl_3$)

**Scheme 118.** Derivatisation of (*S*)-carboxylic acid to diastereomeric alcohols (–)-**220c** and (–)-**220c'.**

Enantioenriched (er 99.5:0.5) *N*-Botc protected alcohol (+)-**219c** underwent a deprotection/protection sequence to place a Boc group on the N, to give alcohol (+)-**220c** (50%, Scheme 119).

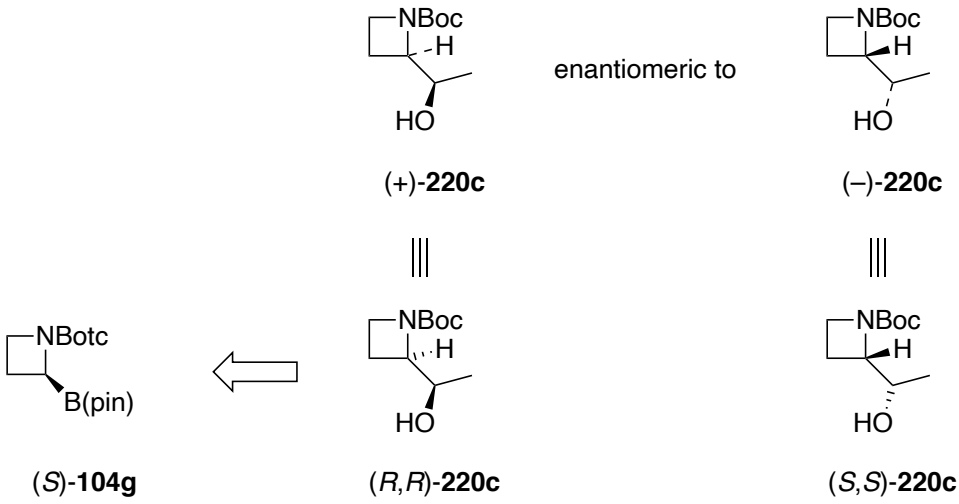



**Scheme 119.** Synthesis of *N*-Boc alcohol (+)-**220c** via asymmetric lithiation-borylation 1,2-metallate rearrangement and oxidation.

Importantly, alcohol (+)-**220c** derived from boronic ester (+)-**223c** gave a positive $[\alpha]_D^{25}$ value. As 1,2-metallate rearrangements are stereospecific with the stereochemistry of the migrating centre remaining unchanged and with inversion of stereochemistry at the carbon bound to the nucleofuge, assignment of absolute stereochemistry can be made. Since α-lithiation of benzoates using (–)-sp **87** is known to preferentially deprotonate the *pro-S* H,[138] the absolute configuration at the carbinol carbon in alcohol (+)-**220c** can be assigned (Scheme 119).

In contrast, in the synthesis of alcohols (–)-**220c** and (–)-**220c'** from (*S*)-carboxylic acid (*S*)-**221**, the stereochemistry at the α-N position remained unchanged, we therefore know the absolute configuration at the α-N carbon in alcohols (–)-**220c** and (–)-**220c'**. NMR

analysis enabled matching of the correct alcohol diastereomer (–)-**220c** to the one derived from boronic ester (+)-**220c**. HPLC analysis confirmed that these two alcohols were enantiomers, allowing the assignment of (*R*,*R*) for (+)-**220c** (Scheme 120).




**Scheme 120.** Determination of absolute configuration by comparison of the two enantiomeric alcohols **220c**.

This also allows assignment of relative configuration for diastereomers from racemic 1,2-metallate rearrangement. This is opposite to what was previously assigned based on formation of benzylic alcohols, suggesting possible erroneous assignment of relative stereochemistry for benzaldehyde-trapped azetidines **104b** and **104b'** by a previous member in the Hodgson group (see section 4.2.2).[93]

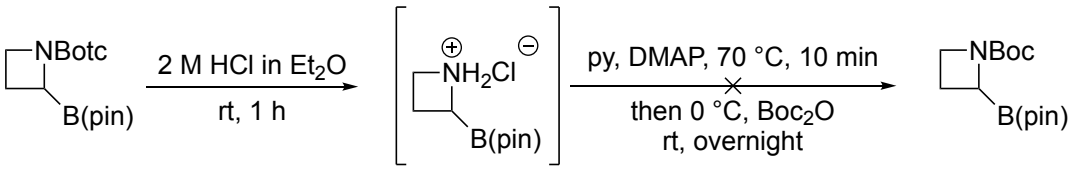
Working backwards through the stereospecific sequence establishes the absolute configuration of starting boronic ester (+)-**104g** as (*S*)-**104g** (Scheme 120). This means that α-lithiation—borylation of azetidine **101a**, using (*S*)-DIANANE (*S*)-**105** results in a borylated product with the opposite sense of asymmetric induction to that occurring during an α-lithiation—methylation of azetidine **101a** with (*S*)-DIANANE (*S*)-**105** ligand.[93] This supports the findings by O'Brien *et al*.[96] who found that the sense and degree of

enantioselectivity in α-lithiation—electrophile trappings on *N*-thiopivaloyl-azetidine **55** was dependent on the electrophile (see chapter 4). This result also suggests that previously synthesised enantioenriched 2-substituted-*N*-Botc-azetidines within the group may have been assigned incorrect absolute stereochemistry.[93]

### 3.2.11 Attempted deprotection/protection of boronic ester 104g

The feasibility of 1,2-metallate rearrangement reactions relies heavily on the nature of the migrating alkyl group on the boronate intermediate. Electron withdrawing groups located near the migrating carbon reduce its propensity to migrate due to decreased nucleophilicity. The Botc group is highly electron withdrawing, due to the high amount of charge transfer from the lone pair on N to S.[193] The electron withdrawing nature of this group could therefore be reducing efficiency for the desired 1,2-metallate rearrangement reaction.

It was thought that a change of the protecting group on boronic ester **104g** to an *N*-Boc group would provide a good comparison of the two protecting groups in the 1,2-metallate rearrangement reaction. Therefore, a deprotection/protection sequence was attempted on racemic boronic ester **104g** (Scheme 121). Acidic deprotection however, resulted in a number of spots appearing on TLC, and $^{1}$H NMR gave inconclusive evidence as to whether successful deprotection had occurred. Crude **151c** was therefore taken through to the next step of the reaction sequence. This however resulted in a number of spots which, on purification, failed to give any desired product **229**.




**104g** **151c** **229**

**Scheme 121.** Attempted deprotection/protection sequence on boronic ester **104g.**

Precedent in the lit.[194] for similar a deprotection on a 2-B(pin)-*N*-Boc-piperidine suggested the boronic ester should be able to survive the acidic protection step; however, in this case, this step was problematic. Since, working conditions for homologation had been established with *N*-Botc boronic ester **104g**, work to access the *N*-Boc equivalent was not further pursued.

### 3.2.12 Optimisation using boronic ester 104g as the limiting reagent

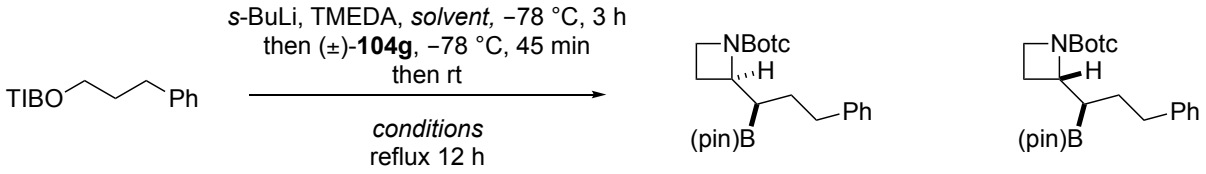
One of the main limitations in the previously 'optimised' conditions for 1,2-metallate rearrangement was that the starting azetidine boronic ester **104g** was being used in excess (1.5 equiv). This meant that the reaction was costly (more precious/expensive azetidine starting material **104g** in excess) and time consuming (greater time spent synthesising starting material **104g**). It was therefore important to optimise conditions of the reaction for which starting azetidine boronic ester **104g** would be the limiting reagent. This would also provide a complimentary set of two optimised conditions for 1,2-metallate rearrangement; depending on the preciousness of the starting material (azetidine boronic ester **104g** or benzoate ester **179**), either could be used as the limiting reagent and ideally give good yields.

Work by Aggarwal *et al*.[161] following 1,2-metallate rearrangements using *in situ* IR spectroscopy showed the nature of the solvent had a profound effect on the rate of lithiation and boronate complex formation. Their results showed that the non-polar solvent PhMe was most effective for lithiation of benzoate esters. PhMe, however, showed the slowest rate for the formation of the boronate complex, which was rationalised by strong co-ordination of (–)-sp **87** with lithiated benzoate esters in non-polar solvent, sterically preventing rapid boronate complex formation.

When 1,2-rearrangement reaction was performed in my hands using PhMe as the solvent for the reaction, only 72% starting benzoate **179a** was recovered (Table 6, entry 1). Performing the lithiation and borylation in $Et_2O$ followed by a solvent switch to PhMe prior to refluxing to enable 1,2-migration also failed to give the desired product and returned only 22% starting benzoate **179a** (Table 6, entry 2). A reaction performed using TBME as the solvent for lithiation and 1,2-metallate rearrangement gave boronic esters **223b** and **223b'** in 41 % yield (dr 71:29) (Table 6, entry 3). The reaction was then examined using $Et_2O$ as the lithiation—borylation solvent and $CHCl_3$ as the solvent for the migration step, which gave product in 34% yield (dr 80:20) (Table 6, entry 4). The low yield was because the reaction was sampled for following by $^{11}B$ NMR, so as to give an approximate extent of boronate complex formation and subsequently the extent of migration.

Taking an initial aliquot of the reaction mixture following addition of boronic ester **104g** and warming to rt and analysis by $^{11}B$ NMR indicated complete conversion of the starting material to boronate (no peak at δ 32 ppm and single peak at δ 6 ppm). A second aliquot was taken following refluxing overnight in $CHCl_3$, which revealed complete consumption of

the boronate complex (no peak at δ 6 ppm) and a main peak corresponding to the product boronic esters **223b** and **223b'** (peak at δ 33 ppm). Another much smaller peak was also seen at δ 22 ppm, corresponding to an unknown borate or amino borate compound.




**179a** **223b** **223b'**

| Entry | Lithiation solvent | Migration solvent | Reflux temp/ °C | % Yield | dr (223b:223b') | % Recovered 179a |
|---|---|---|---|---|---|---|
| 1 | PhMe | PhMe | 111 | 0 | n/a | 72 |
| 2 | $Et_2O$ | PhMe | 111 | 0 | n/a | 22 |
| 3 | TBME | TBME | 55 | 41 | 71:29 | 33 |
| 4 | $Et_2O$ | $CHCl_3$ | 63 | 34[a] | 80:20 | 27[a] |

[a] (note, two samples taken from reaction mixture for NMR analysis).

**Table 6.** Optimisation of lithiation/1,2-rearrangement with benzoate **179a** and boronic ester **104g.**

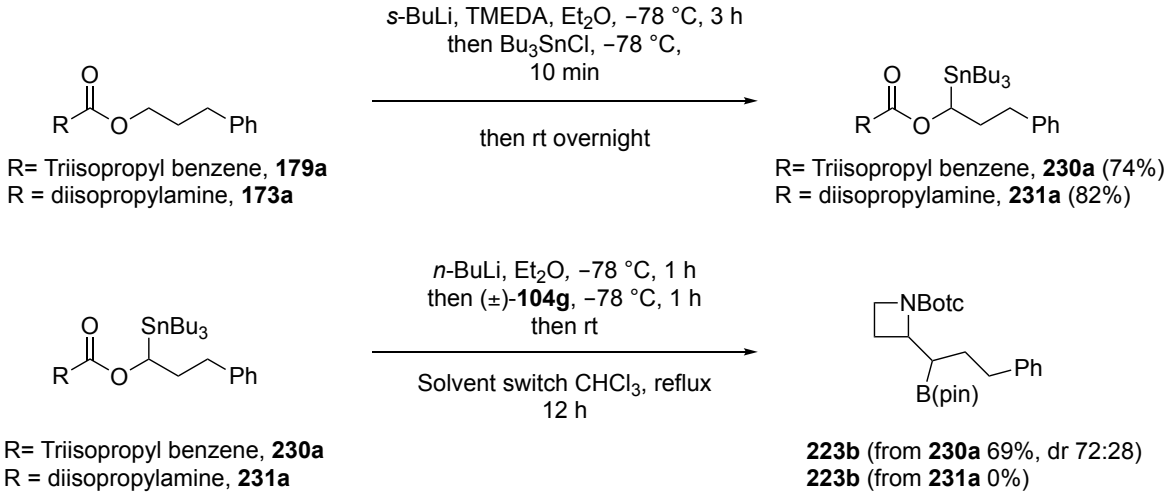
Despite the modest yields, useful information from the reaction monitoring was obtained. Spectroscopic evidence supported complete consumption of starting material to a boronate species as well as complete conversion of the boronate species following reflux overnight in $CHCl_3$. Formation of an undesired borate/amino borate species, either by decomposition of the boronic ester product or by a competing reaction with the boronate complex, was also observed which may account for reduced reaction yields.

### 3.2.13 Investigations of 1,2-metallate rearrangement via stannanes

1,2-Metallate rearrangement reactions frequently utilise Sn–Li exchange to access lithiated benzoates/carbamates, in preference to direct lithiation with *s*-BuLi/diamine ligand. The use of stannanes was essential in Aggarwals' work performing iterative homologations to synthesise (+)-hydroxyphthioceranic acid.[195] This was partly due to clean and efficient Sn–Li exchange reducing the requirement for excess *s*-BuLi which could add irreversibly to the boronic ester. Additionally, transmetallation removes the need for a diamine ligand. This has been hypothesised to reduce the steric hindrance around the $Li^+$ cation as the reaction solvent (usually $Et_2O$) is the only species present to ligate with the organolithium species. Indeed, for many sterically challenging transformations, use of benzoate stannanes instead of direct benzoate lithiation has proved optimal.[141,196] As our azetidine boronic ester **104g** was considered sterically challenging, an investigation of 1,2-metallate rearrangement reaction using benzoate stannane **230a** and carbamate stannane **231a** was undertaken to, hopefully, give improved yields (boronic ester **104g** limiting reagent) in the homologation reaction.

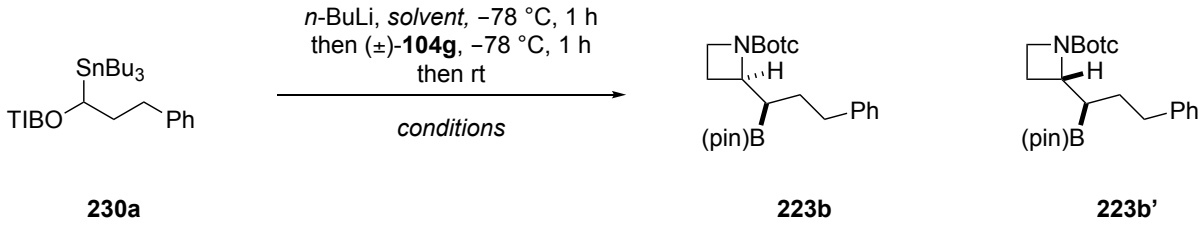
Stannanes **230a** and **231a** were prepared following a lithiation—electrophile trapping sequence using $Bu_3SnCl$ as the electrophile to give benzoate **230a** and carbamoyl **231a** stannanes in 74% and 82% yields, respectively. Both stannanes were then used in the 1,2-metallate rearrangement chemistry, this time, however, in the absence of TMEDA and using *n*-BuLi to effect Sn–Li exchange (Scheme 122). Under these conditions, boronic esters **223b** and **223b'** were effectively synthesised from the benzoate stannane **230a** in 69% yield (72:28 dr) (previous conditions gave boronic ester **223b** and **223b'** in 71% yield, 83:17 dr).

This demonstrated that good yields can be achieved when using starting boronic ester **104g** as the limiting reagent (1.3 equiv of stannane **230a** was used). An attempt at homologation using carbamate stannane **231a** failed to give the desired 1,2-rearranged product (15% RSM **231a**, 12% **173a**) (Scheme 122).




**Scheme 122.** Synthesis of stannanes **230a** and **231a** and subsequent tin/lithium exchange 1,2-metallate rearrangement.

With promising initial results from the homologation reaction using benzoate stannane **230a**, attempts to further optimise the reaction were undertaken (Table 7).




| Entry | Transmetallation solvent | Migration solvent | Reflux temp/ °C | additive | % Yield | dr (223b:223b') |
|---|---|---|---|---|---|---|
| 1 | TBME | TBME | 55 | – | 14 | nd |
| 2 | $Et_2O$ | $CHCl_3$ | 63 | TMSCl | 59 | 65:35 |
| 3 | $Et_2O$ | $CHCl_3$ | 63 | $MgBr_2$/MeOH | 0 | n/a |
| 4 | $Et_2O$ | $CHCl_3$ | 63 | $MgBr_2$●$Et_2O$ | 0 | n/a |

**Table 7.** Optimisation of tin/lithium exchange 1,2-rearrangement with stannane **230a** and boronic ester **104g.**

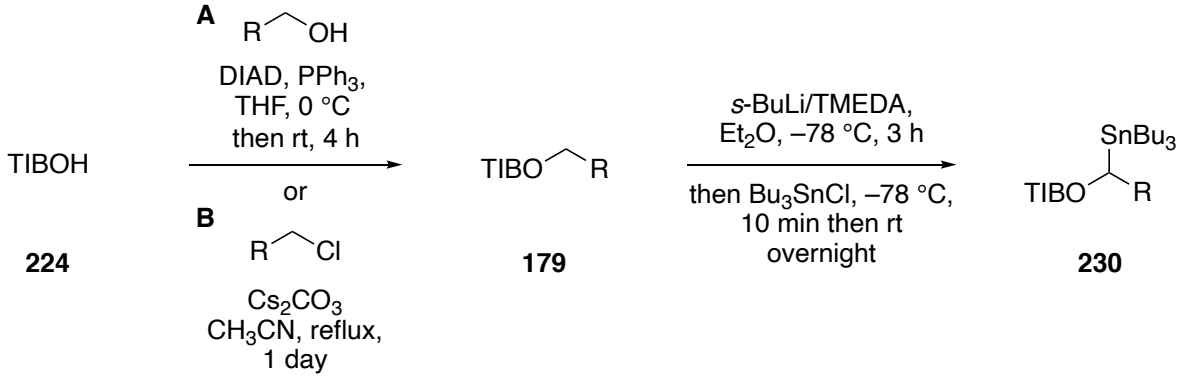
Carrying out the Sn–Li exchange and 1,2-metallate rearrangement steps in TBME resulted in a low yield 14% of homologated boronic esters **223b** and **223b'** and returned 21% protodeborylated *N*-Botc-azetidine **101a** (Table 7, entry 1). Under the solvent switch $Et_2O$ to $CHCl_3$ conditions, addition of a second electrophile following boronate complex formation (to quench any excess anionic species present in the reaction mixture before refluxing) was performed using TMSCl as the electrophile.

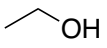
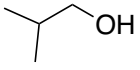
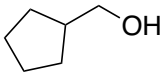
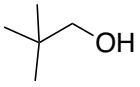
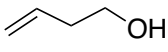
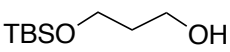
It was considered that this could decrease the diastereoselectivity either by preventing reversible 'ate' complex formation,[186] by trapping any intermediate lithiated species, or by removing any remaining nucleophilic/anionic species in the reaction mixture. This was a concern since in the $^{11}B$ NMR the appearance of a boron species at δ 22 ppm suggested a $B(OR)_3$ species was forming. This could potentially be nullified by the addition of stoichiometric amounts of TMSCl which could effectively prevent unwanted side reactions from occurring.

In the event, the homologation attempt using TMSCl a secondary electrophile gave boronic esters **223b** and **223b'** with slightly decreased diastereoselectivity (dr 65:35); however, the combined yield was also slightly reduced, to 59% (Table 7, entry 2). Use of a Lewis acid additive ($MgBr_2$ in MeOH), failed to give the desired products, with the crude $^{11}B$ NMR spectrum showing two non-product peaks at δ 17 and 21 ppm (Table 7, entry 3). Similarly, using $MgBr_2 \bullet Et_2O$, freshly prepared from Mg and dibromoethane failed to give any of the desired product (Table 7, entry 4).

### 3.2.14 Substrate scope of homologation reaction via stannanes

With the initial stannane homologation conditions (Scheme 122) providing the highest yields, substrate scope was examined. By increasing the alkyl substituents on the carbon β to the tributylstannyl group, tolerance of the reaction to increasing steric hindrance could be studied. With this in mind, a number of stannanes were synthesised starting from triisopropylbenzoic acid via a Mitsunobu reaction, with the appropriate alcohol, followed by directed α-lithiation—electrophile trapping with $Bu_3SnCl$, in good yield (Table 8).[138] Acetal stannane **230h** was also prepared following $S_N2$ substitution of the chloride with triisopropylbenzoic acid,[176] with subsequent directed lithiation—stannylation.




| Entry | Alcohol (or chloride) | 179 (yield %) | 230 (yield %) |
|---|---|---|---|
| 1 |  | **179c** (98%) | **230b** (72%) |
| 2 |  | **179g** (68%) | **230c** (86%) |
| 3 |  | **179h** (88%) | **230d** (77%) |
| 4 |  | **179i** (99%) | **230e** (84%) |
| 5 |  | **179j** (70%) | **230f** (52%) |
| 6 |  | **179k** (20%) | **230g** (30%) |

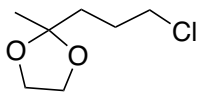
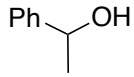
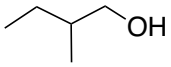
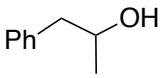
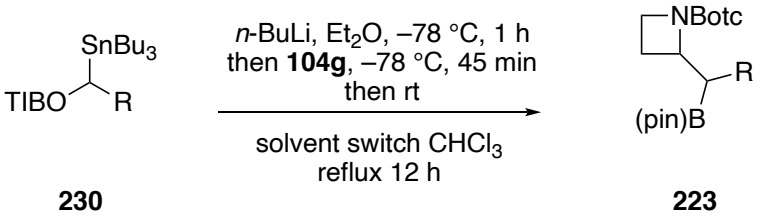
| | | | |
|---|---|---|---|
| 7 |  | **179l** (68%) | **230h** (64%) |
| 8 |  | **179m** (67%) | **230i** (81%) |
| 9 |  | **179n** (76%) | n/a |
| 10 |  | **179o** (99%) | n/a |

**Table 8.** Synthesis of benzoates **179** and stannanes **230.**

Homologations with the stannanes, via Sn–Li exchange followed by 1,2-metallate rearrangement reaction, were performed with boronic ester **104g** (Table 9). With ethyl stannane **230b**, it was found that reducing the reflux time to just 3 h gave optimal yields for homologated boronic ester **223c** (Table 9, entry 1). The diastereoselectivity was noticeably reduced, suggesting an influence of substrate sterics. Increasing the steric bulk with isobutyl stananne **230c** gave homologated isobutyl boronic ester **223e** in 65% (86:14 dr, Table 9, entry 2 (**223e:223e'** relative stereochemistry assigned by analogy to boronic ester **223c** & **223c'**)). The increased diastereoselectivity most likely reflects the increased steric bulk of the isobutyl group with the two pendant methyl groups not being 'tied back' in a cyclic ring system.[197]

With cyclopentylmethyl stannane **230d** the reaction proceeded smoothly to give the desired homologated boronic esters **223f** and **223f'** in 55% overall yield (dr 72:28). The slight decrease in the yield compared with boronic ester **223c** (Table **9**, entries 1 and 2) could be due to the increased steric demands imposed by the branched alkyl group at the β-carbon relative to the stannane **230b**.




**230** **223**

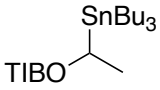
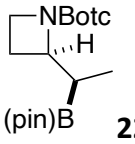
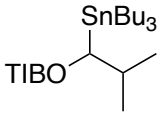
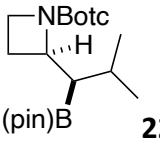
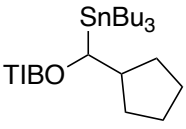
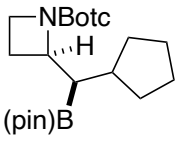
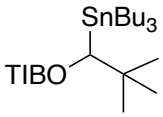
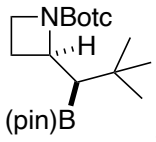
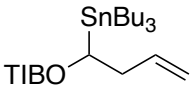
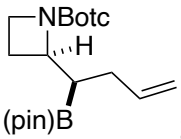
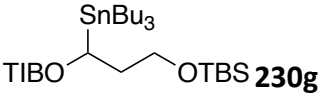
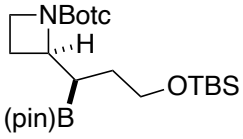
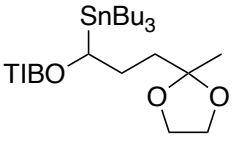
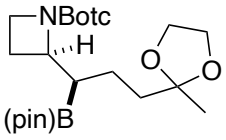
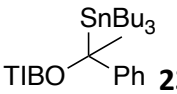
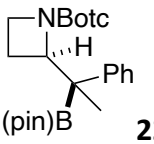
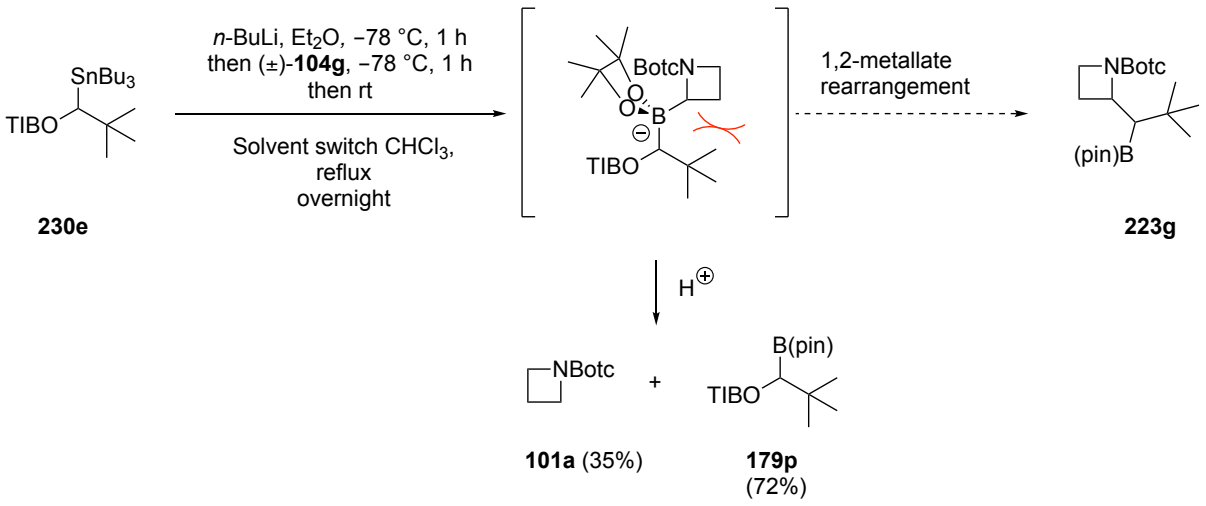
| Entry | Stannane | Product | Yield | dr |
|---|---|---|---|---|
| 1 |  **230b** |  **223c** | 68% | 56:44 |
| 2 |  **230c** |  **223e** | 65% | 86:14 |
| 3 |  **230d** |  **223f** | 55% | 72:28 |
| 4 |  **230e** |  **223g** | 0% | n/a |
| 5 |  **230f** |  **223h** | 50% | 71:29 |
| 6 |  **230g** |  **223i** | 65% | 58:42 |
| 7 |  **230h** |  **223j** | 56% | 67:33 |
| 8 |  **230i** |  **223k** | 0% (86% RSM) | n/a |

**Table 9.** Reaction scope for 1,2-metallate rearrangement.

With the neopentyl stannane **230e**, the reaction failed to undergo 1,2-metallate rearrangement and instead gave benzoate boronic ester **179p** in moderate yield (72%) and *N*-Botc-azetidine **101a** (35%) (Scheme 123). The formation of these products suggests that the boronate complex forms, however, it is unable to align correctly to be anti-periplanar with the migrating terminus to allow for successful migration. This presumably means that the boronate complex remains until the addition of water and then collapses to give *N*-Botc-azetidine **101a** and boronic ester **179p** (Scheme 123). The lower yield of *N*-Botc-azetidine **101a** relative to the boronic ester **179p**, however, suggests potential collapse of the boronate complex occurs during refluxing in $CHCl_3$, with the proton source here possibly being $CHCl_3$ itself. If collapse of the 'ate' complex occurs relatively easily, then *N*-Botc-azetidine **101a** could be prone to decompose during the remainder of the refluxing period.




**Scheme 123.** Attempted 1,2-metallate rearrangement on neopentyl stannane **230e.**

When homologation was performed with alkenyl stannane **230f**, the reaction proceeded smoothly to give boronic ester **223h** and **223h'** in 50% yield (71:29 dr, Table 9, entry 5). In this instance, the reaction also produced 4% yield of triisopropyl benzoate boronic ester **179q**, suggesting that either 1,2-migration had not gone to completion after 12 h, or that

boronate formation was partially reversible. Silyl ether stannane **230g** was also well tolerated in the homologation reaction, giving boronic esters **223i** and **223i'** in 66% yield (58:42 dr). The decrease in diastereoselectivity may be a result of the ability of oxygen in the stannane substrate to co-ordinate to the $Li^+$ cation during boronate formation. Acetal stannane **230h** was also able to give homologated boronic ester **223j** and **223j'** in 56% yield (67:33 dr); however, in this case the diastereomers were inseparable by column chromatography.

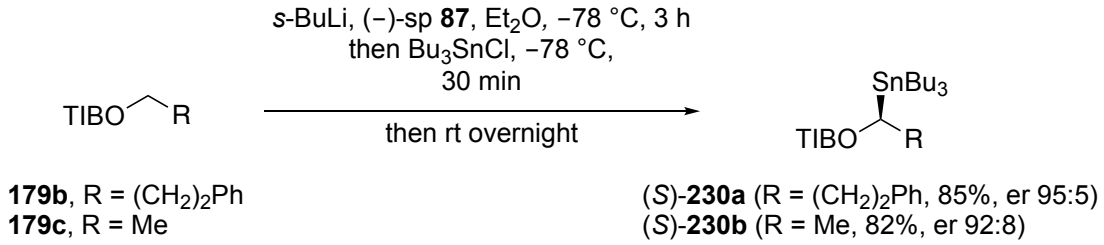
Aggarwal and co-workers have been able to apply boronic ester homologation to synthesise quaternary carbon centres.[198] An attempt at homologation of boronic ester **104g** to create a quaternary centre was therefore attempted using stannane **230i**, the latter being prepared following a reduction, Mitsunobu, lithiation—stannylation sequence. The attempted homologation only resulted in 86% RSM of stannane **230i** and 20% *N*-Botc-azetidine **101a**. This result suggests that Sn–Li exchange is significantly more challenging on this sterically hindered benzoate, with the resulting excess unreacted *s*-BuLi promoting deborylation.

### 3.2.15 Asymmetric homologation via enantioenriched stannanes

The asymmetric variant of the reaction was now investigated, with the hope that without the presence of a bulky (–)sp **87** ligand improved yields could be obtained. Sn–Li exchange is believed to occur with complete retention of configuration[79] and formation of enantiopure benzoate stannanes **230** is well-documented in the lit.[138] The asymmetric

reaction could therefore be carried out using the exact conditions previously developed for the racemic 1,2-metallate rearrangement, but with enantioenriched starting materials.

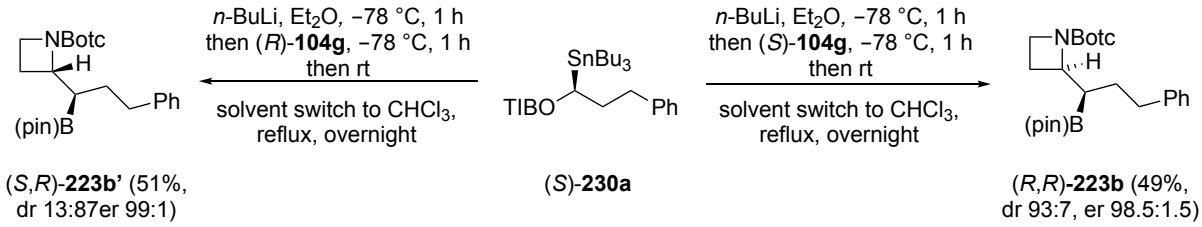
Enantioenriched stannanes (*S*)-**230a** and (*S*)-**230b** were synthesised using an asymmetric lithiation—electrophile trapping reaction with $Bu_3SnCl$ as the electrophile and (–)-sp **87** as the chiral diamine ligand (Scheme 124).




**Scheme 124.** Asymmetric lithiation—electrophile trapping of benzoates **179b** and **179c.**

Boronic esters (*S*)-**104g** and (*R*)-**104g** were then subjected to 1,2-metallate rearrangement conditions with the enantioenriched stannanes. This would give insight into a possible 'matched/mis-matched' effect which could be operating, based on the diastereoselectivity for the reaction using racemic starting materials (Scheme 122, p 118).

The 'matched' reaction case, using (*S*)-boronic ester **104g** and (*S*)-stannane **230a** (i.e., which would lead to the major diastereomer **223b** in the racemic reaction), gave the desired boronic ester **223b** in moderate 49% yield with high enantio- and diastereo-selectivities ((major-(*R*,*R*)-**223b** 98.5:1.5 er), (minor-(*S*,*R*)-**223b'** 71:29 er), 93:7 dr) (Scheme 125). Despite the high enantio and diastereoselectivities, the yield was disappointingly low — especially considering the 'matched' case should be expected to facilitate the 1,2-metallate rearrangement.




(*S*,*R*)-**223b'** (51%, dr 13:87er 99:1) (*S*)-**230a** (*R*,*R*)-**223b** (49%, dr 93:7, er 98.5:1.5)

**Scheme 125**. Asymmetric Sn—Li exchange 1,2-metallate rearrangement with stannane (*S*)-**230a.**

The diastereoselectivity for the reaction was slightly higher than expected. Assuming the reaction did not have any 'matched/mis-matched' influences, diastereoselectivity would be expected to be ~88:12 dr based on the amounts of minor enantiomers of **230** and **104g** present in the reaction mixture (Scheme 112, p 107). This could be an indication of a slight 'matched' effect, however, analysis of the minor diastereomer by $^{1}$H NMR spectroscopy following chromatography revealed the presence of an alkene impurity **232a**, believed to be formed via β-elimination of the boronic ester **223b** and **22b'** with subsequent ring-opening (multiplets, $\delta_H$ = 5.60 – 5.50 & 5.38 – 5.26 ppm) (Figure 8).

The minor diastereomer required an additional chromatographic purification before being isolated sufficiently pure; these additional steps required to isolate the minor diastereomer would have a detrimental effect on the yield and therefore could be responsible for the slightly higher dr (than expected) for the reaction.

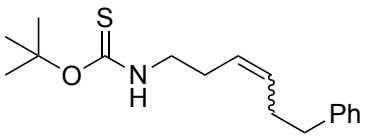



**Figure 8.** Alkene impurity **232a**

For the 'mis-matched' case, the reaction proceeded with strikingly similar results compared to the 'matched' (yield 51%, (major-(*S*,*R*)-**223b'** 99:1 er), (minor-(*R*,*R*)-**223b** 78:28 er) 87:13 dr) (Scheme 125). The similarity between the 'matched/mis-matched' reactions suggest that both diastereomers can be formed with the same relative ease. It also implies that any

diastereoselectivity in the racemic reaction has a minimal effect on the asymmetric reaction and any potential 'matched/mis-matched' effect can be overridden. This does not, however, help explain why such diastereoselectivities are present during the racemic reaction and why yields for the asymmetric reaction decreased by ~ 20%.

The same set of reactions was also performed with ethyl stannane (*S*)-**230b** and enantioenriched boronic ester **104g** (Scheme 126). For the 'matched' reaction the 1,2-rearranged boronic ester **223c** was formed in 52% yield ((major (*R*,*R*)-**223c** 99:1 er), (minor-(*S*,*R*)-**223c'** 55:45 er), 85:15 dr). These results follow a similar pattern to the asymmetric 1,2-rearrangement reactions involving stannane (*S*)-**230a**. The minor diastereomer could not be separated during chromatography, eluting with a significant amount of an alkene impurity **232b** seen during $^{1}$H NMR analysis (multiplets, $\delta_H$ = 5.65 – 5.49 & 5.42 – 5.25 ppm, Figure 9).

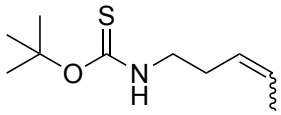
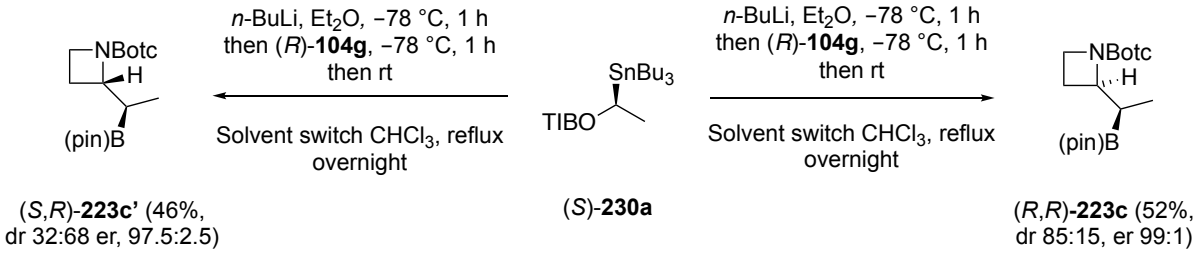



**Figure 9.** Alkenyl impurity **232b.**

The 'mis-matched' reaction in this case did give boronic ester **223c'** in decreased diastereoselectivity, suggesting a possible 'mis-matched' effect (46%, (major-(*S*,*R*)-**223c'** er 97.5:2.5), (minor-(*R*,*R*)-**223c** er 75:25), dr 68:32). This, however, would contradict the three previous results which showed no such effect.

The reaction also produced trace alkene impurities seen by $^{1}$H NMR analysis for both diastereomers. The alkene impurity was not, however, observed in the crude $^{1}$H NMR spectra for all of the previous asymmetric reactions, although this could be due to relatively

weak signal intensities compared to other side-products formed (e.g. $Bu_4Sn$). The increased amount of alkenyl impurity seen in the reactions involving the ethyl stannyl benzoate **230b** compared with the 1-phenyl-propyl stannane **230a** suggests that the formation of the undesired alkenyl compound occurs more favourably when the size of the alkyl chain is reduced.




(*S*,*R*)-**223c'** (46%, dr 32:68 er, 97.5:2.5)

(*S*)-**230a**

(*R*,*R*)-**223c** (52%, dr 85:15, er 99:1)

**Scheme 126.** Asymmetric tin/lithium exchange 1,2-metallate rearrangement with stannane (*S*)-**230b.**

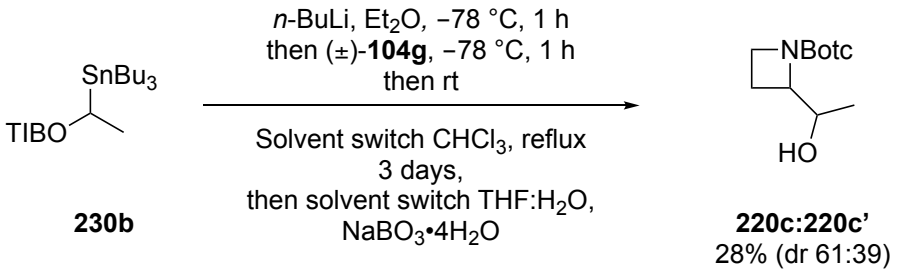
### 3.2.16 Experiments to probe the origins of diastereoselectivity

It was speculated that the formation of alkenyl impurities could be influencing the apparent reaction diastereoselectivity by selective decomposition of the homologated boronic esters. This decomposition may explain the appearance of an unknown borate impurity peak in the $^{11}B$ NMR spectrum at δ 22 ppm.

To test whether alkenyl impurities were being formed due to prolonged reaction times under reflux, racemic stannane **230b** and racemic boronic ester **104g** were subjected 1,2-metallate rearrangement with an extended reflux time of 3 days. On analysis of the crude $^1H$ NMR spectrum, peaks corresponding to product boronic esters **223c** and **223c'** (dr 58:42) were seen along with peaks in the alkenyl range. There was, however, no peak at $\delta_H$ 3.49 ppm corresponding to a proton environment seen for alkene impurity **232b** and therefore, at most, only trace amounts of the alkene impurity could be present. This was supported by TLC analysis of the crude mixture, which showed spots corresponding to the

boronic esters **223c** and **223c'**, and no spots corresponding to the alkenyl impurity. Purification of the crude mixture via column chromatography, however, resulted in 26% yield of the alkenyl impurity **232b** (~1:1 *E*/*Z*), along with boronic esters **223c** and **223c'** in 7% yield (dr 60:40).

A repeat reaction (3 day reflux) with *in situ* oxidation gave the corresponding alcohols **220c** and **220c'** in 28% yield (61:39 dr, Scheme 127) with no trace of alkene impurity **232b**. This suggests that ethyl boronic esters **223c** and **223c'** are unstable to column chromatography using silica. With this result, the possibility of alkene impurity **232b** forming during the reaction conditions cannot be ruled out; however, if it is the case that the alkene impurity is being formed during reflux, it is then decomposing following its formation. This would explain the appearance of unknown alkenyl peaks in the reaction crude by $^{1}$H NMR analysis. The alkene impurity **232b**, isolated following chromatography showed peaks corresponding to the Botc group, which could decompose thermally via a Chugaev reaction during reflux.[199] Thermolysis via abstraction of β-H from the *tert*-butyl group had been previously shown to proceed in refluxing ethanol.[93]



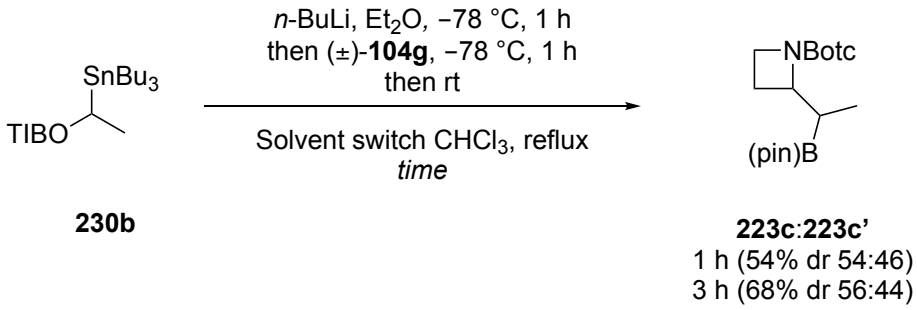

**230b** **220c:220c'** 28% (dr 61:39)

**Scheme 127.** Extended 1,2-metallate rearrangement time with oxidation.

The reaction was run with reduced refluxing times of 1 h and 3 h (no oxidation). In the reaction with only a 1 h reflux time, boronic esters **223c** and **223c'** were formed in 54%

combined yield (dr 54:46). The reaction performed with 3 h reflux time gave boronic esters **223c** and **223c'** in a combined yield of 68% (dr 56:44) (Scheme 128). These results suggest 1,2-metallate rearrangement occurs relatively quickly and non-selectively between the two diastereomers with this benzoate. This means that the origin of the diastereoselectivity in this case cannot be due to preferential 1,2-metallate rearrangement of one of the diastereomeric boronate complexes. It therefore could arise from selective decomposition of the homologated boronic esters and/or selective decomposition during column chromatography.

To test the stability on silica, 26 mg of boronic esters **223c** and **223c'** (dr 54:46) were subjected to column chromatography through 3.1 g of silica. Only 75% of the mass was recovered with 12% yield of alkene **232b** formed, demonstrating that decomposition had taken place. Interestingly, the diastereomeric ratio of the recovered boronic esters **223c** and **223c'** had changed to dr 46:54. This contradicts the observed diastereoselectivity for the homologation reaction, since it indicates that the major diastereomer **223c** preferentially decomposes on silica.



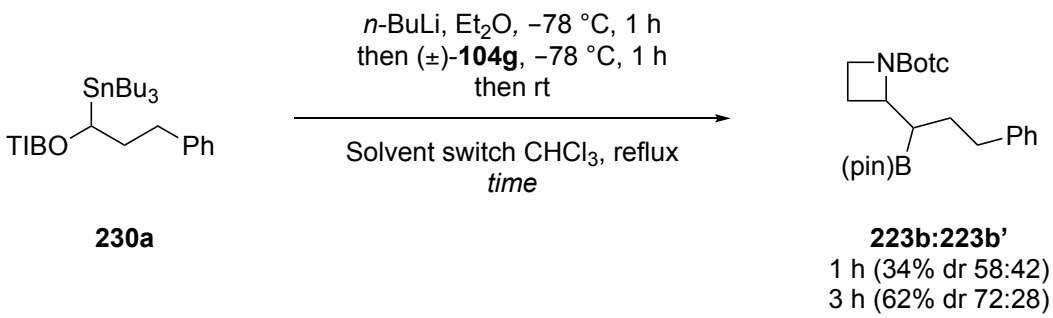

**Scheme 128.** Sn—Li exchange 1,2-metallate rearrangement with reduced migration time.

The same reactions with shortened reflux times (1 h and 3 h) were performed on the benzoate stannane **230a**. The yield after 1 h reflux of boronic esters **223b** and **223b'** was 34% (dr 58:42) (Scheme 129), suggesting incomplete migration had occurred. The

diastereoeselectivity was reduced, however, relative to conditions with refluxing overnight (dr 72:28), again suggesting that migration for both diastereomeric boronate complexes occur at similar rates. The reaction with a 3 h reflux time gave boronic esters **223b** and **223b'** in 62% yield (dr 72:28) (Scheme 129).

The similar yields obtained for this reaction compared with the reaction with refluxing overnight (68%) suggest that most 1,2-metallate rearrangement occurred within 3 h. Interestingly, the diastereoselectivities between the reactions refluxing at 3 h and overnight (12 h) were the same. It would be expected that if one boronic ester was decomposing preferentially, then the additional refluxing time should increase the diastereoselectivity. Since this was not seen, it suggests that the diastereoselectivity was not caused by selective decomposition in this case and instead could have been caused by selective boronate formation.

Comparing the diastereoselectivities for the ethyl and 1-phenylpropyl stannanes **230a** and **230b** suggests that potential diastereoselectivity could be a consequence of the size of the alkyl group attached to the stannane: the less sterically demanding ethyl substituent giving lower selectivity compared with the bulkier 1-phenylpropyl substituent.

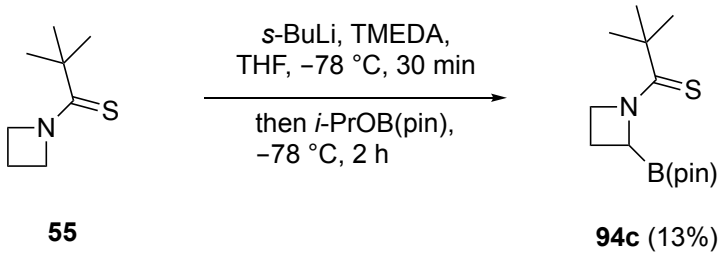



**230a**

**223b:223b'**
1 h (34% dr 58:42)
3 h (62% dr 72:28)

**Scheme 129**. Sn—Li exchange 1,2-metallate rearrangement with reduced migration time.

To further probe the diastereoselectivity of the homologation reaction, *N*-thiopivaloyl-azetidine boronic ester was synthesised following a lithiation—electrophile trapping sequence (Scheme 130). The reaction failed to give high yield (13%) due to significant decomposition/loss of the product boronic ester **94** during column chromatography, performed using C-2 deactivated silica.[200]




**55** **94c** (13%)

**Scheme 130.** Lithiation—borylation of N-thiopivaloyl-azetidine **94c.**

It was hoped that the greater stability of the thiopivaloyl group to removal might prevent decomposition of boronic ester **94c** during reflux. The thiopivaloyl protecting group has been shown within the group to withstand harsh deprotection conditions, such as refluxing in ethylene diamine overnight.[90] It was also believed that *N*-thiopivaloyl boronic ester **94c** would have a greater degree of conformational rigidity compared with *N*-Botc-azetidine boronic ester **104g**. This would be in part due to closer proximity of the *t*-butyl group of the thiopivaloyl to the α-positions on the azetidine ring.

*N*-Thiopivaloyl boronic ester **94c** was found to exist almost entirely as a single rotamer by analysis of the $^{1}$H NMR spectrum. The favoured rotamer would most likely have the *t*-butyl group pointing away from the bulky B(pin) group.[102] This would mean that the sulfur atom would be positioned to potentially interact with the empty p-orbital on the boron atom, essentially forming a rigid bicyclic molecule. There was, however, no evidence of such interaction since the peak seen in the $^{11}$B NMR spectrum was at $\delta_B$ 31 ppm, which

corresponds to a three coordinated $RB(OR)_2$ species. Any interactions from the sulfur lone pair to the boron p-orbital would be expected to increase the shielding on the boron atom and change the chemical shift of the $^{11}B$ peak to a lower ppm (although it was marginally lower than *N*-Botc boronic ester **104g** at $\delta_B$ 32 ppm).

If such a rigid structure were formed, then the transition state of the boronate formation step would be much more closed in nature and potentially give a higher degree of diastereoselectivity (Figure 10). There could also be a certain degree of facial selectivity that could significantly affect the amount of diastereoselectivity.

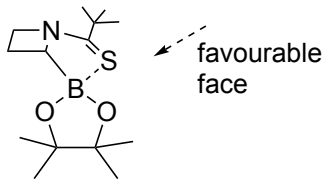
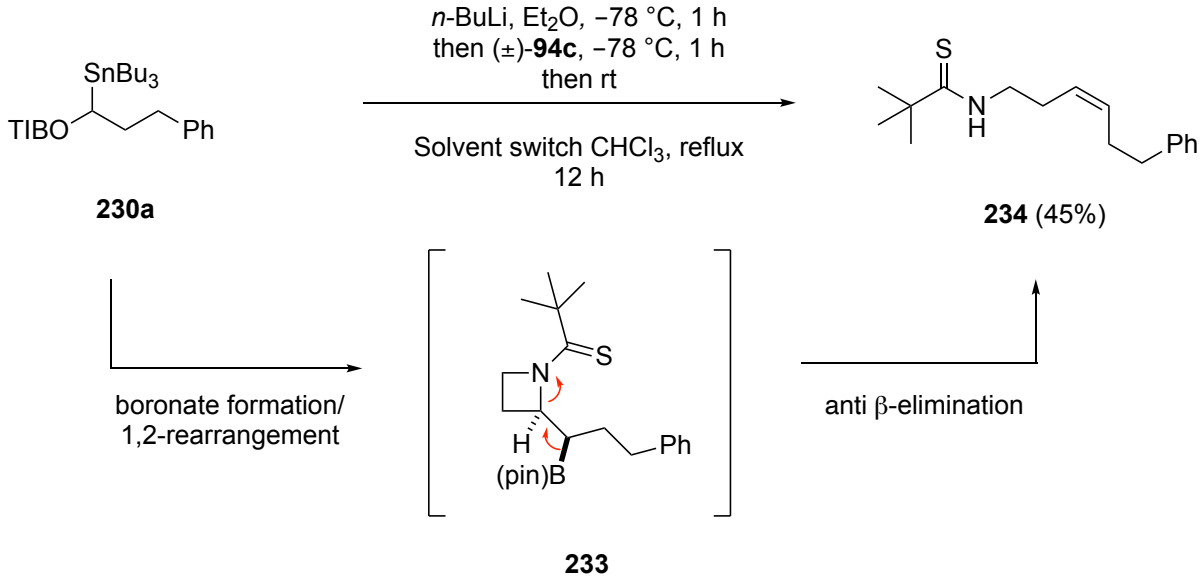



**Figure 10.** Potential bicyclic nature of N-thiopivaloyl boronate **94c**

When boronic ester **94c** was subjected to homologation with stannane **230a**, the reaction exclusively gave alkene **234** as a single *Z* isomer. The stereochemistry was determined via $^1H$ NMR analysis of alkenyl proton coupling constants, with *J* = 10.5 Hz suggesting a *cis* relationship between the two alkenyl protons (NOESY analysis gave allylic cross-peaks). The formation of the alkene most likely occurred following initial boronate formation and 1,2-metallate rearrangement which gave homologated boronic ester **233** (Scheme 131). Boronic ester **233** would then have undergone rapid β-elimination with ring-opening to give alkene **234** (probably due to the greater electron withdrawing nature of the thiopivaloyl group compared to Botc).

The observation that only a single alkene stereoisomer was formed could be due to a number of reasons; firstly it could be that diastereoselectivity in the initial boronate/1,2-metallate rearrangement is sufficiently selective to afford a single diastereomeric boronic ester **233**; secondly, there could be favourable β-elimination of diastereomeric boronic esters — there could be selective decomposition of the other diastereomer during the reaction.

The fact that the *Z*-isomer was isolated would rule out preferential β-elimination since, assuming anti-elimination, this would occur through a more sterically hindered transition state compared with the β-elimination to give the *E*-isomer. Assuming that anti-elimination is the mechanism to form *Z*-alkene **234**, it would be expected that only a single diastereomer of boronic ester **233** is being formed. This diastereomer **233** also corresponds with the major diastereomer formed in the boronate/1,2-metallate rearrangement reactions with boronic ester **104g**.

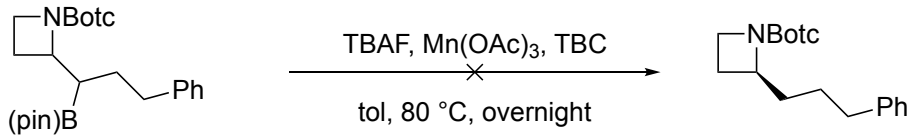



**Scheme 131.** Boronate/1,2-metallate rearrangement followed by anti β-elimination.

### 3.2.17 Functionalisations of homologated boronic ester

The only transformation that was successfully performed on homologated boronic esters **223b** and **223b'** was oxidation to the corresponding alcohols. So as to increase the synthetic value of the homologation reaction, various attempts at functionalising the homologated boronic esters into a variety of different functional groups were performed.

Proto-deborylation might enable access to highly enantioenriched alkyl substituted azetidines. This would be a desirable transformation if the homologation reaction was ever used in a natural product synthesis (e.g. alkyl substituent of penaresidins). Aggarwal and co-workers have described a TBAF mediated proto-deborylation for non-benzylic boronic esters.[201] However, attempted proto-deborylation on boronic ester **223b** and **223b'** (1:1 dr) resulted in decomposition of the starting material with no discernible product (Scheme 132), $^{1}$H NMR analysis of reaction crude showed the disappearance of any *N*-Botc peaks (1.50-1.70 ppm) suggesting the protecting group had been removed during the reaction.

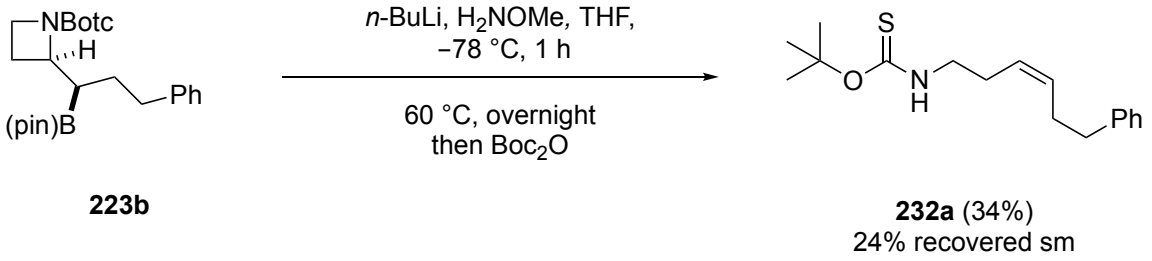



**223b:223b'** (1:1 dr) **235**

**Scheme 132.** Attempted de-borylation.

Morken *et al*.[202] reported direct amination of boronic esters via the addition of lithiated methoxylamine to boronic esters to form a boronate intermediate, which can then collapse via 1,2-metallate rearrangement to give the desired aminated compound. Attempts at performing amination following these conditions on boronic ester **223b**, however, resulted

in the formation of alkene (*Z*)-**232a** in 34% yield and recovered starting material 24% (Scheme 133).



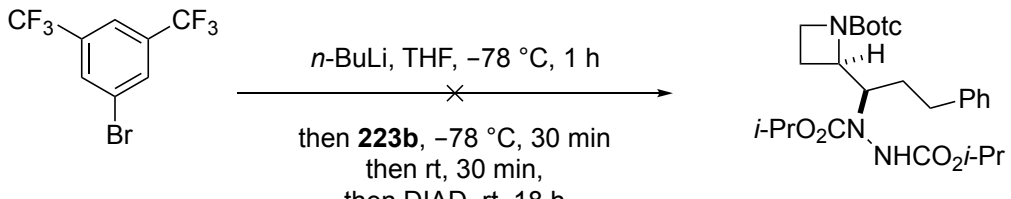

**223b**

**232a** (34%)
24% recovered sm

**Scheme 133.** Attempted boronic ester amination.

The boronate complex was most likely forming, however, upon heating, competing collapse of the 'ate' complex via β-elimination resulted in the formation of the alkene in similar fashion seen for the *N*-thiopivaolyl substrate (see p 134).

To reduce the "nucleophilicity" of the boronate complex, addition of lithiated species with electron-withdrawing groups was considered. Aggarwal *et al*.[203] has shown that formation of boronate complexes using lithiated 3,5-bis(trifluoromethyl) benzene **236** as the nucleophile to form the 'ate' complex allows stereoretentive trappings with electrophiles. Addition of lithiated benzene **236** to boronic ester **223b**, followed by electrophilic trapping with DIAD, resulted in 56% recovered starting material and a complex mixture of unknown side products. Encouragingly, none of the side products contained any peaks corresponding to the unwanted alkene (Scheme 134).

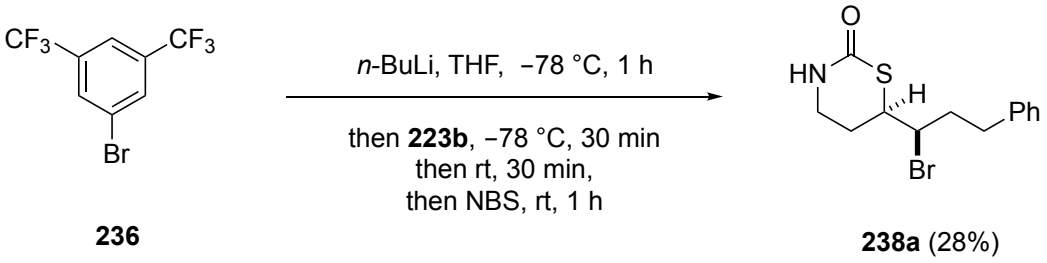



**236**

**237** (0%),
56% recovered sm

**Scheme 134.** Attempted hydrazination of boronic ester **223b.**

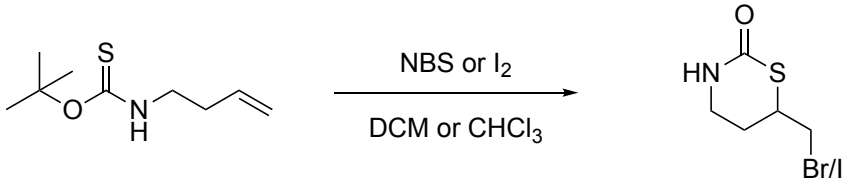
It was thought that a more reactive electrophile would be more effective at trapping the boronate complex; therefore the same reaction was attempted, this time, however, NBS was used as the electrophile (Scheme 135). The reaction failed to give any of the desired brominated product; however, it did give 28% of 1,3-thiazinan-2-one **238**. This most likely forms via a β-elimination of the boronate complex, followed by bromocyclisation to give the cyclised product **238** (Scheme 135)**.** To account for the poor mass recovery, a test reaction in which NBS was added to *N*-Botc-azetidine **104g** resulted in decomposition of the starting material. It is likely that NBS interacts with the thiocarbonyl group which subsequently results in the removal of the protecting group from the azetidine.




**236** **238a** (28%)

**Scheme 135.** Thiazinan-2-one **238a** synthesis via bromocyclisation.

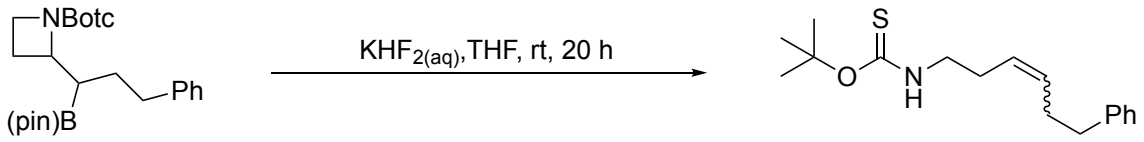
Attempts to form 1,3-thiazinan-2-ones through iodocyclisation and bromocyclisation were made in order to establish whether or not it was an effective method to synthesise such heterocyclic compounds. However, initial results failed to give products in good yields that could be easily isolated and therefore further investigation was not pursued (Scheme 136).




**232c** **238b** and **238c** impure (5-16%)

**Scheme 136.** Attempted bromo/iodocyclisation.

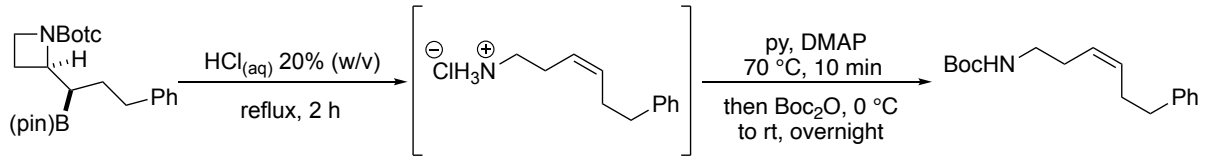
An attempt to form the trifluoroboronate salt from boronic ester **223b** and **223b'** was performed to access boronate compounds more readily reactive to cross-coupling conditions.[204] Treating a mixture of boronic esters **223b** and **223b'**in THF with aqueous $KHF_2$ resulted in the formation of the undesired alkene **232a** in good yield (81%) (Scheme 137). The formation of the alkene could be due to the acidic reaction conditions, as silica has also been shown to encourage elimination, or it could be a result of boronate formation promoting elimination.




**223b:223b'** (dr 72:28) **232a** (81%, *E*/*Z* ~ 30:70)

**Scheme 137.** Attempted synthesis of trifluoroborate salt.

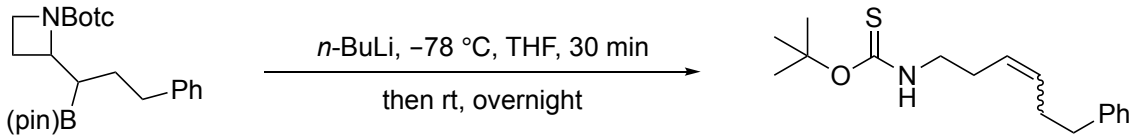
Conversion of boronic ester **223b** to boronic acid under aqueous acidic conditions was also attempted, since boronic acids are desirable compounds with an increasing number of boronic acids appearing as potential drug targets.[205] Stirring boronic ester **223b** and **223b'** in 20% aq HCl w/w for two hours at rt gave 78% RSM. The same reaction performed on boronic ester **223b**, but with heating to reflux for 2 h, gave deprotected ring-opened unsaturated ammonium salt **239** (43% NMR yield). This was subsequently Boc protected, giving alkene **240** in 23% yield (over 2 steps). $^1$H NMR analysis revealed stereochemistry of the alkene to be *Z* (*J* = 10.3 Hz and NOESY cross-peaks between allylic protons). The appearance of a single alkene from the single diastereomeric boronic ester suggested that the ring-opening elimination was stereospecific, most likely via anti-elimination.




**223b** **239** (43%, NMR yield) **240** (23%, over two steps)

**Scheme 138.** Synthesis of homoallyic amine **240.**

Intentional alkene formation was performed under basic conditions by simply treating a mixture of boronic esters **223b** and **223b'** with *n*-BuLi in THF and allowing the mixture to warm to room temperature. This gave the desired alkene **232a** in 45% yield as (40:60) mixture of *E*/*Z* isomers (Scheme 139).

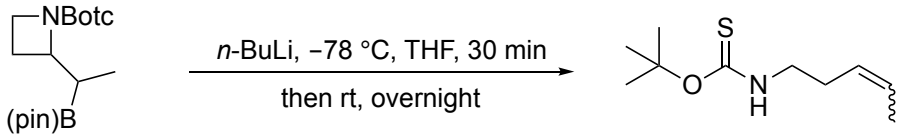



**223b:223b'** (dr 58:42) **232a** (45%, *E*/*Z* ~ 40:60)

**Scheme 139.** Boronate formation followed by β-elimination.

The same reaction was performed with boronic ester **223c** and **223c'** (54:46 dr), resulting in the formation of in an *E*/*Z* (54:46) mixture of alkene **232c** in 58% yield (Scheme 140). The corresponding alkene ratio demonstrates that both boronic esters eliminate/ring-open with the same level of fidelity. Further evidence supporting a similar rate for ring-opening elimination was obtained when the same reaction was performed on boronic esters **223c** and **223c'** (54:46 dr) but with the temperature kept at –78 °C for 30 min before quenching. $^{1}$H NMR analysis of the crude showed the reaction had proceeded with 31% conversion to the alkene with remaining boronic ester **223c** and **223c'** in a 54:46 dr. The unchanged dr lends further support to origin of diastereoselectivity in the homologation reaction being during boronate formation and not due to a selective ring-opening elimination pathway.

This reaction also illustrates the large challenge faced for derivatisation of the homologated boronic esters due to the ease with which these systems undergo ring-opening elimination.

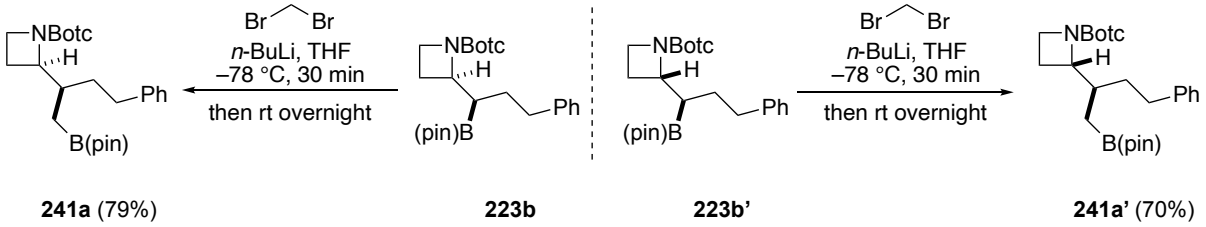



**223c:223c'** (dr 54:46) **232b** (58%, *E*/*Z* 46:54)

**Scheme 140.** Nucleophilic boronate/elimination.

It was therefore decided to explore boronic ester functionalisations which would occur at – 78 °C, in the hope that 1,2-migration/rearrangement would occur in preference to ring-opening elimination. Such transformations were possible, as it had been shown with oxidation of the homologated boronic esters to the alcohols — a reaction which occurred without the formation of any alkene side-product. Matteson homologations are known to undergo 1,2-migration at temperatures below zero[206] and it was therefore decided that this functionalisation would be suitable for boronic esters **223b** and **223b'**.

When the reaction was attempted with $CH_2BrLi$ as the homologating reagent, pleasingly, the reaction proceeded smoothly to give boronic ester **241a** and **241a'** in 79% and 70% yield, respectively (Scheme 141). In both cases, no alkene impurity was observed, suggesting complete selectivity for 1,2-migration. These homologated boronic esters should in theory be able to undergo further transformations without the issues of competing β-elimination. Oxidation of these boronic esters to alcohols would be the synthetic equivalent to *N*-Botc-azetidine **101a** lithiation—epoxide trapping with regioselective trapping at the substituted site of the epoxide.

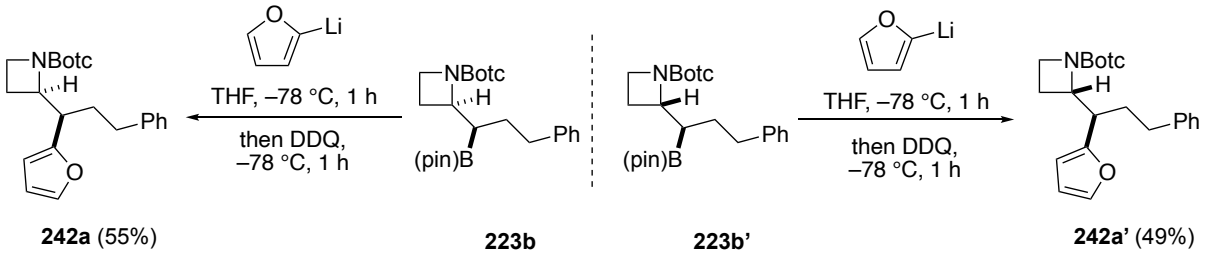



**241a** (79%) **223b** **223b'** **241a'** (70%)

**Scheme 141.** Matteson homologation on diastereomers **223b** and **223b'.**

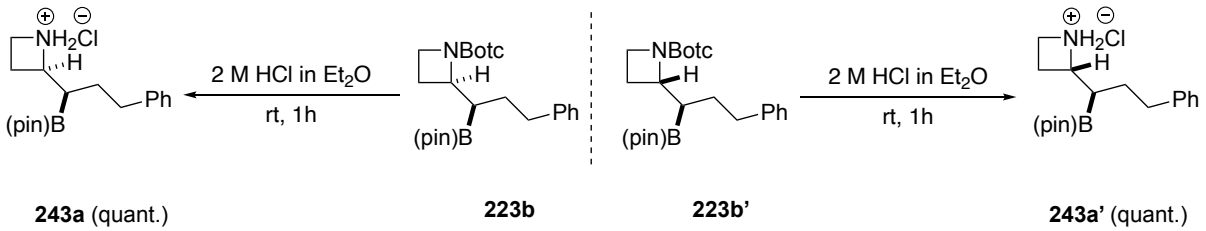
Another transformation that has been shown to occur at –78 °C was Aggarwal's boronate arylation with 1,2-migration triggered by $S_EAr$ (see p 84). In the original paper,[170] the authors describe two suitable electrophiles to trigger $S_EAr$, NBS and DDQ. Having already established that NBS is incompatible with the *N*-Botc functional group, a test reaction to establish functional group tolerance of *N*-Botc-azetidine **101a** with DDQ was performed. After 1 h at –78 °C in THF with DDQ (1.5 equiv), the reaction gave 55% recovered azetidine **101a**.

Although there was significant decomposition of the starting material, it was hoped that during the reaction the majority of the DDQ would be consumed during the $S_EAr$ step. The reaction was therefore attempted with both diastereomeric boronic esters **223b** and **223b',** giving the desired furanylated products **242a** and **242a'** in 55% and 49% yield, respectively (Scheme 142). In the case of boronic ester **223b**, 28% yield of undesired alkene (*Z*)-**232a** was observed, however, in the reaction with boronic ester **223b'**, only trace alkene (*E*)-**232a** was observed in the reaction crude by $^1$H NMR spectroscopy. This is surprising, given it suggests that the formation of *Z*-alkene (*Z*)-**232a** occurs with greater ease (although these results support observations made during boronic esters **223c** and **223c'** silica stability tests, p 130).




**Scheme 142.** Furanylation of diastereomers **223b** and **223b'.**

Finally, examination of protecting group removal was performed on boronic esters **223b** and **223b'**. This was potentially problematic, as attempted deprotection of boronic ester **104g** under acidic conditions had resulted in product decomposition (see p 113-114). Deprotection of boronic ester **223b** and **223b'** with HCl (in $Et_2O$) resulted in the quantitative formation of the desired deprotected ammonium azetidines **243a** and **243a'** (Scheme 143). This transformation is of significance as it would allow alterations of the electronics at the nitrogen group. As discussed earlier (see above), the *N*-Botc group is electron withdrawing and it may be facilitating undesired β-elimination/ring-opening. Being able to modify the *N*-group of the homologated boronic esters may allow for a greater range transformations to be performed on such compounds, without competing elimination and or *N*-Botc decomposition.




**Scheme 143.** Deprotection of homologated boronic esters **223b** and **223b'.**

## 3.3 Summary

Synthesis of a 2-B(pin)-*N*-Botc-azetidine has been achieved in both high yields and enantioselectivity. Conditions in which the boronic ester **104g** can be synthesised in sufficiently high purity allow for simple purification (volatile impurities removed under hi-

vac). Issues still remain surrounding an effective means to purify boronic ester **104g**, especially in cases where there is significant impurity present in the reaction crude. This prevents efficient means of forming boronic ester **104g** under more convenient THF/TMEDA lithiation conditions. Recent work by Glorius *et al.* on similar α-amino boronic ester utilises a celite filtration purification,[207] which may offer a possible means to boronic ester **104g** purification without incurring significant loss of product.

A range of functionalisations on boronic ester **104g** have been attempted and it has been shown that Aggarwal-type homologation reactions are effective to access functionalised 1,2-amino boronic ester azetidines. The reaction conditions have been optimised under direct lithiation conditions (suitable with boronic ester **104g** in excess) and under Sn–Li exchange conditions (suitable with boronic ester **104g** as limiting reagent). The reaction scope has been examined (Sn–Li conditions) and shown to tolerate ethyl, β-branched (except neopentyl), alkenyl, siloxy and acetal benzoates. Diastereoselectivity has been obtained in all cases for this transformation, with the origins of diastereoselectivity most likely occurring during selective irreversible boronate formation. The asymmetric homologation has been shown to occur without an influence of a matched/mismatched effect and is able to give highly enantioenriched homologated boronic esters. This sequence of transformations is therefore able to give enantioenriched azetidines with contiguous stereocentres with complete stereocontrol. Further derivatisation of the homologated boronic esters has been demonstrated, with the key to further functionalisation being to utilise conditions in which 1,2-migration of the formed boronate intermediate occurs at a greater rate than competing β-elimination ring-opening. This has resulted in the development of boronic ester oxidation, Matteson homologation and

furanylation on both diastereomers of homologated boronic ester **223b**. Additionally the homologated boronic esters can be deprotected which will allow for a greater range of functionalisation at N and potentially a greater range of boronic ester functionalisations. Overall, this has effectively demonstrated the possibility of utilising an α-boronic ester as a synthetic 'building block' and has enabled access to a range of functionalised 2-substituted-azetidines that would be previously inaccessible via a direct α-lithiation—electrophile trapping methodology.

Finally, determination of absolute configuration has been achieved, which shows that the asymmetric induction for boronic ester **104g** formation is opposite to that seen during asymmetric lithiation—methylation. This is an interesting observation as it demonstrates that asymmetric induction for the lithiation—electrophile trapping is dependent on the electrophile (similar to what was found on the *N*-thiopivaloyl system, see p 152**,** chapter 4). This is an important finding with respect to previous work in the group, as previous assignment of stereochemistries of 2-substituted-azetidines were by analogy to 2-methyl-azetidine **104a**. As the sense of enantioinduction is dependent on the electrophile, it became important to re-evaluate previously assigned stereochemistry and to probe possible origins for why the sense of asymmetric induction is dependent on the electrophile. This will form the results and discussion in the next chapter.

# 4. Mechanistic studies on the enantiodetermining step in asymmetric α-lithiation—electrophile trapping of *N*-Botc azetidine 101a

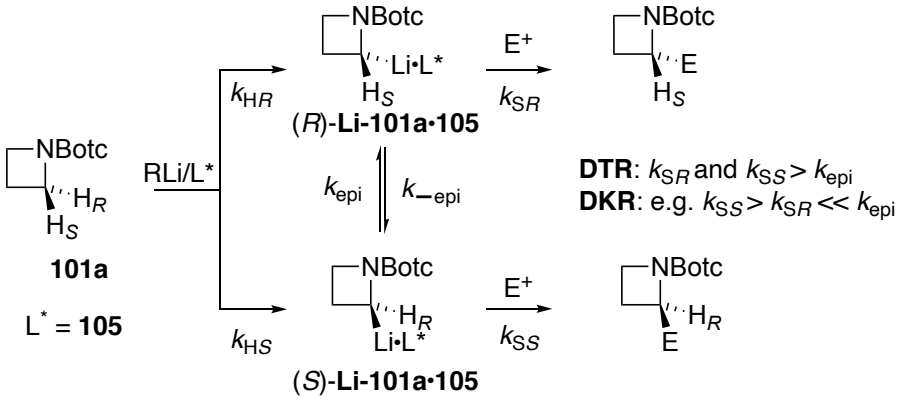
## 4.1 Introduction

### 4.1.1 Mechanistic considerations for asymmetric α-lithiation—electrophile trapping

Mechanistically, enantioselectivity in asymmetric α-lithiation—electrophile trapping can occur as a result of three distinct pathways (Scheme 144).[208] Firstly, combination of the organolithium base with a chiral ligand can result in a chiral base. This base can selectively remove either the *pro-R* or *pro-S* hydrogen, which subsequently forms a configurationally stable anion. The anion is then able to react with an introduced electrophile in a stereospecific manner ($S_E2$ retentive or $S_E2$ invertive)[208] to give enantioenriched products.

Two other pathways for asymmetric induction both occur after deprotonation. A dynamic kinetic resolution (DKR) occurs when a configurationally unstable anion is able to epimerise at a rate faster than trapping with an electrophile (e.g., $k_{SR} > k_{SS} << k_{epi}$). As a result, the enantioselectivity follows Curtin-Hammett principles and the levels of enantioselectivity are dictated by the difference in rates of trapping between the electrophile and two diastereomeric organolithium complexes ($\Delta\Delta G^{\ddagger}$). Lithiation—electrophile trappings which follow this pathway require a rapidly epimerising organolithium intermediate — often the carbanion is mesomerically stabilised or an α- heteroatom is from a lower row in the periodic table (S or Se).[208] The third possible mechanistic pathway is a dynamic thermodynamic resolution (DTR).[208-209] This occurs when the diastereomeric organolithium complexes are configurationally unstable and are able to equilibrate into a thermodynamically controlled ratio. Reaction with an introduced electrophile occurs at a

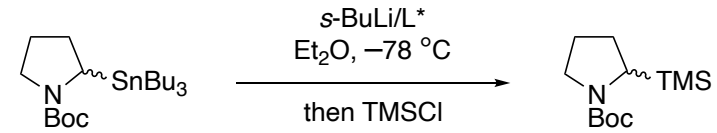
rate faster than epimerisation ($k_{SR}$ and $k_{SS} > k_{epi}$) with the enantioselectivity reflecting the thermodynamic ratio of the diastereomeric lithiated complexes. Reactions which follow such pathways are often controlled by employing a warm-cool cycle, in which the organolithium complexes are warmed to allow thermal equilibration followed by cooling to lock the thermodynamically controlled ratio of the complexes before the addition of an electrophile.




**Scheme 144.** Enantiodetermining pathways for asymmetric lithiation electrophile trapping.

An example of an enantioselective deprotonation mechanism is Beak's (–)-sp **87** mediated asymmetric lithiation—electrophile trapping of *N*-Boc-pyrrolidine **65b** (see chapter 1, Scheme 24, p 26).[82] To confirm that the reaction proceeded via an asymmetric deprotonation pathway, the authors performed Sn–Li exchange studies, which demonstrated that the organolithium intermediate is configurationally stable at the reaction temperatures.[82] Such experiments work on the assumption of a stereospecific transmetallation (a reaction with considerable precedent for occurring in a stereoretentive manner),[79] and measures any erosion in ers observed when starting from an enantioenriched stannane (or absence of enantioselectivity when starting from a racemic stannane). The lack of significant erosion seen with α-lithio-*N*-Boc-pyrrolidine indicates configurational stability of the anion (Scheme 145). Deuteration studies were also

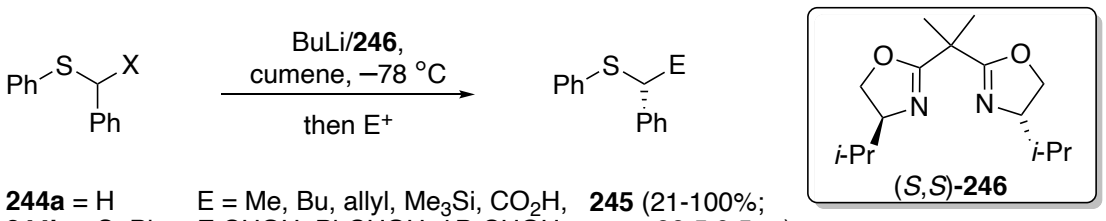
performed, which demonstrated that there was a high kinetic preference for the removal of the *pro-S* hydrogen by a *s*-BuLi/(–)-sp coordinated base.[82]




| | L* | |
|---|---|---|
| (±)-**86c** | (–)-sp **87** | (±)-**86d** (51.5:48.5 er) |
| (*S*)-**86c** (98:2 er) | none | (*S*)-**86d** (96.5:3.5 er) |
| (*S*)-**86c** (98:2 er) | TMEDA | (*S*)-**86d** (87:13 er) |

**Scheme 145.** Confirmation of configurationally stability via Sn-Li exchange.[82]

An example of a DKR reaction pathway was observed in the enantioselective α-lithiation—electrophile trapping of mesomerically stabilised benzylsulfide (Scheme 146).[210] The use of chiral bisoxazoline ligands (e.g., (*S*,*S*)-**246**) enabled asymmetric electrophile trapping of the organolithium complexes with a variety of electrophiles with high selectivity (up to 99.5:0.5 er). The degree of enantioselectivity was found to be dependent on the electrophile (a common trait in DKR mechanisms) with carbonyl electrophiles giving the highest levels of enantioselectivity.




**244a** = H
**244b** = SePh
**244c** = $SnBu_3$

E = Me, Bu, allyl, $Me_3Si$, $CO_2H$, EtCHOH, PhCHOH, *i*-PrCHOH, CyCHOH, $Me_2COH$, $Ph_2COH$

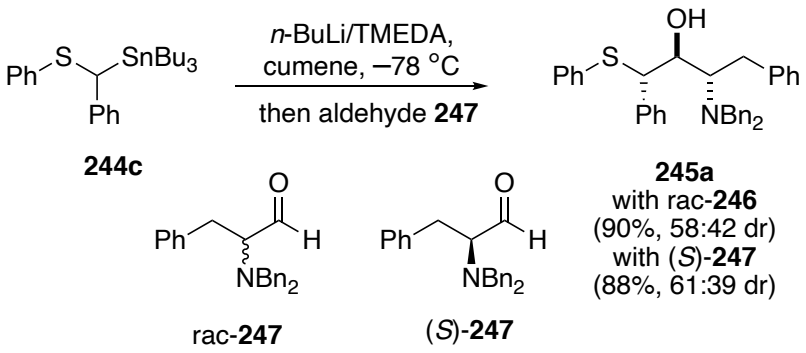
**245** (21-100%; up to 99.5:0.5 er)

**Scheme 146.** DKR of α-S carbanion with bix-oxazlidone ligand (*S*,*S*)-**246.**[210]

To determine the mechanism, Toru and co-workers conducted a number of experiments. Firstly, Sn–Li exchange was performed with racemic stannane **224c** (Scheme 146). Following formation of organolithium, chiral bisoxazoline (*S*,*S*)-**246** was added to the reaction mixture prior to addition of the electrophile. This gave matching levels of

enantioselectivity to those when the ligand was present during deprotonation, indicating that the organolithium complexes are configurationally unstable; however, this experiment does not differentiate between a DKR and DTR mechanism.

In order to discriminate between DTR and DKR, a Hoffmann test[211] and a "poor man's Hoffmann test"[212] were performed. The Hoffmann test utilises a chiral electrophile which is first introduced as the racemate. The diastereoselectivity that arises from trapping with the organolithium complexes will reflect the energy difference ($\Delta\Delta G^{\ddagger}$) between the two diastereomeric pathways. The second step of the test involves use of the enantiopure chiral electrophile; if the complexes are configurationally stable relative to electrophile trapping, then the diastereoselectivity will be expected to be 1:1. However, if the diastereoselectivity is similar to that determined with the racemic electrophile, then the anion is configurationally unstable relative to trapping with the electrophile (DKR). In this case Toru *et al.* found that diastereoselectivity when trapping with chiral aldehyde **247** was same (~60:40 dr) with both the racemic and enantioenriched electrophile indicating DKR (Scheme 147).

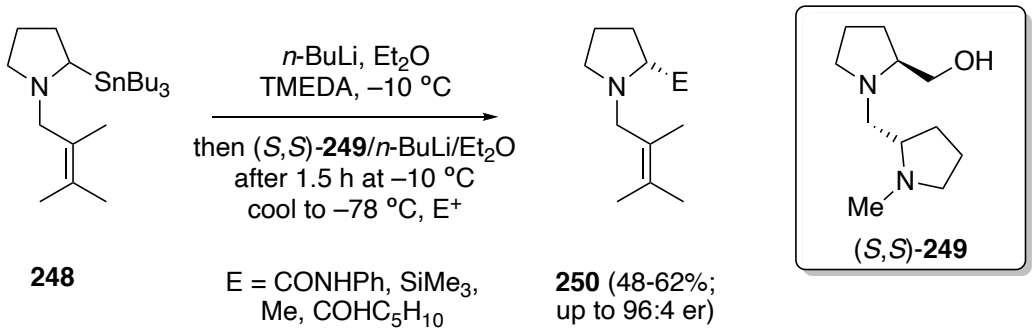



**Scheme 147.** Hoffmann test to determine configurational stability/instability. [210]

The "poor man's Hoffmann test" reacts a chiral organolithium complex with excess and sub-stochiometric amounts of the electrophile.[212] When trapping is performed with excess

electrophile, complete consumption of the organolithium complex is observed and therefore the enantioselectivity will reflect the ratio of the two diastereomeric complexes (if DTR). In the reaction with sub-stoichiometric amounts of electrophile, the enantioselectivity is influenced to a greater degree by the reaction kinetics, due to incomplete consumption of the organolithium complexes. If there is an observable difference in the levels of enantioselectivity between trapping with excess and sub-stoichiometric amounts of electrophile, then it demonstrates anionic configurationally stability relative to trapping with the electrophile. This therefore demonstrates a DTR mechanism, since if the reaction was occurring through a DKR mechanism the enantioselectivity would be independent of the reaction conversion. However, a DKR mechanism cannot be differentiated from a DTR mechanism by a "poor man's Hoffmann test", since it is possible that the selectivity derived from kinetics may coincide with the thermodynamically controlled selectivity (e.g., $k_{SR} \approx k_{SS}$). [212]

An example of a reaction controlled by DTR was demonstrated by Coldham and co-workers in the transmetallation and enantioselective electrophile trapping of *N*-alkyl/allyl-pyrrolidines.[213] The DTR was exploited following a Sn–Li exchange of *N*-prenyl stannane **248** to form a racemic organolithium complex. Introduction of diamino-alcohol ligand (*S*,*S*)-**249** followed by incubation for 1.5 h at –10 °C (a temperature at which the anion is configurationally unstable) allowed thermal equilibration of the lithiated complexes. On cooling the complexes to –78 °C (a temperature at which the anion is configurationally stable), an introduced electrophile led to highly enantioenriched 2-substituted-pyrrolidines **250** (49%-62%, up to 96:4 er, Scheme 148).




**248** **250** (48-62%; up to 96:4 er)

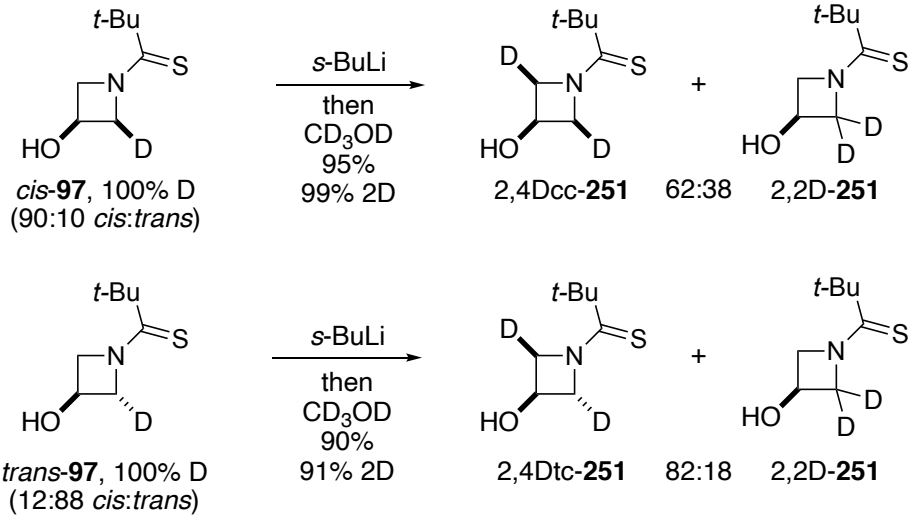
**Scheme 148.** DTR of N-prenyl-pyrrolidine **248.**[213]

### 4.1.2 Previous mechanistic studies on the α-lithiation of azetidines

The origins of diastereoselectivity in the lithiation of *N*-thiopivaloyl-azetidin-3-ol **96** (see chapter 1, p 30) were previously investigated through the lithiation of *cis*-2D-azetidine **97** and *trans*-2D-azetidine **97** with subsequent trapping with either $CD_3OD$, MeOH or benzylbromide.[91]

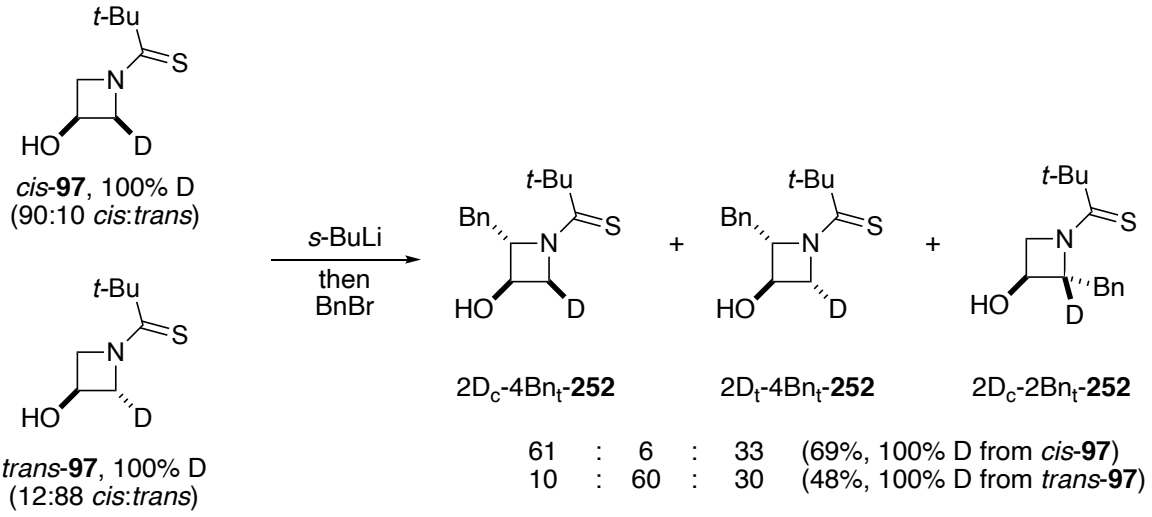
Comparison of lithiation between deuterated diastereomers *cis*-2D-**97** and *trans*-2D-**97** found that lithiation occurred preferentially *trans* to the hydroxyl group. This was determined as increased amount of 2,2-dideuterated-azetidine 2,2D-**251** formed from lithiation and deuteration of azetidine *cis*-2D-**97** compared to the reduced amount of 2,2-dideuterated-azetidine 2,2D-**251** formed from the corresponding azetidine *trans*-2D-**97** (Scheme 149). Since the "removal" of deuterium by lithiation is often accompanied by a very high kinetic isotope effect (KIE), the deuterium can act as a protecting group for lithiation.[214] In the case of azetidine *trans*-2D-**97**, the deuterium is effectively blocking *trans* lithiation at the deuterated site of the compound reducing the amount of 2D,2-lithio-azetidine formed. This diminishes the total of 2,2-dideuterated-azetidine 2,2D-**251** produced, compared with azetidine *cis*-2D-**97** as the starting material, thus demonstrating

a preference for *trans* lithiation. However, the fact that 2,2-dideuterated-azetidine 2,2D-**251** is observed from *trans*-2D-**97** lithiation demonstrates the occurrence of *cis*-lithiation.



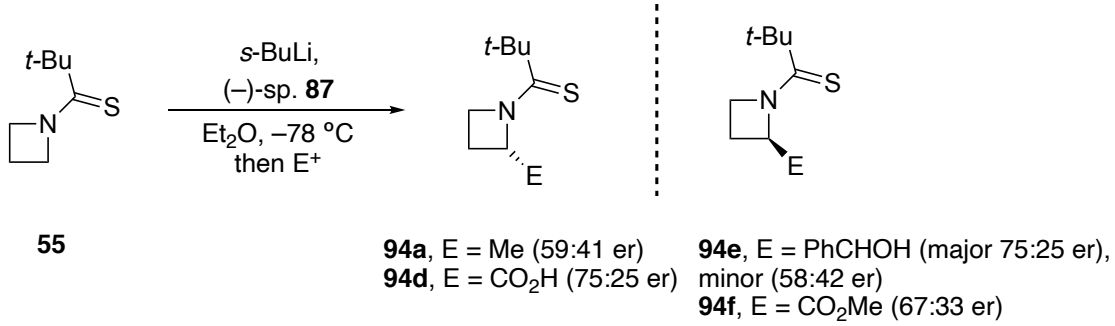

**Scheme 149.** Determination of favoured cis or trans lithiation of deuterated **97.**[91]

Deuterated azetidines *cis*-2D-**97** and *trans*-2D-**97** were lithiated and trapped with benzyl bromide, giving exclusively *trans* benzylated products $2D_c$-$4Bn_t$-**252**, $2D_t$-$4Bn_t$-**252** and $2D_t$-$2Bn_t$-**252** (Scheme 150), regardless of starting material. If the trapping occurs stereospecifically, then it would suggest that the organolithium species is configurationally unstable as both diastereomers *cis*-2D-**97** and *trans*-2D-**97** react to give the same $2D_c$-$2Bn_t$-**252** product. However, a firm conclusion about the configurational stability of the anion cannot be made as it is possible that the same product arises from competing trapping mechanisms (inversion, retention or SET).[208]




**Scheme 150.** Supporting evidence for configurational instability of lithiated **97.**[91]

Mechanistic studies by O'Brien and co-workers also demonstrated an interesting feature in the enantioselective α-lithiation—electrophile trapping of *N*-thiopivaloyl-azetidine **55**.[96] After determining the absolute configurations of a variety of enantioenriched 2-substituted azetidines, it was found that the sense of asymmetric induction was dependent on electrophile (Scheme 151).



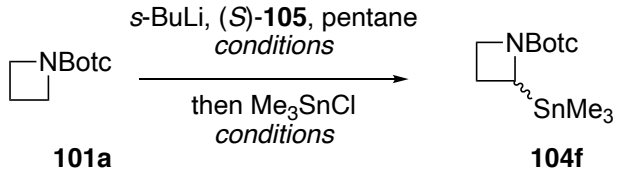

**Scheme 151.** Electrophile dependent sense of asymmetric induction.[96]

This is extremely uncommon in the enantioselective α-lithiation—electrophile trapping of dipole-stabilised non-benzyl C(sp$^3$) carbanions. With mesomerically dipole-stabilised anions it is speculated that a more C(sp$^2$)/planar carbanion is formed which results in a less sterically demanding access to the opposite face of the carbanion.[215] O'Brien and co-workers also showed that lithiated *N*-thiopivaloyl-azetidine **55** is configurationally

unstable through Sn–Li exchange experiments. However, despite demonstrating the occurrence of a post-deprotonation enantio-determining mechanism, no differentiation was made between DTR and DKR.[96]

Previous studies on the origins of asymmetric induction for the enantioselective α-lithiation—electrophile trapping of *N*-Botc azetidine **101a** failed to clarify the mechanism of the enantiodetermining step.[94] Sn–Li exchanges in the presence of DIANANE (*S*)-**105** on an enantioenriched 2-stannyl-azetidine (+)-**104f** (68:32 er) with subsequent electrophile trapping gave azetidine products with similar levels of enantioenrichment (~70:30 er), making it difficult to assess configurationally stability.[94]

Interestingly, during asymmetric stannylation studies it was noted that the sense of asymmetric induction (albeit small) was dependent on the reaction temperature and lithiation time (Table 10).[94]




**101a** **104f**

| Entry | Lithiation temp (time) | Stannylation temp (time) | % Yield 104f | er | $[\alpha]_D^{25}$ |
|---|---|---|---|---|---|
| 1 | –78 °C (1 h) | –78 °C (30 min) then rt (30 min) | 90% | 66:34 | +166.3 |
| 2 | –78 °C (1 h) | –78 °C (30 min) | 80% | n/a | +120.9 |
| 3 | –78 °C (5 min) | –78 °C (30 min) then rt (30 min) | 62% | 46:54 | –42.3 |
| 4 | –98 °C (3 h) | –98 °C (30 min) | 77% | n/a | +145.1 |
| 5 | –98 °C (1 h) | –98 °C (30 min) | 70% | n/a | –33.9 |

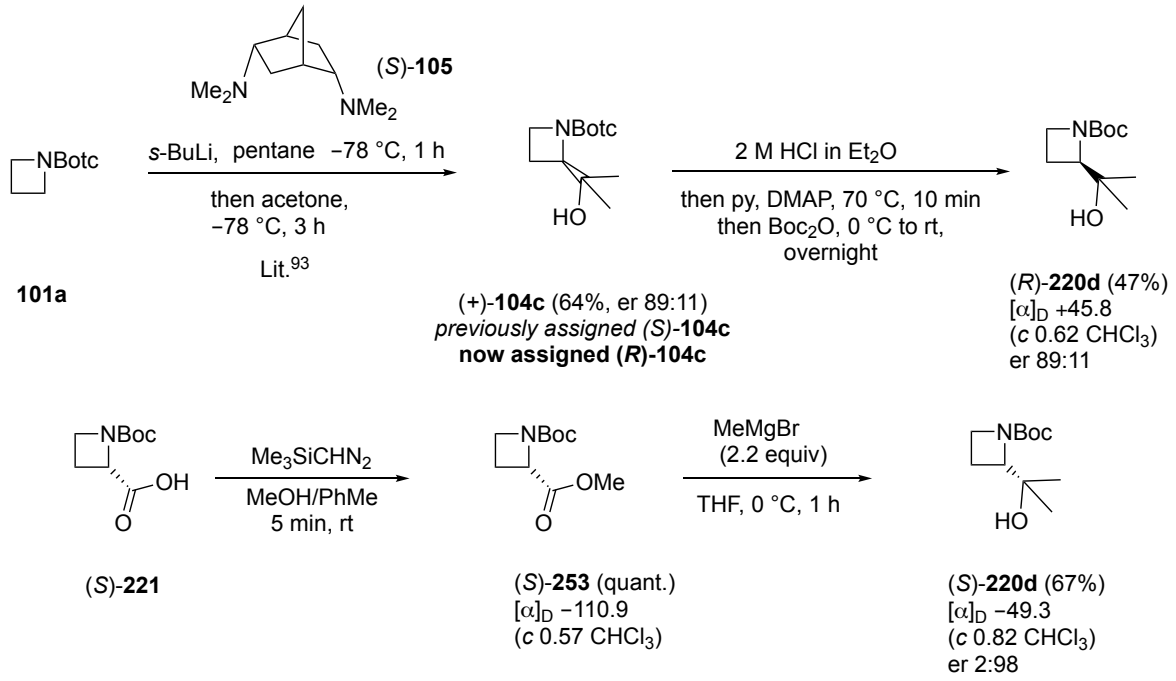
**Table 10**. Asymmetric stannylation of *N*-Botc azetidine **101a**.[94]

It was also observed in the asymmetric lithiation—electrophile trapping of *N*-Botc azetidine **101a** that optimal conditions were dependent on the electrophile. In the case of acetone trapping, a 92:8 er was achieved after just 1 h at –78 °C, however, under the same conditions with MeI trapping the enantioselectivity was 73:27 er.[94] These initial observations indicate a complex reaction mechanism which required further investigation to determine the enantiodetermining mechanism(s).

## 4.2 Results and discussion

### 4.2.1 Determination of absolute configuration for acetone adduct 104c

Having found electrophile dependence on the sense of asymmetric induction for the asymmetric α-lithiation—electrophile trapping of *N*-Botc azetidine **101a** with DIANANE **105**, confirmation of absolute configuration for previously trapped enantioenriched azetidines was carried out. This was studied since absolute configuration had been assigned by analogy to 2-methyl-azetidine (*R*)-**101a**.[94] To determine the absolute stereochemistry of acetone-trapped azetidine (+)-**104c**, enantioenriched alcohol (+)-**104c** was converted into *N*-Boc-protected alcohol (+)-**220d** following a deprotection/protection sequence (47%, Scheme 152). The specific rotation of *N*-Boc alcohol (+)-**220d** was compared with a sample synthesised from enantiopure (*S*)-carboxylic acid (*S*)-**221** (Scheme 152).




**Scheme 152**. Determination of absolute stereochemistry for alcohol **104c.**

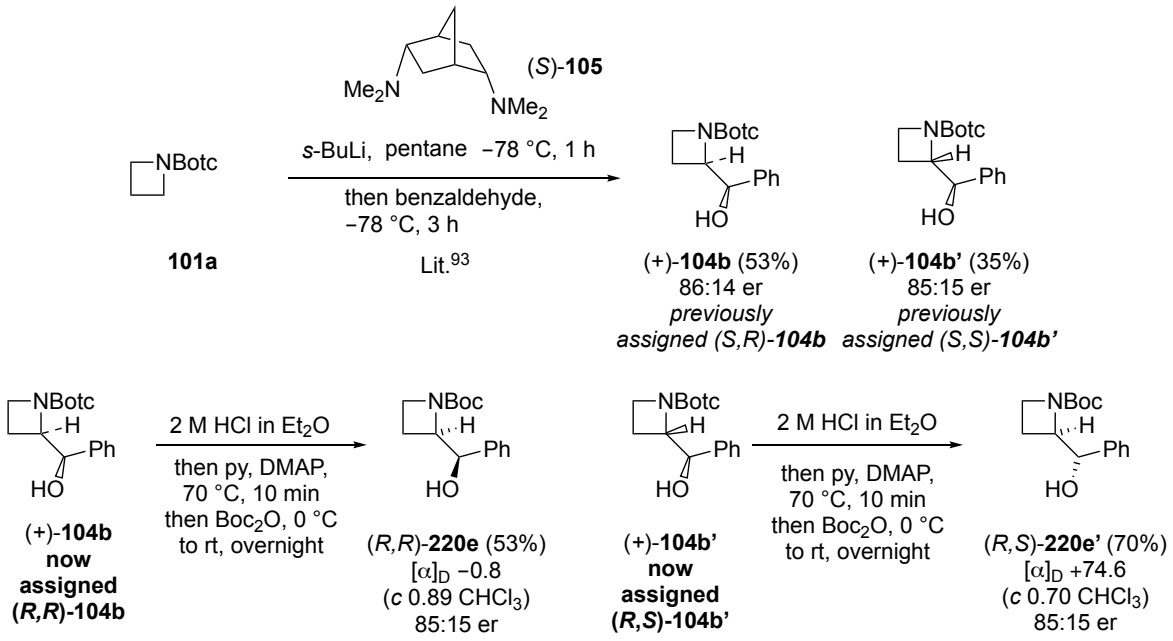
Comparison of specific rotation and HPLC data of enantiomeric alcohols (+)-**220d** and (–)-**220d** indicated that alcohol (+)-**104f** synthesised from (*S*)-**105** DIANANE can be assigned as (*R*)-**104f** (reversing the previous assignment).[93] This agrees with the findings of O'Brien *et al.,*[96] who found in the asymmetric α-lithiation—electrophile trapping of *N*-thiopivaloyl-azetidine **55**, that carbonyl electrophiles reacted to give opposite sense of enantioinduction to alkyl halide electrophiles.

### 4.2.2 Benzaldehyde-trapped azetidines

The absolute configurations of benzylic alcohols (+)-**104b** (86:14 er) and (+)-**104b'** (85:15 er), previously synthesised by asymmetric α-lithiation of *N*-Botc azetidine **101a** in the presence of DIANANE (*S*)-**105** and trapping with benzaldehyde,[93] were also investigated. Following *N*-Botc to Boc conversion by acidic deprotection (HCl in $Et_2O$) (Scheme 153) and analysis (NMR, specific rotation and chiral HPLC), determination could be made by comparison with data recently reported by O'Brien and co-workers.[96] This gave the

absolute configuration assignments of *RR* and *RS* for major-**104b** and minor-**104b'**, respectively.

These assignments reverse those indicated in our earlier work, [93] including the relative configuration which was made by a now apparent erroneous correlation of major alcohol **104b'** with crystallographically determined benzaldehyde-derived adduct from *N*-thiopivaloyl-azetidine. The relative stereochemistry of major-alcohol (*R*,*R*)-**104b**, matches that of the major benzaldehyde adduct formed in α-lithiation—electrophile trapping of *N*-thiopivaloyl-azetidine **55**[61] and *N*-thiopivaloyl-azetidin-3-ol **96**.[91]



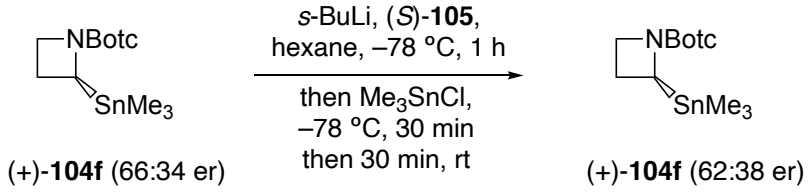

**Scheme 153.** Determination of absolute configuration for benzaldehyde-trapped azetidines (+)-**104b** and (+)-**104b'.**

The newly established absolute configurations for alcohols major-(*R*,*R*)-**104b** and minor-(*R*,*S*)-**104b** were used to re-assign relative and absolute stereochemistry for *p*-chlorobenzaldehyde trapped adducts major-(*R*,*R*)-**104m** and minor-(*R*,*S*)-**104m'**.[94] A high degree of confidence is given for these latter assignments, as one would reasonably

assume similar reactivity patterns between benzaldehyde and *p*-chlorobenzaldehyde with 2-lithio-*N*-Botc-azetidine.

### 4.2.3: Mechanistic studies for acetone trapping

To determine the origins of the electrophile dependent sense of asymmetric induction in the asymmetric α-lithiation—electrophile trapping of *N*-Botc azetidine **101a**, mechanistic investigations on the enantiodetermining step(s) were undertaken. Previous mechanistic studies had given inconclusive results regarding the configurationally stability of diastereomeric anions, with Sn–Li exchange studies on enantioenriched stannane (+)-**104f** (66:34 er) with DIANANE (*S*)-**105** giving trapped products in similar levels of enantioenrichment (Scheme 154).[94]

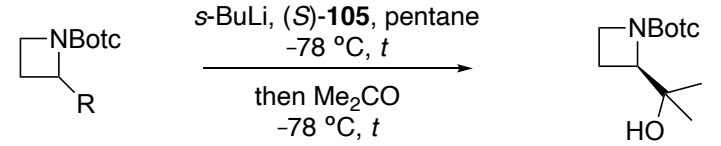



**Scheme 154**. Previous Sn-Li exchange studies for determination of absolute configuration.

However, previous results demonstrating time and temperature dependence of the enantioselectivity (for certain electrophiles, see p 153) indicated configurational instability. The latter was also suggested by an earlier result (see p 44) in which deprotonation at –78 °C before methylation at –98 °C gave identical levels of enantioenrichment to the reaction being run entirely at –98 °C, potentially indicating asymmetric deprotonation is not enantiodetermining.

The configurational stability of 2-lithiated *N*-Botc azetidine complexes ((*R*)-**Li-101a•105** and (*S*)-**Li-101a•105**) with chiral diamine ligand DIANANE (*S*)-**105** was assessed by comparison of α-deprotonation and Sn–Li exchange (Table 11). A control asymmetric deprotonation reaction was performed using previously optimised conditions for lithiation and for

enantioselectivity with acetone as the electrophile, which gave alcohol (*R*)-**104c** in 89:11 er (61% yield, Table 11, entry 1; lit.[94] 47%, 91:9). With the yield and enantioselectivity within experimental error to that previously obtained in the group, a comparative Sn–Li exchange was performed on racemic stannane (±)-**104f** in the presence of (*S*)-**105**. Following incubation of 1 h at –78 °C, trapping with acetone gave alcohol (*R*)-**104c** in 90:10 er (57% yield, Table 11, entry 2). The matching levels of enantioenrichment from these first two experiments show the intermediate organolithium complexes are configurationally unstable at –78 °C and the enantiodetermining step arises after formation of the organolithium. If DTR is occurring (p 149), then altering incubation time and temperature may influence enantioselectivity.[216] Following Sn–Li exchange, decreasing the duration of incubation to just 5 min gave enantioenriched alcohol (*R*)-**104c** in 85:15 er (64% yield, Table 11, entry 3), indicating either equilibration of the lithiated diastereomeric complexes formed from transmetallation is essentially complete after 5 min at –78 °C, or a DKR process (p 152).




**101a** R = H
**104f** R = $SnMe_3$

(*R*)-**104c**

| Entry | 101a or (±)-104f | Metallation time | Trapping time | Yield (*R*)-104c | er | Recovered 101a |
|---|---|---|---|---|---|---|
| 1 | **101a** | 60 min | 60 min | 61% | 89:11 | 21% |
| 2 | **(±)-104f** | 60 min | 60 min | 57% | 90:10 | 30% |
| 3 | **(±)-104f** | 5 min | 60 min | 64% | 85:15 | 25% |
| 4 | **101a** | 1 min | 5 min | 28% | 58:42 | 70% |
| 5 | **(±)-104f** | 60 min (–98 °C) | 60 min (–98 °C) | 41% | 84:26 | 25% |

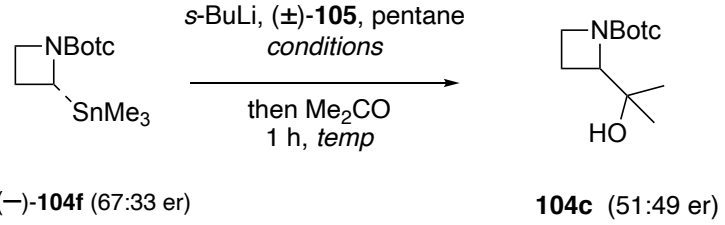
**Table 11**. Comparison of deprotonation with Sn–Li exchange.

Although the enantiodetermining step occurs post-deprotonation, asymmetric deprotonation could still be occurring.[217] However, 1 min lithiation at –78 °C of azetidine **101a** in the presence of DIANANE (*S*)-**105** before acetone trapping gave alcohol (*R*)-**104c** in 58:42 er (28% yield, Table 11, entry 4). Time dependent enantioselectivity through lithiation (entries 1 and 4) suggests DTR. The reduced er after 1 min indicates the lithiated diastereomeric complexes have not fully equilibrated (unlike after 1 h), and there is no favourable initial formation of one organolithium complex by asymmetric deprotonation that is then reduced on equilibration.

Enantioenriched stannane (–)-**104f** (91%, 67:33 er) was prepared via asymmetric α-lithiation—stannylation of *N*-Botc-azetidine in the presence of (*R*)-**105**. It was hoped that by performing a series of Sn–Li exchanges experiments with racemic DIANANE (±)-**105** with different incubation time an estimate of rate of racemisation could be determined. However, transmetallations with stannane (–)-**104f** in the presence of (±)-**105** at –78 °C (Table 12) gave racemic acetone adducts **104c** even after a 1 min incubation time (Table 12, entry 2). The reactions with 1 and 5 min incubation time returned trace unreacted stannane (–)-**104f** which was found to have a similar level of enantioenrichment (66:34 er & 65:35 er) to the starting material.

These results suggest that resolution of stannane (–)-**104f** is not occurring during transmetallation, which could have accounted for the rapid racemisation. Reducing the temperature of Sn–Li exchange to –98 °C for 1 min with enantioenriched stannane (–)-**104f** (67:33 er) in the presence of racemic DIANANE (±)-6 before acetone trapping, resulted in

essentially racemic alcohol **104c** (51:49 er, 39% yield, Table 12, entry 3). Assuming stereoretentive Sn–Li exchange, this demonstrates the high configurational instability of the organolithium complexes even at –98 °C, when the anion is formed by transmetallation.



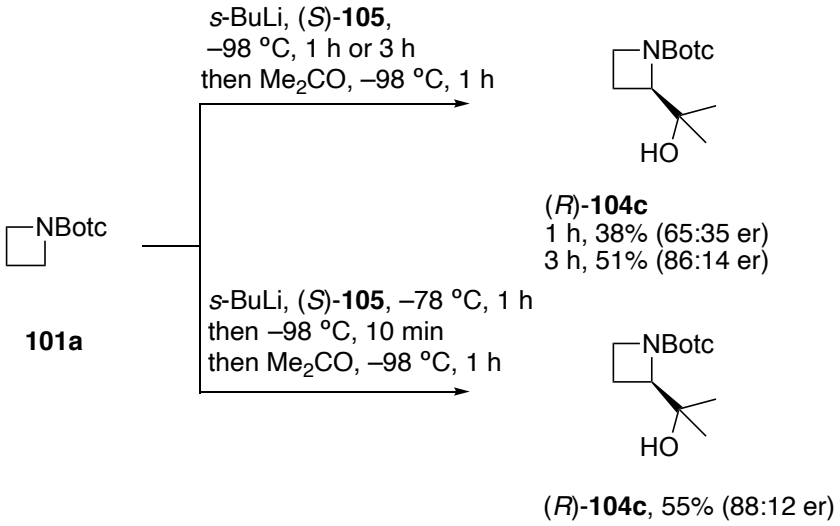

(–)-**104f** (67:33 er) **104c** (51:49 er)

| Entry | Transmetallation time (temp) | Trapping temp | 104c yield (er) | Recovered 104f er |
|---|---|---|---|---|
| 1 | 5 min (–78 °C) | –78 °C | 47% (50:50) | 65:35 |
| 2 | 1 min (–78 °C) | –78 °C | 25% (50:50) | 66:34 |
| 3 | 1 min (–98 °C) | –98 °C | 39% (51:49) | 58:42 |

**Table 12.** Configurational instability from stannane (–)-**104f**

In contrast to anion generation through Sn–Li exchange, partial configurational stability was demonstrated in *deprotonations* with different incubation temperatures and times (Scheme 155). Lithiation of azetidine **101a** in the presence of DIANANE (*S*)-**105** and incubation for 1 h at –98 °C before trapping gave alcohol (*R*)-**104c** with moderate enantioselectivity (65:35 er, 38% yield), showing incomplete equilibration (assuming DTR). However, when deprotonation and incubation were performed at –78 °C for 1 h, then cooling to –98 °C before trapping, this led to alcohol (*R*)-**104c** with good enantioselectivity (88:12 er, 55% yield), indicating that high enantioselectivity can be achieved with trapping at –98 °C. Deprotonation and incubation at –98 °C for 3 h before trapping gave alcohol (*R*)-**104c** in 86:14 er (51% yield); the high er suggests equilibration is almost complete at –98 °C after 3 h. These time dependent enantioselectivities imply DTR, with acetone, and

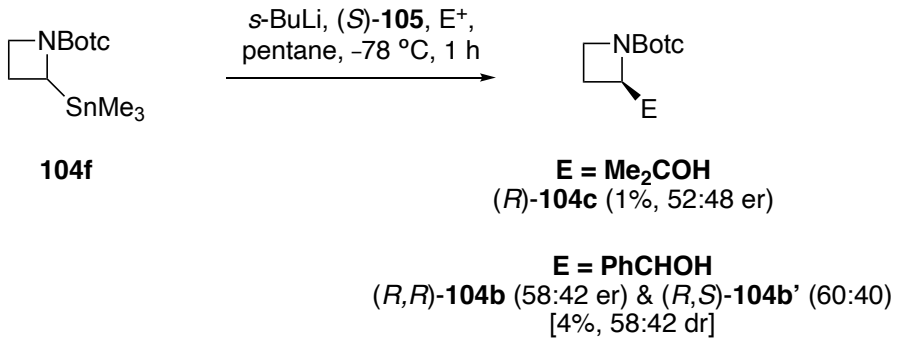
indicate the organolithium complexes possess greater configurational stability at –98 °C when formed through deprotonation.




**Scheme 155.** Temperature and time dependent enantioselectivity.

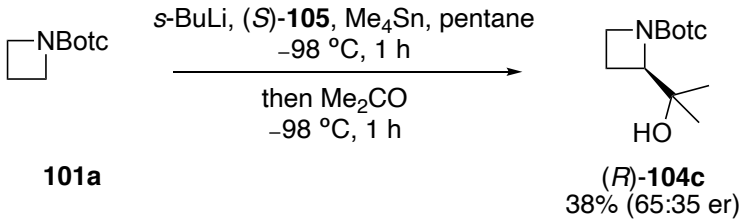
Remarkably, compared to 65:35 er obtained from deprotonation for 1 h at –98 °C (Scheme 155), *increased* enantioselectivities were observed from Sn–Li exchange of stannane (±)-**104f** when carried out under the same conditions in the presence of DIANANE (*S*)-**105**, giving alcohol (*R*)-**104c** in 84:16 er (41% yield, Table 11, entry 5, p 157). At –98 °C, the difference in enantioselectivity from Sn–Li exchange compared to deprotonation can be rationalised by an "unproductive" kinetic deprotonation at –98 °C, with initial formation of a greater proportion of the thermodynamically less stable lithiated complex. In this scenario, deprotonation *at –98 °C* would require a longer incubation period to increase the enantioselectivity, relative to transmetallation. Alternatively, Sn–Li exchange with racemic stannane **104f** could be occurring non-stereospecifically in the presence of DIANANE (*S*)-**105** ligand, although precedent for non-retentive Sn–Li exchange is very limited;[218] no transmetallation occurred without the ligand present. A non-retentive transmetallation could explain the rapid racemisation observed at –98 °C after 1 min for the Sn–Li exchange of enantioenriched stannane (*R*)-**104f** noted earlier (Table 12, p 160).

To test the possibility of a non-stereospecific Sn–Li exchange, transmetallation was performed on stannane (±)-**104f** with DIANANE (*S*)-**105** and *in situ* acetone. This gave trace amounts (1% yield) of essentially racemic alcohol **104c** (52:48 er), indicating that Sn–Li exchange was occurring stereospecifically with some degree of "microscopic"[219] configurational stability with respect to the rate of addition to acetone. An identical experiment was also performed with *in situ* benzaldehyde giving (*R*,*R*)-**104b** (58:42 er) and (*R*,*S*)-**104b'** (60:40 er) in 4% yield (58:42 dr), further supporting a non-enantioselective Sn–Li exchange.



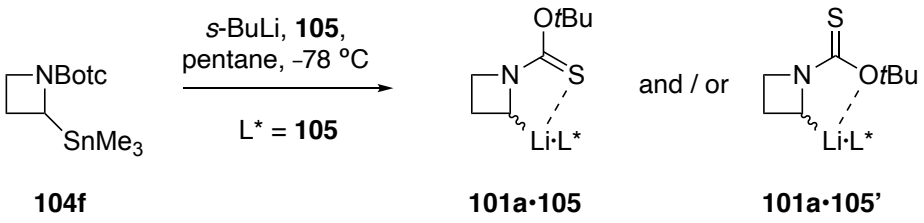

**Scheme 156.** Transmetallation in situ trapping of *N*-Botc stannane **104f.**

To test if the $Me_3SnBu$ generated during Sn-Li exchange could be influencing configurational stability of the anion, deprotonation was carried out in the presence of $Me_4Sn$ (1 equiv) at –98 °C.[220] Following trapping with acetone, alcohol (*R*)-**104c** was formed in 38% and 65:35 er (Scheme 157); this is the same level of enantioselectivity obtained from deprotonation in the absence of $Me_4Sn$ at –98 °C and indicates the presence of $Me_4Sn$ is not the origin of decreased configurational stability from transmetallation.




**Scheme 157.** Lithiation—electrophile trapping in the presence of $Me_4Sn$.

One speculative rationalisation for the difference in enantioselectivity through Sn–Li exchange could be the formation of oxygen-coordinated lithiated complexes from stannane **104f** (Scheme 158). Rotamer interconversion does not occur on the reaction timescale at the low reaction temperatures used.[102] Therefore, transmetallation could lead to the formation of a sulfur-coordinated anion as well as an oxygen-coordinated anion, since the rotamer ratio of stannane **104f** is 2:1 (at rt). In contrast, as lithiation is directed by the thiocarbonyl group,[102] only the sulfur-coordinated lithiated complex would be expected from deprotonation. The possible oxygen-coordinated anion from Sn–Li exchange could lead to a lithiated complex with different configurational stability and altered reactivity, due to the different nature of coordination at Li.




**Scheme 158.** Possible complexes from Sn–Li exchange.

Additionally, transmetallation would result in the formation of different mixed aggregates which could change the nature of the organolithium complexes. The formation of mixed aggregates is confirmed by the isolation of traces of 2,4-disubstituted stannane **108e** (1-7% yield, ~95:5 dr, Figure 11) when performing transmetallation on stannane **104f**, showing that α'-lithiation competes slightly with Sn–Li exchange.

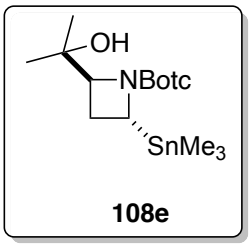
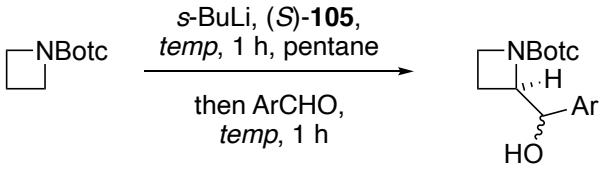


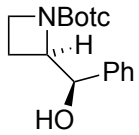
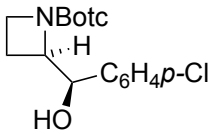

**Figure 11.** 2,4-disubstituted stannane **108e** formed via competing α'-lithiation—electrophile trapping.

Previously, variations in configurational stability depending on the method of carbanion formation have been observed for 2-lithio-*N*-Boc-piperidine,[221] which may arise due to different Li ligation/aggregation states formed by deprotonation or transmetallation. The authors did not investigate the origins further; however, rotamers in the starting 2-tributylstannyl-*N*-Boc-piperidine may facilitate formation of different carbanionic species.

Further support for a partially configurationally stable anion forming from asymmetric α-lithiation—electrophile trapping had previously been obtained in the group.[94] Reduced enantioselectivities were observed for lithiation—electrophile trapping of *N*-Botc-azetidine **101a** with aromatic aldehydes after 1 h at –98 °C compared to at –78 °C (Table 12). If DKR was occurring an improvement in enantioselectivity would be expected at lower temperatures. Aromatic aldehydes are fast trapping electrophiles[118] and therefore would be predicted to trap the lithiated complexes at a rate faster than epimerisation. Reduced enantioselectivities at –98 °C suggest that the lithiated complexes have not fully equilibrated after 1 h (as seen with acetone), again supporting the idea that the lithiated complexes are partially configurationally stable at –98 °C.




**101a** **104b or 104m**

| Entry[a] | Product (major diastereomer shown) | Lithiation temp | $E^+$ trapping temp | % Yield (dr) | er[b] | % SM |
|---|---|---|---|---|---|---|
| 1 | | –78 °C | –78 °C | 88 (60:40) | 86:15 | 7 |
| 2 |  **104b** | –98 °C | –98 °C | 51 (71:29) | 65:35 | 49 |
| 3 | | –78 °C | –78 °C | 64 (69:31) | 80:20 | 25 |
| 4 |  **104m** | –98 °C | –98 °C | 14 (64:36) | 69:31 | 86 |

[a] ***Work performed by Claire Mortimer.***[94]

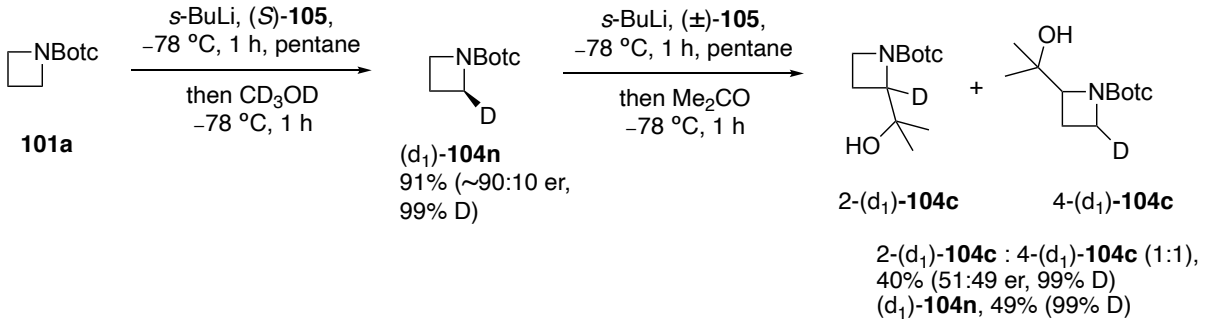
[b] Er of major diastereomer (er of minor diastereomer er identical for entries 1 & 3, 60:40 and 65:35 for entries 2 & 4, respectively)

**Table 12.** Partial configurational stability of α-Li at –98 °C when trapping with aromatic aldehydes.[94]

### 4.2.4 Configurational stability deuterium studies

An enantioenriched azetidine ($d_1$)-**104n** was synthesised following lithiation of azetidine **101a** at −78 °C for 1 h, followed by trapping with $CD_3OD$. This gave monodeuterated azetidine ($d_1$)-**104n** in 91% yield and 99% D incorporation as determined by $^1H$ NMR spectroscopy (Scheme 159). Under the assumption that $CD_3OD$ traps very rapidly (i.e. similar to acetone) and with retention,[222] we predicted that the enantioenrichment of monodeuterated ($d_1$)-**104n** azetidine would be approximately 90:10 er. Although enantioenrichment could not be determined following conversion to a Mosher amide, a non-zero specific rotation value was observed for monodeuterated azetidine ($d_1$)-**104n**

($[\alpha]_D^{25}$ –0.35 *c* 10.9). Enantioenriched monodeuterated azetidine ($d_1$)-**104n** then underwent lithiation in pentane with DIANANE (±)-**105** followed by trapping with acetone. This gave essentially racemic deuterated alcohol ($d_1$)-**104c** in 40% yield (51:49 er, 99% D) and recovered monodeuterated azetidine ($d_1$)-**104n** in 49% yield (99% D). The high levels of deuteration in the recovered starting material ($d_1$)-**104n** and product ($d_1$)-**104c** suggest that a high kinetic isotope effect is occurring, effectively preventing lithio-dedeuteration.[223] The fact that alcohol ($d_1$)-**104c** is essentially racemic suggest that the organolithium complexes are configurationally unstable and have fully racemised after 1 h at –78 °C.

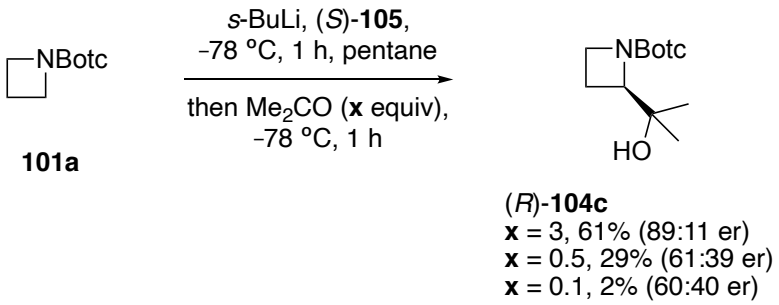



**Scheme 159.** Asymmetric deuteration followed by racemic lithiation—electrophile trapping.

### 4.2.5 Hoffmann tests with acetone

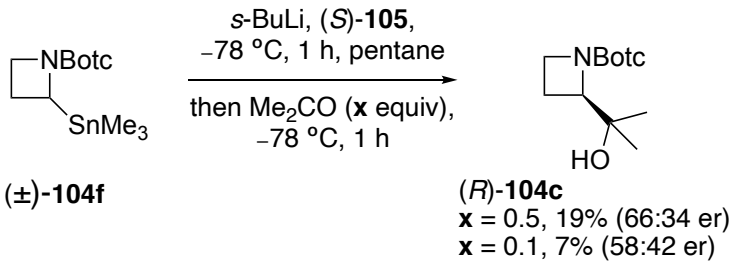
Experiments to probe whether the enantiodetermining process with acetone operates through DTR or DKR were carried out using a "poor man's Hoffmann test."[208] This test involves reacting the lithiated complexes with an excess and with a sub-stoichiometric amount of electrophile. If the reaction proceeds via DKR then enantioselectivity will be independent of conversion. However, for a DTR mechanism if the two diastereomeric complexes react with the electrophile at different rates then variation in enantioselectivity will be observed.

Azetidine **101a** was deprotonated (1 h, –78 °C) with DIANANE (*S*)-**105** and reacted with excess and sub-stoichiometric amounts of acetone to give alcohol (*R*)-**104c**, giving differing levels of enantioselectivity (Scheme 160). Decreased enantioselectivity for reactions with substoichiometric acetone suggests that the minor lithiated complex reacts marginally faster than the major complex[217] ((*R*)-**Li-101a•105** faster than (*S*)-**Li-101a•105**, assuming retentive substitution, $S_E2$ret, with acetone[224]). The difference in enantioselectivity shows epimerisation is not occurring on the timescale of the reaction and confirms that trapping with acetone proceeds via DTR at –78 °C.




**Scheme 160.** "Poor man's Hoffmann test" with acetone trapping

A "poor man's Hoffmann test" was also undertaken on racemic stannane (±)-**104f** in the presence of DIANANE (*S*)-**105** to examine any potential differences between the intermediate organolithium complexes formed by transmetallation compared to deprotonation. Sn–Li exchange on stannane (±)-**104f**, followed by trapping with substoichiometric amounts of acetone (0.5 equiv and 0.1 equiv) gave alcohol (*R*)-**104c** in 19% (66:34 er) and 7% (58:42 er), respectively (Scheme 161). These results show the enantiodetermining step for reaction of the anion generated by Sn–Li exchange occurs by DTR and the 'minor' organolithium complex is the faster reacting species, i.e., like deprotonation.



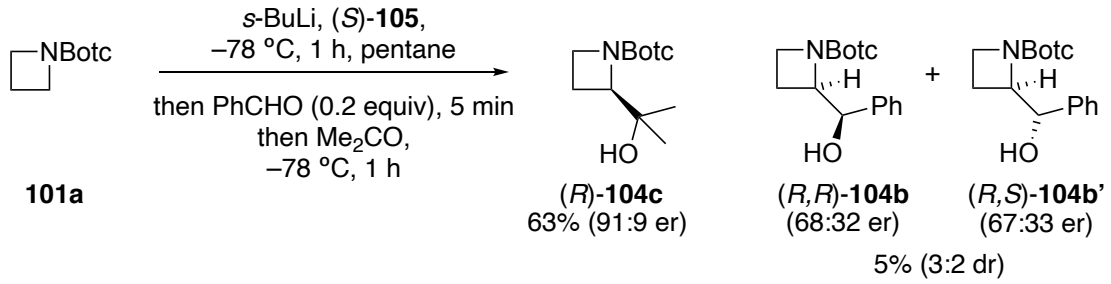

(±)-**104f**

(*R*)-**104c**
**x** = 0.5, 19% (66:34 er)
**x** = 0.1, 7% (58:42 er)

**Scheme 161.** "Poor man's Hoffmann test" with stannane (±)-**104f.**

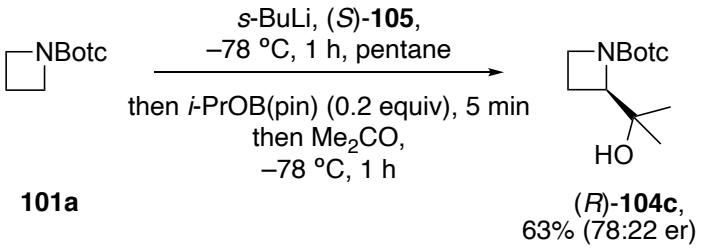
A sacrificial electrophile technique has been previously used to improve enantioselectivity in a reaction where DTR operates.[225] This works by introducing substoichiometric amounts of an electrophile which reacts faster with the minor diastereomeric organolithium complex, altering the diastereomeric ratio between complexes before introducing a second electrophile in excess.

Three sacrificial electrophiles were tested (MeI, benzaldehyde and *i*-PrOB(pin)); although none were able to improve enantioselectivity, some interesting results were obtained. When using benzaldehyde as a sacrificial electrophile in sub-stoichiometric amounts (0.2 equiv, Scheme 162), followed by acetone in excess, a very minor increase in enantioselectivity was observed for alcohol (*R*)-**104c**; however, the increase was within experimental error. Interestingly, a reduction in er seen for both diastereomers of the benzaldehyde-trapped adducts (*R*,*R*)-**104b** (68:32 er) and (*R*,*S*)-**104b'** (67:33 er) compared to when the reaction was performed with only benzaldehyde in excess (see p 165), suggests that the reaction proceeds via DTR with the minor diastereomeric complex being the faster reacting intermediate.[217]



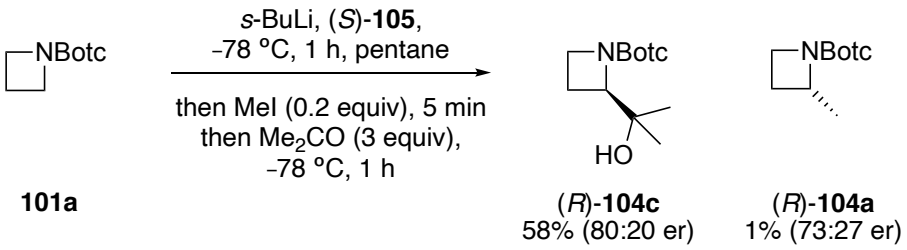

**Scheme 212.** Benzaldehyde as a sacrificial electrophile.

When *i*-PrOB(pin) was used as a sacrificial electrophile it was planned that the small traces of boronic ester **104g** formed during the reaction could easily be removed from the reaction crude using column chromatography (see section 3.2.1). This could potentially enable this method to be applicable with a range of electrophiles, as possible issues of product separation with sacrificial electrophile side products would be avoided. It was assumed that *i*-PrOB(pin) trapped in a similar fashion as acetone (i.e., DTR), based on the similar levels (and sense) of enantioselectivity observed for the two electrophiles under identical conditions (*cf.* (*S*)-**104g** (92:8) & (*R*)-**104g** (91:9)). Additionally, *i*-PrOB(pin) is an electrophile with precedent to trapping in a retentive manner[158a] (similar to acetone). However, using *i*-PrOB(pin) as a sacrificial electrophile (0.2 equiv) followed by acetone trapping, led to alcohol (*R*)-**104c** in reduced enantioselectivity (78:22 er, 44% yield, Scheme 163). The lower er suggests either a preference of *i*-PrOB(pin) to react with the major diastereomeric organolithium complex, or a potential non-beneficial influence on the diastereomeric ratio by the presence of the lithium alkoxide salts (such as *i*-PrOLi) formed during trapping with the sacrificial electrophile.




**Scheme 163.** Sacrificial *i*-PrOB(pin) reaction.

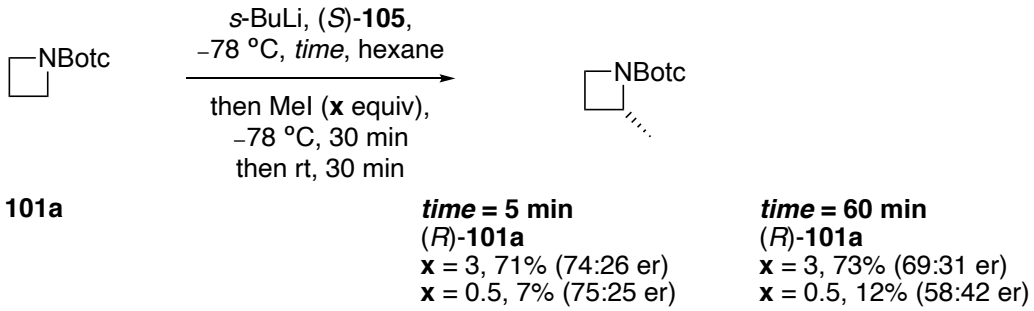
Using MeI (0.2 equiv) as a sacrificial electrophile failed to improve the enantioselectivity for alcohol (*R*)-**104c** (80:20 er, 58%, Scheme 164). However, the enantioselectivity for 2-methyl-azetidine (*S*)-**104a** (73:27 er) was similar to when alkylation was performed using excess MeI (79:21 er, Table 1, p 44). This potentially supports a DKR process with this electrophile—although a "poor man's Hoffmann test" cannot distinguish between the two asymmetric substitution mechanisms (DTR and DKR) if the enantioselectivities are the same, as reaction rates could be approximately equal ($k_{SR} \approx k_{SS}$). Nevertheless, the extent of enantioenrichment obtained with MeI compared with the assumed diastereomeric ratio (~90:10) of organolithium complexes further supports a DKR process. Alkyl halides are slow trapping electrophiles,[118,226] which could allow the rate of epimerisation between diastereomeric complexes to compete with the rate of electrophile trapping.




**Scheme 164.** Sacrificial MeI reaction.

Previous attempts at performing a "poor man's Hoffmann test" with MeI as an electrophile were inconclusive with two attempts giving varying results (Scheme 165).[94] These attempts included a warming phase to rt during quenching; this was potentially problematic as

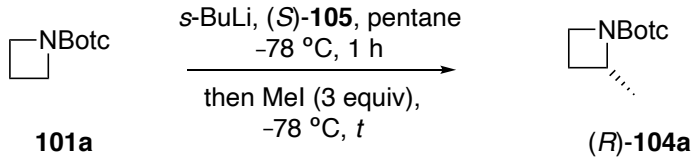
previous optimisation studies performed on the asymmetric methylation with a warming phase to rt generally gave more varied levels of enantioselectivity. [94]




**Scheme 165.** Previous inconclusive "poor man's Hoffmann test" tests.[94]

To remove any doubt about these results, a "poor man's Hoffmann test" was carried out on azetidine **101a** at –78 °C with MeI as the electrophile, in which aliquots of the reaction mixture were quenched at different times. By measuring the product to starting material ratio (**101a**:**104a**) and the er of product from these different time intervals, we could determine if enantioselectivity was conversion dependent; this is essentially the same as a "poor man's Hoffmann test" (Scheme 166).[220]

It was found with MeI as the electrophile that enantioselectivity is independent of reaction conversion, indicating a DKR mechanism is occurring. Further supporting evidence for DKR with MeI is the improved levels of enantioenrichment at –98 °C after 1 h (91:9 er),[93] in contrast to electrophiles that react via DTR which show decreased levels of enantioselectivity under the same conditions (see p 165).



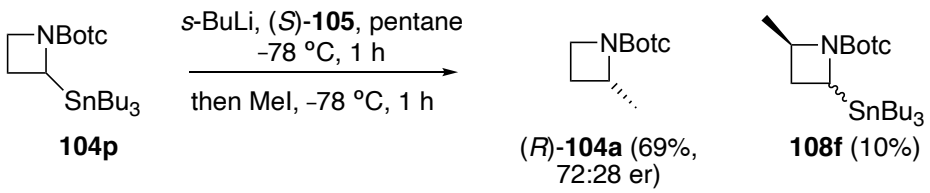

**101a** (*R*)-**104a**

| *t* | **104a**:**101a** | er |
|---|---|---|
| 5 min | 55:45 | 77:23 |
| 10 min | 64:36 | 78:22 |
| 30 min | 72:28 | 79:21 |
| 60 min | 74:26 | 77:23 |
| 120 min | 76:24 | 77:23 |

**Scheme 166.** Poor man's Hoffmann test with MeI trapping.

In reaction in which a DKR occurs, the method used to form the organolithium complexes should not affect enantioselectivity since epimerisation of the carbanion occurs at a faster rate to trapping with the electrophile. A series of Sn–Li exchange experiments were performed to determine whether or not similar levels of enantioselectivity could be achieved via this approach.

Performing a transmetallation on tributyl stannane **104p** in the presence of DIANANE (*S*)-**105**, at –78 °C gave 2-methyl-azetidine (*R*)-**104a** in 72:28 er (69% yield) (Scheme 167). This represents a level of enantioselectivity similar to what was achieved by asymmetric α-lithiation—methylation, further supporting a DKR mechanism. Significant amounts of 2-stannyl,4-methyl-azetidine **108f** in 10% yield was formed, showing that competing lithiation is occurring, likely for the rotamer in which the thiocarbonyl group is facing away from the stannyl substituent. (see p 39).




**104p** (*R*)-**104a** (69%, 72:28 er) **108f** (10%)

**Scheme 167.** Sn—Li exchange and methylation of stannane **104p.**

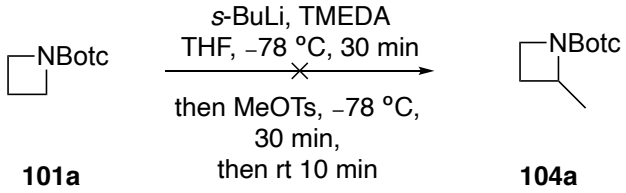
An attempt at performing Sn–Li exchange on stannane **104p** at –98 °C in the presence of DIANANE (*S*)-**105**, followed by methylation gave 2-methyl-azetidine (*R*)-**104a** in 81:19 er (47% yield); similarly, 2-stannyl,4-methyl-azetidine **108f** was formed in 8% yield. Although the enantioselectivity is slightly reduced to the levels previously reported, they are within experimental error of the results obtained in my hands (see p 44). The reduced levels of enantioselectivity could possibly be a further example of discrepancies observed between deprotonation and Sn–Li exchange.

It is interesting that the sense of asymmetric induction with MeI trapping is opposite to electrophiles such as acetone, benzaldehyde and *i*-PrOB(pin). This maybe a consequence of a difference in the mode of trapping (i.e., $S_E2ret$ Vs $S_E2inv$);[208] indeed, alkyl halides are known to trap with inversion at the carbanion in preference to retention.[217] However, this is predominantly observed in the trapping of benzylic/allylic carbanions with very little precedent for such a phenomenon occurring on non-mesomerically dipole-stabilised carbanions.[224] DFT studies have calculated a large degree of conjugation between N-lone pair and thiocarbonyl π-system for *N*-Botc-azetidine **101a**/*N*-thiopivaloyl-azetidine **55**.[102] This could result in more benzylic/allylic like behaviour in the carbanion, which may facilitate inversion with alkyl halides. The opposite sense of asymmetric induction (to acetone and benzaldehyde) was also observed by O'Brien in the asymmetric lithiation—methylation of *N*-thiopivaloyl-azetidine **55**.[96]

An alternative explanation for the opposite sense observed for MeI could be simply that the minor-diastereomeric organolithium is the more reactive complex and reacts at a faster rate via a retentive trapping. This would be in agreement with "poor man's Hoffmann tests"

with acetone, which showed that the minor diastereomeric complex was the faster reacting species.

Controlling the sense of asymmetric induction in the alkylation of carbanions can be achieved by changing the nucleofuge of the electrophile. For example, the use of alkyl tosylates has been demonstrated to give alkylated products with the opposite sense of asymmetric induction to when the same reaction is performed with alkyl halides.[227] This is believed to be due to the co-ordinating ability of the electrophile, resulting in the approach of the electrophile to the same side as the $Li^+$ cation. An attempt at α-lithiation—electrophile trapping using MeOTs with TMEDA in THF however resulted in only recovered starting material **101a** 19% (Scheme 168). Due to the failed reaction on the racemic system, the asymmetric variant was not attempted.

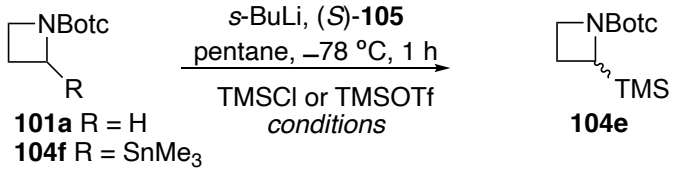



**Scheme 168.** Attempted α-lithiation—electrophile trapping of *N*-Botc azetidine **101a** with methyl tosylate.

### 4.2.6 Asymmetric silylation of *N*-Botc azetidine

Use of an internal electrophile such as TMSCl has been previously used to ascertain the degree of an asymmetric deprotonation.[217] These experiments are performed with TMSCl *in situ*, which in theory allows for rapid trapping of the carbanion as it is being formed. This is possible since TMSCl is relatively slow reacting with *s*-BuLi, which allows deprotonation to occur preferentially. This allows an excess of TMSCl to be present in the reaction mixture to quench the organolithium complexes at a rate faster than equilibration.

Two parallel '*in situ*' trapping experiments were performed at –78 °C using *N*-Botc azetidine **101a** and stannane (±)-**104f** (Table 13), which gave silane (–)-**104e** in identical enantioenrichment (70:30 er, Table 13, entries 1 and 2). These results failed to demonstrate asymmetric deprotonation; however, they do show the level of asymmetric induction with this electrophile is independent of the method of anion generation (an indication of DKR).[228] TMSCl is a slower reacting electrophile[118,226] and a possible explanation for the matching enantioselectivity could therefore be the result of DKR. If that is the case, enantioselectivity will be independent of incubation time of the organolithium intermediates. A deprotonation reaction with a 1 h incubation period at –78 °C before external addition of TMSCl gave silane (–)-**104e** in 52% yield and essentially the same enantioselectivity (68:32 er, Table 13, entry 3). A "poor man's Hoffmann test" was performed with 0.5 equiv of TMSCl, giving (–)-**104e** in 69:31 er (34% yield, Table 13, entry 4), providing further evidence that DKR is occurring.



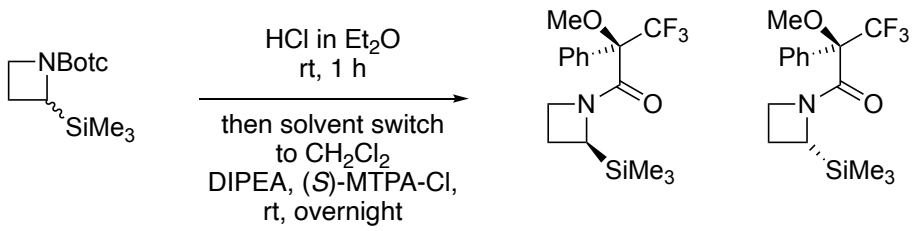

| Entry | Substrate 101a or 104f | Electrophile (equiv) | Incubation time | Yield 12 | er (*R*:*S*) |
|---|---|---|---|---|---|
| 1 | **101a** | TMSCl (10) | *In situ* | 29% | 70:30 |
| 2 | **104f** | TMSCl (10) | *In situ* | 39% | 70:30 |
| 3 | **101a** | TMSCl (3) | 1 h | 52% | 68:32 |
| 4 | **101a** | TMSCl (0.5) | 1 h | 34% | 69:31 |
| 5 | **101a** | TMSOTf (3) | 1 h | 28% | 42:58 |

**Table 13.** Asymmetric silylation of *N*-Botc azetidine **101a**

Interestingly, the sign of specific rotation for silane (–)-**104e** was the same for the enantioenriched 2-methyl-azetidine (*R*)-**101a** and opposite to that of those adducts formed by DTR (using acetone, benzaldehyde). It was therefore predicted that the sense of asymmetric induction was the same as that observed in the formation of 2-methyl-azetidine (*R*)-**104a** (this was confirmed following Mosher amide analysis, see next section). It was speculated that by using a more reactive silylating electrophile, the sense of asymmetric induction could be inverted, as it would more likely proceed by DTR (different diastereoselectivities between TMSCl and TMSOTf have been obtained before).[229] Pleasingly, using TMSOTf as a more reactive silylating agent[230] did result in a change in the sense of asymmetric induction, giving (+)-**104e** in 58:42 er (28% yield, Table 13, entry 5).

### 4.2.7 Determination of absolute configurations by conversion to Mosher amides

The absolute configuration of silane (–)-**104e** was determined by conversion to the Mosher amide and analysis of the $^{1}$H NMR spectra. Transformation of silane (±)-**104e** to the diastereomeric chromatographically separable Mosher amides (*R,S*)-**253a** and (*R*,*R*)-**253a'** was achieved by acidic deprotection of the *N*-Botc group,[93] followed by amide formation with (*S*)-MPTA-Cl (52%, 55:45 dr, Scheme 169).




| | (*R*,*S*)-**253a** | : | (*R*,*R*)-**253a'** |
|---|---|---|---|
| (±)-**104e** | 55 | : | 45 |
| (–)-**104e** (69:31 er) | 26 | : | 74 |

**Scheme 169.** Conversion of silane **104e** to Mosher amides (*R*,*S*)-**253a** and (*R*,*R*)-**253a'.**

For all the Mosher amides analysed, only single rotamers were observed. The rotamers for the two silyl amides (*R,S*)-**253a** and (*R*,*R*)-**253a'** were assigned *cis* from 2D-NOSEY cross-peaks, both between methoxy and a deshielded H of $NCH_2$, and between the shielded H of $NCH_2$ and the phenyl group (Figure 12-15); this is consistent with the previously established rotamer preference for an analogous 2-trimethylsilyl-*N*-thiopivaloyl-azetidine.[102] These cross-peaks allow assignment of the $NCH_2$ protons in both diastereomers. With the rotameric form established, the relative stereochemistry of the silyl group could then be assigned from NOE cross-peaks between either the methoxy or Ph group of the Mosher amide, depending on the diastereomer. Additional cross-peaks between the $SiMe_3$ group and the ring protons were used to establish relative configuration of the remaining ring protons (Figure 12-15). These assignments were supported by vicinal proton-proton coupling constants around the ring: azetidines typically show larger values for mutually *cis* protons (~9-11 Hz) compared to *trans* protons (~5-7 Hz).[231]

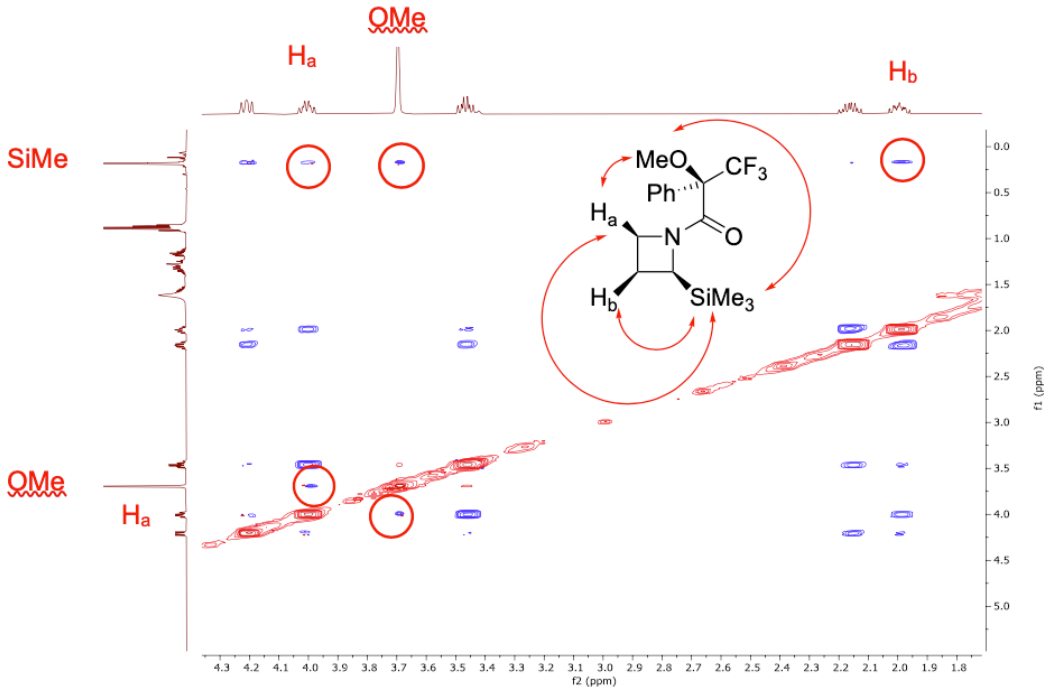



**Figure 12.** NOESY spectrum of minor diastereomer silane (*R*,*S*)-**253a.**

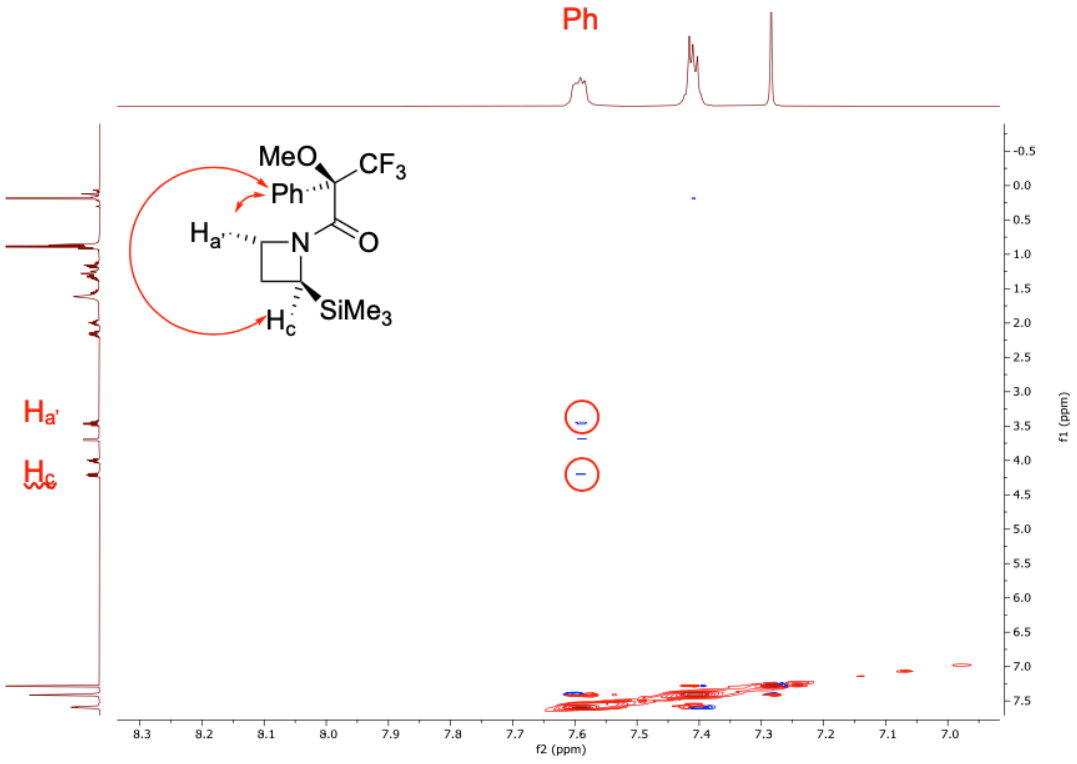



**Figure 13.** NOESY spectrum of minor diastereomer (aromatic region) silane (*R*,*S*)-**253a.**

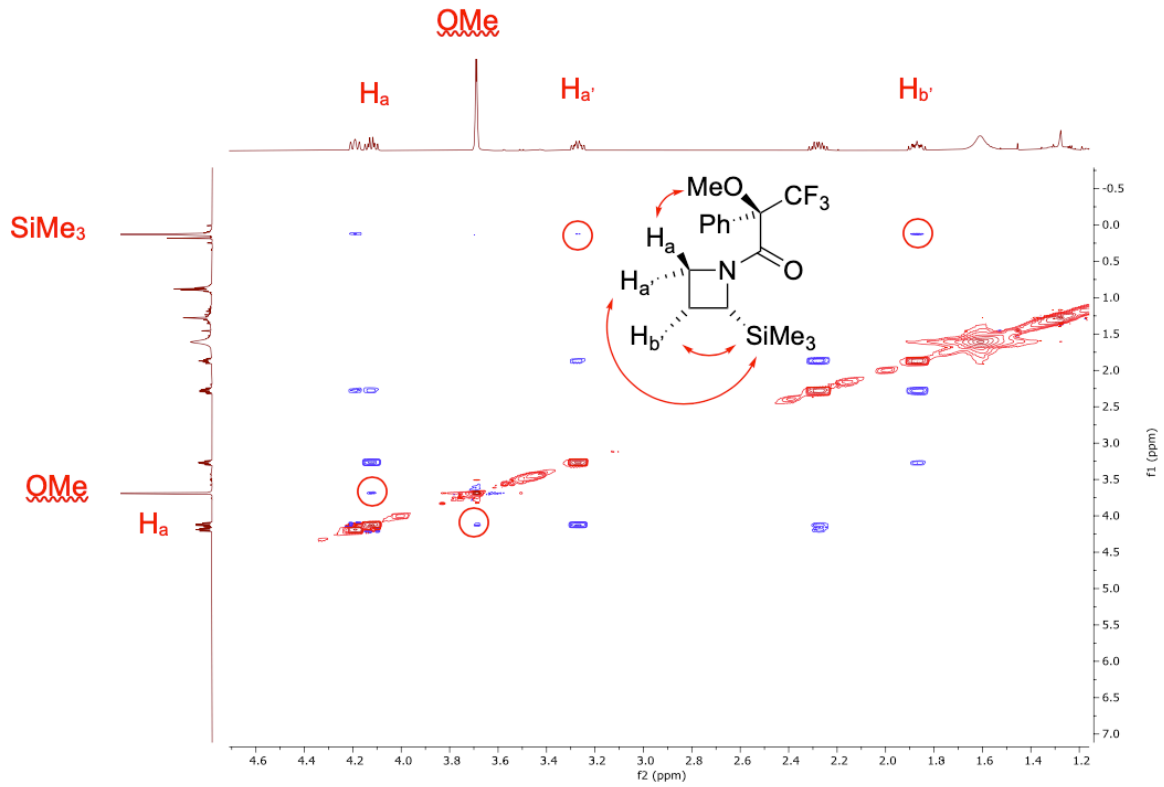



**Figure 14.** NOESY spectrum of major diastereomer silane (*R*,*R*)-**253a'.**

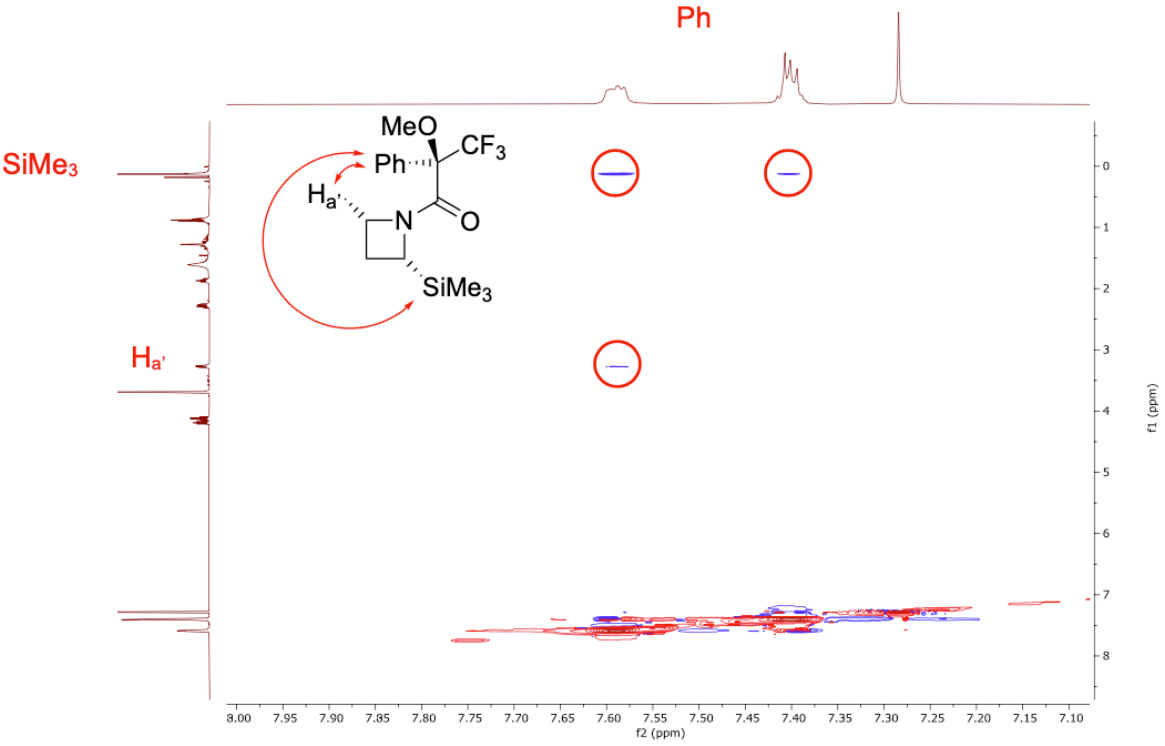



**Figure 15.** NOESY spectrum of major diastereomer (aromatic region) silane (*R*,*R*)-**253a'.**

The silane diastereomers possessed distinctive chemical shift patterns, with the $NCH_2$ and NCHC$H_2$ protons showing significant Δδ ppm values (Figure 16, Table 14). The lack of any significant Δδ ppm for the NCH proton (Table 14, entry 5) further supports the *cis* rotamer assignment, with the C=O group pointing towards the substituted side of the azetidine ring.[232] The chemical shift patterns for the silanes indicate the phenyl group has a shielding effect on the $NCH_2$ and NCHC$H_2$ protons which occupy the same space below the ring ($H_{a'}$ & $H_{b'}$, as drawn). Additionally, the trimethylsilyl group influences chemical shift values; mutually *cis* protons being shielded relative to those that are *anti*. The latter is particularly apparent for $H_b$, which for (*R*,*S*)-**253a** is more shielded than the (*R*,*R*)-**253a'** $H_b$ proton (Table 14 entry 3). Importantly, these chemical shift patterns are observable with other substituted azetidines and therefore allow for assignment of relative/absolute configurations of other similarly substituted azetidines, following conversion to Mosher amides.

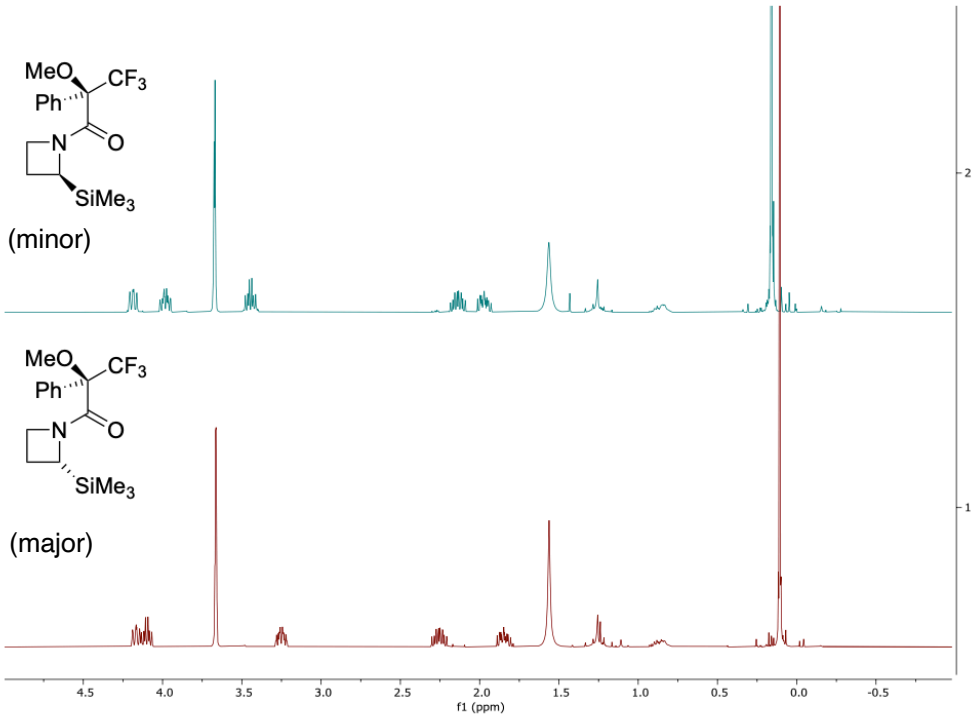
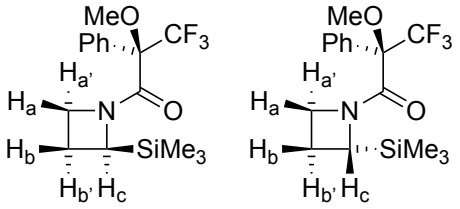



**Figure 16.** Overlapped $^1H$ NMR spectra of Mosher silanes (*R*,*S*)-**253a** and (*R*,*R*)-**253a'.**




(*R*,*S*)-**253a** (*R*,*R*)-**253a'**

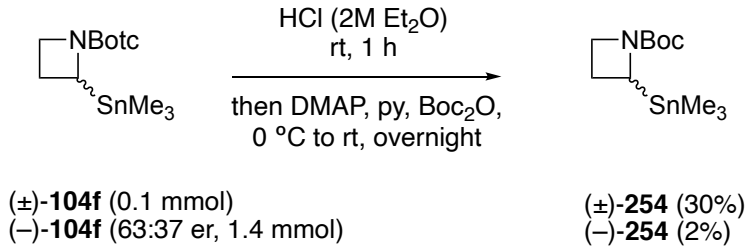
| Entry | Proton | (*R*,*S*)-253a | (*R*,*R*)-253a' | $\Delta\delta_{(\delta S-\ \delta R)}$ |
|---|---|---|---|---|
| 1 | $H_a$ | 3.98 | 4.10 | -0.12 |
| 2 | $H_{a'}$ | 3.44 | 3.25 | 0.19 |
| 3 | $H_b$ | 1.97 | 2.25 | -0.28 |
| 4 | $H_{b'}$ | 2.14 | 1.85 | 0.29 |
| 5 | $H_c$ | 4.18 | 4.17 | 0.01 |
| 6 | $SiMe_3$ | 0.16 | 0.11 | 0.05 |

**Table 14.** Chemical shifts differences between (*R*,*S*)-**253a** and (*R*,*R*)-**253a'** silanes.

Having determined the relative and absolute configuration of the two diastereomeric Mosher silanes (*R*,*S*)-**253a** and (*R*,*R*)-**253a'**, enantioenriched silane (–)-**104e** (69:31 er) was converted to Mosher silanes following the same deprotection/amide formation sequence (41%, 88:12 dr (isolated), Scheme 169). $^{19}F$ NMR analysis of the crude reaction mixture indicated a 74:26 dr, by integration of the corresponding $CF_3$ peaks, with (*R,R*)-**253a'** being the major diastereomer; this result enabled assignment of the absolute configuration of silane (–)-**104e** as *R* (confirming the same sense of asymmetric induction as MeI).

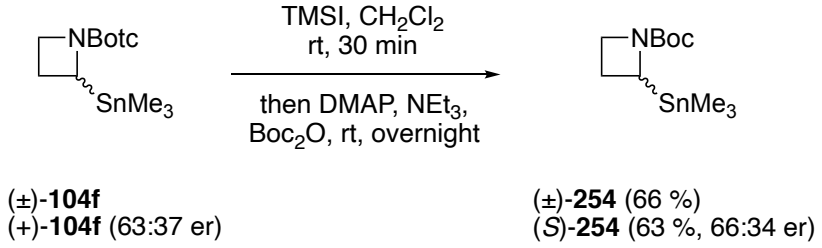
Assignment of absolute configuration for the enantioenriched stannane (+)-**104f** was determined following conversion to the Mosher amide. However, the Mosher amide was not immediately accessible, as *N*-Botc stannane **104f** could not be easily deprotected under acidic conditions. An initial test *N*-Botc to *N*-Boc conversion was attempted on racemic stannane **104f** (0.1 mmol scale), resulting in 30% yield of the desired *N*-Boc stannane **254**, with significant protodestannylation occurring. However, performing the reaction on

enantioenriched stannane (–)-**104f** on an increased scale (1.4 mmol) resulted in only trace amounts (2%) of *N*-Boc stannane **254** (Scheme 170).




**Scheme 170.** Stannane **104f** protecting group interconversion to *N*-Boc stannane **254** under acidic conditions.

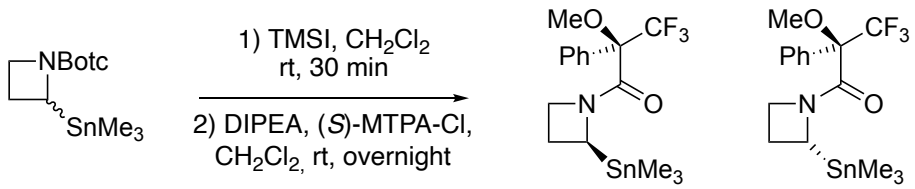
Thermal deprotection in EtOH was also attempted,[93] however that only returned unreacted stannane **104f** (88% RSM). Therefore, in order to determine the absolute configuration of enantioenriched stannane **104f**, a new method for *N*-Botc deprotection was developed. Gawley and co-workers previously described *N*-Boc deprotection of 2-stannyl-pyrrolidines using TMSI.[233] Application of this procedure to *N*-Botc stannane **104f** allowed clean removal of the directing group; subsequent trapping with $Boc_2O$ gave *N*-Boc stannane **254** in moderate yield 66% (Scheme 171). Similarly, enantioenriched stannane (+)-**104f** (63:37 er) gave enantioenriched *N*-Boc stannane (+)-**254** in 66:34 er (63% yield). This demonstrates a new "milder" method for *N*-Botc deprotection and serves as a viable alternative when acid labile substituents are present.




**Scheme 171.** Synthesis of N-Boc stannane 254 via deprotection of stannane **254** using TMSI.

Stannane **104f** was converted to the corresponding stannyl Mosher amides (*R,S*)-**253b** and (*R,R*)-**253b'** following the modified deprotection (TMSI), with subsequent amide formation

using (*S*)-MPTA-Cl (28%, 52:48 dr (isolated), Scheme 172). The two diastereomers were formed in a 1:1 ratio, determined by $^{19}F$ NMR analysis of the crude. Following separation by column chromatography, the diastereomers were analysed by $^{1}H$ NMR spectroscopy and their absolute and relative configurations assigned by analogy to the corresponding silyl Mosher amides (*R,S*)-**253a** and (*R,R*)-**253a**, due to the observation of similar chemical shift patterns (Figure 17 and Table 15, *cf.* Figure 16 and Table 14).




| | (*R,S*)-**253b** | : | (*R,R*)-**253b'** |
|---|---|---|---|
| (±)-**104f** | 50 | : | 50 |
| (+)-**104f** (62:38 er) | 59 | : | 41 |

**Scheme 172.** Conversion of stannane 10 to Mosher amides (*R,S*)-**253b** and (*R,R*)-**253b'.**

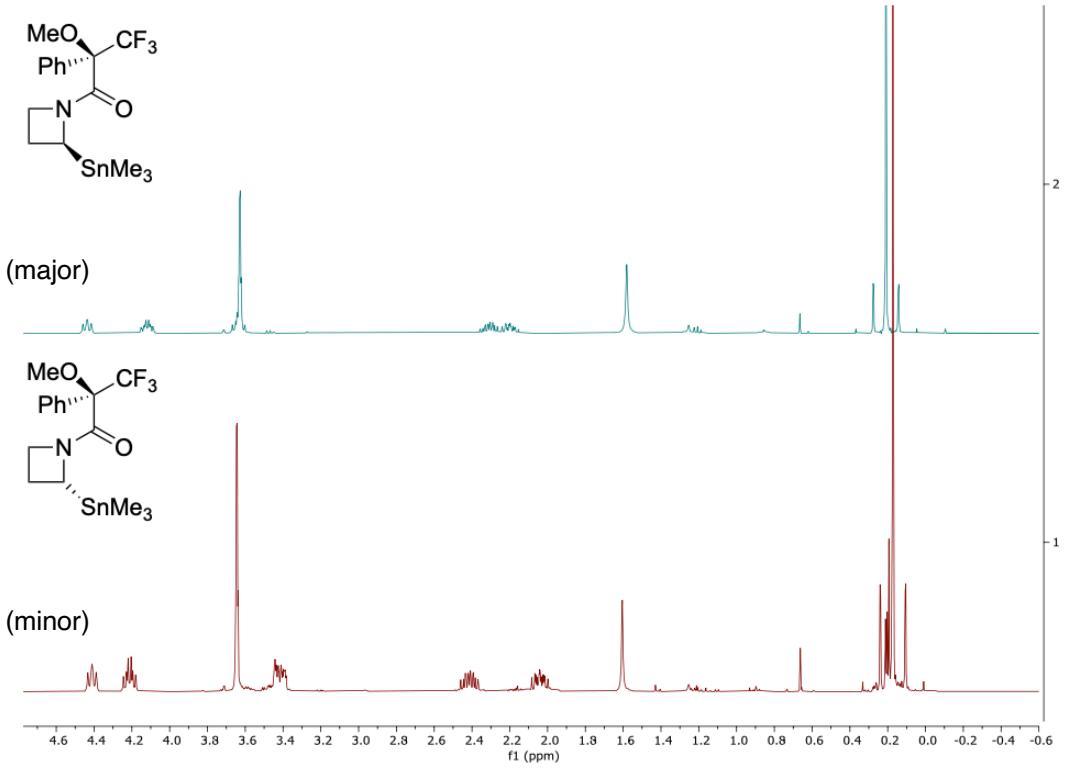
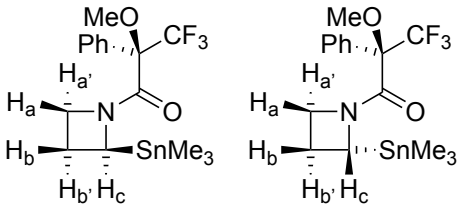



**Figure 17.** Overlapped $^{1}H$ NMR spectra of Mosher stannanes (*R,S*)-**253b** and (*R,R*)-**253b'.**




(*R*,*S*)-**253b** (*R*,*R*)-**253b'**

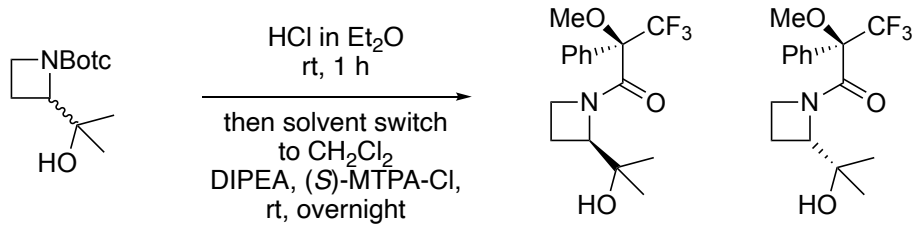
| Entry | Proton | (*R*,*S*)-253b | (*R*,*R*)-253b' | $\Delta\delta_{(\delta S - \delta R)}$ |
|---|---|---|---|---|
| 1 | $H_a$ | 4.12 | 4.21 | -0.09 |
| 2 | $H_{a'}$ | 3.64[a] | 3.43[a] | 0.21 |
| 3 | $H_b$ | 2.20 | 2.41 | -0.21 |
| 4 | $H_{b'}$ | 2.31 | 2.04 | 0.27 |
| 5 | $H_c$ | 4.44[a] | 4.41 | 0.03 |
| 6 | $SnMe_3$ | 0.21 | 0.17 | 0.04 |

[a] For multiplets, peak position was determined as the mean of the multiplet range.
**Table 15.** Chemical shifts differences between (*R*,*S*)-**253b** and (*R*,*R*)-**253b'** stannanes.

Enantioenriched stannane (+)-**104f** (62:38 er) was converted to the corresponding Mosher amides following the previously developed route (51%, 54:46 dr (isolated), Scheme 172). Analysis of the crude by $^{19}F$ NMR spectrum gave a 59:41 dr, in good agreement with the enantioenrichment of the starting material. The major $^{19}F$ NMR peak corresponded to stannane (*R*,*S*)-**253b**, which was used to assign the absolute configuration of stannane (+)-**104f** as *S*.

Additional confirmation of accurate Mosher amide analysis for the assignment of absolute configuration was obtained by converting alcohol (±)-**104c**, into the corresponding hydroxy Mosher amides (*R,S*)-**253c** and (*R,R*)-**253c'** (Scheme 173). With racemic alcohol (±)-**104c** a 1:1 mixture of diastereomers was formed (confirmed by $^{19}F$ NMR analysis of the crude). Separation of the diastereomers and $^{1}H$ NMR analysis revealed similar chemical shift patterns (Figure 18, Table 16), comparable to those previously observed for the silyl and stannyl Mosher amides. Enantioenriched alcohol (*R*)-**104c** (80:20 er) of known absolute configuration was subsequently converted into hydroxy Mosher amides (*R,S*)-**253c** and

(*R,R*)-**253c'** ($^{19}$F NMR analysis of crude gave 82:18 dr). Purification of the resulting hydroxy Mosher amides (*R,S*)-**253c** and (*R,R*)-**253c'** showed the major diastereomer ((*R,R*)-**253c'**) to have similar $^{1}$H NMR shift patterns to the major stannyl Mosher amide (*R,S*)-**253b**.




(±)-**104c**
(*R*)-**104c** (80:20 er)

(*R,R*)-**253c'** : (*R,S*)-**253c**
49 : 51
82 : 18

**Scheme 173.** Conversion of hydroxy **104c** to Mosher amides (*R,R*)-**253c'** and (*R,S*)-**253c.**

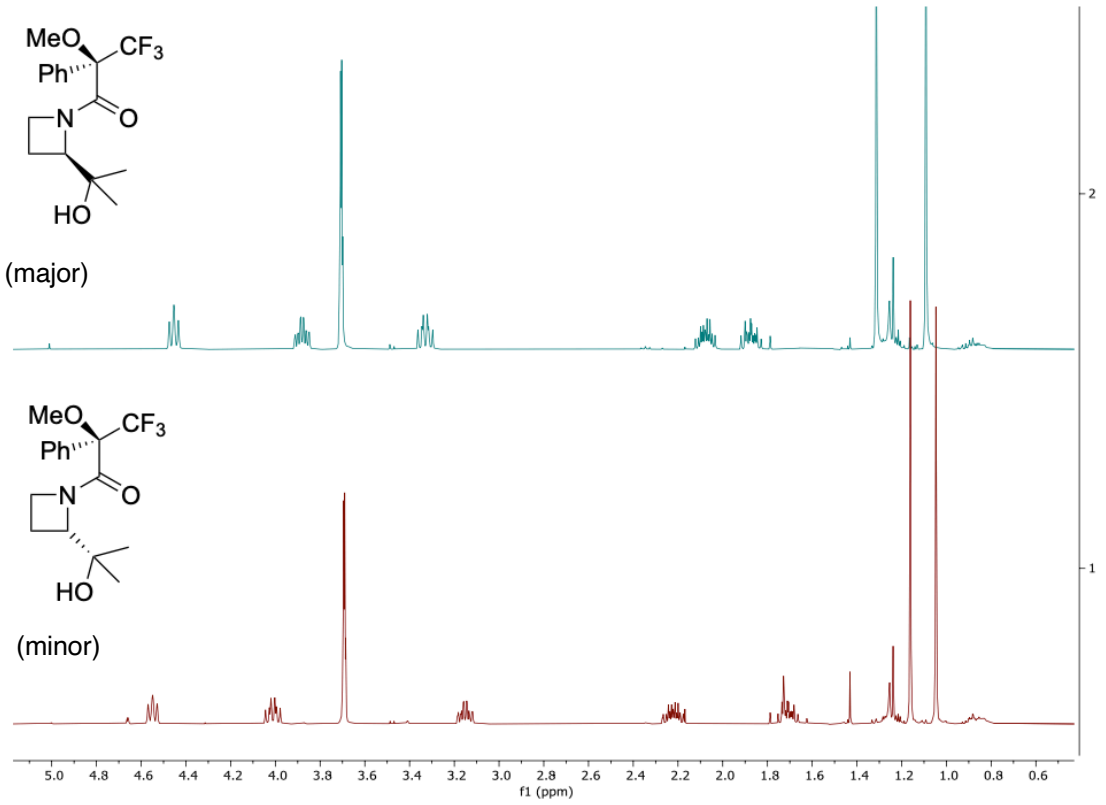
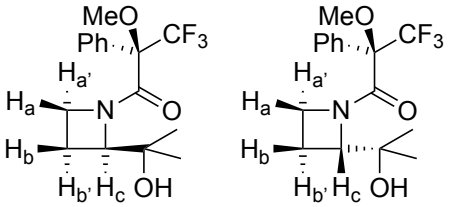



**Figure 18.** Overlapped $^{1}$H NMR of Mosher alcohols (*R,R*)-**253c'** and (*R,S*)-**253c.**




(*R*,*R*)-**253c'** (*R*,*S*)-**253c**

| Entry | Proton | (*R*,*R*)-253c' | (*R*,*S*)-253c | $\Delta\delta_{(\delta R-\delta S)}$ [a] |
|---|---|---|---|---|
| 1 | $H_a$ | 3.88 | 4.01 | -0.13 |
| 2 | $H_{a'}$ | 3.33 | 3.15 | 0.18 |
| 3 | $H_b$ | 1.87 | 2.22 | -0.35 |
| 4 | $H_{b'}$ | 2.08 | 1.71 | 0.37 |
| 5 | $H_c$ | 4.45 | 4.55 | -0.10 |
| 6 | Me | 1.31 | 1.16 | 0.15 |
| 7 | Me' | 1.09 | 1.05 | 0.04 |

[a] δR-δS due to change in CIP priority assignment.

**Table 16.** Chemical shifts differences between (*R*,*R*)-**253c'** and (*R*,*R*)-**253c** alcohols.

Verification of stannane (*S*)-**104f** absolute configuration was confirmed when a single crystal suitable for X-ray crystallographic analysis of stannane (*R*,*S*)-**253b** was grown (following separation of the two diastereomers by chromatography),[234] showing identical absolute and relative stereochemistry to that assigned by Mosher amide analysis (fig **19**).

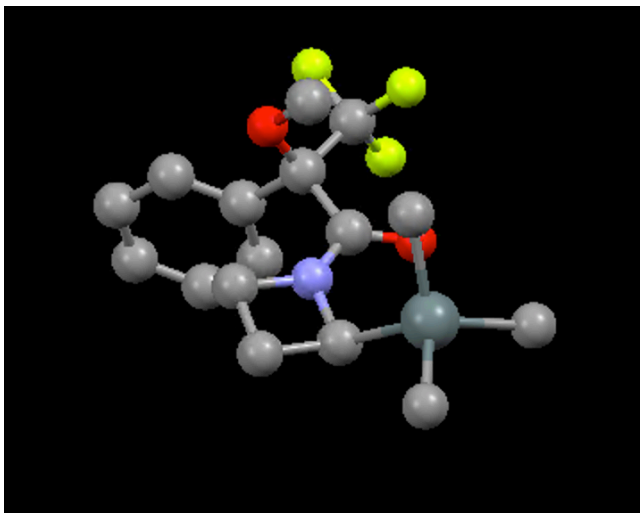


**Figure 19.** X-ray crystal structure of Mosher amide (*R*,*S*)-**253b.** Hydrogen atoms hidden in diagram for clarity.

### 4.2.8 Analysis of previous asymmetric stannylation results

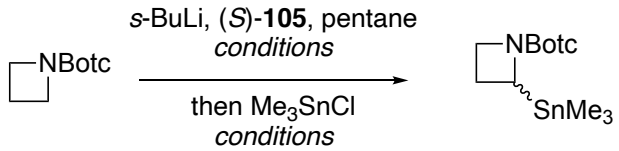
Work on asymmetric stannylation of *N*-Botc azetidine **101a** previously performed within the group had given results which, at the time, could not be explained (Table 17).[94] However, having established that the enantiodetermining mechanism is electrophile dependent, a rationalisation of the obtained results was re-attempted. Additionally, in-house HPLC conditions were developed which allowed er analysis of former samples which previously had not be analysed (optical purity was previously used).

With $Me_3SnCl$ as the electrophile, both variation in reaction time and temperature altered the sense of asymmetric induction (Table 17). Lithiation of *N*-Botc azetidine **101a** in the presence of DIANANE (*S*)-**105** at –78 °C for 1 h led to stannane (*S*)-**104f** in 67:33 er (90% yield, Table 17, entry 1). An otherwise identical reaction, but without warming to rt following $Me_3SnCl$ addition, resulted in stannane (*S*)-**104f** in similar enantioselectivity (61:39 er, Table 17, entry 2) in 80% yield — indicating that warming the reaction to rt had minimal effect on enantioselectivity. However, reducing the lithiation time to 5 min before stannylation *inverted* the sense of asymmetric induction, to give stannane (*R*)-**104f** in 46:54 er (62% yield).

The dependence of asymmetric induction on lithiation time indicates DTR and also suggests organolithium complex equilibration is incomplete after 5 min at –78 °C. The reduced overall levels of enantioselectivity compared with optimised conditions for acetone trapping suggests either an interfering DKR mechanism, in which the thermodynamically less stable complex reacts at a faster rate with $Me_3SnCl$, or possible competing non-

stereospecific electrophile trapping ($S_E2$ret and $S_E2$inv).[224] Stannylation is a reaction which has precedent for both retentive and invertive organolithium trapping, as well as a examples in which both occur competitively.[235]

Decreasing the lithiation temperature to –98 °C for 3 h before trapping at the same temperature gave stannane (*S*)-**104f** in 64:36 er (77% yield, Table 17, entry 4). However, reducing the lithiation time to 1 h at –98 °C resulted in a change in the sense of asymmetric induction to 46:54 er (Table 17, entry 5). This shows again the increased time required for complex equilibration at –98 °C, demonstrating a less configurationally labile anion at –98 °C. Despite the reduced enantioselectivity (*cf.* acetone and benzaldehyde), the stannylation results support a DTR mechanism as the enantioselectivity is highly dependent on incubation time and temperature.




**101a** **104f**

| Entry | Lithiation temp (time) | Stannylation temp (time) | % Yield 104f | er | (*R*)/(*S*)-104f | Recovered 101a |
|---|---|---|---|---|---|---|
| 1 | –78 °C (1 h) | –78 °C (30 min) then rt (30 min) | 90% | 67:33 | (*S*) | 0% |
| 2 | –78 °C (1 h) | –78 °C (30 min) | 80% | 61:39 | (*S*) | 0% |
| 3 | –78 °C (5 min) | –78 °C (30 min) then rt (30 min) | 62% | 46:54 | (*R*) | 38% |
| 4 | –98 °C (3 h) | –98 °C (30 min) | 77% | 64:36 | (*S*) | 21% |
| 5 | –98 °C (1 h) | –98 °C (30 min) | 70% | 46:54 | (*R*) | 24% |

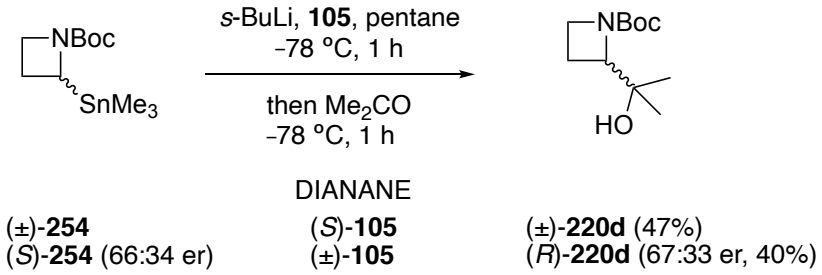
***Experiments performed by Claire Mortimer[94]***

**Table 17.** Asymmetric stannylation of *N*-Botc azetidine **101a** with complete HPLC data.

### 4.2.9 Studies into the origins of configurational instability of 2-lithio-*N*-Botc-azetidine

O'Brien and co-workers previously established with *N*-thiopivaloyl-azetidine **55** that asymmetric induction occurs post deprotonation; however, no distinction between DTR or DKR was made.[96] They also speculated that the origin of configurational instability may due to the longer C=S bond.[96] To test whether the C=S group or azacycle size was responsible for the configurational instability of *N*-Botc azetidine lithiated **Li-101a•105**, we sought to access the lithiated *N*-Boc azetidine equivalents. Our group had previously found that direct α-lithiation of *N*-Boc azetidine is problematic,[90] but access to α-lithiated *N*-Boc azetidine could be achieved by Sn–Li exchange from *N*-Boc stannane **254** (Scheme 174).

Under identical transmetallation conditions used for stannane **104f** in the presence of DIANANE (*S*)-**105**, stannane (±)-**254** underwent Sn–Li exchange and trapping with acetone to give racemic *N*-Boc alcohol (±)-**220d** (47% yield) (Scheme 174). Transmetallation with racemic DIANANE (±)-**105** using enantioenriched *N*-Boc stannane (*S*)-**254** (66:34 er) gave enantioenriched alcohol (*R*)-**220d** in 67:33 er (40% yield) (Scheme 174). These results show α-lithiated *N*-Boc azetidine is configurationally stable in pentane at –78 °C for 1 h, indicating that the C=S group is responsible for the configurational instability. It also demonstrates, for the first time, access to a configurationally stable α-lithiated azetidine.



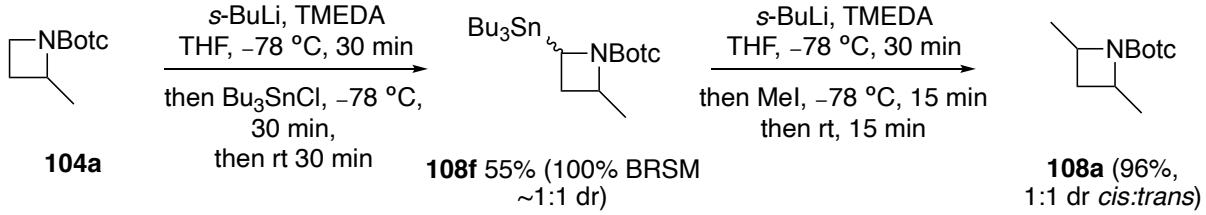

**Scheme 174.** Transmetallation of *N*-Boc stannane **254**

### 4.2.10 The syntheses of 2,4-disubstituted-azetidines by transmetallation

It was hoped that access to 2,4-disubstituted-azetidines could be achieved in high yields via transmetallation. As enantioinduction had been shown to occur post deprotonation, it was envisioned that quantitative access to an α'-lithiated 2-methyl-azetidine **104a** could be achieved by Sn–Li exchange on a stannane precursor **108f** (Scheme 175). Since stannane **108f** could be accessed under racemic α'-lithiation—electrophile trapping conditions, it was hoped that yields of up to ~70% could be achieved (corresponding to near complete conversion of the major rotamer).

Attempted racemic α'-lithiation—stannylation with $Bu_3SnCl$ was performed on 2-methyl-azetidine (±)-**104a**, giving 2-stannyl,4-methyl-azetidine **108f** in 55% yield (100% BRSM, ~ 1:1 dr, Scheme 175). Pleasingly, the yield corresponded to almost complete stannylation of the major rotamer of starting material **104a**. No formation of 2-stannyl,2-methyl-azetidine was observed, further supporting only α'-lithiation occurs (see p 38) of azetidine **104a**.[102] The reaction proceeded with no diastereoselectivity, showing no stereochemical influence of the methyl substituent in the stannylation step (as was seen for alkylation). Performing transmetallation on the diastereomeric mixture of stannane **108f** in the presence of TMEDA in THF, followed by methylation gave

2,4-methyl-azetidine **108a** in 96% yield (~1:1 dr, Scheme 175). The high yield demonstrates that both diastereomers (and both rotamers) of stannane **108f** can efficiently undergo Sn–Li exchange to form the intermediate 2-methyl,4-lithio-azetidine.



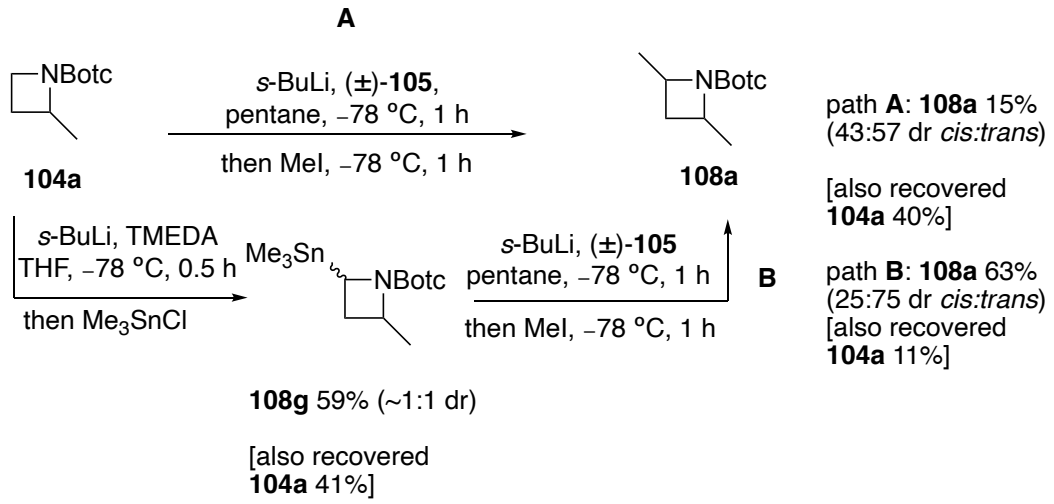

**Scheme 175.** 2,4-methyl azetidine 108a synthesis via transmetallation.

To allow for a closer comparison between previous Sn–Li exchange and deprotonation studies, similar reactions were performed with trimethyl stannane equivalent **108g**. Additionally, synthesis of 2,4-dimethyl-azetidine **108a** was performed following α'–lithiation—electrophile trapping on 2-methyl-azetidine (±)-**104a** (Scheme 176). Lithiation at –78 °C for 1 h in pentane with racemic DIANANE (±)-**105** then trapping with MeI gave 2,4-dimethyl-azetidine **108a** in 15% yield (57:43 dr), with a slight preference for the *trans*-2,4-dimethyl-azetidine. This result indicates that the steric and stereoelectronic influence of the pre-existing methyl group is minimal during α'–lithiation—methylation in pentane with DIANANE (±)-**105**, as seen earlier (p 45).

However, when 2,4-dimethyl-azetidine **108a** was prepared by transmetallation from 4-methyl-2-trimethylstannyl-azetidine **108g**, different diastereoselectivity was observed (Scheme 176). Similar to the $Bu_3Sn$ analogue (see above), 4-methyl-2-trimethylstannyl-azetidine **108g** was prepared by α'–lithiation of racemic 2-methyl-azetidine **104a** in THF with TMEDA, followed by trapping with $Me_3SnCl$; this gave an ~1:1 dr (inseparable) of stannane **108g** in 59% yield (100% BRSM). Transmetallation of stannane **108g** in pentane in the presence of racemic DIANANE (±)-**105** at –78 °C for 1 h followed by trapping with

MeI gave 2,4-dimethyl-azetidine **108a** in 63% yield (75:25 dr). The major diastereomer is *trans*-2,4 disubstituted-azetidine *trans*-**108a**.

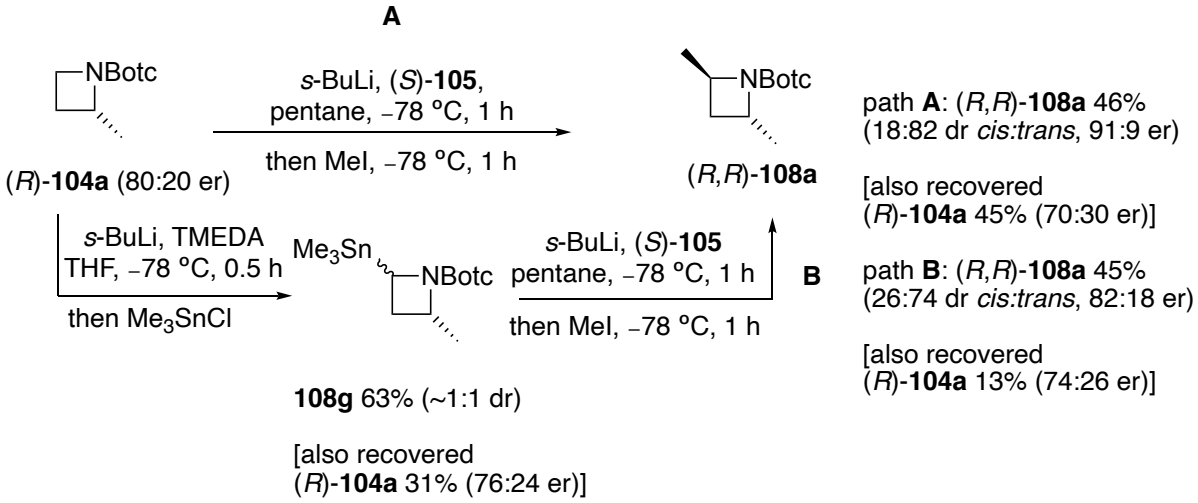
Interestingly, the diastereoselectivity of the reaction via transmetallation was higher compared to lithiation. Although, the yield via α'–lithiation is low, if we assume that (like α–methylation) the reaction is proceeding via DKR, then the selectivity should not be influenced by the conversion. These results again suggest that an anion formed by transmetallation has slightly different characteristics compared to the anion formed by lithiation (*cf*. p 160-163)




**Scheme 176.** Syntheses of 2,4-dimethylazetidine **108a.**

Similar differences in anion reactivity were observed between lithiation and transmetallation in the asymmetric synthesis of 2,4-dimethyl-azetidine (*R*,*R*)-**108a** (Scheme 177). Deprotonation of (*R*)-**104a** (80:20 er) at –78 °C for 1 h before trapping with MeI gave 2,4-dimethyl-azetidine (*R*,*R*)-**108a** in 46% yield (82:18 dr, 91:9 er). Interestingly, starting material (*R*)-**104a** 45% was recovered with reduced enantioenrichment (70:30 er). This most likely is due to the reaction's small diastereoselective preference for formation of *trans*-2,4-dimethyl-azetidine *trans*-**108** over the *meso*-**108** diastereomer.

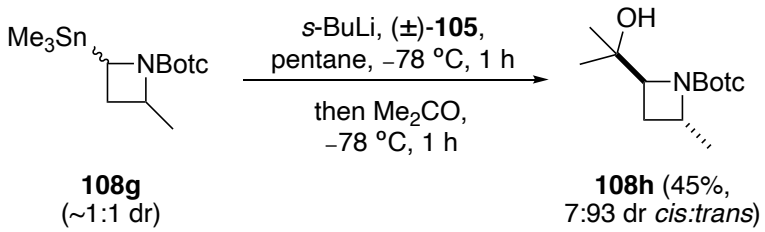
An attempt to improve the yield of the overall transformation was examined via stannane **108g** as an intermediate (Scheme 177). Lithiation–stannylation of (*R*)-**104a** (80:20 er) with TMEDA in THF, gave stannane **108g** in 63% yield (~1:1 dr). Transmetallation of stannane **108g** in the presence of DIANANE (*S*)-**105** gave 2,4-dimethyl-azetidine (*R*,*R*)-**108a** in 45% yield (74:26 dr, 82:18 er). The reduced diastereo- and enantioselectivity from this approach again highlights differences in behaviour of the anionic complexes formed from deprotonation and transmetallation. The same results obtained by transmetallation under asymmetric conditions would be expected if the transmetallation was run in the presence of racemic DIANANE(±)-**105**. This suggests that for anion formed by transmetallation, the substrate, rather than the ligand, is controlling the selectivity in the methylation step.




**Scheme 177.** Asymmetric syntheses of 2,4-dimethylazetidine (*R*,*R*)-**108a.**

Interestingly, when the same transmetallation of racemic stannane (±)-**108g** was performed with acetone trapping, it gave 2,4-disubstituted azetidine **108h** in 45% yield (54% BRSM, 93:7 dr, Scheme 178). If we assume acetone traps with retention via a DTR mechanism, then that would suggest that equilibration of 2-methyl,4-lithio-azetidine

complexes favours the *trans* diastereomeric complex when formed by transmetallation. This would make sense on steric grounds.




**Scheme 178.** 2,4-disubstituted azetidine **108h** synthesis via transmetallation.

## 4.3 Conclusions

The absolute configurations for a range of electrophiles used to trap complexes of lithiated **101a** asymmetrically have been determined (including novel Mosher amide analysis for monosubstituted azetidines). Additionally the enantiodetermining mechanism has been investigated for these electrophiles and interestingly, the mechanism has been shown to be dependent on the electrophile.

For the two electrophiles which trap through DKR (MeI and TMSCl), the predominant sense of asymmetric induction is opposite to those electrophiles which proceed through DTR (acetone, benzaldehyde and $Me_3SnCl$ also likely *i*-PrOB(pin)). This could be due either to preferential *invertive* $S_E2inv$ trapping, not uncommon for mesomerically stabilised organolithiums trapped by alkyl halides,[208] or to retentive trapping in which the minor diastereomeric organolithium complex is the faster reacting species, as was observed by the "poor man's Hoffman test" using acetone as the electrophile (Scheme 160). Nevertheless, it is an interesting observation that the enantiodetermining mechanism is dependent on the electrophile and may explain previous examples with electrophile dependent asymmetric induction.

The origins of the anion configurational stability have been probed and the results indicate that the thiocarbonyl group is responsible for the increased instability. Although the exact reason(s) why the thiocarbonyl group decreases anion configurational stability are unknown, increased N-lone pair charge transfer to the thiocarbonyl group[236] and/or increased (C=S) bond length may facilitate enantiomerisation. Configurationally stability has been shown to be dependent on the method of preparing the organolithium complexes (*R*)-**Li-101a•105** faster than (*S*)-**Li-101a•105**, with deprotonation showing a greater degree of configurationally stability compared to transmetallation. This is speculated to be due to the formation of different anionic species/different mixed-aggregates. Interestingly, the *N*-Boc azetidine equivalent shows configurational stability when formed by transmetallation, which could in future be exploited synthetically.

Finally, 2,4-disubstituted-azetidines have been prepared via 4-methyl-2-stannyl-azetidines. Although it was shown to be an inefficient method to access 2,4-disubstituted systems, it did again further highlight subtle differences between organolithium species formed by deprotonation compared to transmetallation.

## 4.4 Future work

Potential future work on the subjects presented in this thesis include:

- Further development of transformations on synthetic 'handle' boronic ester **104g**, with particular focus on developing conditions to access enantioenriched 2-aryl/vinyl azetidines stereospecifically.

- Further investigations into 1,2-metallate ring-opening of azetidine **104g** to access enantioenriched γ-amino boronic esters. This may be triggered by introducing a suitable thiophilic Lewis acid to inducing boronate migration.
- Application of boronic ester homologation chemistry in natural product synthesis (e.g. penaresidins A and B, Figure 1, p 3).
- Exploration of spectroscopic evidence for enantiodetermining mechanism in the asymmetric lithiation—electrophile trapping of *N*-Botc azetidine **101a**. Diastereomeric ratios between complexes (*R*)-**Li-101a•105** faster than (*S*)-**Li-101a•105** could be obtained by $^{1}$H, $^{6/7}$Li, $^{13}$C NMR low temperature analysis which may confirm a ~90:10 dr. Additionally, establish spectroscopic evidence to demonstrate the subtle differences in anions formed by deprotonation and transmetallation.

# 5. Experimental conditions

## 5.1 General information

Commercially available chemicals/reagents were purchased from major suppliers and unless stated otherwise were used without further purification. TMEDA, (–)-sparteine [(–)-sp], $Et_3N$, TMSCl, were distilled from $CaH_2$; DIANANE **105** and *i*-PrOB(pin) were distilled under reduced pressure before use. MeI and TMSCl was passed through basic alumina immediately before use. *s*-BuLi was titrated on arrival, and periodically thereafter, using 2-propanol solution in PhMe with 0.2% 1,10-phenanthroline indicator solution or diphenyl acetic acid for quantitative analysis of BuLi. All reactions were stirred using Teflon-coated magnetic stirrer bars. All reactions requiring anhydrous conditions were conducted under an atmosphere of nitrogen, glassware was flame-dried and with solvents degassed and dried using a Pure Solv-MD solvent purification system and transferred under nitrogen. The following cooling baths were used: 0 °C (ice/water), –78 °C (dry ice/acetone) and –98 °C (liquid $N_2$/MeOH). For reactions above rt, pre-heated paraffin oil baths on stirrer hotplates were used and the temperature was controlled via an external temperature probe. Reactions were monitored by TLC using Merck silica gel 60 F254 (aluminium support) TLC plates, which were developed using standard visualising agents: UV fluorescence (254 nm), potassium permanganate /Δ or vanillin /Δ. Column chromatography was carried out on silica gel (43-63 μm) in the solvent system indicated. Petroleum ether refers to the fraction boiling between 40 °C to 60 °C. Melting points were measured in open capillaries using Stuart Scientific melting point apparatus and are uncorrected. Infra-red spectra were recorded neat and the intensity of the peaks are reported as s, m, w, br, denoting strong,

medium, weak, and broad, respectively. NMR spectra were recorded on Brüker DPX200 ($^{1}$H = 200 MHz), Brüker AVF400 ($^{1}$H = 400 MHz, $^{13}$C = 101 MHz, $^{19}$F = 377 MHz), AVC 500 ($^{1}$H = 500 MHz, $^{13}$C 125 MHz) or AVB400 ($^{11}$B = 128 MHz) machines in commercial, deuterated, TMS free solvents at 25 °C. Chemical shifts (δ) are given in ppm relative to TMS, calibrated using residual solvent peaks. Where rotamers/diastereomers are discernible, signals due to the minor rotamer/diastereomer are given in parentheses. $^{13}$C NMR spectra were recorded using the UDEFT or PENDANT pulse sequences from the Brüker standard pulse program library. $^{13}$C DEPT spectra and 2D COSY, HSQC, HMBC, NOESY spectra were recorded so as to assist with assignment when required. Multiplicity is denoted in $^{1}$H NMR by: s (singlet), d (doublet), t (triplet), q (quartet), quin (quintet), sext (sextet), hept (heptet) m (multiplet). Proton coupling constants *J* are reported to the nearest 0.1 Hz. NMR spectra were processed using MestReNova software. High resolution mass spectra were obtained by FI (Micromass GCT), or by ESI (LCT Premier reflectron TOF and Brüker MicroTOF) using tetraoctylammonium bromide or sodium dodecyl sulfate as lock mass; values are quoted as ratio of mass to charge in Daltons, and relative intensities of assignable peaks observed are quoted as a percentage value of the base peak. Chiral HPLC was performed on a Dionex UltiMate 3000 system comprising a Dionex LPG-3400A pump, WPS-3000SL autosampler, TCC-3000SD column compartment and DAD-3000 diode-array detector, fitted with the appropriate Daicel Chiralpak column (dimensions: 0.46 cm ø x 25 cm) and corresponding guard column (0.4 cm ø x 1 cm). Wavelengths (λ) are reported in nm, retention times ($\tau_R$) are reported in mins and solvent flow rates are reported in mL min$^{-1}$.

## 5.2 General procedures

**General procedure A: TMEDA mediated lithiation—electrophile trapping**

A solution of TMEDA (2.4 equiv) and azetidine carbothioate **X** (1 equiv) in THF (4.7 mL/mmol **X**) was cooled to –78 °C and *s*-BuLi (1.3 M in cyclohexane/hexane, 1.3 equiv) was added dropwise (~1 min). The reaction mixture was stirred for the time stated at (–78 °C or – 98 °C) before addition of electrophile (amount stated) dropwise. The reaction mixture was stirred for the time and temperature stated, then quenched with sat. aq $NH_4Cl$ (20 mL /mmol **X**), and extracted with $Et_2O$ (3 × 20 mL /mmol **X**). The combined organic extracts were washed with water (20 mL /mmol **X**), then brine (20 mL /mmol **X**), dried ($MgSO_4$) and concentrated under reduced pressure.

**General procedure B: DIANANE mediated lithiation—electrophile trapping**

A solution of DIANANE **105** (1.3 equiv) and azetidine carbothioate **X** (1 equiv) in pentane (8 mL/mmol **X**) was cooled to (–78 °C or –98 °C) and *s*-BuLi (1.3 M in cyclohexane/hexane, 1.3 equiv) was added dropwise (~1 min). The reaction mixture was stirred for the time stated at (–78 °C or –98 °C) before addition of electrophile (amount stated) dropwise. The reaction mixture was stirred for the time stated at (–78 °C or –98 °C), then quenched with sat. aq $NH_4Cl$ (20 mL /mmol **X**), and extracted with $Et_2O$ (3 × 20 mL /mmol **X**). The combined organic extracts were washed with water (20 mL /mmol **X**), then brine (20 mL /mmol **X**), dried ($MgSO_4$) and concentrated under reduced pressure.

**General procedure C: boronate homologation via direct lithiation**

A solution of benzoate (1.0 equiv) and TMEDA (1.1 eq) in $Et_2O$ (0.1 M) was cooled to –78 °C. *s*-BuLi (1.3 equiv, 1.3 M in hexanes) was added dropwise and the reaction mixture was stirred for 3 h at –78 °C. A solution of 2-B(pin)-azetidine **104g** (1.5 equiv) in $Et_2O$ (0.4 M)

was then added dropwise and the reaction mixture was stirred for 1 h at –78 °C. The solution was then warmed to rt over 15 min and the reaction mixture evaporated under vacuum (1 mbar), then $CHCl_3$ was added to give a 0.06 M solution w.r.t. starting 2-B(pin)-azetidine **104g**. The solution was heated under reflux (63 °C, oil bath) overnight (12 h). The reaction mixture was then quenched with water (3 mL) and the layers separated. The organic layer was washed with brine (2 x 2 mL) and the combined aq layers extracted with $CH_2Cl_2$ (3 x 5 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure to give an orange oil.

**General procedure D: preparation of triisopropylbenzoate stannanes**

A solution of the triisopropylbenzoate (1 equiv) and TMEDA (1.3 equiv) [or (–)-sp (1.09 equiv) for asymmetric reaction] in $Et_2O$ (0.2 M) was cooled to –78 °C. *s*-BuLi (1.3 equiv, 1.3 M in cyclohexane/hexane) was added dropwise and the reaction was stirred for 4 h at –78 °C. $Bu_3SnCl$ (1.3 equiv) was then added dropwise to the reaction. After 30 min at –78 °C, the reaction mixture was allowed to warm to rt, then quenched with water (10 mL) and extracted with $Et_2O$ (3 x 10 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$), concentrated under reduced pressure and purified by column chromatography.

**General procedure E: boronate homologation via tin–lithium exchange**

A solution of the stannane (1.3 equiv) in $Et_2O$ (0.1 M) was cooled to –78 °C. *n*-BuLi (1.3 equiv, 2.1 M in hexanes) was added dropwise and the reaction mixture was stirred for 1 h at –78 °C. A solution of 2-B(pin)-azetidine **104g** (1 equiv) in $Et_2O$ (0.4 M) was then added dropwise and the reaction mixture was stirred for 1 h at –78 °C. The solution was then warmed to rt over 15 min and the reaction mixture evaporated under vacuum (1 mbar),

then $CHCl_3$ was added to give a 0.06 M solution w.r.t. starting 2-B(pin)-azetidine **104g**. The solution was heated under reflux (63 °C, oil bath) overnight (12 h). The reaction mixture was then quenched with water (3 mL) and the layers separated. The organic layer was washed with brine (2 x 2 mL) and the combined aq layers extracted with $CH_2Cl_2$ (3 x 5 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure to give an orange oil.

**General procedure F: *N*-Botc deprotection–*N*-Boc reprotection**

To the *N*-Botc protected azetidinyl alcohol (1 equiv) was added HCl (2 M in $Et_2O$, 15 equiv) and the mixture was stirred for 1 h at rt. The reaction was concentrated under a stream of nitrogen. py (0.07 M w.r.t azetidinyl alcohol) and DMAP (0.1 equiv) were added to the resulting residue, which was then heated to 70 °C (oil bath) for 10 min and then cooled to 0 °C. $Boc_2O$ (1.1 equiv) was added and the reaction mixture warmed to rt and stirred for 12 h. Aq HCl (2 M, 2 mL) was added and the reaction mixture was extracted with $CH_2Cl_2$ (3 x 2 mL). The combined organic layers were washed with aq HCl (2 M, 2 mL), $H_2O$ (2 mL) and brine (2 mL). The organic layer was dried ($MgSO_4$), concentrated under reduced pressure and purified by column chromatography.

**General procedure G: Sn–Li exchange—electrophile trapping**

A solution of DIANANE **105** (1.3 equiv) and stannane **X** (1 equiv) in pentane (8 mL/mmol **X**) was cooled to (–78 °C or –98 °C) and *s*-BuLi (1.3 M in cyclohexane/hexane, 1.3 equiv) was added dropwise (~1 min). The reaction mixture was stirred for the time stated at (–78 °C or –98 °C) before addition of electrophile (amount stated) dropwise. The reaction mixture was stirred for the time stated at (–78 °C or −98 °C), then quenched with sat. aq $NH_4Cl$ (20

mL /mmol **X**), and extracted with $Et_2O$ (3 × 20 mL /mmol **X**). The combined organic extracts were washed with water (20 mL /mmol **X**), then brine (20 mL /mmol **X**), dried ($MgSO_4$) and concentrated under reduced pressure.

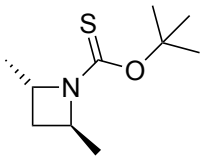
**General procedure H: Formation of Mosher amides**

To the 2-substituted *N*-Botc azetidine **104** (1 equiv) was added HCl (2 M in $Et_2O$, 8 equiv) and the mixture was stirred for 1 h at rt. The reaction was concentrated under a stream of nitrogen and the crude dissolved in $CH_2Cl_2$ (0.1 M). DIPEA (2.2 equiv) and (*S*)-MTPA-Cl (1.2 equiv) was added and the reaction was stirred at rt overnight. The reaction mixture was concentrated under reduced pressure and to the crude was added sat. aq $NH_4Cl$ (20 mL /mmol **104**), and extracted with $CH_2Cl_2$ (3 × 20 mL /mmol **104**). The combined organic extracts were washed with brine (20 mL /mmol **104**), dried ($MgSO_4$) and concentrated under reduced pressure.

## 5.3 Experimental conditions

### 5.3.1 Compounds from chapter 2

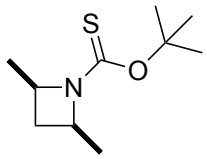
***O*-*t*-Butyl 2,4-dimethylazetidine-1-carbothioate 108a**




A solution of DIANANE (*R*)-**105** (95 mg, 0.51 mmol) in pentane (1.6 mL) was cooled to –78 °C and s-BuLi (0.42 mL, 0.51 mmol) was added dropwise. The reaction mixture was stirred for 10 min, and then transferred dropwise via cannula to a precooled (–98 °C) solution of (*S*)-2-methyl-*N*-Botc-azetidine (*S*)-**104a** (73 mg, 0.39 mmol, 85:15 er) in pentane (1.6 mL). The reaction mixture was stirred for 1 h at –98 °C before the addition of MeI (72 µL, 1.17

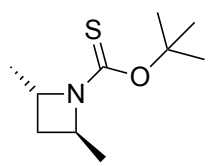
mmol). The reaction mixture was stirred for a further 1 h at –98 °C, quenched with sat aq HCl (1 M, 10 mL), and extracted with $Et_2O$ (4 × 10 mL). The combined organic extracts were washed with water (20 mL) then brine (20 mL), dried (MgSO4) and concentrated under reduced pressure. Purification of the resulting pale yellow oil by column chromatography (0–2% $Et_2O$/petroleum ether) first eluted a colourless oil, *N*-Botc-2,4-dimethylazetidine *cis*-**108a** (3 mg, 4%, 8% brsm). Second eluted a colourless oil, *N*-Botc-2,4-dimethylazetidine (*S*,*S*)-**108a** (21 mg, 27%, 47% brsm, 95:5 er by HPLC: Chiralcel I-C column, eluent: *n*-hexane/*i*-PrOH (99:1), flow rate = 1 mL/min). $\tau_R$ (*S*,*S*) = 11.8 min, $\tau_R$ (*cis*) = 13.0 min, $\tau_R$ (*R*,*R*) = 21.3 min).

***O*-*t*-Butyl 2,4-dimethylazetidine-1-carbothioate *meso*-108a**



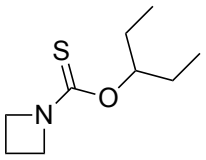

$R_f$ 0.37 (5% $Et_2O$/petroleum ether); IR (neat/$cm^{-1}$) 1469 (s), 1434 (s), 1390 (m), 1269 (s), 1224 (m), 1142 (s); $\delta_H$ (400 MHz, $CDCl_3$) (Rotation of *N*-Botc slow on NMR timescale) 4.37 (4.24) (2H, dquin, *J* = 8.6, 6.3 Hz (*J* = 8.6, 6.3 Hz), NC*H*), 2.54 (1H, dt, *J* = 11.2, 8.6 Hz, $NCHCH_{cis}\mathit{H}_{trans}$), 1.64 (9H, s, $C(C\mathit{H}_3)_3$), 1.56 (1.42) (6H, d, *J* = 6.3 Hz, $NCHC\mathit{H}_3$), 1.39 – 1.30 (1H, m, $NCHC\mathit{H}_{cis}H_{trans}$); $\delta_C$ (100 MHz, $CDCl_3$) (Rotation of *N*-Botc slow on NMR timescale) 185.6 (C=S), 84.6 ($\mathit{C}(CH_3)_3$), 58.74 (58.72) (NCH), 31.3 ($NCH\mathit{C}H_2$), 28.7 ($C(\mathit{C}H_3)_3$), 22.2 (21.5) ($CH\mathit{C}H_3$); HRMS ($FI^+$) calcd for [M+H] $C_{10}H_{20}NOS$ 202.1260, found 202.1262.

***O*-*t*-Butyl (*S*,*S*)-2,4-dimethylazetidine-1-carbothioate *trans*-108a**



$R_f$ 0.35 (5% $Et_2O$/petroleum ether); $[\alpha]_D^{25}$ +40.2 (*c* 0.26, $CHCl_3$); IR (neat/$cm^{-1}$) 1427 (m), 1390 (s), 1365 (m), 1270 (s), 1226 (m), 1139 (s); $\delta_H$ (400 MHz, $CDCl_3$) (Rotation of *N*-Botc slow on NMR timescale) 4.56 – 4.45 (4.45 – 4.35) (2H, m, NC*H*), 1.99 – 1.87 (2H, m, NCHC$H_2$), 1.64 (9H, s, C(C$H_3$)$_3$), 1.55 (1.40) (6H, d, *J* = 6.3 Hz, NCHC$H_3$); $\delta_C$ (100 MHz, $CDCl_3$) (Rotation of *N*-Botc slow on NMR timescale) 184.4 (C=S), 84.7 (*C*$(CH_3)_3$) , 58.3 (57.8) (NCH), 31.4 (NCH*C*$H_2$), 28.8 (C(*C*$H_3$)$_3$), 19.2 (20.5) (CH*C*$H_3$); HRMS ($FI^+$) calcd for [M+H] $C_{10}H_{20}NOS$ 202.1260, found 202.1262.

**_O_-(Pentan-3-yl) azetidine-1-carbothioate 139**



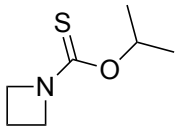

To a solution of 1,1'-thiocarbonyldiimidazole (1.25 g, 7 mmol) in THF (4.7 mL) was added 3-pentanol (0.40 mL, 3.5 mmol). The mixture was heated to 50 °C and stirred for 16 h. The mixture was cooled and diluted with water (10 mL) and EtOAc (20 mL). The layers were separated and the organic layer was washed with 0.5 M HCl (4 x 2 mL), water (3 x 10 mL) and brine (10 mL). The organic layer was dried ($Na_2SO_4$) and concentrated under reduced pressure to give the crude imidazole carbothioate **137**[115] as a dark orange oil (520 mg, 80%).

To a solution of crude imidazole carbothioate **137** (500 mg, 2.69 mmol) in THF (1.3 mL) and DMF (1.3 mL) was added azetidine (0.20 mL, 3.0 mmol). The reaction mixture was stirred at rt overnight (15 h). The mixture was diluted with water (10 mL) and EtOAc (20 mL). The layers were separated and the organic layer was washed with 0.5 M HCl (4 x 2 mL), water (3 x 8 mL) and brine (8 mL). The organic layer was dried ($Na_2SO_4$), concentrated under reduced pressure to give a crude residue which was purified by column chromatography

(20% EtOAc/petroleum ether) to give a colourless oil, azetidine carbothioate **139** (360 mg, 55% over two steps).

$R_f$ 0.92 (50% EtOAc/petroleum ether); IR (neat/cm$^{-1}$) 2967 (m), 2881 (m), 1499 (s), 1472 (s), 1444 (s), 1270 (s), 1245 (s), 1219 (s), 1150 (m); $\delta_H$ (400 MHz, $CDCl_3$) (Rotation of thiocarbamate slow on NMR timescale) 5.24 (1H, quin, *J* = 7.1 Hz, OCH), 4.18 (2H, t, *J* = 7.8 Hz, $NCH_2$), 4.07 (2H, t, *J* = 7.8 Hz, $NCH_2$), 2.25 (2H, quin, *J* = 7.8 Hz, $NCH_2C\mathit{H}_2$), 1.64 (4H, quin, *J* = 7.1 Hz ($CH_3C\mathit{H}_2)_2$), 0.90 (6H, t, *J* = 7.1 Hz, ($C\mathit{H}_3CH_2)_2$); $\delta_C$ (125 MHz, $CDCl_3$) (Rotation of thiocarbamate slow on NMR timescale) 187.1 (C=S), 83.2 (OCH), 52.4 ($NCH_2$), 50.5 ($NCH_2$), 26.2(($CH_3\mathit{C}H_2)_2$), 15.0 ($NCH_2\mathit{C}H_2$), 9.5 (($\mathit{C}H_3CH_2)_2$); HRMS (FTMS) calcd for [M+H] $C_9H_{18}NOS$ 188.1103, found 188.1103.

***O*-(Isopropyl) azetidine-1-carbothioate 140**



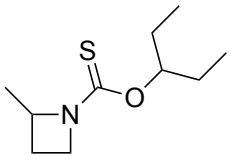

To a solution of 1,1'-thiocarbonyldiimidazole (0.96 g, 5.4 mmol) in THF (6.5 mL) was added IPA (0.37 mL, 4.9 mmol). The mixture was heated to 50 °C and stirred for 16 h. The mixture was cooled and diluted with water (10 mL) and EtOAc (20 mL). The layers were separated and the organic layer was washed with 0.5 M HCl (4 x 2 mL), water (3 x 10 mL) and brine (10 mL). The organic layer was dried ($Na_2SO_4$) and concentrated under reduced pressure to give the crude imidazole carbothioate **138**[115] as a dark orange oil (301 mg, 1.76 mmol, 36%).

To a solution of crude imidazole carbothioate **138** (290 mg, 1.61 mmol) in THF (0.7 mL) and DMF (0.7 mL) was added azetidine (0.11 mL, 1.65 mmol). The reaction mixture was stirred at rt overnight (15 h). The mixture was diluted with water (7 mL) and EtOAc (15 mL). The layers were separated and the organic layer was washed with 0.5 M HCl (4 x 1 mL), water

(3 x 5 mL) and brine (5 mL). The organic layer was dried ($Na_2SO_4$), concentrated under reduced pressure to give a crude residue which was purified by column chromatography (20% EtOAc/petroleum ether) to give a colourless oil, azetidine carbothioate **140** (150 mg, 66 %).

$R_f$ 0.92 (50% EtOAc/petroleum ether); IR (neat/$cm^{-1}$) 2977 (m), 1499 (s), 1473 (s), 1443 (s), 1372 (m), 1274 (s), 1246 (s), 1222 (s), 1150 (s), 1101 (s), 1028 (m); $\delta_H$ (400 MHz, $CDCl_3$) (Rotation of thiocarbamate slow on NMR timescale) 5.48 (1H, hept, *J* = 6.2 Hz, OCH), 4.17 (2H, t, *J* = 7.5 Hz, $NCH_2$), 4.06 (2H, t, *J* = 7.5 Hz, $NCH_2$), 2.24 (2H, quin, *J* = 7.5 Hz, $NCH_2CH_2$), 1.29 (6H, d, *J* = 6.2 Hz, $CH(CH_3)_2$); $\delta_C$ (125 MHz, $CDCl_3$) (Rotation of thiocarbamate slow on NMR timescale) 186.4 (C=S), 74.3 (OCH), 52.3 ($NCH_2$), 50.5 ($NCH_2$), 22.1 ($CH(CH_3)_2$), 14.9 ($NCH_2CH_2$); HRMS (FTMS) calcd for [M+H] $C_7H_{14}NOS$ 160.0791, found 160.0791.

***O*-(Pentan-3-yl)-2-methyl azetidine-1-carbothioate 141**

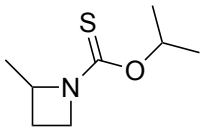



2-methyl-azetidine carbothioate was prepared following general procedure **A**, using azetidine carbothioate **139** (80 mg, 0.44 mmol) and TMEDA (0.15 mL, 1.00 mmol), with a –78 °C lithiation temp (30 min). MeI (0.1 mL, 1.26 mmol) was then added dropwise at –78 °C (10 min) and then warmed to rt over 10 min. The crude material was purified by column chromatography (1-2% $Et_2O$/petroleum ether) gave a colourless oil, 2-methyl azetidine carbothioate **141** (67 mg, 78%, 80% BRSM).

$R_f$ 0.82 (20% $Et_2O$/petroleum ether); IR (neat/$cm^{-1}$) 2966 (m), 1485 (S), 1464(s), 1439(s), 1372(w), 1338 (m), 1264 (s), 1239 (m), 1216 (s), 1145 (m), 1103 (m), 1035 (w); $\delta_H$ (400 MHz, $CDCl_3$) (2.5:1 rotamer mixture by analysis of NCH signals in the 4.64-4.40 region) 5.29 (1H,

quin, *J* = 6.2 Hz,OCH), 4.50-4.40 (4.64-4.52) (1H, m, NCH), 4.17 – 3.93 (2H, m,$NCH_2$), 2.50 – 2.31 (m, 1H, NCHC*H*H'), 1.88-1.77 (1H,m, NCHCH*H'*), 1.71 – 1.53 (4H, m, $(CH_3CH_2)_2$), 1.45 (1.58) (2H, d, *J* = 6.3 Hz, NCHC$H_3$), 0.91 (6H, t, *J* = 7.4 Hz, $(CH_3CH_2)_2$); $\delta_C$ (125 MHz, $CDCl_3$) 187.5 (187.1) (C=S), 83.0 (82.2) (OCH), 60.0 (61.6) (NCH), 49.5 (48.8) ($NCH_2$), 26.3 (26.11) $(CH_3CH_2)_2$), 23.0 (23.6) (NCH$CH_2$), 21.0 (19.9) (NCH$CH_3$), 9.6 (9.4) $(CH_3CH_2)_2$); HRMS (FTMS) calcd for [M+H] $C_{10}H_{20}NOS$: 202.1260, found 202.1264.

**_O_-(Isopropyl)-2-methyl azetidine-1-carbothioate 142**

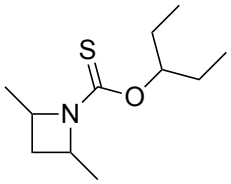



2-methyl-azetidine carbothioate was prepared following general procedure **A**, using azetidine carbothioate **140** (75 mg, 0.46 mmol) and TMEDA (0.15 mL, 1.00 mmol), with a –78 °C lithiation temp (30 min). MeI (0.1 mL, 1.26 mmol) was then added dropwise at –78 °C (10 min) and then warmed to rt over 10 min. The crude material was purified by column chromatography (1-2% $Et_2O$/petroleum ether) gave a colourless oil, 2-methyl-azetidine carbothioate **142** (47 mg, 59%).

$R_f$ 0.82 (20% $Et_2O$/petroleum ether); IR (neat/$cm^{-1}$) 2976 (m), 1486 (s), 1468 (s), 1439 (s), 1372 (m), 1338 (m), 1267 (s), 1239 (m), 1219 (s), 1144 (s), 1103 (s), 1039 (s); $\delta_H$ (400 MHz, $CDCl_3$) (2.5:1 rotamer mixture by analysis of NCH signals in the 4.61-4.39 region) 5.50 (1H, quin, *J* = 6.3 Hz, OCH), 4.49-4.39 (4.61-4.52) (1H, m, NCH), 4.18 – 3.90 (2H, m, ($NCH_2$)), 2.45-2.33 (1H, m, NCHC*H*H'), 1.86-1.75 (1H, m, NCHCH*H'*), 1.43 (1.53) (3H, d, *J* = 6.4 Hz, NCHC$H_3$), 1.33 – 1.27 (6H, m, CH(C$H_3$)$_2$); $\delta_C$ (125 MHz, $CDCl_3$) 186.7, (186.4) (C=S), 74.0 (73.4) (OCH), 60.0 (61.6) (NCH), 49.4 (48.9) ($NCH_2$), 23.00 (23.5) (NCH$CH_2$), 22.24 (22.21) (CH($CH_3$)$_2$), 21.9

(22.0) (CH(*C*'$H_3$)$_2$), 20.8 (19.8) (NCH*C*$H_3$); HRMS (FTMS) calcd for [M+H] $C_8H_{16}NOS$ 174.0947, found 174.0950.

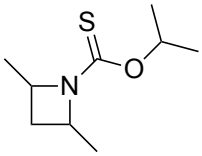
***O*-(*P*entan-3-yl) 2,4-dimethylazetidine-1-carbothioate 143**




2,4-dimethyl-azetidine carbothioate was prepared following general procedure **A**, using azetidine carbothioate **141** (20 mg, 0.10 mmol) and TMEDA (0.03 mL, 0.24 mmol), with a – 78 °C lithiation temp (30 min). MeI (0.02 mL, 0.30 mmol) was then added dropwise at – 78 °C (30 min) and then warmed to rt over 20 min. The crude material was purified by column chromatography (1-2 % $Et_2O$/petroleum ether) to give a colourless oil, 2,4-dimethyl-azetidine carbothioate **143** (8 mg, 37%, 56:44 dr (*trans*:*cis*)) as a mixture of inseparable diastereomers.

$R_f$ 0.83 (10% $Et_2O$/petroleum ether); IR (neat/cm$^{-1}$) 2966 (m), 1472 (s), 1437 (s), 1348 (m), 1262 (s), 1215 (s), 1163 (m), 1142 (m), 1100 (w), 1034 (m); $\delta_H$ (400 MHz, $CDCl_3$) (1.3:1 mixture of diastereomers) 5.39 – 5.27 (1H, m, OCH), 4.58 – 4.27 (2H, m, NCH), 2.59 (1H, dt, *J* = 11.3, 8.5 Hz, NCHC$H_{trans}H_{cis}$), 2.05 – 1.92 (2H, m, NCHC$H_2$), 1.71 – 1.61 (4H, m, C$H_2CH_3$), 1.59 (1.58) (3H, d, *J* = 6.3 Hz (*J* = 6.3 Hz), NCHC$H_3$), 1.49 – 1.41 (4H, m, NCHC$H_3$ and NCHCH$_{trans}H_{cis}$), 0.94 – 0.86 (6H, m, $CH_2CH_3$); $\delta_C$ (125 MHz, $CDCl_3$) (diastereomer mixture) 188.3 (186.1) (C=S), 81.88 (81.91), 58.9 (58.1) (NCH), 58.4 (57.8) (NCH), 31.6 (31.7) (NCH$CH_2$), 26.2 (26.0) ($CH_2CH_3$), 26.0 (25.8) ($CH_2CH_3$), 22.4 (20.8) (NCH$CH_3$), 21.3 (19.2) (NCH$CH_3$) , 9.6 ($CH_3CH_2$)$_2$) , 9.28 (9.34) ($CH_3CH_2$)$_2$); HRMS (FTMS) calcd for [M+H] $C_{11}H_{22}NOS$ 216.1417, found 216.1418.

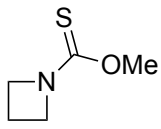
***O*-(Prop-3-yl) 2,4-dimethylazetidine-1-carbothioate 144**




2,4-dimethyl-azetidine carbothioate was prepared following general procedure **A**, using azetidine carbothioate **142** (15 mg, 0.09 mmol) and TMEDA (0.03 mL, 0.24 mmol), with a –78 °C lithiation temp (30 min). MeI (0.02 mL, 0.30 mmol) was then added dropwise at –78 °C (30 min) and then warmed to rt over 20 min. The crude material was purified by column chromatography (1-2 % $Et_2O$/petroleum ether) to give a colourless oil, 2,4-dimethyl- azetidine carbothioate **144** (6 mg, 36%, 57:43 dr (*trans*:*cis*)) as a mixture of inseparable diastereomers.

$R_f$ 0.79 (10% $Et_2O$/petroleum ether); IR (neat/$cm^{-1}$) 2978 (w), 1488 (s), 1439 (s), 1266 (s), 1220 (s); $\delta_H$ (400 MHz, $CDCl_3$) (1.3:1 mixture of diastereomers) 5.62 – 5.44 (2H, m, OCH), 4.61 – 4.27 (4H, m, NCH), 2.58 (1H, dt, *J* = 11.1, 8.6 Hz, $NCHCH_{cis}\mathit{H}_{trans}$), 1.98 (2H, ddd, *J* = 7.7, 6.0, 3.6 Hz, $NCHC\mathit{H}_2$), 1.60 – 1.55 (3H, m, $NCHC\mathit{H}_3$), 1.48 – 1.38 (4H, m, $NCHC\mathit{H}_3$ and $NCHC\mathit{H}_{cis}H_{trans}$), 1.33 – 1.26 (6H, m, $OCH(C\mathit{H}_3)_2$); $\delta_C$ (100 MHz, $CDCl_3$) (diastereomer mixture) 186.5 (185.7) (C=S), 73.3 (73.1) (OCH), 59.0 (58.6) (NCH), 58.3 (58.0) (NCH), 22.4 (22.3) ($NCH\mathit{C}H_2$), 22.2 (22.0) ($OCH\mathit{C}H_3$), 21.9 (21.3) ($OCH\mathit{C}H_3$), 20.6 (19.3) ($NCH\mathit{C}H_3$). HRMS not found.

***O*-Methyl azetidine-1-carbothioate 147**



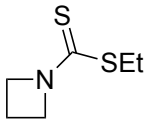

A flask charged with thiophosgene (0.20 mL, 2.61 mmol) in $Et_2O$ (13 mL) was cooled to –78 °C. Azetidine (0.35 mL, 5.19 mmol) was added dropwise, the mixture was warmed to 0 °C

and stirred for 2 h. The reaction was warmed to rt and filtered. The filtrate was concentrated under reduced pressure to give azetidine-1-carbothionyl chloride **146** (370 mg, quant.) sufficiently pure to be taken to the next step.

To a flask charged with azetidine-1-carbothionyl chloride **146** (100 mg, 0.74 mmol) under $N_2$ was added MeOH (5 mL, 124 mmol). The mixture was stirred and heated to reflux for 1 h. The reaction mixture was cooled to rt and concentrated under reduced pressure. The residue was purified by column chromatography (10% $Et_2O$/petroleum ether) to give a yellow oil carbothioate **147** (62 mg, 64%).

$R_f$ 0.52 (50% $Et_2O$/petroleum ether); IR (neat/$cm^{-1}$) 2945 (w), 2881 (w), 1503 (s), 1472 (m), 1440 (s), 1270 (s), 1244 (s), 1217 (s), 1147 (s); $\delta_H$ (400 MHz, $CDCl_3$) 4.18 (2H, t, *J* = 7.6 Hz,$NCH_2$), 4.09 (2H, t, *J* = 7.6 Hz, $NCH_2$), 3.97 (3H, s, $CH_3$), 2.25 (2H, quin, *J* = 7.6 Hz, $NCH_2C\mathit{H_2}$); $\delta_C$ (125 MHz, $CDCl_3$) 187.8 (C=S), 57.5 ($CH_3$), 52.6 ($NCH_2$), 50.8 ($NCH_2$), 14.9 ($NCH_2\mathit{C}H_2$); HRMS (FTMS) calcd for [M+H] $C_5H_{10}NOS$ 132.0479, found 132.0478.

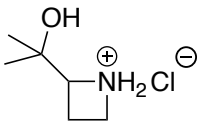
**Ethyl azetidine-1-carbodithioate 150**




Ethyl-azetidine carbothioate was prepared following general procedure **A**, using azetidine carbothioate **149** (380 mg, 0.10 mmol) and TMEDA (0.96 mL, 6.43 mmol), with a –78 °C lithiation temp (30 min). MeI (0.5 mL, 8.05 mmol) was then added dropwise at –78 °C (30 min). The crude material was purified by column chromatography (10% $Et_2O$/petroleum ether) to give a mixture of starting material and ethyl azetidine-1-carbodithioate **150** (152 mg (28:82 (**149**:**150**)), 33%). An analytically pure sample of product was obtained by prep-TLC (10% $Et_2O$/petroleum ether).

$R_f$ 0.36 (5% EtOAc/petroleum ether); IR (neat/cm$^{-1}$) 2923 (w) 1479 (m), 1461 (m), 1435 (s), 1151 (m); $\delta_H$ (400 MHz, $CDCl_3$) 4.31 – 4.25 (2H, m, $NCH_2$), 4.20 – 4.13 (2H, m, $NCH_2$), 3.25 (2H, q, *J* = 7.4 Hz, $SCH_2$), 2.46 – 2.28 (2H, m, $NCH_2CH_2$), 1.33 (3H, t, *J* = 7.4 Hz, $SCH_2CH_3$); $\delta_C$ (100 MHz, $CDCl_3$) 194.6 (C=S), 54.6 ($NCH_2$), 53.1 ($NCH_2$), 30.1 ($SCH_2$), 15.5 ($NCH_2CH_2$), 14.5 ($SCH_2CH_3$); HRMS (FTMS) calcd for [M+H] $C_6H_{12}NS_2$ 162.0406, found 162.0405.

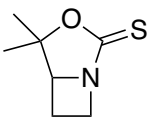
**2-(2-Hydroxypropan-2-yl)azetidin-1-ium chloride 151a**




HCl (1.80 mL, 2 M in $Et_2O$, 3.60 mmol) was added to *O*-*t*-butyl 2-(2-hydroxypropan-2-yl)azetidine-1-carbothioate **104c** (560 mg, 2.42 mmol) at rt. The mixture was stirred for 1 h at rt, then concentrated under reduced pressure to give a pale yellow solid, azetidinium chloride **151a** (354 mg, quant).

mp 95–97 °C; IR (neat/cm$^{-1}$) 2972 (w), 2361 (s), 2341 (s), 958 (w), 653 (s); $\delta_H$ (400 MHz, $D_2O$) 4.38 (1H, t, *J* = 8.8 Hz, NCH), 3.97 (1H, q, *J* = 9.9 Hz, NC*H*H'), 3.68 (1H, td, *J* = 9.9, 5.4 Hz,NCH*H'* ), 2.63 – 2.16 (2H, m, $NCH_2CH_2$), 1.11 (3H, s, $CH_3$), 1.10 (3H, s, $CH_3$); $\delta_C$ (125 MHz, $CDCl_3$) 69.3 (COH), 68.7 (NCH), 42.0 ($NCH_2$), 25.8 ($CH_3$), 23.9 ($CH_3$), 19.6 ($NCH_2CH_2$); HRMS (FTMS) calcd for [M-Cl] $C_6H_{14}NO$ 116.1070, found 116.1069.

**4,4-Dimethyl-3-oxa-1-azabicyclo[3.2.0]heptane-2-thione 152**

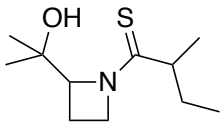



To a solution of chloride salt **151a** (40 mg, 0.28 mmol) in $CHCl_3$ (5.1 mL) and $Et_3N$ (0.12 mL, 0.8 mmol) was added thiophosgene (20 µL, 0.28 mmol) in $CHCl_3$ (0.70 mL) dropwise. The

mixture was stirred overnight at rt. The reaction was concentrated under reduced pressure, diluted with sat. aq $NaHCO_3$ (2 mL) and extracted with EtOAc (3 x 1.5 mL). The combined organic layers were dried ($MgSO_4$), concentrated under reduced pressure. The residue was purified by column chromatography (40% $Et_2O$/petroleum ether) to give a pale yellow solid, azabicycle **152** (33 mg, 75%).

$R_f$ 0.28 (50% $Et_2O$/petroleum ether); mp 73–74 °C; IR (neat/$cm^{-1}$) 2980 (m), 1349 (s), 1260 (s), 1226 (m), 1193 (w), 1140 (s); $\delta_H$ (400 MHz, $CDCl_3$) 4.53 – 4.42 (2H, m, NC*H* & NCH*H'*), 4.02 (1H, tdd, *J* = 9.5, 3.7, 0.7 Hz, NC*H*H' ), 2.82 (1H, dddd, *J* = 11.5, 9.5, 8.8, 8.0 Hz, $NCH_2CH$H'), 2.38 (1H, dtd, *J* = 11.5, 7.0, 3.7 Hz, $NCH_2CH$*H'*), 1.55 (3H, s, $CH_3$), 1.50 (3H, s, $CH_3$); $\delta_C$ (125 MHz, $CDCl_3$) 199.9 (C=S), 90.4 (O*C*$(CH_3)_2$ , 72.1 (NCH), 57.3 ($NCH_2$), 28.0 ($CH_3$), 25.5 (NCH*C*$H_2$), 23.0 ($CH_3$); ); LRMS ($ESI^+$) 180.0 ($[M+Na]^+$, 100 %); HRMS (FTMS) calcd for [M+H] $C_7H_{12}NOS$: 158.0634, found 158.0634.

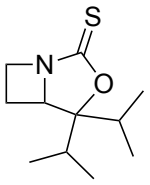
**1-(2-(2-Hydroxypropan-2-yl)azetidin-1-yl)-2-methylbutane-1-thione 153**




Thioamide was prepared following general procedure **A**, using azabicycle **152** (15 mg, 0.10 mmol) and TMEDA (0.04 mL, 0.24 mmol), with a –78 °C lithiation temp (30 min). MeI (0.02 mL, 0.30 mmol) was then added dropwise at –78 °C (30 min) and then warmed to rt over 10 min. The crude material. The crude material was purified by column chromatography (20% $Et_2O$/ 20% petroleum ether/ DCM) to give a colourless oil, thioamide **153** (10 mg, 50%, 61% brsm, 50:50 dr), as a ~1:1 mixture of inseparable diastereomers.

$R_f$ 0.52 (20% $Et_2O$/20% petroleum ether/DCM); IR (neat/$cm^{-1}$) 3279 (br), 2967 (m), 2924 (m), 1491 (s), 1462 (m), 1444 (m); $\delta_H$ (400 MHz, $CDCl_3$) (mixture of diastereomers) 6.08 (6.02) (1H, s, OH), 4.74 (1H, t, *J* = 7.6 Hz, NCH), 4.27 – 4.07 (2H, m, $NCH_2$), 2.59 – 2.36 (2H, m, C*H* $CH_3$ & $NCH_2CH$*H'*), 2.03-1.91 (1H, m, $NCH_2C$*H*H'), 1.87 – 1.69 (1H, m, CH*H'* $CH_3$), 1.59 – 1.46 (1H, m, *CH*H'$CH_3$), 1.28 (1.27) (3H, s, C(OH)C$H_3$), 1.17 (3H, d, *J* = 6.7 Hz CHC$H_3$), 1.14 (3H, s, C(OH) C$H_3$), 0.87 (3H, q, *J* = 7.5 Hz, $CH_2CH_3$); $\delta_C$ (125 MHz, $CDCl_3$) 208.8 (C=S), 77.4 (76.8) (NCH), 72.3 (72.2) (COH), 51.9 (51.6) ($NCH_2$), 43.7 (43.6) (*C*$HCH_3$), 30.9 (29.11) (*C*$H_2CH_3$), 25.2 (25.1) (C(OH)*C*$H_3$), 23.4 (23.0) (C(OH)*C*$H_3$), 21.4 (19.9) (CH*C*$H_3$), 18.85 (18.82) ($NCH_2CH_2$), 12.3 (12.2) ($CH_2CH_3$); HRMS (FTMS) calcd for [M+H] $C_{11}H_{22}NOS$ 216.1417, found 216.1416.

**4,4-Diisopropyl-3-oxa-1-azabicyclo[3.2.0]heptane-2-thione 156**

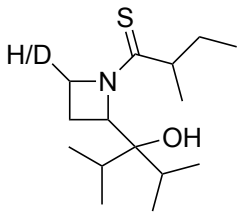



Azabicycle was prepared following general procedure **A**, using *N*-Botc-azetidine **101a** (200 mg, 1.15 mmol) and TMEDA (0.41 mL, 2.76 mmol), with a –78 °C lithiation temp (30 min). 2,4-Dimethyl-3-pentanone (0.21 mL, 1.50 mmol) was then added dropwise at – 78 °C (30 min) and then warmed to rt over 3 h. The crude material was purified by column chromatography (5% EtOAc/ petroleum ether) to give a crystalline solid, azabicycle **156** (164 mg, 67%).

$R_f$ 0.25 (20% EtOAc/ petroleum ether); mp 71–72 °C; IR (neat/$cm^{-1}$) 2962 (m), 1355 (s), 1327 (s), 1267 (s), 1247 (s), 1223 (s), 1183 (m), 1141 (m); $\delta_H$ (400 MHz, $CDCl_3$) 4.64 (1H, dd, *J* = 8.5, 6.8 Hz, NCH), 4.45 (1H, td, *J* = 9.2, 6.8 Hz, NC*H*H'), 4.01 (1H, td, *J* = 9.2, 3.5 Hz, NCH*H'*), 3.00 (1H, ddt, *J* = 11.3, 9.2, 8.5 Hz, NCHC*H*H'), 2.49 – 2.41 (1H, m, NCHCH*H'*), 2.40 – 2.24

(2H, m, C*H*($CH_3$)$_2$), 1.15 (3H, d, *J* = 6.9 Hz, CH(C*H*$_3$)$_2$), 0.96 – 0.90 (9H, m, CH(C*H*$_3$)$_2$); $\delta_C$ (100 MHz, $CDCl_3$) 199.6 (C=S), 99.7 (OC), 67.2 (NCH), 57.5 ($NCH_2$), 33.7 (*C*H($CH_3$)$_2$), 32.5 ((*C*H($CH_3$)$_2$), 27.0 (NCH*C*H$_2$), 18.7 (CH(*C*H$_3$)$_2$), 17.5 (CH(*C*H$_3$)$_2$), 17.4 (CH(*C*H$_3$)$_2$), 17.3 (CH(*C*H$_3$)$_2$); HRMS (FTMS) calcd for [M+H] $C_{11}H_{20}ONS$ 214.1260, found 214.1263.

**1-(2-(3-Hydroxy-2,4-dimethylpentan-3-yl)azetidin-1-yl)-2-methylpentane-1-thione 157**

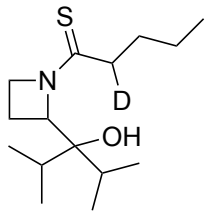



Thioamide was prepared following general procedure **A**, using azabicycle **156** (25 mg, 0.12 mmol) and TMEDA (0.04 mL, 0.29 mmol), with a –78 °C lithiation temp followed by warming to –45 °C (30 min). $CD_3OD$ (0.1 mL, 2.3 mmol) was then added dropwise at – 45 °C (5 min) and then warmed to rt (10 min). The crude material was purified by column chromatography (20% EtOAc/ petroleum ether) to give a colourless oil, thioamide **157** (12 mg, 37%, 50% D) as a ~1:1 mixture of inseparable diastereomers.

$R_f$ 0.74 (75% $Et_2O$/ petroleum ether); IR (neat/$cm^{-1}$) 3327 (br), 3007 (m), 2960 (m), 2926 (w), 1519 (s), 1496 (m), 1453 (m), 1386 (m), 1359 (w), 1335 (m), 993 (m); $\delta_H$ (400 MHz, $CDCl_3$) (mixture of diastereomers) 5.79 (1H, s, OH), 5.71 (1H, s, OH), 5.10 – 4.91 (2H, m, NCH), 4.36 – 4.09 (3H, m, $NCH_2$ & NCHD), 2.57 – 2.29 (6H, m, C(S)CH & NCHC*H*$_2$), 2.26 – 2.14 (2H, m, C*H*($CH_3$)$_2$), 2.05 – 1.94 (2H, m, C*H*($CH_3$)$_2$), 1.85 – 1.71 (2H, m, C*H*H'$CH_3$), 1.59 – 1.45 (2H, m, CH*H'*$CH_3$), 1.17 – 1.09 (12H, m, CHC*H*$_3$ & CH(C*H*$_3$)$_2$), 1.08 – 1.01 (12H, m, CH(C*H*$_3$)$_2$), 0.93 – 0.86 (6H, m, CH(C*H*$_3$)$_2$ & $CH_2$C*H*$_3$), 0.84 (3H, t, *J* = 7.4 Hz, $CH_2$C*H*$_3$); $\delta_C$ (100 MHz, $CDCl_3$) (mixture of diastereomers) 209.8 (C=S), 209.5 (C=S), 78.1 (COH), 77.9 (COH),

76.6 (NCH), 76.2 (NCH), 52.4 ($NCH_2$), 52.1 ($NCH_2$), 43.8 (C(S)*C*H), 43.5 (C(S)*C*H), 33.4 (*C*H($CH_3$)$_2$), 33.2 (*C*H($CH_3$)$_2$), 33.0 (*C*H($CH_3$)$_2$), 30.7 (*C*$H_2CH_3$), 29.2 (*C*$H_2CH_3$), 20.9 (CH*C*$H_3$), 19.6 (CH*C*$H_3$), 19.1 (CH(*C*$H_3$)$_2$), 19.0 ($NCHCH_2$), 18.92 ($NCHCH_2$), 18.88 (CH(*C*$H_3$)$_2$), 18.8 (CH(*C*$H_3$)$_2$), 18.2 (CH(*C*$H_3$)$_2$), 18.1 (CH(*C*$H_3$)$_2$), 17.84 (CH(*C*$H_3$)$_2$), 17.82 (CH(*C*$H_3$)$_2$), 17.7 (CH(*C*$H_3$)$_2$), 12.3 ($CH_2$*C*$H_3$), 12.2 ($CH_2$*C*$H_3$); HRMS (FTMS) calcd for [M+H] $C_{15}H_{30}ONS$ 272.2043, found 272.2044 and [M+1+H (base peak)] 273.2102.

**1-(2-(3-Hydroxy-2,4-dimethylpentan-3-yl)azetidin-1-yl)pentane-1-thione-2-d 158**



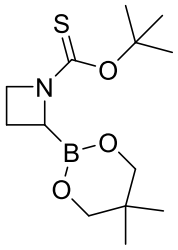

A solution of azabicycle **156** (50 mg, 0.23 mmol) in THF (2.3 mL) was cooled to –78 °C before the addition of TMEDA (80 µL, 0.55 mmol). *n*-BuLi (230 µL, 2.1 M in hexanes, 0.48 mmol) was added dropwise and the mixture was stirred for 1 h at –78 °C. $CD_3OD$ (0.1 mL, 2.3 mmol) was added and the mixture was allowed to warm to rt. The reaction was quenched with sat. aq $NH_4Cl$ (5 mL) and extracted with $Et_2O$ (4 x 5 mL). The combined organic extracts were washed with water (10 mL) and brine (10 mL), dried ($Na_2SO_4$) and concentrated under reduced pressure to give a colourless oil. This crude material was purified by column chromatography (20% EtOAc/petroleum ether) to give a colourless oil, thioamide **158** (23 mg, 36%, 61% brsm >90% D by NMR).

$R_f$ 0.52 (50% EtOAc/ petroleum ether); IR (neat/$cm^{-1}$) 3273 (br), 2960 (m), 2875 (w), 1474 s), 1383 (w); $\delta_H$ (400 MHz, $CDCl_3$) 5.62 (1H, s, OH), 4.97 (1H, dd, *J* = 9.4, 7.0 Hz, NCH), 4.33 – 4.08 (2H, m, $NCH_2$), 2.50 – 2.28 (3H, m, NCHC*H*$_2$ & CDH), 2.19 (1H, hept, *J* = 7.0 Hz,

C*H*($CH_3$)$_2$), 1.98 (1H, hept, *J* = 6.8 Hz, C*H*($CH_3$)$_2$), 1.66 (2H, q, *J* = 7.7 Hz, CDHC*H*$_2$), 1.43 – 1.31 (2H, m, C*H*$_2$$CH_3$), 1.11 (3H, d, *J* = 7.0 Hz, CH(C*H*$_3$)$_2$), 1.05 (3H, d, *J* = 7.0 Hz, (CH(C*H*$_3$)$_2$), 1.02 (3H, d, *J* = 6.8 Hz, CH(C*H*$_3$)$_2$), 0.96 – 0.87 (6H, m, CH(C*H*$_3$)$_2$ & $CH_2$C*H*$_3$); $\delta_C$ (100 MHz, $CDCl_3$) 204.1 (C=S), 78.0 (COH), 76.6 (NCH), 52.5 ($NCH_2$), 40.1 (T, *J* = 19.7 Hz, CDH), 33.3 (*C*H($CH_3$)$_2$), 32.9 (*C*H($CH_3$)$_2$), 30.5 (CDH*C*H$_2$), 22.4 (*C*H$_2$$CH_3$), 18.83 (NCH*C*H$_2$), 18.75 (CH(*C*H$_3$)$_2$), 18.1 (CH(*C*H$_3$)$_2$), 17.8 (CH(*C*H$_3$)$_2$), 17.7 (CH(*C*H$_3$)$_2$), 13.9 (CH$_2$*C*H$_3$); HRMS (FTMS) calcd for [M+H] $C_{15}H_{29}$DONS 273.2105, found 273.2105.

### 5.3.2. 2-Boryl azetidine synthesis and functionalisation

**_O_-(_t_-Butyl) 2-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)azetidine-1-carbothioate 104i**



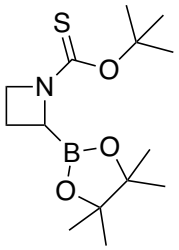

Boronic etser was prepared following general procedure **A**, using *N*-Botc-azetidine **101a** (40 mg, 0.23 mmol) and TMEDA (0.08 mL, 2.76 mmol), with a –78 °C lithiation temp (30 min). B(*i*-PrO)$_3$ (0.11 mL, 0.46 mmol) was then added dropwise at – 78 °C (120 min). The crude material was dissolved in PhMe (1 mL) and neopentylglycol (30 mg, 0.28 mmol) was added. The reaction was stirred overnight at rt. The reaction was quenched with $H_2O$ (6 mL) and extracted with DCM (3 x 6 mL). The combined organic phases were washed with $H_2O$ (1 x 6 mL), dried ($Na_2SO_4$) and concentrated under reduced pressure to give desired boronic ester **104i** (11 mg, 16%).

Available data for **104i**

$R_f$ 0.00 (50% $Et_2O$/petroleum ether); $\delta_H$ (400 MHz, $CDCl_3$) (1.5:1 rotamer mixture by analysis of $OCH_2$ signals in the 3.65 – 3.62 region) 4.14 (1H, t, *J* = 7.7 Hz, NCH), 4.10 – 3.84 (2H, m,

$NCH_2$), 3.62 (3.65) (4H, s, $OCH_2$), 2.45 – 2.12 (1H, m, NCHNCH*H'*), 2.09 – 1.96 (1H, m, NCHNC*H*H'), 1.61 (9H, s, $C(CH_3)_3$), 0.98 (0.99) (6H, s, $CH_3$); $\delta_C$ (100 MHz, $CDCl_3$) (mixture of rotamers) 185.6 (185.3) (C=S), 84.3 (84.2) ($C(CH_3)_3$, 72.3 (72.2) ($OCH_2$), 52.0 ($NCH_2$), 32.0 (32.1) ($C(CH_3)_2$), 28.62 (28.64) ($C(CH_3)_3$), 22.0 (22.3) ($C(CH_3)_2$), 16.4 (16.1) ($NCHCH_2$). BCH carbon not observed due to quadrupolar relaxation. LRMS found [M+Na] 308.2.

***O*-(*t*-Butyl)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)azetidine-1-carbothioate 104g**



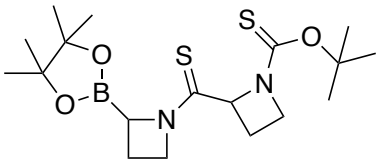

The boronic ester was prepared following general procedure **B**, using *N*-Botc azetidine **101a** (625 mg, 3.60 mmol) and DIANANE (±)-**105** (850 mg, 3.30 mmol), with a –78 °C lithiation temp (1 h). *i*-PrOB(pin) (0.96 mL, 4.70 mmol) was then added dropwise at –78 °C (2 h). The reaction mixture was quenched with aq HCl (1 M, 50 mL), and extracted with petroleum ether/$Et_2O$ (9:1) (4 × 30 mL). The combined organic extracts were washed with water (20 mL), then brine (20 mL), dried ($MgSO_4$) and concentrated under reduced pressure to give a pale-yellow oil which solidified under hi-vaccum (1 mbar) to give boronic ester **104g** (960 mg, 89%).

mp 55–57 °C; IR (neat/$cm^{-1}$) 2977 (w), 1491 (m), 1444 (m), 1416 (m), 1381 (m), 1338 (m), 1267 (m), 1226 (m), 1138 (s); $\delta_H$ (400 MHz, $CDCl_3$) (1.5:1 rotamer mixture, by analysis of $C(CH_3)_3$ signals in the 1.63-1.57 region) 4.21 – 3.95 (3H, m, NCH & $NCH_2$), 2.35 – 2.10 (1H, m, NCHC*H*H'), 2.06 – 1.94 (1H, m, NCHCH*H'*) 1.61 (1.59) (9H, s, $C(CH_3)_3$), 1.31 – 1.23 (12H,

m, $OC(CH_3)_2$); $\delta_C$ (100 MHz, $CDCl_3$) (mixture of rotamers) 184.0 (184.6) (C=S), 84.6 (84.3) ($C(CH_3)_3$), 84.2 (84.1) ($OC(CH_3)_2$), 51.9 (50.8) ($NCH_2$), 28.6 ($C(CH_3)_3$), 25.1 (24.8) ($OC(CH_3)_2$), 16.2 (15.6) ($NCHCH_2$). BCH carbon not observed due to quadrupolar relaxation. $\delta_B$ (128 MHz, $CDCl_3$) 32; HRMS (FTMS) calcd for [M+Na] $C_{14}H_{26}O_3N^{11}B^{32}SNa$ 322.1619, found 322.1620.

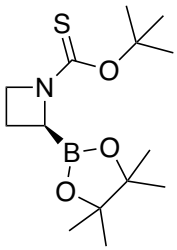
*Boronic ester was also prepared following general procedure **A**, using N-Botc-azetidine **101a** (2.00 g, 11.5 mmol) and TMEDA (4.1 mL, 27.6 mmol), with a –78 °C lithiation temp (30 min). i-PrOB(pin) (3.1 mL, 15.0 mmol) was then added dropwise at – 78 °C (30 min) and then warmed to rt over 2 h. The crude material was taken up in a minimal amount of hexane and left in the freezer overnight. The resulting crystals were filtered, washed with cold hexane (3 x 10 mL) and dried to give boronic ester **199** (301 mg, 7%). The mother liquor was concentrated under reduced pressure. To the crude was added MeOH:$H_2O$ (1:1) (25 mL) which was then concentrated under reduced pressure. The resulting solid was recrystallise from hexane (with activated carbon) and left in the freezer overnight. The resulting solid was filtered, washed with cold hexane (3 x 10 mL) and dried to give boronic ester **104g** (2.20 g, 64%). All data described as above.*

**_O_-(_t_-Butyl) 2-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)azetidine-1-carbonothioyl)azetidine-1-carbothioate 199**



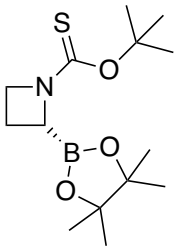
$R_f$ 0.01 ($Et_2O$); 2975 (w), 2932 (w), 1519 (m), 1475 (m), 1446 (m), 1430 (m), 1380 (m), 1373 (m), 1338 (m), 1285 (m), 1270 (m), 1143 (s);$\delta_H$ (400 MHz, $CDCl_3$) (mixture of diastereomers and rotamers) 5.10 – 4.98 (1 H, m, (C=S)CH), 4.54 – 4.16 (4.91 – 4.81) (3H, m, BCH and (C=S)$NCH_2$), 4.14 – 3.83 (2H, m, Botc$NCH_2$), 2.68 – 2.09 (4 H, m, $NCH_2CH_2$), 1.63 (1.60) (9 H, s, $C(CH_3)_3$), 1.28 (1.25) (12 H, s, $OC(CH_3)_2$); $\delta_C$ (100 MHz, $CDCl_3$) (mixture of diastereomers and rotamers) 193.9 (194.4) ((*C*=S)CH), 185.7 (185.6) ((*C*=S)O*t*-Bu), 86.1 (85.4) ($C(CH_3)_3$), 84.4 (84.3) ($OC(CH_3)_2$), 65.3 (63.1) ((C=S)*C*H), 54.1 (54.3) ((C=S)$NCH_2$), 49.4 (50.3) (Botc$NCH_2$), 28.4 (28.5) ($C(CH_3)_3$), 24.94 (25.0) ($OC(CH_3)_2$), 24.89 (24.8) ($OC(CH_3)_2$), 22.4 (22.0) ((C=S)$CHCH_2$), 17.0 (16.4) ($BCHCH_2$). ). BCH carbon not observed due to quadrupolar relaxation. $\delta_B$ (96 MHz, $CDCl_3$) 32; HRMS (FTMS) calcd for [M+Na] $C_{18}H_{32}N_2O_3BS_2$ 398.1978 found 398.1974.

**_O_-(_t_-Butyl) (_S_)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)azetidine-1-carbothioate (_S_)-104g**



The boronic ester was prepared following general procedure **B**, using *N*-Botc-azetidine **101a** (500 mg, 2.88 mmol) and DIANANE (*S*)-**105** (685 mg, 3.77 mmol), with a –78 °C lithiation temp (1 h). *i*-PrOB(pin) (0.77 mL, 3.75 mmol) was then added dropwise at –78 °C (2 h). The reaction mixture was quenched with aq HCl (1 M, 50 mL), and extracted with petroleum ether/$Et_2O$ (9:1) (4 × 30 mL). The combined organic extracts were washed with water (20 mL), then brine (20 mL), dried ($MgSO_4$) and concentrated under reduced pressure to give a pale-yellow oil which solidified under hi-vaccum (1 mbar) to give boronic ester (*S*)-**104g** (838 mg, 92%, 92:8 er by HPLC: Chiralcel AD-H column; eluent; *n*-hexane/*i*-PrOH (99:1); flow rate = 1 mL $min^{-1}$; $\tau_R$ ((*R*) minor) = 10.2 min, $\tau_R$ ((*S*) major) = 13.9 min); $[\alpha]_D^{25}$ +96.9 (*c* 1.05, $CHCl_3$); all other data as described for racemic **104g**.

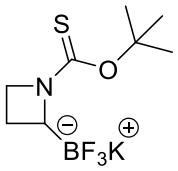
***O*-(*t*-Butyl) (*R*)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)azetidine-1-carbothioate (*R*)-104g**




The boronic ester was prepared following general procedure **B**, using *N*-Botc-azetidine **101a** (500 mg, 2.88 mmol) and DIANANE (*R*)-**105** (685 mg, 3.77 mmol), with a –78 °C lithiation temp (1 h). *i*-PrOB(pin) (0.77 mL, 3.75 mmol) was then added dropwise at –78 °C (2 h). The reaction mixture was quenched with aq HCl (1 M, 50 mL), and extracted with petroleum ether/$Et_2O$ (9:1) (4 × 30 mL). The combined organic extracts were washed with water (20 mL), then brine (20 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The crude material was purified by column chromatography (35% wt $H_2O$ $SiO_2$,

0-5% EtOAc/petroleum ether) gave a white solid, boronic ester (*R*)-**104g** (0.541 mg, 63%, 89:11 er by HPLC: Chiralcel AD-H column, eluent: *n*-hexane/*i*-PrOH (99:1), flow rate = 1 mL $min^{-1}$; $\tau_R$ ((*R*) major) = 10.2 min, $\tau_R$ ((*S*) minor) = 13.9 min); $[\alpha]_D^{25}$ −87.2 (*c* 0.98, $CHCl_3$); all other data as described for racemic **104g**.

**Potassium (1-(*t*-butoxycarbonothioyl)azetidin-2-yl)trifluoroborate 203**

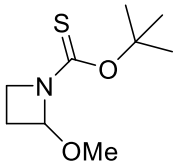



Boronic ester **104g** (155 mg, 0.52 mmol) was dissolved in acetone (1 mL) and was cooled to 0 °C. $KHF_2$ (120 mg, 1.55 mmol) and $H_2O$ (0.25 mL) was added to the solution at 0 °C. The reaction was was stirred for 30 min at rt. The mixture was concentrated under reduced pressure and dried overnight. The crude mixture was extracted with acetone (3 x 1 mL) and the combined organic extracts were concentrated. $Et_2O$ (2 mL) was added to precipitate the product. The solution was sonicated for 15 min and stored in the refridgerator overnight. The solid was filtered and dried *in vacuo* to give impure boronate salt **203** (127 mg, 88%)

Discernible data for boronate salt **203**

$\delta_H$ (400 MHz, acetone-$d_6$) 3.98 – 3.60 (3H, m, NCH & $NCH_2$), 2.00 – 1.80 (2H, m, NCHNC$H_2$), 1.57 (9H, s, $C(CH_3)_3$); $\delta_c$ (100 MHz, acetone-$d_6$) 182.9 (C=S), 82.1 ($C(CH_3)_3$), 52.5 ($NCH_2$), 28.8 ($C(CH_3)_3$), 25.2 (NCH$CH_2$). BCH carbon not observed due to quadrupolar relaxation. $\delta_F$ (377 MHz, acetone-$d_6$) (mixture of rotamers) –149.6 (–150.1) (Q, *J* = 49.3 Hz, (*J* = 48.8 Hz)); $\delta_B$ (128 MHz, acetone-$d_6$) 3 (Q, *J* = 55.2 Hz).

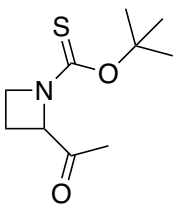
**_O_-(_t_-Butyl) 2-methoxyazetidine-1-carbothioate 210**




To a solution of boronic ester **104g** (60 mg, 0.20 mmol) in THF (1 mL) at 0 °C was added vinylmagnesium bromide (1 M in THF, 0.30 mL, 0.30 mmol). The mixture was stirred at rt for 30 mins before being cooled to –78 °C. A solution of iodine (0.5 M in MeOH, 0.48 mL, 0.24 mmol) was added dropwise and the reaction was stirred at –78 °C for 20 min. A solution of NaOMe (3 M in MeOH, 0.53 mL, 1.60 mmol) was added dropwise and the reaction mixture was warmed to 0 °C over 30 min. The reaction mixture was quenched with aq. $Na_2S_2O_3$ (5 mL), extracted with $Et_2O$ (3 x 5 mL), the combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The crude material was purified by column chromatography (10% $Et_2O$/petroleum ether) to give a coloulress oil, suspected methyoxyazetidine **210** (12 mg, 30%).

$R_f$ (10% $Et_2O$/petroleum ether) 0.51; $\delta_H$ (400 MHz, $CDCl_3$) (1:2.7 rotamer mixture by analysis of NCH signals in the 5.50 – 5.15 region) 5.24 (5.46) (1H, s br, NCH), 4.05 – 3.91 (1H, m, NCH*H*'), 3.92 – 3.80 (3.80 – 3.71) (1H, m, NC*H*H'), 3.48 (3.62) (3H, s br, $OCH_3$), 2.52 – 2.32 (1H, m, NCHCH*H*'), 2.23 – 1.98 (1H, m, NCHC*H*H'), 1.67 (9H, s br, $C(CH_3)_3$); $\delta_C$ (125 MHz, $CDCl_3$) 187.5 (188.6) (C=S), 91.7 (93.4) (NCH), 86.1 (85.7) ($C(CH_3)_3$), 56.7 (56.9) ($OCH_3$), 47.6 (47.0) ($NCH_2$), 28.5 ($C(CH_3)_3$), 23.7 (24.2) ($NCHCH_2$).

**_O_-(_t_-Butyl) 2-acetylazetidine-1-carbothioate 104l**

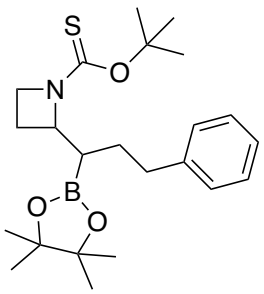


2-acetylazetidine was prepared following general procedure **A**, using *N*-Botc-azetidine **101a** (200 mg, 1.15 mmol) and TMEDA (0.41 mL, 2.76 mmol), with a –78 °C lithiation temp (30 min). A solution of *N*-methoxy-*N*-methylacetamide in THF (6.90 mL, 0.3M 3.45 mmol) was then added dropwise at – 78 °C (180 min). The crude material was purified by column chromatography (10% $Et_2O$/petroleum ether) to give a colourless oil, 2-acetylazetidine **104l** (56 mg, 23%, 31% BRSM).

$R_f$ 0.43 (50% $Et_2O$/petroleum ether); IR (neat/$cm^{-1}$) 2975 (w), 1716 (m), 1474 (m), 1436 (s), 1392 (m), 1365 (m), 1285 (s), 1145 (s); $\delta_H$ (400 MHz, $CDCl_3$) (1.3:1 rotamer mixture by analysis of the NCH signals in the 4.85 – 4.63 region) 4.67 (4.82) (1H, dd, *J* = 9.7, 5.9 Hz, (dd, *J* = 9.6, 5.8 Hz NCH), 4.10 (4.07 – 3.95) (2H, t, *J* = 7.6 Hz, (m), $NCH_2$ ), 2.51 – 2.35 (1H, m, NCHC*H*H'), 2.20 (2.29) (3H, s, NCHCOC$H_3$), 2.12 – 1.96 (1H, m, NCHCH*H*'), 1.58 (1.62) (9H, s, $C(CH_3)_3$); $\delta_C$ (100 MHz, $CDCl_3$) (mixture of rotamers) 204.8 (205.8) (C=S), 185.8 (186.7) (C=O), 86.1 (85.8) (*C*$(CH_3)_3$), 68.2 (68.6) (NCH), 49.8 (49.3) ($NCH_2$), 28.35 (28.39) (C(*C*$H_3)_3$), 25.6 (26.7) (NCHCO*C*$H_3$), 18.70 (18.6) (NH*C*$H_2$); HRMS (FTMS) calcd for [M+Na] $C_{10}H_{17}O_2NSNa$ 238.0872, found 238.0874.

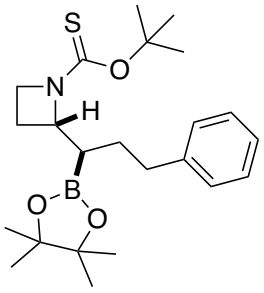
### 5.3.3 Boronic ester 104g homologation

***O*-*t*-Butyl 2-(3-phenyl-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propyl)azetidine-1-carbothioate (*R**,*R**)-223b and (*R**,*S**)-223b'**



Boronic ester **223b** was prepared following general procedure **C**, using benzoate **179a** (155 mg, 0.42 mmol), TMEDA (70 µL, 0.46 mmol) and boronic ester **104g** (190 mg, 0.63 mmol) with heating (63 °C) overnight (12 h). This residue was purified by chromatography (3% EtOAc/petroleum ether). First eluted, a colourless oil, benzoate **179a** (20 mg, 13%). Second eluted a colourless oil, which solidified on standing, minor diastereomer (*R*,S**)-**223b'** (22 mg, 12%). Thirdly eluted a colourless oil, which solidified on standing, major diastereomer (*R*,R**)-**223b** (104 mg, 59%).

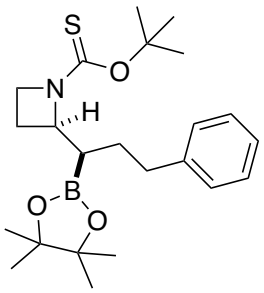
**_O_-_t_-Butyl (_R_*)-2-((_S_*)-3-phenyl-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propyl)azetidine-1-carbothioate (_R_*,_S_*)-223b'**




$R_f$ 0.38 (10% EtOAc/petroleum ether); mp 63-64 °C; IR (neat/cm$^{-1}$) 2978 (w), 2927 (w), 1477 (m), 1437 (m), 1390 (m), 1366 (m), 1330 (m), 1280 (m), 1141 (s); $\delta_H$ (500 MHz, $CDCl_3$) (7.4:1 rotamer mixture by analysis of the NCH signals in the 4.67 – 4.37 region) 7.35 – 7.11 (5H, m, Ph), 4.41 (4.64) (1H, q, *J* = 6.5 Hz, (*J* = 6.0 Hz), NCH), 3.99 (3.91 – 3.83) (2H, t, *J* = 7.7 Hz, (m), $NCH_2$), 2.74 – 2.52 (2.42 – 2.35) (2H, m, $PhCH_2$), 2.27 – 2.07 (2H, m, NCHC*H*$_2$), 1.96 (1H, dt, *J* = 9.8, 6.5 Hz, BCH), 1.74 (1H, dtd, *J* = 13.1, 9.8, 5.6 Hz, $PhCH_2CHH'$), 1.61 (1.63) (9H, s, $C(CH_3)_3$), 1.59 – 1.54 (1H, m, $PhCH_2CHH'$), 1.28 (1.27) (12H, s, $C(CH_3)_2$); $\delta_C$ (125 MHz, $CDCl_3$) (mixture of rotamers) 185.5 (185.3) (C=S), 142.3 (*i*-Ph), 128.49 (*o*-Ph), 128.46 (*m*-Ph), 126.0 (*p*-Ph), 85.0 (84.2) ($C(CH_3)_3$), 83.4 (83.2) ($OC(CH_3)_2$), 65.3 (66.1) (NCH), 49.7 (49.6) ($NCH_2$),

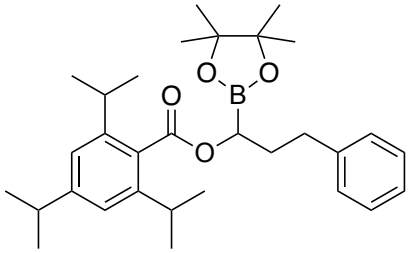
35.6 (35.8) ($PhCH_2$), 29.4 (29.9) ($PhCH_2CH_2$), 28.5 (28.7) ($C(CH_3)_3$), 25.22 (25.15) ($OC(CH_3)_2$), 25.1 (25.0) ($OC(CH_3)_2$), 18.8 (19.7) ($NCHCH_2$). BCH carbon not observed due to quadrupolar relaxation. $\delta_B$ (128 MHz, $CDCl_3$) 34; HRMS (FTMS) calcd for [M+Na] $C_{23}H_{37}O_3N^{11}B^{32}SNa$ 440.2401, found 440.2403.

**_O_-_t_-Butyl (_R_*)-2-((_R_*)-3-phenyl-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propyl)azetidine-1-carbothioate (_R_*,_R_*)-223b**




$R_f$ 0.29 (10% EtOAc/petroleum ether); mp 75-76 °C; IR (neat/$cm^{-1}$) 2978 (w), 1479 (m), 1439 (m), 1367 (m), 1323 (m), 1275 (m), 1242 (m), 1140 (s); $\delta_H$ (400 MHz, $CDCl_3$) (4.9:1 rotamer mixture by analysis of the NCH signals in the 4.70 – 4.44 region) 7.36 – 7.09 (m, 5H, Ph), 4.55 (4.73) (1H, dt, *J* = 9.7, 5.5 Hz, (*J* = 9.7, 5.2 Hz), NCH), 3.99 – 3.78 (2H, m, $NCH_2$), 2.80 (1H, ddd, *J* = 13.9, 10.3, 4.9 Hz, PhC*H*H'), 2.64 – 2.43 (2.44) (1H, m, (dt, *J* = 9.8, 4.5 Hz), PhCH*H'*), 2.25 – 1.64 (5H, m, $NCHCH_2$, BCH and $PhCH_2CH_2$), 1.55 (1.61) (9H, s, $C(CH_3)_3$), 1.26 – 1.23 (12H, m, $C(CH_3)_2$); $\delta_C$ (100 MHz, $CDCl_3$) (mixture of rotamers) 185.5 (C=S), 142.6 (*i*-Ph), 128.7 (128.6) (*o*-Ph), 128.5 (128.3) (*m*-Ph), 125.9 (*p*-Ph), 84.8 (84.3) ($C(CH_3)_3$), 83.5 (83.3) ($OC(CH_3)_2$), 65.5 (66.4) (NCH), 49.6 (49.9) ($NCH_2$), 35.8 (35.9) ($PhCH_2$), 28.6 (28.7) ($C(CH_3)_3$), 26.6 (26.8) ($PhCH_2CH_2$), 25.08 (25.11) ($OC(CH_3)_2$), 24.8 (24.9) ($OC(CH_3)_2$), 18.3 (19.1) ($NCHCH_2$). BCH carbon not observed due to quadrupolar relaxation. $\delta_B$ (128 MHz, $CDCl_3$) 34; HRMS (FTMS) calcd for [M+H] $C_{23}H_{37}O_3N^{10}B^{32}S$ 417.2624, found 417.2627.

**3-Phenyl-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propyl 2,4,6-triisopropylbenzoate 179f**



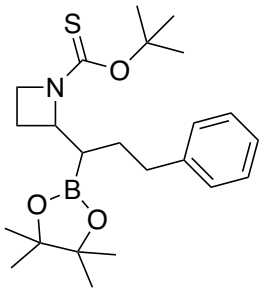
A solution of triisopropyl benzoate **179a** (215 mg, 0.59 mmol) and TMEDA (0.11 mL, 0.71 mmol) in $Et_2O$ (1.2 mL) under $N_2$ was cooled to –78 °C. *s*-BuLi (0.55 mL, 1.3 M in hexanes, 0.71 mmol) was added dropwise and the reaction mixture was stirred for 4 h at –78 °C. *i*-PrOB(pin) (0.15 mL, 0.71 mmol) was then added dropwise, the mixture was stirred at –78 °C for 1 h and then warmed to rt. After 10 min, the reaction mixture was quenched with sat. aq $NH_4Cl$ (1 mL) and extracted with EtOAc (3 x 2 mL). The combined organic extracts were dried ($Na_2SO_4$) and concentrated under reduced pressure to give a crude residue as a colourless oil. The residue was purified by column chromatography (5% $Et_2O$/petroleum ether) to give a colourless oil which solidified on standing to give a white solid, boronic ester **179f** (244 mg, 84%).

$R_f$ 0.35 (25% $Et_2O$/petroleum ether); mp 83–84 °C; IR (neat/$cm^{-1}$) 2961 (m), 2929 (m), 1709 (s), 1460 (m), 1383 (s), 1343 (s), 1288 (m), 1246 (s), 1139 (s), 1105 (m), 1076 (s), 968 (m), 876 (m), 850 (m), 748 (m), 700 (s); $\delta_H$ (400 MHz, $CDCl_3$) 7.31 – 7.24 (2H, m, *m*-Ph), 7.21 – 7.15 (3H, m, *o*- & *p*-Ph), 7.02 (2H, s, *m*-Ar), 4.20 (1H, dd, *J* = 9.3, 4.7 Hz, BCH), 3.08 (2H, hept, *J* = 6.8 Hz, 2 x *o*-ArC*H*$(CH_3)_2$), 2.95 – 2.79 (2H, m, *p*-ArC*H*$(CH_3)_2$ & PhC*H*H'), 2.71 (1H, ddd, *J* = 13.7, 10.2, 6.4 Hz, PhCH*H'*), 2.19 – 1.96 (2H, m, $PhCH_2CH_2$), 1.32 – 1.22 (30H, m, 10 x Me); $\delta_C$ (100 MHz, $CDCl_3$) 172.5 (C=O), 150.2 (*p*-Ar), 145.4 (*o*-Ar), 141.8 (*i*-Ph), 130.1 (*i*-Ar), 128.6

(*o*-Ph), 128.5 (*m*-Ph), 126.0 (*p*-Ph), 121.0 (*m*-Ar), 84.0 (O*C*($CH_3$)$_2$), 34.6 (*p*-Ar*C*H($CH_3$)$_2$), 33.3 (Ph*C*$H_2$), 32.3 (PhC$H_2$*C*$H_2$), 31.1 (*o*-Ar*C*H($CH_3$)$_2$), 25.0 (OC(*C*$H_3$)$_2$), 24.8 (OC(*C*$H_3$)$_2$), 24.5 (*o*-ArCH(*C*$H_3$)$_2$), 24.1 (*p*-ArCH(*C*$H_3$)$_2$). BCH carbon not observed due to quadrupolar relaxation. $\delta_B$ (128 MHz, $CDCl_3$) 32; HRMS (FTMS) calcd for [M+H] $C_{31}H_{46}{}^{10}BO_4$ 492.3520, found 492.3527.

**Reversal of boronic ester and lithiated intermediate**

***O*-*t*-Butyl 2-(3-phenyl-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propyl)azetidine-1-carbothioate (*R**,*R**)-223b and (*R**,*S**)-223b'**

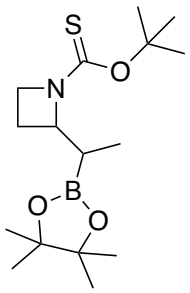



To a solution of *N*-Botc azetidine **101a** (26 mg, 0.15 mmol) and TMEDA (50 µL, 0.34 mmol) in THF (0.75 mL) under $N_2$ was cooled to –78 °C. *s*-BuLi (0.15 mL, 1.3 M in cyclohexane/hexanes, 0.20 mmol) was added dropwise and the reaction mixture was stirred for 1 h at –78 °C. A solution of boronic ester **179f** (0.45 mL, 0.5 M in THF, 0.22 mmol) was added dropwise and the mixture was stirred at –78 °C for 45 min. The mixture was warmed to rt, solvents removed under vacuum, then $CHCl_3$ (1.2 mL) was added. The solution was heated under reflux (63 °C) overnight (12 h). The reaction mixture was then quenched with water (3 mL) and the layers separated. The organic layer was washed with brine (2 x 2 mL) and the combined aq layers extracted with $CH_2Cl_2$ (3 x 5 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure to give a colourless oil. This residue was purified by column chromatography (3% EtOAc/petroleum

ether). First eluted a colourless oil, minor diastereomer (*R*,S**)-**223b'** (8 mg, 13%). Second eluted a colourless oil, major diastereomer (*R*,R**)-**223b** (15 mg, 24%).

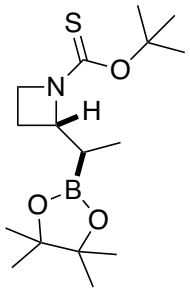
All data matched those described previously (p 223 – 224).

**O-(*t*-Butyl) 2-(1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)ethyl)azetidine-1-carbothioate 223c**



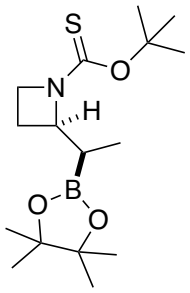

Boronic ester **223c** was prepared following general procedure **C**, using benzoate **179c** (155 mg, 0.56 mmol), TMEDA (90 µL, 0.62 mmol) and boronic ester **104g** (251 mg, 0.84 mmol) with heating (63 °C) overnight (12 h). This residue was purified by chromatography (3% EtOAc/petroleum ether). First eluted, a colourless oil, minor diastereomer (*R*,S**)-**223c;** (46 mg, 25%). Second eluted a colourless oil, major diastereomer (*R*,R**)-**223c** (93 mg, 51%).

***O*-(*t*-Butyl) (*R**)-2-((*S**)-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)ethyl)azetidine-1-carbothioate (*R**,*S**)-223c'**



$R_f$ 0.25 (10% $Et_2O$/petroleum ether); 2976 (m), 2918 (m), 1479 (m), 1465 (m), 1438 (m), 1391 (m), 1380 (m), 1366 (m), 1330 (m), 1281 (m), 1266 (s), 1144 (s); $\delta_H$ (400 MHz, $CDCl_3$) (5.4:1 rotamer mixture by analysis of the NCH signals in the 4.58 – 4.25 region) 4.29 (4.58 – 4.49) (1H, pseudo q, *J* = 7.5 Hz, (m), NCH), 4.06 – 3.79 (2H, m, $NCH_2$), 2.40 – 1.96 (2H, m, NCHC*H*$_2$), 1.88 (1H, pseudo quin, *J* = 7.5 Hz, BCH), 1.64 (1.61) (9H, s, $C(CH_3)_3$), 1.23 (1.25) (12H, s, $C(CH_3)_2$), 0.93 (0.96) (3H, d, *J* = 7.5 Hz, BCHC*H*$_3$); $\delta_C$ (100 MHz, $CDCl_3$) (mixture of rotamers) 185.4 (C=S), 84.9 (*C*$(CH_3)_3$), 83.3 (O*C*$(CH_3)_2$), 66.8 (NCH), 49.8 ($NCH_2$), 28.6 (28.7) (C(*C*$H_3)_3$), 25.1 (25.0) (OC(*C*$H_3)_2$), 24.8 (OC(*C*$H_3)_2$), 19.5 (NCH*C*$H_2$), 11.7 (BCH*C*$H_3$). BCH not observed due to quadrupolar relaxation. $\delta_B$ (128 MHz, $CDCl_3$) 34; HRMS (FTMS) calcd for [M+Na] $C_{16}H_{30}{}^{11}BNO_3{}^{32}SNa$ 350.1932, found 350.1931.

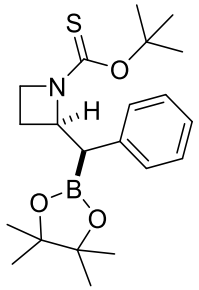
**_O_-(_t_-Butyl) (_R*_)-2-((_R*_)-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)ethyl)azetidine-1-carbothioate (_R*_,_R*_)-223c**




$R_f$ 0.16 (10% $Et_2O$/petroleum ether); IR (neat/$cm^{-1}$) 2976 (m), 2929 (w), 2880 (w), 1481 (m), 1452 (m), 1440 (m), 1390 (m), 1363 (s), 1322 (m), 1277 (s), 1268 (s), 1235 (m), 1224 (m), 1143 (s), 1102 (m), 1022 (w); $\delta_H$ (400 MHz, $CDCl_3$) (3.7:1 rotamer mixture by analysis of the NCH signals in the 4.80 – 4.54 region) 4.64 – 4.54 (4.80 – 4.72) (1H, m, NCH), 4.05 – 3.72 (2H, m, $NCH_2$), 2.28 – 2.09 (1H, m, NCHCH*H'*), 1.98 – 1.82 (2.48) (2H, m, (qd, *J* = 7.5, 4.6 Hz, $BCH_{minor\ rot}$), NCHC*H'*H and BCH), 1.62 (1.61) (9H, s, $C(CH_3)_3$), 1.22 – 1.19 (12H, m, $OC(CH_3)_2$), 1.00 (1.01) (2H, d, *J* = 7.5 Hz, (*J* = 7.5 Hz), BCHC*H*$_3$); $\delta_C$ (100 MHz, $CDCl_3$) (mixture of

rotamers) 185.2 (184.8) (C=S), 84.8 (84.3) (*C*$(CH_3)_3$), 83.5 (83.2) (O*C*$(CH_3)_2$), 65.8 (66.5) (NCH), 49.7 (49.9) ($NCH_2$), 28.7 (C(*C*$H_3)_3$), 25.0 (OC(*C*$H_3)_2$), 24.7 (OC(*C*$H_3)_2$), 17.7 (18.4) (NCH*C*$H_2$), 8.1 (7.7) (BCH*C*$H_3$). BCH carbon not observed due to quadrupolar relaxation. $\delta_B$ (128 MHz, $CDCl_3$) 34; HRMS (FTMS) calcd for [M+Na] $C_{16}H_{30}{}^{11}BNO_3{}^{32}SNa$ 350.1932, found 350.1933.

**_O_-(_t_-Butyl) (_R_*)-2-((_R_*)-phenyl(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl)azetidine-1-carbothioate 223d**

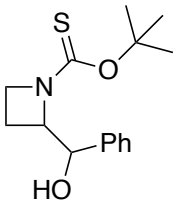



Boronic ester **223d** was prepared following general procedure **C**, using benzoate **179e** (130 mg, 0.38 mmol), TMEDA (60 µL, 0.42 mmol) and boronic ester **104g** (170 mg, 0.57 mmol) with heating (63 °C) overnight (12 h). This residue was purified by flash chromatography (3% EtOAc/petroleum ether) eluted a colourless oil, major diastereomer (*R*,R**)-**223d** (29 mg, 20%). Minor diastereomer could not be separated from impurities (~8 mg, 5%).

$R_f$ 0.32 (10% $Et_2O$/petroleum ether); IR (neat/$cm^{-1}$) 2975 (w), 1480 (m), 1438 (m), 1364 (m), 1244 (m), 1140 (s); $\delta_H$ (400 MHz, $CDCl_3$) (1.2:1 rotamer mixture by analysis of NCH signals in the 4.90 – 4.68 region) 7.36 – 7.13 (5H, m, Ph), 4.70 (4.88) (1H, dddd, *J* = 9.2, 5.4, 3.9, 1.3 Hz, (dtd, *J* = 8.8, 4.9, 1.4 Hz), NCH), 3.70 (3.59) (1H td, *J* = 10.2, 5.6 Hz, (td, *J* = 10.1, 5.4 Hz), NCH*H*'), 3.23 (3.81) (1H, d, *J* = 3.9 Hz, (d, *J* = 4.9 Hz), BCH), 2.99 (2.91) (1H dddd, *J* = 10.2, 9.2, 6.4, 1.3 Hz, (dddd, *J* = 10.1, 9.2, 6.7, 1.4 Hz), NC*H*H'), 2.31 – 2.14 (1H, m, NCHCH*H*'), 2.00 – 1.84 (1H, m, NCHC*H*H'), 1.73 (1.59) (9H, s, C$(CH_3)_3$), 1.31 – 1.17 (12H, m, OC$(CH_3)_2$);

$\delta_C$ (100 MHz, $CDCl_3$) (rotamers) 185.0 (184.4) (C=S), 136.9 (137.9) (*i*-Ph), 131.1 (131.4) (*m*-Ph), 128.4 (128.0) (*o*-Ph), 126.6 (126.2) (*p*-Ph), 84.9 (84.3) ($C(CH_3)_3$), 83.9 (83.7) ($OC(CH_3)_2$), 65.5 (65.9) (NCH), 49.3 (49.2) ($NCH_2$), 28.9 (28.7) ($C(CH_3)_3$), 24.9 (25.0) ($OC(CH_3)_2$), 24.8 ($OC(CH_3)_2$), 18.1 (19.1) ($NCHCH_2$). BCH carbon not observed due to quadrupolar relaxation. $\delta_B$ (128 MHz, $CDCl_3$) 33; HRMS (FTMS) calcd for [M+H] $C_{21}H_{33}O_3N^{11}BS$ 390.2269, found 390.2265.

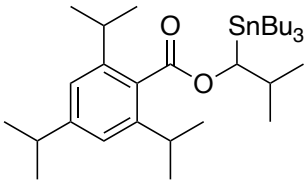
**_O_-(_tert_-butyl) 2-(hydroxy(phenyl)methyl)azetidine-1-carbothioate 104b**




Alcohol **104b** was prepared following general procedure **C**, using benzoate **179e** (98 mg, 0.29 mmol), TMEDA (50 µL, 0.32 mmol) and boronic ester **104g** (130 mg, 0.43 mmol) with heating (63 °C) overnight (12 h). The reaction mixture evaporated under vacuum (1 mbar), then THF:$H_2O$ (1:1) (4.8 mL) and sodium perborate tetrahydrate (225 mg, 1.45 mmoL) was added and the reaction was stirred vigorously at rt for 1 h. The reaction mixture was diluted with water (10 mL) and extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (10 mL0, dried ($MgSO_4$) This residue was purified by flash chromatography (10% $Et_2O$/petroleum ether) to first give a colourless oil, minor diastereomer alcohol (*R*,S**)-**104b'** (14 mg, 18%). Second eluted a colourless oil, major diastereomer alcohol (*R*,R**)-**104b** (35 mg, 43%). All other data as described in lit.[93]

### 5.3.4 Preparation of stannanes and homologation of boronic ester 104g

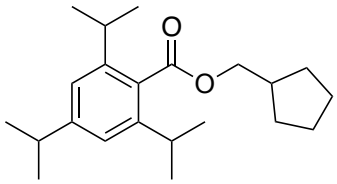
**2-Methyl-1-(tributylstannyl)propyl 2,4,6-triisopropylbenzoate 230c**




Stannane **230c** was prepared following general procedure **D**, using isobutyl triisopropylbenzoate[161] (1.00 g, 3.30 mmol). The crude material was purified by column chromatography (1% $Et_2O$/petroleum ether) to give a colourless oil, stannane **230c** (1.68 g, 86%).

$R_f$ 0.71 (5% $Et_2O$/petroleum ether); IR (neat/$cm^{-1}$) 2958 (s), 2926 (m), 2870 (m), 1707 (m), 1607 (w), 1461 (m), 1250 (m), 1186 (m), 1137 (w), 1064 (m); $\delta_H$ (400 MHz, $CDCl_3$) 6.99 (2H, s, *m*-Ar), 5.15 (1H, d, *J* = 4.2 Hz, OCH), 3.00 – 2.74 (3H, m, ArC*H*$(CH_3)_2$), 2.30 – 2.18 (1H, m, OCHC*H*$(CH_3)_2$), 1.58 – 1.46 (6H, m, $SnCH_2CH_2$), 1.33 (6H, sext, *J* = 7.3 Hz, $CH_2CH_3$), 1.27 – 1.21 (18H, m, ArCH$(CH_3)_2$), 1.04 (3H, d, *J* = 6.7 Hz, OCHCH$(CH_3)_2$), 0.99 (3H, d, *J* = 6.9 Hz, OCHCH$(CH_3)_2$), 0.98 – 0.93 (6H, m, $SnCH_2$), 0.89 (9H, t, *J* = 7.3 Hz, $CH_2CH_3$); $\delta_C$ (100 MHz, $CDCl_3$) 171.4 (C=O), 149.8 (*p*-Ar), 145.0 (*o*-Ar), 131.2 (*i*-Ar), 120.9 (*m*-Ar), 79.4 (OCH), 34.5 (*o*-Ar*C*H$(CH_3)_2$), 33.0 (OCH*C*H$(CH_3)_2$), 31.6 (*p*-Ar*C*H$(CH_3)_2$), 29.3 ($SnCH_2CH_2$), 27.7 ($CH_2CH_3$), 24.8 (*p*-ArCH(*C*$H_3)_2$), 24.4 (*o*-ArCH(*C*$H_3)_2$), 24.1 (*o*-ArCH(*C*$H_3)_2$), 21.7 (OCHCH(*C*$H_3)_2$), 20.2 (OCHCH(*C*$H_3)_2$), 13.8 ($CH_2CH_3$), 10.55 ($SnCH_2$); HRMS (FTMS) calcd for [M+H] $C_{32}H_{59}O_2{}^{120}Sn$ 595.3536, found 595.3532.

**Cyclopentylmethyl 2,4,6-triisopropylbenzoate 179h**

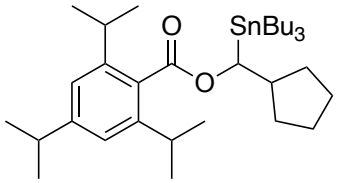


To a solution of cyclopentanemethanol (1.40 mL, 13.2 mmol) in THF (48 mL) were added $Ph_3P$ (3.50 g, 13.2 mmol) and 2,4,6-triisopropylbenzoic acid (3.00 g, 12.0 mmol). The mixture was cooled to 0 °C and DIAD (2.60 mL, 13.2 mmol) was added dropwise. The solution was stirred at 0 °C for 30 min, warmed to rt and stirred for 4 h. The reaction mixture was then quenched with sat. aq $NH_4Cl$ (10 mL) and the layers separated. The organic layer was washed with brine (2 x 10 mL) and the combined aq layers were extracted with $Et_2O$ (3x 10 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. The crude residue was triturated with pentane to remove $Ph_3P=O$ and concentrated under reduced pressure to give a pale yellow oil. This crude material was purified by column chromatography (2% $Et_2O$/petroleum ether) to give a colourless oil, benzoate **179h** (3.51 g, 88%).

$R_f$ 0.50 (20% $Et_2O$/petroleum ether); IR (neat/$cm^{-1}$) 2959 (s), 2870 (w), 1725 (s), 1607 (w), 1461 (w), 1283 (w), 1250 (s), 1137 (m), 1103 (w), 1075 (m); $\delta_H$ (400 MHz, $CDCl_3$) 7.02 (2H, s, *m*-Ar), 4.21 (2H, d, *J* = 7.2 Hz, $OCH_2$), 2.95 – 2.81 (3H, m, Ar*C*H$(CH_3)_2$), 2.32 (1H, hept, *J* = 7.2 Hz, $OCH_2CH$), 1.89 – 1.75 (2H, m, CHCH*H*'), 1.70 – 1.52 (4H, m, $CHCH_2CH_2$), 1.38 – 1.29 (2H, m, CHC*H*H'), 1.26 (12H, d, *J* = 6.7 Hz, *o*-ArCH($CH_3$)$_2$), 1.26 (6H, d, *J* = 6.9 Hz, *p*-ArCH($CH_3$)$_2$; $\delta_C$ (100 MHz, $CDCl_3$) 171.3 (C=O), 150.1 (*p*-Ar), 144.8 (*o*-Ar), 121 (*i*-Ar & *m*-Ar), 69.3 ($OCH_2$), 38.6 ($OCH_2CH$), 34.6 (*p*-Ar*C*H$(CH_3)_2$), 31.7 (*o*-Ar*C*H$(CH_3)_2$), 29.7 ($OCH_2CHCH_2$),

25.6 ($CHCH_2CH_2$), 24.3 (*o*-$ArCH(CH_3)_2$), 24.1 (*p*-$ArCH(CH_3)_2$); HRMS (FTMS) calcd for [M+H] $C_{22}H_{35}O_2$ 331.2632, found 331.2633.

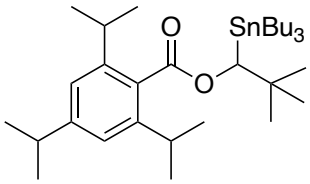
**Cyclopentyl(tributylstannyl)methyl 2,4,6-triisopropylbenzoate 230d**




Stannane **230d** was prepared following general procedure **D**, using cyclopentylmethyl triisopropylbenzoate **179h** (897 mg, 2.71 mmol). The crude material was purified by column chromatography (1% $Et_2O$/petroleum ether) to give a colourless oil, cyclopentylmethyl stannane **230d** (1.28 g, 77%).

$R_f$ 0.71 (5% EtOAc/petroleum ether); IR (neat/$cm^{-1}$) 2957 (s), 2927 (m), 2869 (w), 1706 (m), 1461 (w), 1068 (m); $\delta_H$ (400 MHz, $CDCl_3$) 6.99 (2H, s , *m*-Ar), 5.18 – 5.11 (1H, m, OC*H*), 2.92 – 2.80 (3H, m, ArC*H*$(CH_3)_2$), 2.49 – 2.34 (1H, m, OCHC*H*), 1.82 – 1.69 (2H, m, CHC*H*H'), 1.68 – 1.41 (10H, m, $CH_2CH_2$ & $SnCH_2$), 1.40 – 1.18 (26H, m, $SnCH_2CH_2$, $ArCH(CH_3)_2$ & CHCH*H'*), 1.00 – 0.82 (15H, m, $CH_2CH_3$ & $CH_2CH_3$); $\delta_C$ (100 MHz, $CDCl_3$) 171.3 (C=O) 149.7 (*p*-Ar), 144.9 (*o*-Ar), 131.2 (*i*-Ar), 120.8 (*m*-Ar), 75.9 (OCHSn), 44.5 (OCH*C*H), 34.4 (*p*-Ar*C*$H(CH_3)_2$), 31.5 (*o*-Ar*C*$H(CH_3)_2$), 30.9 ($CHCH_2$), 29.2 ($SnCH_2$), 27.6 ($SnCH_2CH_2$), 25.8 ($CHCH_2CH_2$), 24.6 (*o*-$ArCH(CH_3)_2$), 24.3 (*p*-$ArCH(CH_3)_2$), 13.7 ($CH_2CH_3$), 10.3 ($CH_2CH_3$); HRMS (FTMS) calcd for [M+H] $C_{35}H_{61}O_2{}^{120}Sn$ 621.3688, found 621.3689.

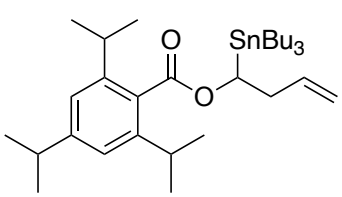
**2,2-Dimethyl-1-(tributylstannyl)propyl 2,4,6-triisopropylbenzoate 230e**




Stannane **230e** was prepared following general procedure **D**, using neopentyl triisopropylbenzoate[161] (884 mg, 2.78 mmol). The crude material was purified by column chromatography (1% $Et_2O$/petroleum ether) to give a colourless oil, stannane **230e** (1.41 g, 84%).

$R_f$ 0.71 (5% $Et_2O$/petroleum ether); IR (neat/$cm^{-1}$) 2957 (s), 2927 (s), 1710 (s), 1461 (m), 1363 (w) 1251 (s), 1028 (s); $\delta_H$ (400 MHz, $CDCl_3$) 7.00 (2H, s, *m*-Ar), 5.24 – 5.06 (1H, m, OCH), 3.02 – 2.73 (3H, m, ArC*H*$(CH_3)_2$), 1.61 – 1.42 (6H, m, $SnCH_2$), 1.38 – 1.30 (6H, m, C*H*$_2CH_3$), 1.29 – 1.22 (18H, m, ArCH(C*H*$_3)_2$), 1.07 – 0.94 (15H, m, $C(CH_3)_3$ & $SnCH_2CH_2$), 0.92 – 0.85 (9H, m, $CH_2CH_3$); $\delta_C$ (100 MHz, $CDCl_3$) 170.9 (C=O), 149.8 (*p*-Ar), 145.3 (*o*-Ar), 131.0 (*i*-Ar), 121.1 (*m*-Ar), 83.9 (O*C*H), 34.5 (*p*-Ar*C*H$(CH_3)_2$), 36.4 (*C*$(CH_3)_3$), 31.5 (*m*-*C*H$(CH_3)_2$), 29.3 ($SnCH_2$), 28.5 (C(*C*$H_3)_3$), 27.7 (*C*$H_2CH_3$), 24.7 (*o*-ArCH(*C*$H_3)_2$), 24.6 (*o*-ArCH(*C*$H_3)_2$), 24.1 (*p*-ArCH(*C*$H_3)_2$), 13.8 ($CH_2CH_3$), 11.3 ($SnCH_2$); HRMS (FTMS) calcd for [M+H] $C_{33}H_{61}O_2{}^{120}Sn$ 609.3688, found 609.3690.

**1-(Tributylstannyl)but-3-en-1-yl 2,4,6-triisopropylbenzoate 230f**

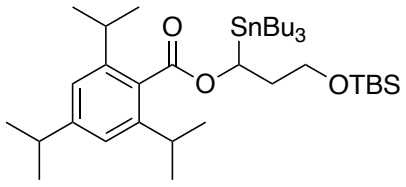



Stannane **230f** was prepared following general procedure **D**, using but-3-enyl triisopropyl benzoate[161] (1.30 g, 4.40 mmol). The crude material was purified by column

chromatography (1% $Et_2O$/petroleum ether) to give a colourless oil, stannane **230f** (1.37 g, 52%).

$R_f$ 0.88 (5% $Et_2O$/petroleum ether); IR (neat/$cm^{-1}$) 2958 (s), 2925 (s), 2870 (m), 1711 (s), 1461 (m), 1250 (s), 1136 (m), 1103 (m), 1066 (s), 876 (m); $\delta_H$ (400 MHz, $CDCl_3$) 6.99 (2H, s, *m*-Ar), 5.84 (1H, ddt, *J* = 17.1, 10.1, 6.8 Hz, $CH_2$=C*H*), 5.27 (1H, dd, *J* = 7.3, 6.3 Hz, OCH), 5.12 (1H, ddt, *J* = 17.1, 2.1, 1.5 Hz C$H_{trans}$H=CH), 5.06 (1H, ddt, *J* = 10.1, 2.1, 1.1 Hz, CH$H_{cis}$=CH), 2.92 – 2.80 (3H, m, ArC*H*$(CH_3)_2$), 2.71 – 2.65 (2H, m, OCHC$H_2$), 1.61 – 1.43 (6H, m, $SnCH_2CH_2$), 1.32 (6H, sext, *J* = 7.3 Hz, C$H_2CH_3$), 1.26 – 1.20 (18H, m, ArCH(C$H_3)_2$), 1.00 – 0.93 (6H, m, $SnCH_2$), 0.89 (9H, t, *J* = 7.3 Hz, $CH_2CH_3$); $\delta_C$ (100 MHz, $CDCl_3$) 171.3 (C=O), 149.9 (*p*-Ar), 145.0 (*o*-Ar), 136.4 ($CH_2$=*C*H), 131.1 (*i*-Ar), 120.9 (*m*-Ar), 117.0 (*C*$H_2$=CH), 70.9 (OCH), 38.9 (OCH*C*$H_2$), 34.5 (*p*-Ar*C*H$(CH_3)_2$), 31.5 (*o*-Ar*C*H$(CH_3)_2$), 29.3 ($SnCH_2CH_2$), 27.7 (*C*$H_2CH_3$), 24.7 (*p*-ArCH(*C*$H_3)_2$), 24.3 (*o*-ArCH(*C*$H_3)_2$), 24.1 (*o*-ArCH(*C*$H_3)_2$), 13.8 ($CH_2CH_3$), 10.0 ($SnCH_2$); HRMS (FTMS) calcd for [M+H] $C_{32}H_{57}O_2{}^{120}Sn$ 593.3380, found 593.3378.

**3-((*t*-Butyldimethylsilyl)oxy)-1-(tributylstannyl)propyl 2,4,6-triisopropylbenzoate 230g**

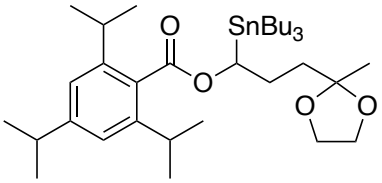



Stannane **230g** was prepared following general procedure **D**, using 3-((*t*-butyldimethylsilyl)oxy)propyl triisopropylbenzoate[188] (460 mg, 1.09 mmol). The crude material was purified by column chromatography (1% $Et_2O$/petroleum ether) to give a colourless oil, stannane **230g** (232 mg, 30%).

$R_f$ 0.67 (3% $Et_2O$/petroleum ether); IR (neat/$cm^{-1}$) 2958 (s), 2927 (s), 1709 (m), 1462 (m), 1251 (m), 1101 (m), 1071 (m); $\delta_H$ (400 MHz, $CDCl_3$) 6.99 (2H, s, *m*-Ar), 5.21 (1H, dd, *J* = 10.0, 3.6 Hz, OCH), 3.73 – 3.63 (2H, m, $OCH_2$), 2.94 – 2.74 (3H, m, Ar*CH*$(CH_3)_2$), 2.17 (1H, dddd, *J* = 14.8, 10.0, 6.5, 5.0 Hz, OCHC*H*H'), 2.03 (1H, dtd, *J* = 14.8, 7.4, 3.6 Hz, OCHCH*H'*), 1.62 – 1.46 (6H, m, $SnCH_2CH_2$), 1.32 (6H, sext, *J* = 7.3 Hz, $CH_2CH_3$), 1.25 – 1.20 (18H, m, ArCH($CH_3$)$_2$), 1.01 – 0.93 (6H, m, $SnCH_2$), 0.92 – 0.86 (18H, m, $CH_2CH_3$ & $C(CH_3)_3$), 0.04 (6H, s, $Si(CH_3)_2$); $\delta_C$ (100 MHz, $CDCl_3$) 171.2 (C=O), 149.9 (*p*-Ar), 145.0 (*o*-Ar), 131.1 (*i*-Ar), 120.9 (*m*-Ar), 68.3 (OCH), 61.4 ($OCH_2$), 37.7 ($OCHCH_2$), 34.5 (*p*-Ar*C*H$(CH_3)_2$), 31.6 (*m*-Ar*C*H$(CH_3)_2$), 29.3 ($SnCH_2CH_2$), 27.7 ($CH_2CH_3$), 26.1 ($C(CH_3)_3$), 24.6 (*p*-ArCH($CH_3$)$_2$), 24.4 (*o*-ArCH($CH_3$)$_2$), 24.10 (*o*-ArCH($CH_3$)$_2$), 18.5 ($C(CH_3)_3$), 13.8 ($CH_2CH_3$), 10.00 ($SnCH_2$), -5.10 ($Si(CH_3)_2$; HRMS (FTMS) calcd for [M+H] $C_{37}H_{71}O_3{}^{28}Si^{120}Sn$ 711.4195, found 711.4192.

**3-(2-Methyl-1,3-dioxolan-2-yl)-1-(tributylstannyl)propyl 2,4,6-triisopropylbenzoate**

**230h**

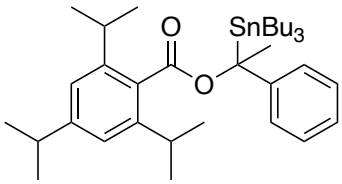



Stannane **230h** was prepared following general procedure **D**, using 3-(2-methyl-1,3-dioxolan-2-yl)propyl triisopropylbenzoate[176] (1.00 g, 2.66 mmol). The crude material was purified by column chromatography (1% $Et_2O$/petroleum ether) to give a colourless oil, stannane **230h** (1.14 g, 64%).

$R_f$ 0.59 (10% $Et_2O$/petroleum ether); IR (neat/$cm^{-1}$) 2958 (s), 2925 (s), 2871 (m), 1707 (m), 1461 (m), 1376 (w), 1286 (w), 1250 (s), 1137 (m), 1103 (m), 1066 (s), 1052 (s); $\delta_H$ (400 MHz, $CDCl_3$) 6.99 (2H, s, *m*-Ar), 5.15 (1H, dd, *J* = 7.0, 5.9 Hz, OCH), 3.98 – 3.87 (4H, m, $OCH_2$), 2.94

– 2.77 (3H, m, ArC*H*($CH_3$)$_2$), 2.07 – 1.99 (2H, m, OCHC$H_2$), 1.87 – 1.67 (2H, m, $CH_2CO_2$), 1.60 – 1.47 (6H, m, $SnCH_2CH_2$), 1.39 – 1.27 (9H, m, $CH_2CH_3$ & $CO_2CH_3$), 1.24 (12H, d, *J* = 6.9 Hz, *o*-ArCH(C$H_3$)$_2$), 1.24 (6H, d, *J* = 6.8 Hz, *p*-ArCH(C$H_3$)$_2$), 1.02 – 0.94 (6H, m, $SnCH_2$), 0.89 (9H, t, *J* = 7.3 Hz, $CH_2CH_3$); $\delta_C$ (100 MHz, $CDCl_3$) 171.3 (C=O), 149.9 (*p*-Ar), 145.0 (*o*-Ar), 131.1 (*i*-Ar), 120.9 (*m*-Ar), 109.9 ($CO_2$), 72.2 (OCH), 64.9 ($OCH_2$), 38.1 ($CH_2CO_2$), 34.5 (*p*-Ar*C*H($CH_3$)$_2$), 31.6 (*o*-Ar*C*H($CH_3$)$_2$), 29.3 ($SnCH_2CH_2$), 29.0 (OCH$CH_2$), 27.7 ($CH_2CH_3$), 24.7 (*p*-ArCH(*C*$H_3$)$_2$), 24.3 (*o*-ArCH(*C*$H_3$)$_2$), 24.1 (*o*-ArCH(*C*$H_3$)$_2$ & $CO_2CH_3$), 13.8 ($CH_2CH_3$), 10.0 ($SnCH_2$); HRMS (FTMS) calcd for [M+H] $C_{35}H_{63}O_4{}^{120}Sn$ 667.3749, found 667.3749.

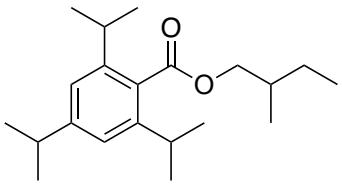
**1-Phenyl-1-(tributylstannyl)ethyl 2,4,6-triisopropylbenzoate 230i**




A solution of 1-phenylethyl triisopropylbenzoate (0.90 g, 2.60 mmol) and TMEDA (0.51 mL, 3.40 mmol) in $Et_2O$ (8 mL) under $N_2$ was cooled to –78 °C. *s*-BuLi (2.60 mL, 1.3 M in hexanes, 3.40 mmol) was added dropwise and the mixture was stirred for 10 min at –78 °C. $Bu_3SnCl$ (0.94 mL, 3.46 mmol) was added dropwise to the reaction mixture and stirred for 30 mins at –78 °C. The reaction mixture was allowed to warm to rt, quenched with water (10 mL) and extracted with $Et_2O$ (3 x 10 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure to give a pale yellow oil. This crude material was purified by column chromatography (petroleum ether) to give a colourless oil, stannane **230i** (1.35 g, 81%).

$R_f$ 0.74 (10% $Et_2O$/petroleum ether); IR (neat/$cm^{-1}$) 2957 (s), 2924 (m), 2869 (w), 1699 (s), 1460 (m), 1288 (m), 1259 (m), 1071 (s), 1029 (m), 877 (m), 696 (s); $\delta_H$ (400 MHz, $CDCl_3$) 7.34 – 7.25 (2H, m, *m*-Ph), 7.24 – 7.19 (2H, m, *o*-Ph), 7.15 – 7.09 (1H, m, *p*-Ph), 6.99 (2H, s, *m*-Ar), 3.04 (2H, hept, *J* = 6.8 Hz, *o*-ArC*H*$(CH_3)_2$), 2.87 (1H, hept, *J* = 6.9 Hz, *p*-ArC*H*$(CH_3)_2$), 1.97 (3H, s, $CCH_3$), 1.49 – 1.32 (6H, m, C*H*$_2CH_3$), 1.30 (6H, d, *J* = 6.8 Hz, *o*-ArCH(C*H*$_3)_2$), 1.28 – 1.20 (6H, m, $SnCH_2CH_2$), 1.25 (6H, d, *J* = 6.8 Hz, *o*-ArCH(C*H*$_3)_2$), 1.23 (6H, d, *J* = 6.9 Hz, *p*-ArCH(C*H*$_3)_2$), 0.94 – 0.80 (15H, m, Sn*CH*$_2CH_2$ and $CH_2CH_3$); $\delta_C$ (100 MHz, $CDCl_3$) 171.9 (C=O), 150.2 (*p*-Ar), 146.8 (*i*-Ph), 145.1 (*o*-Ar), 130.5 (*i*-Ar), 128.2 (*m*-Ph), 125.5 (*p*-Ph), 124.4 (*o*-Ar), 121.0 (*m*-Ar), 82,0 (OCSn), 34.6 (*p*-Ar*C*H$(CH_3)_2$), 31.4 (*o*-Ar*C*H$(CH_3)_2$), 29.1 (*C*$H_2CH_3$), 27.7 ($SnCH_2CH_2$), 24.7 (*p*-ArCH(*C*H$_3)_2$), 24.3 (*o*-ArCH(*C*H$_3)_2$), 24.16 (OC*C*$H_3$), 24.11 (*o*-ArCH(*C*H$_3)_2$), 13.8 ($CH_2CH_3$), 12.0 ($SnCH_2$); HRMS (FTMS) calcd for [M+Na] $C_{36}H_{58}O_2SnNa$ 657.3377, found 657.3375.

**2-Methylbutyl 2,4,6-triisopropylbenzoate 179n**

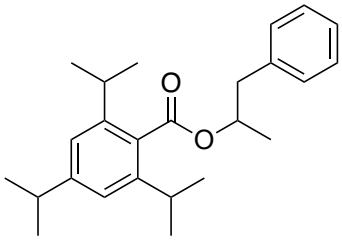



To a solution of 2-methylbutanol (0.48 mL, 4.44 mmol) in THF (16 mL) were added $Ph_3P$ (1.16 g, 4.44 mmol) and triisopropylbenzoic acid (1.00 g, 4.03 mmol). The mixture was cooled to 0 °C and DIAD (0.87 mL, 4.44 mmol) was added dropwise. The solution was stirred at 0 °C for 30 min, warmed to rt and stirred for 4 h. The reaction mixture was then quenched with sat. aq $NH_4Cl$ (10 mL) and the layers were separated. The organic layer was washed with brine (2 x 10 mL) and the combined aq. layers were extracted with $Et_2O$ (3x 10 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under

reduced pressure. The crude residue was triturated with pentane to removed $Ph_3P=O$ and concentrated under reduced pressure to give a colourless oil. This crude material was purified by column chromatography (2% $Et_2O$/petroleum ether) to give a colourless oil, benzoate **179n** (0.98 g, 76%).

$R_f$ 0.76 (20% $Et_2O$/petroleum ether); IR (neat/$cm^{-1}$) 2961 (m), 2931 (w), 2872 (w), 1725 (s), 1461 (m), 1283 (m), 1251 (s), 1137 (m), 1103 (m), 1074 (s); $\delta_H$ (400 MHz, $CDCl_3$) 7.02 (2H, s, *m*-Ar), 4.20 (1H, dd, *J* = 10.8, 5.9 Hz, OC*H*H'), 4.13 (1H, dd, *J* = 10.8, 6.5 Hz, OCH*H'*), 2.96 – 2.79 (3H, m, ArC*H*$(CH_3)_2$), 1.80 (2H, m, $OCH_2C$*H*), 1.51 (1H, dtd, *J* = 13.0, 7.5, 5.5 Hz, $CH_3C$*H*H'), 1.30 – 1.22 (1H, m, $CH_3CH$*H'*), 1.26 (18H, d, *J* = 6.9 Hz, ArCH($C$*H*$_3)_2$), 0.99 (1 H, d, *J* = 6.8 Hz, $OCH_2CHC$*H*$_3$), 0.94 (1H, t, *J* = 7.5 Hz, $CH_2C$*H*$_3$); $\delta_C$ (100 MHz, $CDCl_3$) 171.4 (C=O), 150.1 (*i*-Ar), 144.8 (*o*-Ar), 130.9 (*p*-Ar), 121.0 (*m*-Ar), 69.8 ($OCH_2$), 34.6 (*p*-Ar*C*H$(CH_3)_2$), 34.2 ($OCH_2$*C*H), 31.7 (*o*-Ar*C*H$(CH_3)_2$), 26.2 ($CH_3$*C*$H_2$), 24.3 (*o*-ArCH(*C*$H_3)_2$), 24.1 (*p*-ArCH(*C*$H_3)_2$), 16.7 ($OCH_2CH$*C*$H_3$), 11.3 ($CH_2$*C*$H_3$); HRMS (FTMS) calcd for [M+H] $C_{21}H_{35}O_2$ 319.2632, found 319.2632.

**1-Phenylpropan-2-yl 2,4,6-triisopropylbenzoate 179o**

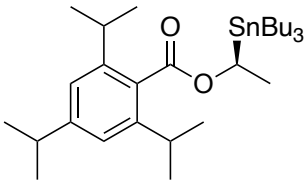



To a solution of 3-phenyl-2-propanol (1.80 mL, 13.2 mmol) in THF (48 mL) were added $Ph_3P$ (3.46 g, 13.2 mmol) and triisopropylbenzoic acid (2.98 g, 12.0 mmol). The mixture was cooled to 0 °C and DIAD (2.60 mL, 13.2 mmol) was added dropwise. The solution was stirred

at 0 °C for 30 min, warmed to rt and stirred for 4 h. The reaction mixture was then quenched with sat. aq $NH_4Cl$ (10 mL) and the layers were separated. The organic layer was washed with brine (2 x 10 mL) and the combined aq. layers were extracted with $Et_2O$ (3x 10 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. The crude residue was triturated with pentane to removed $Ph_3P{=}O$ and concentrated under reduced pressure to give a crude residue as a pale yellow oil. The crude was purified by column chromatography (1% EtOAc/petroleum ether) to give a colourless oil, benzoate ester **179o** (4.36 g, 98%).

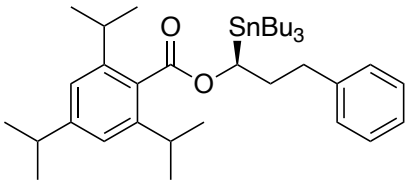
$R_f$ 0.38 (30% $CH_2Cl_2$/petroleum ether); IR (neat/$cm^{-1}$) 2961 (m), 2930 (w), 1720 (s), 1458 (m), 1283 (m), 1251 (s), 1188 (w), 1135 (m), 1104 (m), 1074 (s); $\delta_H$ (400 MHz, $CDCl_3$) 7.34 – 7.20 (5H, m, Ph), 6.97 (2H, s, *m*-Ar), 5.52 (1H, app. dquin, *J* = 7.5, 6.2 Hz, OCH), 3.07 (1H, dd, *J* = 13.8, 7.5 Hz, PhC*H*H'), 2.92-2.81 (2H, m, PhCH*H'* & *p*-ArC*H*$(CH_3)_2$), 2.69 (2H, hept, *J* = 6.9 Hz, *o*-ArC*H*$(CH_3)_2$), 1.37 (3H, d, *J* = 6.2 Hz, OCHC*H*$_3$), 1.23 (6H, d, *J* = 6.9, *p*-ArCH(C*H*$_3)_2$), 1.18 (6 H, d, *J* = 6.9 Hz, *o*-ArCH(C*H*$_3)_2$), 1.16 (6H, d, *J* = 6.9 Hz, *o*-ArCH(C*H*$_3)_2$); $\delta_C$ (100 MHz, $CDCl_3$) 170.5 (C=O), 150.1 (*p*-Ar), 144.7 (*o*-Ar), 137.7 (*i*-Ph), 130.8 (*i*-Ar), 129.4 (*o*-Ph), 128.6 (*m*-Ph), 126.7 (*p*-Ph), 120.9 (*m*-Ar), 72.3 (OCH), 42.5 (Ph*C*$H_2$), 34.6 (*p*-Ar*C*H$(CH_3)_2$), 31.3 (*o*-Ar*C*H$(CH_3)_2$), 24.5 (*o*-ArCH(*C*$H_3)_2$), 24.1 (*o*-ArCH(*C*$H_3)_2$), 24.0 (*p*-ArCH(*C*$H_3)_2$), 19.8 (OCH*C*$H_3$); HRMS (FTMS) calcd for [M+Na] $C_{25}H_{34}O_2Na$ 389.2451, found 389.2448.

**(*S*)-1-(Tributylstannyl)ethyl 2,4,6-triisopropylbenzoate (*S*)-230b**



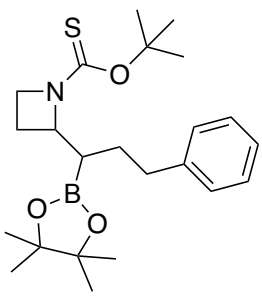
Stannane (*S*)-**230b** was prepared following general procedure **D**, using ethyl triisopropylbenzoate **179c** (975 mg, 3.53 mmol) and (–)-sparteine (0.88 mL, 3.84 mmol). The crude material was purified by column chromatography (1% $Et_2O$/petroleum ether) to give a colourless oil, stannane (*S*)-**230b** (1.39 g, 70%, 92:8 er by HPLC: OD-H column; eluent; *n*-hexane; flow rate = 1 mL $min^{-1}$; $\tau_R$ ((*S*) major) = 3.6 min, $\tau_R$ ((*R*) minor) = 4.2 min); $[\alpha]_D^{25}$ +19.3 (*c* 1.01, $CHCl_3$); all other data as described for racemate in lit.[178]

**(*S*)-3-Phenyl-1-(tributylstannyl)propyl 2,4,6-triisopropylbenzoate (*S*)-230a**




Stannane (*S*)-**230a** was prepared following general procedure **D**, using 3-phenylpropyl triisopropylbenzoate **179a** (1.37 g, 3.74 mmol) and (–)-sparteine (0.94 mL, 4.08 mmol). The crude material was purified by column chromatography (1% $Et_2O$/petroleum ether) to give a colourless oil, stannane (*S*)-**230a** (431 g, 82%) in 94:6 er (conditions for HPLC: OD-H column; eluent; *n*-hexane; flow rate = 1 mL $min^{-1}$; $\tau_R$ ((*S*) major) = 4.1 min, $\tau_R$ ((*R*) minor) = 4.7 min); $[\alpha]_D^{25}$ +20.8 (*c* 1.01, $CHCl_3$); all other data as described for racemate in lit.[138]

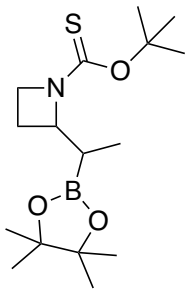
***O*-*t*-Butyl 2-(3-phenyl-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propyl)azetidine-1-carbothioate (*R**,*R**)-223b and (*R**,*S**)-223b'**



Boronic ester **223b** was prepared following general procedure **E**, using stannane **230a** (852 mg, 1.30 mmol) and azetidine boronic ester **104g** (300 mg, 1.00 mmol) with heating (63 °C) in $CHCl_3$ for 12 h. The residue was purified by column chromatography (2% EtOAc/petroleum ether). First eluted a colourless oil, minor diastereomer (*R*,S**)-**223b'** (88 mg, 21%). Second eluted a pale yellow oil, major diastereomer (*R*,R**)-**223b** (197 mg, 47%). All data matched those described previously (p **223** – **224**).

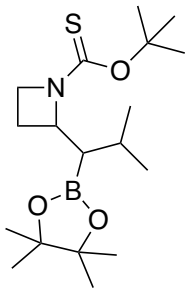
*A 0.42 mmol scale reaction gave (R*,S*)-**223b'** (33 mg, 19%) and (R*,R*)-**223b** (87 mg, 50%) respectively.*

**_O_-(_t_-Butyl) 2-(1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)ethyl)azetidine-1-carbothioate (_R_*,_R_*)-223c and (_R_*,_S_*)-223c'**



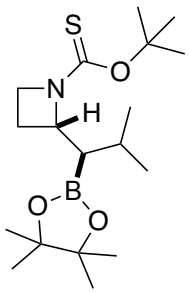

Boronic ester **223c** was prepared following general procedure **E**, using stannane **230b** (311 mg, 0.55 mmol) and azetidine boronic ester **104g** (125 mg, 0.42 mmol) with heating (63 °C) in $CHCl_3$ for 3 h. The residue was purified by column chromatography (2% EtOAc/petroleum ether). First eluted a colourless oil, minor diastereomer (*R*,S**)-**223c'** (41 mg, 30%). Second eluted a pale yellow oil, major diastereomer (*R*,R**)-**223c** (52 mg, 38%)

**_O_-(_t_-Butyl) 2-(2-methyl-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propyl)azetidine-1-carbothioate (_R_*,_R_*)-223e and (_R_*,_S_*)-223e'**




Boronic ester **223e** was prepared following general procedure **E**, using stannane **230c** (326 mg, 0.55 mmol) and azetidine boronic ester **104g** (125 mg, 0.42 mmol). The residue was purified by column chromatography (5% $Et_2O$/petroleum ether). First eluted a colourless oil, minor diastereomer (*R*,S**)-**223e'** (13 mg, 9%). Second eluted a colourless oil, major diastereomer (*R*,R**)-**223e** (83 mg, 56%)

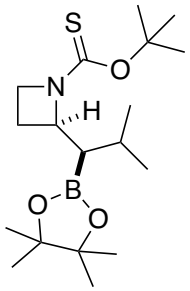
**_O_-(t-Butyl) (_R_*)-2-((_S_*)-2-methyl-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propyl)azetidine-1-carbothioate (_R_*,_S_*)-223e'**




$R_f$ 0.50 (25% $Et_2O$/petroleum ether); IR (neat/$cm^{-1}$) 2961 (w), 2928 (w), 1466 (m), 1436 (m), 1387 (m), 1365 (w), 1326 (w), 1279 (m), 1142 (s); $\delta_H$ (400 MHz, $CDCl_3$) (5.7:1 rotamer mixture by analysis of the NCH signals in the 4.72 – 4.46 region) 4.50 (4.74 – 4.63) (1H, dt, *J* = 8.5, 6.4 Hz, (m), NCH), 3.99 – 3.90 (2H, m, $NCH_2$), 2.27 (1H, ddt, *J* = 11.0, 8.5, 6.4 Hz, NCHC*H*H'), 2.15 – 2.04 (1H, m, NCHCH*H'*), 1.84 – 1.70 (1H, m, C*H*$(CH_3)_2$), 1.64 (1.63) (9H, s,

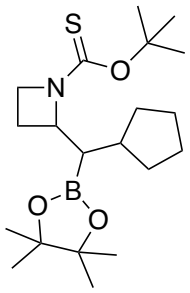
$C(CH_3)_3$), 1.62 – 1.59 (1H, m, BCH), 1.24 (6H, s, OC($CH_3$)$_2$), 1.23 (6H, s, OC($CH_3$)$_2$), 0.93 (3H, d, *J* = 6.7 Hz, CH($CH_3$)$_2$), 0.87 (3H, d, *J* = 6.5 Hz, CH($CH_3$)$_2$); $\delta_C$ (100 MHz, $CDCl_3$) 185.7 (C=S), 84.9 ($C(CH_3)_3$), 83.3 (O$C(CH_3)_2$), 64.6 (NCH), 49.9 ($NCH_2$), 28.6 ($C(CH_3)_3$), 26.6 ($CH(CH_3)_2$), 25.4 (OCH($CH_3$)$_2$), 25.1 (OCH($CH_3$)$_2$), 23.2 (CH($CH_3$)$_2$), 22.6 (CH($CH_3$)$_2$), 18.7 (NCH$CH_2$). BCH carbon not observed due to quadrupolar relaxation. $\delta_B$ (128 MHz, $CDCl_3$) 34; HRMS (FTMS) calcd for [M+Na] $C_{18}H_{34}O_3N^{11}B^{32}SNa$ 377.2245, found 377.2244.

**_O_-(t-Butyl) (_R_*)-2-((_R_*)-2-methyl-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propyl)azetidine-1-carbothioate (_R_*,_R_*)-223e**



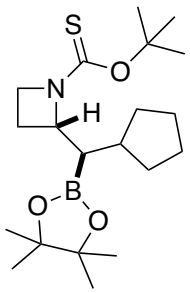

$R_f$ 0.48 (25% $Et_2O$/petroleum ether); IR (neat/$cm^{-1}$) 2975 (w), 1465 (m), 1434 (m), 1379 (m), 1322 (w), 1276 (m), 1141 (s); $\delta_H$ (400 MHz, $CDCl_3$) (5.7:1 rotamer mixture by analysis of the NCH signals in the 4.73 – 4.52 region) 4.60 – 4.52 (4.73 – 4.66) (1H, m, NCH), 4.01 – 3.83 (2H, m, $NCH_2$), 2.32 – 2.00 (3H, m, NCH$CH_2$ & $CH(CH_3)_2$), 1.65 (1.60) (9H, s, $C(CH_3)_3$), 1.36 (1H, dd, *J* = 7.8, 3.2 Hz, BCH), 1.23 (12H, s, OC($CH_3$)$_2$), 0.99 (3H, d, *J* = 3.4 Hz, CH($CH_3$)$_2$), 0.98 (3H, d, *J* = 3.4 Hz, CH($CH_3$)$_2$); $\delta_C$ (100 MHz, $CDCl_3$) (mixture of rotamers) 186.0 (C=S), 85.2 ($C(CH_3)_3$), 83.3 (O$C(CH_3)_2$), 65.2 (NCH), 49.9 ($NCH_2$), 28.7 (28.6) ($C(CH_3)_3$), 26.2 ($CH(CH_3)_2$), 25.2 (OC($CH_3$)$_2$), 25.1 (OC($CH_3$)$_2$), 23.6 (CH($CH_3$)$_2$), 23.5 (CH($CH_3$)$_2$), 20.4 (NCH$CH_2$). BCH carbon not observed due to quadrupolar relaxation. $\delta_B$ (128 MHz, $CDCl_3$) 33; HRMS (FTMS) calcd for [M+Na] $C_{18}H_{34}O_3N^{11}B^{32}SNa$ 378.2245, found 378.2247.

**_O_-(_t_-Butyl)-2-(cyclopentyl(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl)azetidine-1-carbothioate (_R_*,_R_*)-223f and (_R_*,_S_*)-223f'**



Boronic ester **223f** was prepared following general procedure **E**, using stannane **230d** (340 mg, 0.55 mmol) and azetidine boronic ester **104g** (125 mg, 0.42 mmol). The residue was purified by column chromatography (2% EtOAc/petroleum ether). First eluted a colourless oil, minor diastereomer (*R*,S**)-**223f'** (24 mg, 15%). Second eluted a pale yellow oil, major diastereomer (*R*,R**)-**223f** (64 mg, 40%).

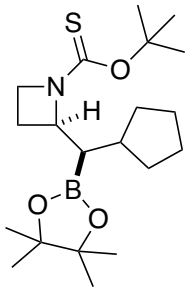
**_O_-(_t_-Butyl) (_R_*)-2-((_S_*)-cyclopentyl(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl)azetidine-1-carbothioate (_R_*,_S_*)-223e'**



$R_f$ 0.68 (20% $Et_2O$/petroleum ether); IR (neat/$cm^{-1}$) 2975 (w), 2953 (w), 1477 (m), 1437 (m), 1388 (m), 1366 (m), 1329 (m), 1278 (s), 1244 (w), 1142 (s); $\delta_H$ (400 MHz, $CDCl_3$) (6.7:1 rotamer mixture by analysis of the NCH signals in the 4.66 – 4.39 region) 4.49 – 4.39 (4.66 – 4.58) (1H, m, NCH), 3.96 – 3.90 (2H, m, $NCH_2$), 2.39 – 2.26 (1H, m, NCHC*H*H'), 2.11 – 2.00 (1H, m, NCHCH*H*'), 1.80 – 1.66 (4H, m, BCH, BCHC*H* & CHC*H*H'), 1.65 – 1.54 (11H, m, $C(CH_3)_3$

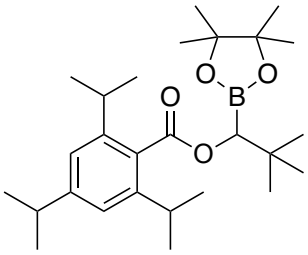
& $CH_2CH_2$), 1.53 – 1.40 (2H, m, $CH_2CH_2$), 1.23 (6H, s, $C(CH_3)_2$), 1.22 (6H, s, $C(CH_3)_2$), 1.18 – 1.10 (1H, m, CHCH*H*'), 1.08 – 0.97 (1H, m, CHCH*H*'); $\delta_C$ (100 MHz, $CDCl_3$) 185.3 (C=S), 84.8 ($C(CH_3)_3$), 83.2 ($C(CH_3)_2$), 65.0 (65.9) (NCH), 49.6 ($NCH_2$), 38.0 (BCH*C*H), 32.9 ($CHCH_2$), 32.6 ($CHCH_2$), 28.5 (28.7) ($C(CH_3)_3$), 25.3 ($C(CH_3)_2$), 24.98 ($C(CH_3)_2$), 24.96 ($CH_2CH_2$), 24.7 ($CH_2CH_2$), 18.2 ($NCHCH_2$). BCH carbon not observed due to quadrupolar relaxation. $\delta_B$ (128 MHz, $CDCl_3$) 34; HRMS (FTMS) calcd for [M+H] $C_{20}H_{37}O_3N^{11}B^{32}S$ 382.2582, found 382.2579.

**_O_-(_t_-Butyl)-(_R_*)-2-((_R_*)-cyclopentyl(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl)azetidine-1-carbothioate (_R_*,_R_*)-223e**




$R_f$ 0.63 (20% $Et_2O$/petroleum ether); IR (neat/$cm^{-1}$) 2975 (w), 2867 (w), 1465 (m), 1434 (m), 1379 (m), 1365 (m), 1323 (m), 1274 (s), 1139 (s), 966 (w); $\delta_H$ (400 MHz, $CDCl_3$) (6.7:1 rotamer mixture by analysis of the NCH signals in the 4.66 – 4.37 region) 4.53 – 4.37 (4.66 – 4.57) (1H, m, NCH), 3.95 – 3.74 (2H, m, $NCH_2$), 2.21 – 1.97 (3H, m, $NCHCH_2$ & BCH*C*H), 1.89 – 1.76 (2H, m, CHC*H*H'), 1.58 (1.54) (9H, s, $C(CH_3)_3$), 1.56 – 1.36 (5H, m, BCH & $CH_2CH_2$), 1.16 (6H, s, $C(CH_3)_2$), 1.15 (6H, s, $C(CH_3)_2$), 1.11 – 0.96 (2H, m, CHCH*H*'); $\delta_C$ (100 MHz, $CDCl_3$) 185.6 (185.4) (C=S), 85.0 (84.1) ($C(CH_3)_3$), 83.2 (83.0) ($C(CH_3)_2$), 65.8 (66.8) (NCH), 49.8 ($NCH_2$), 37.8 (37.6) (BCH*C*H), 33.4 ($CHCH_2$), 33.2 ($CHCH_2$), 28.66 (28.71) ($C(CH_3)_3$), 25.2 ($CH_2CH_2$), 25.0 ($C(CH_3)_2$), 24.9 ($C(CH_3)_2$), 19.7 (19.8) ($NCHCH_2$). BCH carbon not observed due to quadrupolar relaxation. $\delta_B$ (128 MHz, $CDCl_3$) 33; HRMS (FTMS) calcd for [M+H] $C_{20}H_{37}O_3N^{11}B^{32}S$ 382.2582, found 382.2578.

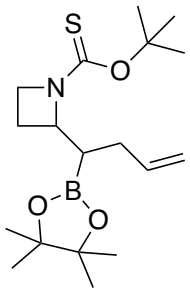
**2,2-Dimethyl-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propyl 2,4,6-triisopropylbenzoate 179p**



Boronic ester **179p** was prepared following general procedure **E**, using stannane **230e** (340 mg, 0.55 mmol) and azetidine boronic ester **104g** (125 mg, 0.42 mmol). The crude material was purified by column chromatography (5% $Et_2O$/petroleum ether) to give a white solid, boronic ester **179p** (132 mg, 71%).

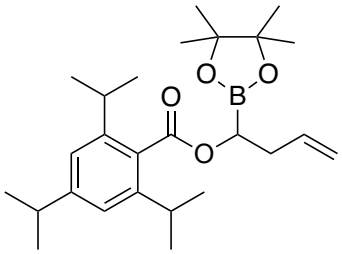
$R_f$ 0.59 (15% $Et_2O$/petroleum ether); mp 76–77 °C; IR (neat/$cm^{-1}$) 2960 (m), 2870 (s), 2360 (w), 1708 (s), 1462 (w), 1371 (s), 1339 (s), 1285 (m), 1271 (m), 1238 (s), 1140 (s), 1079 (m); $\delta_H$ (400 MHz, $CDCl_3$) 7.00 (2H, s, *m*-Ar), 3.83 (1H, s, OCH), 3.06 (2H, hept, *J* = 6.7 Hz, *o*-Ar*CH*$(CH_3)_2$), 2.89 (1H, hept, *J* = 6.9 Hz, *p*-Ar*CH*$(CH_3)_2$), 1.31 (6H, s, C$(CH_3)_2$), 1.28 (6H, s, C$(CH_3)_2$), 1.27 – 1.20 (18H, m, ArCH(C*H*$_3)_2$), 1.03 (9H, s, C$(CH_3)_3$); $\delta_C$ (100 MHz, $CDCl_3$) 172.6 (C=O), 149.9 (*p*-Ar), 145.4 (*o*-Ar), 130.6 (*i*-Ar), 120.9 (*m*-Ar), 83.9 (O*C*$(CH_3)_2$), 34.5 (*p*-Ar*C*H$(CH_3)_2$), 32.8 (*C*$(CH_3)_3$), 30.9 (*o*-Ar*C*H$(CH_3)_2$), 27.5 (C(*C*$H_3)_3$), 25.09 (C(*C*$H_3)_2$), 25.04 (C(*C*$H_3)_2$), 24.6 (*p*-ArCH(*C*$H_3)_2$), 24.3 (*o*-ArCH(*C*$H_3)_2$), 24.1 (*o*-ArCH(*C*$H_3)_2$). BCH carbon not observed due to quadrupolar relaxation. $\delta_B$ (128 MHz, $CDCl_3$) 32; HRMS (FTMS) calcd for [M+H] $C_{27}H_{46}O_4{}^{11}B$ 445.3484, found 445.3485.

**_O_-(_t_-Butyl) 2-(1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)but-3-en-1-yl)azetidine-1-carbothioate (_R_*,_R_*)-223h and (_R_*,_S_*)-223h'**



Boronic ester **223h** was prepared following general procedure **E**, using stannane **230f** (325 mg, 0.55 mmol) and azetidine boronic ester **104g** (125 mg, 0.42 mmol). The crude material was purified by column chromatography (2% EtOAc/petroleum ether). First eluted a colourless oil, boronic benzoate **179q** (8 mg, 4%). second eluted a colourless oil, minor diastereomer (*R*,S**)-**223h'** (21 mg, 14%). Third eluted a pale yellow oil, major diastereomer (*R*,R**)-**223h** (53 mg, 36%).

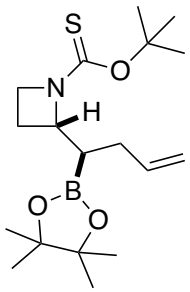
**1-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)but-3-en-1-yl 2,4,6-triisopropylbenzoate 179q**



$R_f$ 0.45 (20% $Et_2O$/petroleum ether); IR (neat/$cm^{-1}$) 2961 (s), 2929 (m), 2870 (w), 1711 (s), 1461 (w), 1428 (w), 1384 (s), 1347 (m), 1252 (m), 1142 (s), 1104 (w), 1078 (m); $\delta_H$ (400 MHz, $CDCl_3$) 6.99 (2H, s, *m*-Ar), 5.87 (1H, ddt, *J* = 17.0, 10.2, 6.7 Hz, $CH_2$=C*H*), 5.13 (1H, dd, *J* = 17.0, 1.4 Hz, C$H_{trans}$H=CH), 5.04 (1H, dd, *J* = 10.2, 1.4 Hz, CH$H_{cis}$=CH), 4.27 (1H, dd, *J* = 8.0, 6.1 Hz, BCH), 3.03 (2H, hept, *J* = 6.7 Hz, *o*-ArC*H*$(CH_3)_2$), 2.88 (1H, hept, *J* = 6.9 Hz, *p*-

ArCH($CH_3$)$_2$), 2.63 – 2.46 (2H, m, BCHC$H_2$), 1.29 (6H, s, OC($CH_3$)$_2$), 1.27 (6H, s, OC($CH_3$)$_2$), 1.26 – 1.20 (18H, m, ArCH(C$H_3$)$_2$); $\delta_C$ (100 MHz, $CDCl_3$) 172.3 (C=O), 150.2 (*p*-Ar), 145.5 (*o*-Ar), 135.1 ($CH_2$=*C*H), 130.0 (*i*-Ar), 120.9 (*m*-Ar), 117.0 (*C*$H_2$=CH), 84.1 (O*C*($CH_3$)$_2$), 34.8 (BCH*C*$H_2$), 34.6 (*p*-Ar*C*H($CH_3$)$_2$), 31.0 (*o*-Ar*C*H($CH_3$)$_2$), 25.1 (OC(*C*$H_3$)$_2$), 24.9 (OC(*C*$H_3$)$_2$), 24.44 (*o*-ArCH(*C*$H_3$)$_2$), 24.42 (*o*-ArCH(*C*$H_3$)$_2$), 24.1 (*p*-ArCH(*C*$H_3$)$_2$). BCH carbon not observed due to quadrupolar relaxation. $\delta_B$ (128 MHz, $CDCl_3$) 31; HRMS (FTMS) calcd for [M+H] $C_{26}H_{42}O_4{}^{11}B$ 429.3172, found 429.3172.

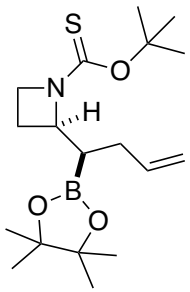
**_O_-(_t_-Butyl) (_R*_)-2-((_S*_)-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)but-3-en-1-yl)azetidine-1-carbothioate (_R*_,_S*_)-223h'**




$R_f$ 0.36 (20% $Et_2O$/petroleum ether); IR (neat/$cm^{-1}$) 2976 (w), 1476 (m), 1437 (m), 1390 (m), 1365 (m), 1332 (w) 1279 (m), 1141 (s); $\delta_H$ (400 MHz, $CDCl_3$) (5.6:1 rotamer mixture by analysis of the NCH signals in the 4.61 – 4.34 region) 5.77 (1H, ddt, *J* = 17.0, 10.1, 6.6 Hz, $CH_2$=C*H*), 5.03 (1H, dt, *J* = 17.0, 1.6 Hz, C$H_{trans}$H=CH), 4.98 – 4.92 (1H, m, CH$H_{cis}$=CH), 4.44 – 4.33 (4.61 – 4.53) (1H, m, NCH), 4.00 – 3.92 (2H, m, $NCH_2$), 2.23 – 1.93 (5H, m, NCHC$H_2$, BCH & BCHC$H_2$), 1.65 (1.63) (9H, s, C($CH_3$)$_3$), 1.22 (12H, s, C($CH_3$)$_2$); $\delta_C$ (100 MHz, $CDCl_3$) (rotamer mixture) 185.5 (C=S), 137.5 ($CH_2$=*C*H), 115.5 (*C*$H_2$=CH), 85.0 (*C*($CH_3$)$_3$), 83.4 (O*C*($CH_3$)$_2$), 65.1 (NCH), 49.7 (50.8) ($NCH_2$), 31.6 (BCH*C*$H_2$), 28.61 (28.58) (C(*C*$H_3$)$_3$), 25.2 (OC(*C*$H_3$)$_2$), 25.0 (OC(*C*$H_3$)$_2$), 19.0 (NCH*C*$H_2$). BCH carbon not observed due to quadrupolar

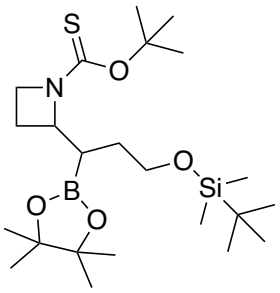
relaxation. $\delta_B$ (128 MHz, $CDCl_3$) 34; HRMS (FTMS) calcd for [M+H] $C_{18}H_{33}O_3N^{11}B^{32}S$ 354.2269, found 354.2271.

**_O_-(_t_-Butyl) (_R_*)-2-((_R_*)-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)but-3-en-1-yl)azetidine-1-carbothioate (_R_*,_R_*)-223h**



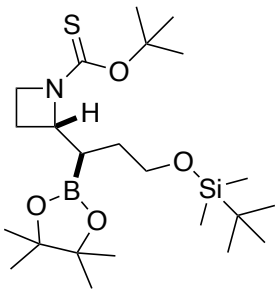

$R_f$ 0.24 (20% $Et_2O$/petroleum ether); IR (neat/$cm^{-1}$) 2976 (w), 1479 (m), 1439 (m), 1365 (m), 1329 (m), 1275 (m), 1140 (s); $\delta_H$ (400 MHz, $CDCl_3$) (4.9:1 rotamer mixture by analysis of the NCH signals in the 4.72 – 4.50 region) 5.85 (1H, ddt, _J_ = 17.0, 10.1, 6.8 Hz, $CH_2$=C_H_), 5.08 – 4.98 (1H, m, C$H_{trans}$H=CH), 4.96 – 4.86 (1H, m, CH$H_{cis}$=CH), 4.54 (4.69) (1H, dtd, _J_ = 8.3, 4.6, 2.5 Hz, (dt, _J_ = 9.4, 5.1 Hz), NCH), 3.99 – 3.75 (2H, m, $NCH_2$), 2.53 – 1.96 (4H, m, NCHC$H_2$ & BCHC$H_2$), 1.85 (1H, dt, _J_ = 10.4, 4.6 Hz, BCH), 1.62 (1.59) (9H, s, $C(CH_3)_3$), 1.19 (12H, s, $OC(CH_3)_2$); $\delta_C$ (100 MHz, $CDCl_3$) (rotamer mixture) 185.4 (185.1) (C=S), 138.2 (138.9) ($CH_2$=CH), 115.0 (114.5) ($CH_2$=CH), 84.9 (84.2) ($C(CH_3)_3$), 83.5 (83.3) (O$C(CH_3)_2$), 65.2 (66.1) (NCH), 49.6 (49.8) ($NCH_2$), 29.2 (29.3) (BCH$CH_2$), 28.70 (28.67) (C($CH_3$)$_3$), 24.97 (25.00) (OC($CH_3$)$_2$), 24.8 (24.9) (OC($CH_3$)$_2$), 18.3 (19.0) (NCH$CH_2$). BCH carbon not observed due to quadrupolar relaxation. $\delta_B$ (128 MHz, $CDCl_3$) 33; HRMS (FTMS) calcd for [M+H] $C_{18}H_{33}O_3N^{11}B^{32}S$ 354.2269, found 353.2272.

**_O_-(_t_-Butyl) 2-(3-((t-butyldimethylsilyl)oxy)-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propyl)azetidine-1-carbothioate (_R_*,_R_*)-223i and (_R_*,_S_*)-223i'**



Boronic ester **223i** was prepared following general procedure **E**, using stannane **230g** (200 mg, 0.28 mmol) and azetidine boronic ester **104g** (63 mg, 0.21 mmol). The residue was purified by column chromatography (5% $Et_2O$/petroleum ether). First eluted a colourless oil, minor diastereomer (*R*,S**)-**223i'** (28 mg, 28%). Second eluted a colourless oil, major diastereomer (*R*,R**)-**223i** (37 mg, 37%).

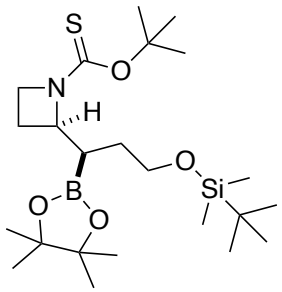
**_O_-(_t_-Butyl) (_R_*)-2-((_S_*)-3-((_t_-butyldimethylsilyl)oxy)-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propyl)azetidine-1-carbothioate (_R_*,_S_*)-223i'**



$R_f$ 0.31 (20% $Et_2O$/petroleum ether); IR (neat/$cm^{-1}$) 2928 (w), 1471 (m), 1438 (m), 1389 (m), 1365 (m), 1329 (w), 1279 (s), 1249 (m), 1142 (s), 1096 (m); $\delta_H$ (400 MHz, $CDCl_3$) (3.6:1 rotamer mixture by analysis of the NCH signals in the 4.63 – 4.36 region) 4.41 (4.63 – 4.54) (1H, q, *J* = 6.8 Hz, (m), NCH), 3.95 (2H, t, *J* = 7.6 Hz, $NCH_2$), 3.69 – 3.50 (2H, m, $OCH_2$), 2.27 – 2.04 (2H, m, NCHC$H_2$), 1.98 (1H, dt, *J* = 9.2, 6.8 Hz, BCH), 1.65 (1.60) (9H, s, OC($CH_3$)$_3$),

1.57 – 1.44 (2H, m, $OCH_2CH_2$), 1.23 (12H, s, $OC(CH_3)_2$), 0.89 (0.88) (9H, s, $SiC(CH_3)_3$), 0.04 (0.03) (6H, s, $Si(CH_3)_2$); $\delta_C$ (125 MHz, $CDCl_3$) (mixture of rotamers) 185.5 (C=S), 85.0 ($OC(CH_3)_3$), 83.3 ($OC(CH_3)_2$), 65.3 (66.0) (NCH), 62.8 ($OCH_2$), 49.6 ($NCH_2$), 30.5 ($OCH_2CH_2$), 28.6 (28.7) ($OC(CH_3)_3$), 26.1 (26.2) ($SiC(CH_3)_3$), 25.2 ($OC(CH_3)_2$), 25.0 ($OC(CH_3)_2$), 18.9 ($NCHCH_2$), 18.5 ($SiC(CH_3)_3$), -5.2 ($Si(CH_3)_2$). BCH carbon not observed due to quadrupolar relaxation. $\delta_B$ (128 MHz, $CDCl_3$) 33; HRMS (FTMS) calcd for [M+Na] $C_{23}H_{46}O_4N^{11}B^{32}S^{28}SiNa$ 494.2905, found 494.2900.

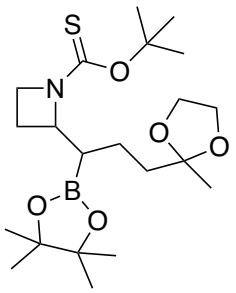
**_O_-(_t_-Butyl) (_R_*)-2-((_R_*)-3-((_t_-butyldimethylsilyl)oxy)-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propyl)azetidine-1-carbothioate (_R_*,_R_*)-223i**




$R_f$ 0.25 (20% $Et_2O$/petroleum ether); IR (neat/$cm^{-1}$) 2928 (w), 1471 (m), 1438 (m), 1366 (m), 1277 (m), 1250 (m), 1143 (s), 1097 (m); $\delta_H$ (400 MHz, $CDCl_3$) (3.8:1 rotamer mixture by analysis of the NCH signals in the 4.74 – 4.51 region) 4.60 – 4.51 (4.70) (1H, m, (dt, *J* = 9.6, 5.2 Hz), NCH), 4.01 – 3.81 (2H, m, $NCH_2$), 3.79 – 3.57 (2H, m, $OCH_2$), 2.33 – 2.08 (1H, m, NCHC*H*H), 1.98 (1H, ddt, *J* = 11.8, 9.3, 6.3 Hz, NCHCH*H*), 1.87 – 1.68 (3H, m, $OCH_2CH_2$ & BCH), 1.64 (1.61) (9H, s, $OC(CH_3)_3$), 1.23 – 1.19 (12H, s, $OC(CH_3)_2$), 0.90 (0.89) (9H, s, $SiC(CH_3)_3$), 0.05 (0.06) (6H, s, $Si(CH_3)_2$); $\delta_C$ (125 MHz, $CDCl_3$) (mixture of rotamers) 185.7 (185.3) (C=S), 85.0 (84.3) ($OC(CH_3)_3$), 83.5 (83.3) ($OC(CH_3)_2$), 65.5 (66.3) (NCH), 63.2 (63.7) ($OCH_2$), 49.7 (49.9) ($NCH_2$), 28.74 (28.71) ($OC(CH_3)_3$), 28.1 (27.8) ($OCH_2CH_2$), 26.27 (26.25) ($SiC(CH_3)_3$), 25.1 ($OC(CH_3)_2$), 24.8 ($OC(CH_3)_2$), 18.6 ($SiC(CH_3)_3$), 18.5 ($NCHCH_2$), –5.0

($Si(CH_3)_2$), –5.1 ($Si(CH_3)_2$). BCH carbon not observed due to quadrupolar relaxation. $\delta_B$ (128 MHz, $CDCl_3$) 33; HRMS (FTMS) calcd for [M+Na] $C_{23}H_{46}O_4N^{11}B^{32}S^{28}SiNa$ 494.2905, found 493.2902.

**_O_-(_t_-Butyl) 2-(3-(2-methyl-1,3-dioxolan-2-yl)-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propyl)azetidine-1-carbothioate 223j**



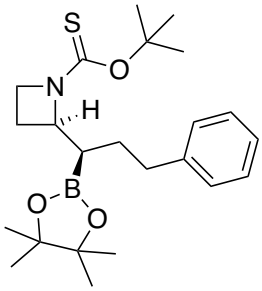

Boronic ester **223j** was prepared following general procedure **E**, using stannane **230h** (366 mg, 0.55 mmol) and azetidine boronic ester **104g** (125 mg, 0.42 mmol). The crude material was purified by column chromatography (5-20% EtOAc/petroleum ether) and eluted a colourless oil, 2:1 inseparable mixture of diastereomers **223j** (100 mg, 56%).

$R_f$ 0.50 (50% $Et_2O$/petroleum ether); IR (neat/$cm^3$) 2976 (w), 1479 (m), 1439 (m), 1367 (m), 1328 (w), 1277 (m), 1142 (s); $\delta_H$ (400 MHz, $CDCl_3$) (2:1 mixture diastereomers by analysis of $C(CH_3)_2$ signals in the 1.24 – 1.17 region and rotamers) 4.75 – 4.29 (1H, m, NCH), 4.03 – 3.82 (6H, m, $NCH_2$ & $OCH_2CH_2O$), 2.34 – 1.93 (2H, m, $NCHCH_2$), 1.86 – 1.75 (1H, m, $C(OCH_2)_2CH$H'), 1.74 – 1.66 (1H, m, BCH), 1.64 (1.63 & 1.60) (10H, s, (m), $C(CH_3)_3$ & BCHCH'), 1.56 – 1.42 (2H, m, $C(OCH_2)_2CH$H' & BCHCHH'), 1.33 (1.35, 1.32 & 1.29) (3H, s, $CH_3$), 1.20 (1.22, 1.21 & 1.19) (12H, s, $C(CH_3)_2$); $\delta_C$ (100 MHz, $CDCl_3$) (diastereomer mixture) 185.6 (185.4) (C=S), 110.2 ($C(OCH_2)_2$), 84.9 (85.0) ($C(CH_3)_3$), 83.5 (83.3) ($C(CH_3)_2$), 65.8 (65.5) (NCH), 64.7 (64.58) ($OCH_2$), 64.62 (64.5) ($OCH_2$), 49.7 (50.0) ($NCH_2$), 38.9 (38.2) ($C(OCH_2)_2CH_2$), 28.7 (28.6) ($C(CH_3)_3$), 25.1 (26.2) ($C(CH_3)_2$), 24.8 (24.9) ($C(CH_3)_2$), 23.8 (23.6)

($CH_3$), 19.3 (19.1) (BCH*C*$H_2$), 18.5 (18.8) (NCH*C*$H_2$). BCH carbon not observed due to quadrupolar relaxation. $\delta_B$ (128 MHz, $CDCl_3$) 34; HRMS (FTMS) calcd for [M+Na] $C_{21}H_{38}O_5N^{11}B^{32}SNa$ 450.2458, found 450.2451.

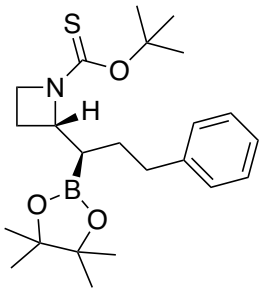
**5.3.5 Asymmetric homologation**

***O*-(*t*-Butyl) (*R*)-2-((*R*)-3-phenyl-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propyl)azetidine-1-carbothioate (*R*,*R*)-223b**



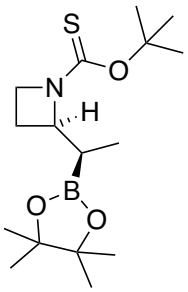

Boronic ester (*R*,*R*)-**223b** was prepared following general procedure **E**, using stannane (*S*)-**230a** (360 mg, 0.55 mmol) and azetidine boronic ester (*S*)-**104g** (125 mg, 0.42 mmol). The residue was purified by column chromatography (5% $Et_2O$/petroleum ether). First eluted a colourless oil, minor diastereomer (*S,R*)-**223b'** (6 mg, 3%, 71:29 er). Second eluted a colourless oil, major diastereomer (*R,R*)-**223b** (80 mg, 46%, 98.5:1.5 er by HPLC: OD-H column; eluent; *n*-hexane/*i*-PrOH (99.8:0.2); flow rate = 1 mL $min^{-1}$; $\tau_R$ ((*S,S*) minor) = 10.4 min, $\tau_R$ ((*R,R*) major) = 12.7 min); $[\alpha]_D^{25}$ +73.9 (*c* 1.01, $CHCl_3$); all other data as described for racemic (*R**,*R**)-**223b** (p **224**).

**_O_-(_t_-Butyl) (_S_)-2-((_R_)-3-phenyl-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propyl)azetidine-1-carbothioate (_S,R_)-223b'**



Boronic ester (_S_,_R_)-**223b'** was prepared following general procedure **E**, using stannane (_S_)-**230a** (360 mg, 0.55 mmol) and azetidine boronic ester (_R_)-**104g** (125 mg, 0.42 mmol). The residue was purified by column chromatography (5% $Et_2O$/petroleum ether). First eluted a colourless oil, major diastereomer (_S,R_)-**223b'** (77 mg, 44%, 99:1 er by HPLC: OD-H column; eluent; _n_-hexane/_i_-PrOH (99.9:0.1); flow rate = 1 mL $min^{-1}$; $\tau_R$ ((_R,S_) minor) = 15.3 min, $\tau_R$ ((_S,R_) major) = 18.4 min); $[\alpha]_D^{25}$ –24.5 (_c_ 0.82, $CHCl_3$); all other data as described for racemic (_R*_,_S*_)-**223b'** (p **223**). Second eluted a colourless oil, minor diastereomer (_R,R_)-**223b** (12 mg, 7%, 72:28 er).

**_O_-(_t_-Butyl) (_R_)-2-((_R_)-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)ethyl)azetidine-1-carbothioate (_R,R_)-223c**

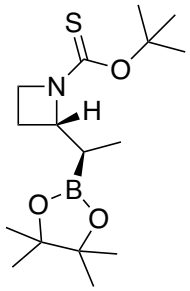


Boronic ester (_R_,_R_)-**223c** was prepared following general procedure **E**, using stannane (_S_)-**230b** (311 mg, 0.55 mmol) and azetidine boronic ester (_S_)-**104g** (125 mg, 0.42 mmol). The

residue was purified by column chromatography (5% $Et_2O$/petroleum ether). First eluted a colourless oil, minor diastereomer (*S,R*)-**223c'** (11 mg, 8%, 55:45 er). Second eluted a colourless oil, major diastereomer (*R,R*)-**223c** (61 mg, 44%, 99:1 er by HPLC: OD-H column; eluent; *n*-hexane/*i*-PrOH (99.9:0.1); flow rate = 1 mL $min^{-1}$; $\tau_R$ ((*S,S*) minor) = 8.1 min, $\tau_R$ ((*R,R*) major) = 9.3 min); $[\alpha]_D^{25}$ +60.5 (*c* 0.93, $CHCl_3$); all other data as described for racemic **223c**. (p **228**).

*The same compound was prepared following general procedure **C**, using (–)-sparteine (0.11 mL, 0.46 mmol), ethyl benzoate **179c** (116,g, 0.42 mmol), s-BuLi (0.35 mL, 1.3 M in hexanes, 0.46 mmol) and azetidine boronic ester (S)-**104g** (190 mg, 063 mmol). To give minor diastereomer (S,R)-**223c'** (9 mg, 7%, 61.5:38.5 er) and major diastereomer (R,R)-**223c** (47 mg, 34%, 99.5:0.5 er).*

**O-(t-Butyl) (S)-2-((R)-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)ethyl)azetidine-1-carbothioate (S,R)-223c'**

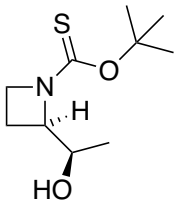



Boronic ester (*S*,*R*)-**223c** was prepared following general procedure **E**, using stannane (*S*)-**230b** (311 mg, 0.55 mmol) and azetidine boronic ester (*R*)-**104g** (125 mg, 0.42 mmol). The residue was purified by column chromatography (5% $Et_2O$/petroleum ether). First eluted a colourless oil, major diastereomer (*S,R*)-**223c'** (43 mg, 31% 97.5:2.5 er by HPLC: OD-H column; eluent; *n*-hexane/*i*-PrOH (99.9:0.1); flow rate = 1 mL $min^{-1}$; $\tau_R$ ((*S,R*) major) = 7.8

min, $\tau_R$ ((*R,S*) minor) = 8.9 min); $[\alpha]_D^{25}$ –36.9 (*c* 0.91, $CHCl_3$); all other data as described for racemic (*R**,*S**)-**223c'** (p **227**). Second eluted a colourless oil, minor diastereomer (*R,R*)-**223c** (20 mg, 15%, 75:25 er).

### 5.3.6 Compounds for determination of absolute configuration of boronic ester (*S*)-104g

### *O*-(*t*-Butyl) (*R*)-2-((*R*)-1-hydroxyethyl)azetidine-1-carbothioate (*R,R*)-219c

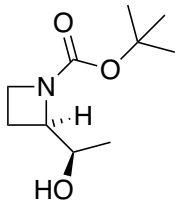



To a solution of boronic ester (*R,R*)-**223c** (46 mg, 0.14 mmol) in THF (1.2 mL) and water (1.2 mL) was added sodium perborate tetrahydrate (108 mg, 0.70 mmol). The reaction mixture was stirred vigorously for 1 h at rt. The reaction mixture was diluted with water (5 mL) and extracted with EtOAc (3 x 5 mL). The combined organic layers were washed with brine (5 mL), dried ($MgSO_4$) and concentrated under reduced pressure to give a pale yellow oil. This residue was purified by column chromatography (10% $Et_2O$/petroleum ether) to give a colourless oil, alcohol (*R*,*R*)-**219c** (16 mg, 52%, 99:1 er by HPLC: Chiralcel OD-H column, eluent; *n*-hexane/*i*-PrOH (97:3); flow rate = 1 mL $min^{-1}$; $\tau_R$ ((*S*,*S*) minor) = 13.5 min, $\tau_R$ ((*R*,*R*) major) = 14.8 min).

$[\alpha]_D^{25}$ +58.2 (*c* 1.05, $CHCl_3$); $R_f$ 0.22 (25% EtOAc/petroleum ether); IR (neat/$cm^{-1}$) 3333 (br), 2975 (m), 2929 (w), 1477 (s), 1438 (s), 1392 (m), 1366 (m), 1279 (s), 1142 (s), 1107 (m), 1022 (w); $\delta_H$ (500 MHz, $CDCl_3$) (1.7:1 rotamer mixture by analysis of the NCH signals in the 4.46 – 4.20 region) 5.33 (3.08) (1H, s, OH), 4.43 (4.24) (1H, td, *J* = 8.6, 6.0 Hz, (pseudo q, *J* = 7.5 Hz), NCH), 4.15 – 3.84 (3H, m, $NCH_2$ and C*H*OH), 2.33 – 2.21 (1H, m, NCHCH*H'*), 1.93 –

1.77 (1H, m, NCHC*H*H'), 1.63 (1.69) (9H, s, $C(CH_3)_3$), 1.12 (1.13) (3H, d, *J* = 6.4 Hz, (d, *J* = 6.4 Hz), CHC*H*$_3$); $\delta_C$ (125 MHz, $CDCl_3$) (mixture of rotamers) 187.3 (C=S), 86.2 (87.2) ($C(CH_3)_3$), 72.3 (70.9) (CHOH), 71.8 (70.6) (NCH), 49.1 (50.1) ($NCH_2$), 28.6 (28.5) ($C(CH_3)_3$), 18.7 (17.7) (NCH*C*H$_2$), 18.2 (17.8) (CH*C*H$_3$); HRMS (FTMS) calcd for [M+Na] $C_{10}H_{19}NO_2{}^{32}SNa$ 240.1029, found 240.1030.

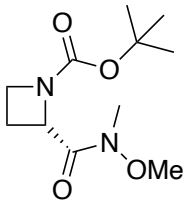
**_t_-Butyl (_R_)-2-((_R_)-1-hydroxyethyl)azetidine-1-carboxylate (_R_,_R_)-220c**




Alcohol (*R*,*R*)-**220c** was prepared following general procedure **F**, using *N*-Botc alcohol (*R*,*R*)-**219c** (14 mg, 0.06 mmol). The crude material was purified by column chromatography (10% EtOAc/petroleum ether) to give a colourless oil, alcohol (*R*,*R*)-**220c** (6 mg, 50%, 99:1 er by HPLC: Chiralcel AD-H column; eluent; *n*-hexane/*i*-PrOH (95:5), flow rate = 1 mL min$^{-1}$; $\tau_R$ ((*R,R*) major) = 9.1 min, $\tau_R$ ((*S,S*) minor) = 16.2 min).

$[\alpha]_D^{25}$ +42.8 (*c* 0.41, $CHCl_3$); $R_f$ 0.48 (EtOAc/petroleum ether); IR (neat/cm$^{-1}$) 3395 (br), 2974 (w), 1699 (m), 1665 (s), 1405 (s), 1366 (s), 1258 (m), 1157 (s), 1138 (s), 1077 (m), 976 (m); $\delta_H$ (400 MHz, $CDCl_3$) 5.14 (1H, br, OH), 4.07 (1H, pseudo q, *J* = 8.0 Hz, NCH), 3.93 – 3.79 (2H, m, C*H*OH & NC*H*H'), 3.73 (1H, td, *J* = 8.9, 4.5 Hz, NCH*H*'), 2.20 – 2.08 (1H, m, NCHC*H*H'), 1.91 – 1.79 (1H, m, NCHCH*H*'), 1.44 (9H, s, OC(C*H*$_3$)$_3$), 1.04 (3H, d, *J* = 6.3 Hz, CHC*H*$_3$); $\delta_C$ (100 MHz, $CDCl_3$) 157.9 (C=O), 80.7 (O*C*$(CH_3)_3$), 72.3 (CHOH), 68.5 (NCH), 46.6 ($NCH_2$), 28.5 (OC(*C*H$_3$)$_3$), 19.1 (NCH*C*H$_2$), 17.4 (CH*C*H$_3$); HRMS (FTMS) calcd for [M+Na] $C_{10}H_{19}O_3NNa$ 224.1257, found 224.1257.

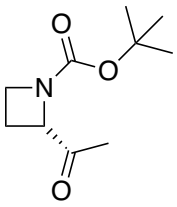
**_t_-Butyl (_S_)-2-(methoxy(methyl)carbamoyl)azetidine-1-carboxylate (_S_)-226**




Prepared following a lit.[2] procedure. To a stirred solution of (*S*)-1-(*t*-butoxycarbonyl) azetidine-2-carboxylic acid (*S*)-**221** (210 mg, 1.04 mmol) and *N*,*O*-dimethylhydroxylamine.HCl (120 mg, 1.25 mmol) in DMF (2.3 mL) at 0 °C was added sequentially *N*-Me morpholine (0.14 mL, 1.25 mmol), HOBt (170 mg, 1.25 mmol) and EDC (240 mg, 1.25 mmol). The reaction mixture was stirred at 0 °C for 2 h, warmed to rt and stirred at rt for 16 h. The reaction mixture was diluted with EtOAc (8 mL) and the solution was washed with aq HCl (1 M, 5 mL), aq NaOH (2 M, 2 x 5 mL) and brine (3 x 5 mL), dried ($MgSO_4$) and concentrated under reduced pressure to give a white crystaline solid Weinreb amide (*S*)-**226** (209 mg, 82%).

mp 58–59 °C; $[\alpha]_D^{25}$ –87.6 (*c* 1.10, $CHCl_3$) IR (neat/$cm^{-1}$) 2974 (w), 1703 (s), 1390 (s), 1366 (m), 1144 (m), 1060 (m); $\delta_H$ (400 MHz, $CDCl_3$) 5.03 (1H, dd, *J* = 9.0, 5.6 Hz, NCH), 4.04 (1H, td, *J* = 9.0, 6.2 Hz, NC*H*H'), 3.86 (1H, td, *J* = 9.0, 5.6 Hz, NCH*H*'), 3.70 (3H, s, $OCH_3$), 3.21 (3H, s, $NCH_3$), 2.46 (1H, dtd, *J* = 11.1, 9.0, 6.2 Hz, NCHC*H*H'), 2.12 (1H, ddt, *J* = 11.1, 9.0, 5.6 Hz, NCHCH*H*'), 1.42 (9H, s, $OC(CH_3)_3$); $\delta_C$ (100 MHz, $CDCl_3$) 171.5 (CHC=O), 155.7 (OC=O), 79.6 (O*C*$(CH_3)_3$), 61.5 ($OCH_3$), 58.4 (NCH), 47.8 ($NCH_2$), 32.3 ($NCH_3$), 28.3 (OC(*C*$H_3)_3$), 20.4 (NCH*C*$H_2$); HRMS (FTMS) calcd for [M+Na] $C_{11}H_{20}O_4N_2Na$ 267.1315, found 267.1314.

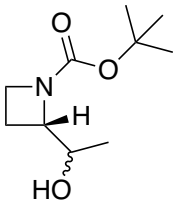
**_t_-Butyl (_S_)-2-acetylazetidine-1-carboxylate (_S_)-228**



A solution of Weinreb amide (*S*)-**226** (100 mg, 0.41 mmol) in THF (1.8 mL) was cooled to –78 °C. MeMgCl (3 M in THF, 0.21 mL, 0.62 mmol) was added dropwise, at the resulting solution was stirred at –78 °C for 2 h. The reaction mixture was quenched with sat. aq $NH_4Cl$ (3 mL) and extracted with EtOAc (3 x 3 mL). The combined organic layers were washed with brine (3 mL), dried ($MgSO_4$) and concentrated under reduced pressure to give a colourless oil. This residue was purified by column chromatography (10% EtOAc/petroleum ether) to give a colourless oil, ketone (*S*)-**228** (71 mg, 86%).

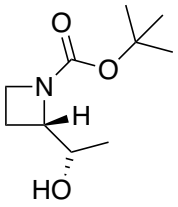
$R_f$ 0.13 (25% EtOAc/petroleum ether); $[\alpha]_D^{25}$ –173.6 (*c* 1.02, $CHCl_3$); IR (neat/$cm^{-1}$) 2976 (w), 1699 (s), 1391 (s), 1366 (s), 1250 (m), 1135 (s); $\delta_H$ (400 MHz, $CDCl_3$) 4.59 (1H, dd, *J* = 9.7, 6.3 Hz, NCH), 3.97 – 3.84 (2H, m, $NCH_2$), 2.52 – 2.38 (1H, m, NCHC*H*H'), 2.26 (3H, s, $CH_3C$=O), 2.12 (1H, ddt, *J* = 12.0, 8.7, 6.3 Hz, NCHCH*H*'), 1.43 (9H, s, $OC(CH_3)_3$); $\delta_C$ (100 MHz, $CDCl_3$) 207.5 (C=O), 155.9 (NC=O), 80.2 (O*C*$(CH_3)_3$), 66.7 (NCH), 46.9 ($NCH_2$), 28.2 (OC(*C*$H_3)_3$), 25.9 (*C*$H_3$C=O), 19.6 (NCH*C*$H_2$); HRMS (FTMS) calcd for [M+Na] $C_{10}H_{17}NO_3Na$ 222.1101, found 222.1101.

**_t_-Butyl (_S_)-2-(-1-hydroxyethyl)azetidine-1-carboxylate (_S_,_S_)-220c and (_S_,_R_)-220c'**



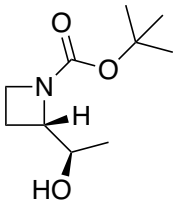

A stirred solution of ketone (*S*)-**228** (60 mg, 0.30 mmol) in MeOH (1 mL) was cooled to 0 °C. $NaBH_4$ (14 mg, 0.36 mmol) was added and the reaction mixture was stirred at rt for 30 min. The solution was then cooled to 0 °C, quenched with sat. aq $NH_4Cl$ (1 mL) dropwise and extracted with EtOAc (3 x 3 mL). The combined organic layers were washed with brine (3 mL), dried ($MgSO_4$) and concentrated under reduced pressure to give a pale yellow oil. This residue was purified by column chromatography (10% EtOAc/petroleum ether). First eluted a colourless oil, alcohol (*S,S*)-**220c** (20 mg, 32%, 96:4 er by HPLC: Chiralcel AD-H column; eluent; *n*-hexane/*i*-PrOH (95:5), flow rate = 1 mL $min^{-1}$; $\tau_R$ ((*R,R*) minor) = 9.0 min, $\tau_R$ ((*S,S*) major) = 16.0 min). Second eluted a colourless oil, alcohol (*S*,*R*)-**220c'** (18 mg, 30%).

**_t_-Butyl (_S_)-2-((_S_)-1-hydroxyethyl)azetidine-1-carboxylate (_S_,_S_)-220c**




$[\alpha]_D^{25}$ –47.4 (*c* 0.82, $CHCl_3$); all other data as described for (*R*,*R*)-**220c** (p **257** – **258**).

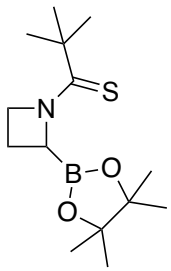
***t*-Butyl (*S*)-2-((*R*)-1-hydroxyethyl)azetidine-1-carboxylate (*S*,*R*)-220c'**




$[\alpha]_D^{25}$ –40.1 (*c* 0.87, $CHCl_3$); $R_f$ 0.28 (EtOAc/petroleum ether); IR (neat/$cm^{-1}$) 3424 (br), 2973 (m), 2930 (m), 2893 (m), 1698 (s), 1677 (s), 1393 (s), 1367 (s), 1256 (m), 1155 (s), 1136 (s); $\delta_H$ (500 MHz, $CDCl_3$) 4.34 (1H, br s, NCH), 3.95 (1H, br s, C*H*OH), 3.84 (1H, q, *J* = 8.2, NC*H'*H), 3.72 (1H, q, *J* = 7.8 Hz, NCH*H'*), 2.11 – 2.06 (2H, m, NCHC$H_2$), 1.44 (9H, s, OC(C$H_3$)$_3$), 1.15 (3H, d, *J* = 6.5 Hz, CHC$H_3$); $\delta_C$ (125 MHz, $CDCl_3$) 157.3 (C=O), 80.2 (O*C*($CH_3$)$_3$), 67.6 (CHOH), 67.2 (NCH), 47.0 ($NCH_2$), 28.5 (OC(*C*$H_3$)$_3$), 16.6 (NCH*C*$H_2$ and CH*C*$H_3$); HRMS (FTMS) calcd for [M+Na] $C_{10}H_{20}O_3N$ 202.1438, found 202.1439.

### 5.3.7 *N*-thiopivaloyl boronic ester 94c and homologation

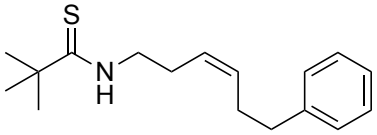
**2,2-Dimethyl-1-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)azetidin-1-yl)propane-1-thione 94c**




Boronic ester **55** was prepared following general procedure **A**, using azetidine thiopivaloyl **104g** (500 mg, 3.20 mmol) and TMEDA (1.20 mL, 7.7 mmol), with a –78 °C lithiation temp (30 min). *i*-PrOB(pin) (0.86 mL, 4.2 mmol) was then added dropwise, the mixture was stirred at –78 °C for 2 h and then warmed to rt over 20 min. The crude material was purified by column chromatography (C-2 deactivated $SiO_2$,[200] 0-5% EtOAc/petroleum ether) to give a yellow oil, boronic ester **94c** (120 mg, 13%).

$R_f$ 0.00 (10% EtOAc/ petroleum ether); IR (neat/cm$^{-1}$) 2973 (m), 1472 (m), 1439 (w), 1370 (s), 1328 (m), 1141 (s); $\delta_H$ (400 MHz, $CDCl_3$) 4.64 – 4.47 (2H, m, $NCH_2$), 4.31 – 4.22 (1H, m, NCH), 2.36 – 2.24 (1H, m, NCHC*H*H'), 2.07 (1H, ddt, *J* = 10.9, 9.1, 6.4 Hz, NCHCH*H*'), 1.34 (9H, s, $C(CH_3)_3$), 1.28 (6H, s, $C(CH_3)_2$), 1.24 (7 H, s, $C(CH_3)_2$); $\delta_C$ (100 MHz, $CDCl_3$) 207.0 (C=S), 83.9 ($OC(CH_3)_2$), 56.9 ($NCH_2$), 42.6 ($C(CH_3)_3$), 29.8 ($C(CH_3)_3$), 25.1 ($C(CH_3)_2$), 24.9 ($C(CH_3)_2$), 16.1 ($NCHCH_2$). BCH carbon not observed due to quadrupolar relaxation. $\delta_B$ (96 MHz, $CDCl_3$) 31; HRMS (FTMS) calcd for [M+H] $C_{14}H_{27}O_2NBS$ 283.1886, found 283.1888.

**(*Z*)-2,2-Dimethyl-N-(6-phenylhex-3-en-1-yl)propanethioamide 234**



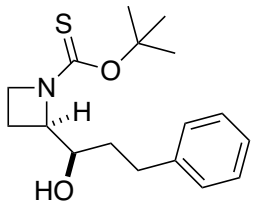

Alkene (*Z*)-**234** was prepared following general procedure **E**, using stannane **230a** (360 mg, 0.55 mmol) and azetidine boronic ester **94c** (120 mg, 0.42 mmol). The crude material was purified by flash chromatography (0-5% EtOAc/petroleum ether) to give a yellow oil, alkene (*Z*)-**234** (52 mg, 45%).

$R_f$ 0.41 (25% $Et_2O$/ petroleum ether); IR (neat/cm$^{-1}$) 3327 (br), 2960 (m), 2926 (m), 1519 (s), 1496 (m), 1453 (m), 1386 (m), 1359 (w), 1335 (m); $\delta_H$ (400 MHz, $CDCl_3$) 7.35 – 7.23 (2H, m, *o*-Ph), 7.23 – 7.15 (3H, m, *m*-Ph & *p*-Ph), 5.67 – 5.56 (1H, m, $PhCH_2CH_2CH$), 5.38 (1H, dtt, *J* = 10.6, 7.4, 1.6 Hz, $NCH_2CH_2CH$), 3.61 (2H, td, *J* = 6.8, 5.1 Hz, $NCH_2$), 2.69 (2H, t, *J* = 7.6 Hz, $PhCH_2$), 2.44 – 2.30 (4H, m, $NCH_2CH_2$ & $PhCH_2CH_2$), 1.32 (9H, s, $C(CH_3)_3$); $\delta_C$ (100 MHz, $CDCl_3$) 213.2 (C=S), 141.6 (*i*-Ph), 132.4 ($PhCH_2CH_2CH$), 128.6 (*m*-Ph), 128.5 (*o*-Ph), 126.3 ($NCH_2CH_2CH$), 126.1 (*p*-Ph), 45.7 ($NCH_2$), 44.6 ($C(CH_3)_3$), 35.9 ($PhCH_2$), 30.2 ($C(CH_3)_3$), 29.4

($PhCH_2CH_2$), 25.7 ($NCH_2CH_2$); HRMS (FTMS) calcd for [M+H] $C_{17}H_{26}NS$ 276.1781, found 276.1780.

**5.3.8 Derivatision of homologated boronic esters**

***O*-*t*-Butyl (*R**)-2-((*R**)-1-hydroxy-3-phenylpropyl)azetidine-1-carbothioate (*R**,*R**)-219b**

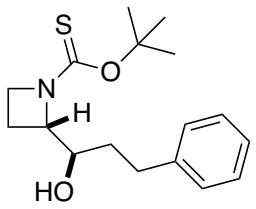



To a solution of boronic ester (*R**,*R**)-**223b** (160 mg, 0.38 mmol) in THF (3.20 mL) and water (3.20 mL) was added sodium perborate tetrahydrate (290 mg, 1.90 mmol). The mixture was stirred vigorously for 1 h at rt. The reaction mixture was then diluted with water (15 mL) and extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure to give a pale-yellow oil. This residue was purified by column chromatography (10% $Et_2O$/petroleum ether) to give a colourless oil, alcohol (*R**,*R**)-**219b** (77 mg, 66%).

$R_f$ 0.13 (25% $Et_2O$/petroleum ether); IR (neat/$cm^{-1}$) 3325 (br), 2926 (w), 2361 (m), 2342 (m) 1476 (m), 1438 (s), 1392 (m), 1366 (m), 1274 (s), 1143 (s); $\delta_H$ (400 MHz, $CDCl_3$) (1.15:1 rotamer mixture by analysis of the NCH signals in the 4.57 – 4.25 region) 7.33 – 7.15 (5H, m, Ph), 5.42 (3.04) (1H, br s, OH), 4.52 (4.30) (1H, q, *J* = 8.6 Hz, (*J* = 7.5 Hz), NCH), 3.98 – 3.76 (4.07 – 3.99) (3H, m, $NCH_2$ and C*H*OH), 2.96 – 2.84 (1H, m, PhC*H*H'), 2.80 – 2.66 (1H, m, PhCH*H'*), 2.31 – 2.15 (1H, m, NC*H*H'), 1.92 – 1.74 (1H, m, NCH*H'*), 1.73 – 1.63 (2H, m, $PhCH_2CH_2$), 1.63 (1.67) (9H, s, $C(CH_3)_3$); $\delta_C$ (100 MHz, $CDCl_3$) (mixture of rotamers) 187.4 (186.1) (C=S), 142.3 (141.7) (*i*-Ph), 128.6 (128.52) (*m*-Ph), 128.46 (128.4) (*o*-Ph), 125.8

(126.0) (*p*-Ph), 86.1 (87.0) (*C*($CH_3$)$_3$), 74.9 (73.4) (CHOH), 70.8 (69.5) (NCH), 49.2 (50.1) ($NCH_2$), 34.3 (33.7) ($PhCH_2CH_2$), 31.2 (31.5) ($PhCH_2$), 28.4 (28.5) (C(*C*$H_3$)$_3$), 18.5 (17.6) (NCH*C*$H_2$); HRMS (FTMS) calcd for [M+Na] $C_{17}H_{25}O_2N^{32}SNa$ 330.1498, found 330.1496.

**_O_-_t_-Butyl (_R_*)-2-((_S_*)-1-hydroxy-3-phenylpropyl)azetidine-1-carbothioate (_R_*,_S_*)-219b'**

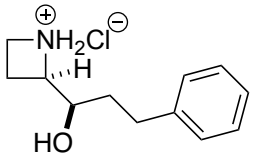



To a solution of boronic ester (*R**,*S**)-**223b'** (14 mg, 0.03 mmol) in THF (0.26 mL) and water (0.26 mL) was added sodium perborate tetrahydrate (25 mg, 0.16 mmol). The mixture was stirred vigorously for 1 h at rt. The reaction mixture was diluted with water (5 mL) and extracted with EtOAc (3 x 2 mL). The combined organic layers were washed with brine (2 mL), dried ($MgSO_4$) and concentrated under reduced pressure to give pale yellow oil. This residue was purified by column chromatography (10% $Et_2O$/petroleum ether) to give a colourless oil, alcohol (*R**,*S**)-**219b'** (6 mg, 64%).

$R_f$ 0.29 (25% $Et_2O$/petroleum ether); IR (neat/$cm^{-1}$) 3418 (br), 2926 (m), 2361 (m), 2343 (m), 1482 (s), 1437 (s), 1391 (m), 1366 (m), 1281 (s), 1144 (s); $\delta_H$ (400 MHz, $CDCl_3$) (1.15:1 rotamer mixture by analysis of the NCH signals in the 4.71 – 4.27 region) 7.32 – 7.16 (5H, m, Ar), 4.69 (4.29) (1H, t, *J* = 7.3 Hz, (*J* = 7.2 Hz), NCH), 4.10 (4.06 –4.01) (1H, br d, *J* = 7.3 Hz, (m), C*H*OH), 4.00 – 3.79 (2H, m, $NCH_2$), 3.53 (1H, br d, *J* = 7.3 Hz, OH), 3.03 – 2.94 (2.90 – 2.82) (1H, m, PhC*H*H'), 2.74 – 2.66 (1H, m, PhCH*H'*), 2.28 – 2.12 (1H, m, NCHC*H*H'), 2.10 – 1.94 (1H, m, NCHCH*H'*), 1.84 – 1.66 (1.61 – 1.58) (2H, m, $PhCH_2CH_2$), 1.62 (1.57) (9H, s, C($CH_3$)$_3$); $\delta_C$ (100 MHz, $CDCl_3$) (mixture of rotamers) 186.5 (186.6) (C=S), 142.4 (*i*-Ph), 128.7

(128.62) (*m*-Ph), 128.55 (128.59) (*o*-Ph), 126.0 (126.2) (*p*-Ph), 85.7 (85.8) ($C(CH_3)_3$), 70.8 (69.2) (CHOH), 70.2 (68.7) (NCH), 49.4 (50.4) ($NCH_2$), 33.3 (33.1) ($PhCH_2CH_2$), 32.5 (32.0) ($PhCH_2$), 28.6 ($C(CH_3)_3$), 16.8 (15.0) ($NCHCH_2$); HRMS (FTMS) calcd for [M+Na] $C_{17}H_{25}O_2N^{32}SNa$ 330.1498, found 330.1498.

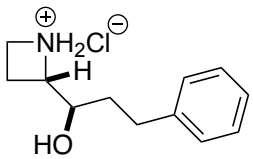
**(*R**)-2-((*R**)-1-Hydroxy-3-phenylpropyl)azetidin-1-ium chloride 151b**




HCl (0.50 mL, 2 M in $Et_2O$, 1 mmol) was added to alcohol **219b** (77 mg, 0.25 mmol) at rt. The mixture was stirred for 1 h at rt, then concentrated under reduced pressure to give a white solid, azetidinium chloride **151b** (50 mg, 88%).

mp 108–110 °C; IR (neat/$cm^{-1}$) 3334 (br), 3025 (br), 2930 (br), 2361 (s), 2341 (m), 1495 (m), 1454 (m), 1315 (m), 1261 (m); $\delta_H$ (400 MHz, $D_2O$) 7.37 – 7.19 (5H, m, Ph), 4.43 – 4.30 (1H, m, NCH), 4.09 – 3.95 (1H, m, NC*H*H'), 3.90 – 3.70 (2H, m, NCH*H*' & C*H*OH), 2.84 – 2.72 (1H, m, PhC*H*H'), 2.70 – 2.59 (1H, m, PhCH*H*'), 2.49 – 2.24 (2H, m, $NCH_2CH_2$), 1.80 – 1.54 (2H, m, $PhCH_2CH_2$); $\delta_C$ (100 MHz, $D_2O$) 141.5 (*i*-Ph), 128.7 (*o*-Ph), 128.5 (*m*-Ph), 126.2 (*p*-Ph), 69.8 (CHOH), 64.1 (NCH), 42.9 ($NCH_2$), 33.0 ($PhCH_2CH_2$), 30.5 ($PhCH_2$), 21.1 ($NCH_2CH_2$); HRMS (FTMS) calcd for [M−Cl] $C_{12}H_{18}ON$ 192.1383, found 192.1383.

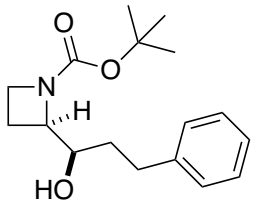
**(*S**)-2-((*R**)-1-Hydroxy-3-phenylpropyl)azetidin-1-ium chloride 151b'**



HCl (0.24 mL, 2 M in $Et_2O$, 0.48 mmol) was added to alcohol **219b'** (18 mg, 0.06 mmol) at rt. The mixture was stirred for 1 h at rt, then concentrated under reduced pressure to give a white solid, azetidinium chloride **151b'** (14 mg, quant).

mp 135–137 °C; IR (neat/$cm^{-1}$) 3322 (br), 2992 (br), 1265 (m), 1145 (m); $\delta_H$ (400 MHz, $CDCl_3$) 9.57 (1H, br s, NH), 8.77 (1H, br s, NH), 7.32 – 7.16 (5H, m, Ph), 4.65 (1H, br s, OH) 4.48 – 4.34 (1H, m, NCH), 4.11 – 3.73 (3H, m, NC*H*$_2$ & C*H*OH), 2.94 – 2.80 (1H, m, PhC*H*H'), 2.79 – 2.54 (2H, m, PhCH*H*' & $NCH_2CHH$'), 2.35 – 2.25 (1H, m, $NCH_2CH$*H'*), 1.76 – 1.65 (2H, m, $PhCH_2CH_2$); $\delta_C$ (100 MHz, $CDCl_3$) 141.3 (*i*-Ph), 128.66 (*o*-Ph), 128.63 (*m*-Ph), 126.3 (*p*-Ph), 67.5 (CHOH), 64.6 (NCH), 43.4 ($NCH_2$), 32.9 ($PhCH_2CH_2$), 31.7 ($PhCH_2$), 18.1 ($NCH_2CH_2$); HRMS (FTMS) calcd for [M−Cl] $C_{12}H_{18}ON$ 192.1383, found 192.1382.

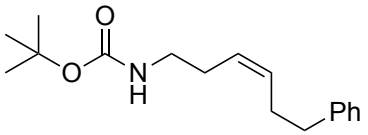
**_t_-Butyl (_R_*)-2-((_R_*)-1-hydroxy-3-phenylpropyl)azetidine-1-carboxylate 220b**




To a solution of azetidinium chloride **151b** (39 mg, 0.17 mmol) in py (2.5 mL) was added DMAP (5 mg, 0.04 mmol). The mixture was heated to 70 °C for 10 min, then cooled to 0 °C. $Boc_2O$ (39 mg, 0.18 mmol) was added and the reaction mixture was stirred at rt for 12 h. Aq. HCl (2M, 15 mL) was added and the reaction mixture was extracted with $CH_2Cl_2$ (3 x 10 mL). The combined organic layers were successively washed with aq HCl (2 M, 10 mL), $H_2O$ (10 mL) and brine (10 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure to give the crude residue as a pale yellow oil. The crude was purified by column chromatography (20% EtOAc/ petroleum ether) to give a colourless oil, alcohol **220b** (32 mg, 65%).

$R_f$ 0.14 (20% EtOAc/petroleum ether); IR (neat/cm$^{-1}$) 3380 (br), 2975 (w), 1665 (s), 1453 (m), 1407 (m), 1366 (s), 1256 (m), 1152 (s), 1112 (m), 1092 (m); $\delta_H$ (400 MHz, $CDCl_3$) 7.32 – 7.15 (5H, m, Ph), 5.19 (1H, br s, OH), 4.17 (1H, td, *J* = 8.3, 7.1 Hz, NCH), 3.83 (1H, q, *J* = 8.8 Hz, NC*H*H'), 3.78 – 3.67 (2H, m, NCH*H*' & C*H*OH), 2.89 (1H, ddd, *J* = 13.8, 9.7, 5.4, Hz, PhC*H*H'), 2.72 (1H, ddd, *J* = 13.8, 9.7, 7.0 Hz, PhCH*H*'), 2.16 – 2.06 (1H, m, $NCH_2CH$H'), 1.85 (1H, ddt, *J* = 11.4, 8.8, 7.1 Hz, $NCH_2CH$*H*'), 1.70 – 1.53 (2H, m, $PhCH_2CH_2$), 1.45 (9H, s, $C(CH_3)_3$); $\delta_C$ (100 MHz, $CDCl_3$) 158.0 (C=O), 142.5 (*i*-Ph), 128.7 (*o*-Ph), 128.5 (*m*-Ph), 125.9 (*p*-Ph), 80.8 ($OC(CH_3)_3$, 75.0 (CHOH), 67.4 (NCH), 46.7 ($NCH_2$), 33.7 ($PhCH_2CH_2$), 31.5 ($PhCH_2$), 28.5 ($OC(CH_3)_3$), 19.1 ($NCH_2CH_2$); HRMS (FTMS) calcd for [M+Na] $C_{17}H_{25}O_3NNa$ 314.1727, found 314.1724.

**_t_-Butyl (Z)-(6-phenylhex-3-en-1-yl)carbamate (*Z*)-240**



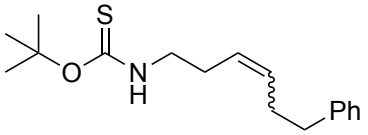

A mixture of boronic ester **223b** (38 mg, 0.09 mmol) and HCl (0.24 mL, 5.4 M in HCl, 1.30 mmol) was heated at reflux for 2h. Solvent was then removed under reduced pressure and the residue was azetropically dried with PhMe (3 x 1 mL) to give a crude residue alkenyl ammonium chloride **239** (18 mg).

To a crude mixture solution of alkenyl ammonium chloride **239** (18 mg, 0.09 mmol) in py (1.3 mL) was added DMAP (3 mg, 0.03 mmol). The mixture was heated to 70 °C for 10 min, then cooled to 0 °C. $Boc_2O$ (21 mg, 0.09 mmol) was added and the reaction mixture was stirred at rt for 12 h. Aq. HCl (2M, 5 mL) was added and the reaction mixture was extracted with $CH_2Cl_2$ (3 x 5 mL). The combined organic layers were successively washed with aq HCl (2M, 5 mL), $H_2O$ (5 mL) and brine (5 mL). The organic layer was dried ($MgSO_4$) and

concentrated under reduced pressure to give the crude residue as a brown solid. The crude was purified by column chromatography (25% $Et_2O$/ petroleum ether) to give a colourless oil, carbamate (*Z*)-**240** (5 mg, 18%).

$R_f$ 0.24 (25% $Et_2O$/petroleum ether); IR (neat/$cm^3$) 3359 (br), 3007 (w), 2976 (w), 1699 (s), 1507 (m), 1454 (w), 1365 (m), 1250 (m), 1171 (s); $\delta_H$ (400 MHz, $CDCl_3$) 7.35 – 7.11 (5H, m, Ph), 5.53 (1H, dt, *J* = 10.3, 7.6 Hz, $PhCH_2CH_2CH$), 5.40 – 5.28 (1H, m, $NCH_2CH_2CH$), 4.46 (1H, br s, NH), 3.15 – 3.01 (2H, m, $NCH_2$), 2.67 (2H, t, *J* = 7.6 Hz, $PhCH_2$), 2.37 (2H, q, *J* = 7.6 Hz, $PhCH_2CH_2$), 2.16 (2H, q, *J* = 6.8 Hz, $NCH_2CH_2$), 1.43 (9H, s, $C(CH_3)_3$); $\delta_C$ (100 MHz, $CDCl_3$) 156 (C=O), 141.9 (*i*-Ph), 131.6 ($PhCH_2CH_2CH$), 128.6 (*o*-Ph), 128.4 (*m*-Ph), 126.9 ($NCH_2CH_2CH$), 126.0 (*p*-Ph), 79.3 ($C(CH_3)_3$) 40.3 ($NCH_2$), 36.0 ($PhCH_2$), 29.4 ($PhCH_2CH_2$), 28.6 ($C(CH_3)_3$), 27.9 ($NCH_2CH_2$); HRMS (FTMS) calcd for [M+Na] $C_{17}H_{25}O_2NNa$ 298.1778, found 298.1779.

**O-(t-Butyl) (6-phenylhex-3-en-1-yl)carbamothioate 232a**



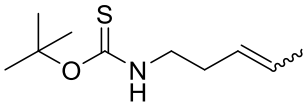

A solution of boronic esters **223b:223b'** (58 mg, 0.14 mmol, 58:42 dr) in THF (1.4 mL) was cooled to –78 °C. *n*-BuLi (0.09 mL, 2.1 M in hexanes, 0.14 mmol) was added dropwise, the mixture stirred at –78 °C for 30 mins and warmed to rt overnight. The reaction mixture was then quenched with sat. aq $NH_4Cl$ (2 mL), extracted with $Et_2O$ (3 x 3 mL), the combined organic extracts were washed (brine) and dried ($MgSO_4$) and concentrated under reduced pressure. Purification of the resulting pale yellow oil by flash chromatography (5% $Et_2O$/petroleum ether) gave a colourless oil, alkene thiocarbamate **232a** (18 mg, 45%, 40:60 *E*/*Z*) as a mixture of inseparable isomers.

*Alkene **232a** was also prepared following attempted potassium trifluoroborate salt formation:*

*To a solution of boronic ester **223b:223b'** (110 mg, 0.26 mmol, 72:28 dr) in THF (2.6 mL) was added aq $KHF_2$ (0.23 mL, 4.5 M, 1.04 mmol). The mixture was stirred at rt for 20 h. The mixture was concentrated under reduced pressure and the residue triturated with hot acetone (3 x 1 mL). The combined organic extracts were concentrated and purified by flash column chromatography (5% $Et_2O$/petroleum ether) to give a colourless oil, alkene thiocarbamate **232a** (62 mg, 81%, 30:70 E/Z) as a mixture of inseparable isomers.*

$R_f$ 0.50 (25% $Et_2O$/ petroleum ether); IR (neat/$cm^{-1}$) 3236 (br), 2977 (w), 2927 (w), 1453 (m), 1391 (m), 1365 (m), 1336 (m), 1251 (m), 1194 (w), 1140 (s); $\delta_H$ (400 MHz, $CDCl_3$) (mixture of rotamers and *E*/*Z* isomers) 7.32 – 7.24 (2H, m, *m*-Ph), 7.21 – 7.18 (3H, m, *p*-Ph & *o*-Ph), 6.06 (6.39) (1H, br s, NH), 5.62 – 5.49 (1H, m, $PhCH_2CH_2CH$), 5.40 – 5.26 (1H, m, $NCH_2CH_2CH$), 3.54 – 3.37 (3.17 (*E*)) (3.07) (2H, m, (td, *J* = 6.8, 5.7 Hz, (td, *J* = 7.0, 5.8 Hz), $NCH_2$), 2.73 – 2.64 (2H, m, $PhCH_2$), 2.43 – 2.30 (2H, m, $PhCH_2CH_2$), 2.29 – 2.21 (2.20 – 2.11) (2H, m, $NCH_2CH_2$), 1.65 (1.68) (9H, s, $C(CH_3)_3$ (*E*)), 1.62 (1.67) (9H, s, $C(CH_3)_3$ (*Z*)); $\delta_C$ (100 MHz, $CDCl_3$) (mixture of rotamers and *E*/*Z* isomers) 188.34 (188.08) (C=S) (*Z*), 188.28 (188.04) (C=S) (*E*), 141.89 (141.87) (*i*-Ph) (*E*), 141.84 (141.78) (*i*-Ph) (*Z*), 132.7 (133.1) ($PhCH_2CH_2CH$) (*E*), 132.1 (132.2) ($PhCH_2CH_2CH$) (*Z*), 128.63 (*o*-Ph) (*Z*), 128.61 (*o*-Ph) (*E*), 128.4 (*m*-Ph) (*E* & *Z*), 127.4 (126.7) ($NCH_2CH_2CH$) (*E*), 126.4 ($NCH_2CH_2CH$) (*Z*), 126.04 (125.92) (*p*-Ph) (*Z*), 125.97 (*p*-Ph) (*E*), 84.97 (86.36) ($OC(CH_3)_3$) (*Z*), 84.94 (86.31) ($OC(CH_3)_3$) (*E*), 44.0 (43.1) ($NCH_2$) (*Z*), 43.2 (*E*), 35.94 (35.86) ($PhCH_2$) (*Z*), 35.91 ($PhCH_2$) (*E*), 34.47 (34.54) ($PhCH_2CH_2$) (*E*), 31.6 (32.2) ($NCH_2CH_2$) (*E*), 29.37 (29.39) ($PhCH_2CH_2$) (*Z*), 28.68 (28.46) ($C(CH_3)_3$) (*E*), 28.65 (28.44) ($C(CH_3)_3$) (*Z*), 26.4 (27.1) ($NCH_2CH_2$) (*Z*); HRMS (FTMS) calcd for [M+Na] $C_{17}H_{25}ON^{32}SNa$ 314.1549, found 314.1551.

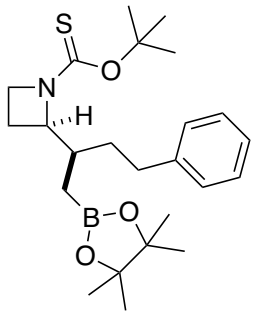
**_O_-(_t_-Butyl) pent-3-en-1-ylcarbamothioate 232b**



A solution of boronic esters **223c:223c'** (58 mg, 0.17 mmol, 54:46 dr) in THF (1.7 mL) was cooled to –78 °C. n-BuLi (0.1 mL, 2.1 M in hexanes, 0.20 mmol) was added dropwise, the reaction stirred at –78 °C for 30 mins and warmed to rt overnight. The reaction mixture was then quenched with sat. aq $NH_4Cl$ (2 mL), extracted with $Et_2O$ (3 x 3 mL), the combined organic extracts were washed (brine) and dried ($MgSO_4$) and concentrated under reduced pressure. Purification of the resulting pale yellow oil by flash chromatography (5% $Et_2O$/petroleum ether) gave a colourless oil, alkene thiocarbamate **232b** (21 mg, 58%, 46:54 *E/Z*) as a mixture of inseparable isomers.

$R_f$ 0.62 (50% $Et_2O$/petroleum ether); IR (neat/$cm^{-1}$) 3206 (br), 2989 (w), 2943 (w), 1516 (m), 1184 (s); $\delta_H$ (400 MHz, $CDCl_3$) (rotamers and diastereomers) 6.40 (6.12) (1H, br s, NH), 5.67 – 5.47 (1H, m, CH=C*H*$CH_3$), 5.45 – 5.24 (1H, m, C*H*=CH$CH_3$), 3.56 – 3.44 (3.25 – 3.14) (2H, m, $NCH_2$), 2.39 – 2.30 (2.29 – 2.12) (2H, m, $NCH_2CH_2$), 1.68 (3H, d, *J* = 2.5 Hz, CHC*H*$_3$), 1.63 (1.68) (9H, s, $C(CH_3)_3$); $\delta_C$ (100 MHz, $CDCl_3$) (rotamers and diastereomers) 128.5, (128.1, 127.5, 127.4, 127.2, 127.0, 126.4, 125.9) (*C*H=*C*H), 84.8 (*C*$(CH_3)_3$), 44.0 (43.9, 43.1, 43.0) ($NCH_2$), 32.0 (31.5, 26.6, 25.9) (*C*$H_2$CH=CH) 28.5 (28.3) (C(*C*$H_3)_3$), 18.0 (12.9) (CH*C*$H_3$). Hi-res mass spectra not found.

**_O_-(_t_-Butyl) (_R*_)-2-((_R*_)-4-phenyl-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butan-2-yl)azetidine-1-carbothioate (_R*_,_R*_)-241a**

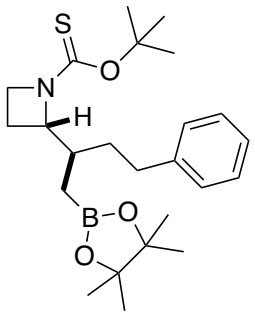



A solution of boronic ester (*R**,*R**)-**223b** (34 mg, 0.08 mmol) and $CH_2Br_2$ (20 µL, 0.20 mmol) in THF (0.8 ml) under $N_2$ was cooled to –78 °C. *n*-BuLi (90 µL, 2.1 M in hexanes, 0.19 mmol) was added slowly dropwise (10 seconds per drop). The mixture was then stirred at –78 °C for 30 min then before being warmed to rt. After 12 h the reaction mixture was diluted with $Et_2O$ (1 mL) and water (1 mL) and the layers separated. The aq layer was extracted with $Et_2O$ (3 x 1 mL), the combined organic layers washed with brine (1 x 2mL), dried ($MgSO_4$) and concentrated under reduced pressure to give a pale-yellow oil. This residue was purified by column chromatography (5% $Et_2O$/petroleum ether) to give a colourless oil, boronic ester (*R**,*R**)-**241a** (27 mg, 79%).

$R_f$ 0.35 (25% $Et_2O$/petroleum ether); IR (neat/$cm^{-1}$) 2975 (w), 2927 (w), 1479 (m), 1440 (m), 1365 (m), 1325 (m), 1278 (m), 1143 (s); $\delta_H$ (400 MHz, $CDCl_3$) (6.2:1 rotamer mixture by analysis of the NCH signals in the 4.65 – 4.37 region) 7.32 – 7.13 (5H, m, Ph), 4.46 – 4.37 (4.65 – 4.57) (1H, m, NCH), 3.99 (1H, ddd, *J* = 9.9, 9.5, 6.1 Hz, NC*H*H'), 3.87 (1H, dddd, *J* = 10.6, 9.5, 6.0, 1.3 Hz, NCH*H'*), 2.76 (2.93 – 2.82) (1H, ddd, *J* = 13.6, 10.6, 5.0 Hz, (m), PhC*H*H'), 2.54 (2.69 – 2.60) (1H, ddd, *J* = 13.6, 10.4, 6.5 Hz, (m), PhCH*H'*), 2.42 – 2.31 (1H, m, NCHC*H*), 2.09 (2.23 – 2.14) (1H, dtd, *J* = 11.5, 9.9, 6.0 Hz, (m), NCHC*H*H'), 1.97 – 1.89

(1H, m, NCHCH*H'*), 1.82 (1H, dddd, *J* = 14.1, 10.6, 6.5, 3.6 Hz, $PhCH_2CHH'$), 1.59 (1.62) (9H, s, $C(CH_3)_3$), 1.53 – 1.39 (1H, m, $PhCH_2CHH'$), 1.25 (12H, s, $OC(CH_3)_2$), 0.96 (1H, dd, *J* = 15.8, 5.2 Hz, BC*H*H'), 0.57 (1H, dd, *J* = 15.8, 9.3 Hz, BCH*H'*); $\delta_C$ (100 MHz, $CDCl_3$) 185.9 (C=S), 142.5 (*i*-Ph), 128.6 (*m*-Ph), 128.5 (*o*-Ph), 125.9 (*p*-Ph), 84.9 ($C(CH_3)_3$), 83.3 ($OC(CH_3)_2$), 68.5 (NCH), 49.7 ($NCH_2$), 35.6 (NCH*C*H), 34.0 ($PhCH_2$), 32.4 ($PhCH_2CH_2$), 28.7 ($C(CH_3)_3$), 25.1 ($OC(CH_3)_2$), 25.0 ($OC(CH_3)_2$), 16.4 ($NCHCH_2$). BCH carbon not observed due to quadrupolar relaxation. $\delta_B$ (128 MHz, $CDCl_3$) 34; HRMS (FTMS) calcd for [M+Na] $C_{24}H_{38}O_3N^{11}B^{32}SNa$ 454.2560, found 454.2557.

**_O_-(_t_-Butyl) (_R*_)-2-((_S*_)-4-phenyl-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butan-2-yl)azetidine-1-carbothioate (_R*_,_S*_)-241a'**

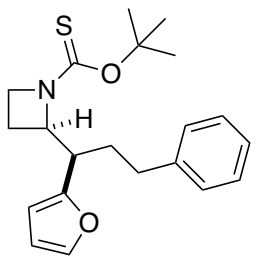



A solution of boronic ester (*R**,*S**)-**223b'** (34 mg, 0.08 mmol) and $CH_2Br_2$ (20 µL, 0.20 mmol) in THF (0.8 ml) under $N_2$ was cooled to –78 °C. *n*-BuLi (90 µL, 2.1 M in hexanes, 0.19 mmol) was added dropwise (10 seconds per drop). The mixture was stirred at –78 °C for 30 mins then the mixture was warmed to rt and further stirred for 12 h. The reaction mixture was diluted with $Et_2O$ (1 mL) and water (1 mL) and the layers separated. The aq layer was extracted with $Et_2O$ (3 x 1 mL), the combined organic layers washed with brine (1 x 2 mL), dried ($MgSO_4$) and concentrated under reduced pressure to give a pale yellow oil. This

residue was purified by column chromatography (5% $Et_2O$/petroleum ether) to give a colourless oil, boronic ester (*R**,*S**)-**241a'** (24 mg, 70%).

$R_f$ 0.52 (25% $Et_2O$/petroleum ether); IR (neat/$cm^3$) 2976 (w), 2927 (w), 1480 (m), 1440 (m), 1390 (m), 1365 (m), 1318 (m), 1278 (s), 1142 (s); $\delta_H$ (400 MHz, $CDCl_3$) (8.7:1 rotamer mixture by analysis of the NCH signals in the 4.76 – 4.39 region) 7.29 – 7.12 (5H, m, Ph), 4.45 (4.73 – 4.61) (1H, dt, *J* = 9.3, 5.5 Hz, (m), NCH), 3.99 (1H, td, *J* = 9.9, 6.2 Hz, NC*H*H'), 3.90 (1H, td, *J* = 9.9, 6.0 Hz, NCH*H*'), 2.60 (2H, t, *J* = 8.1 Hz, $PhCH_2$), 2.52 – 2.40 (2.90 – 2.82) (1H, m, NCHC*H*), 2.18 – 1.98 (1H, m, NCHC*H*H'), 1.98 – 1.88 (1H, m, NCHCH*H*'), 1.59 (1.62) (9H, s, $C(CH_3)_3$), 1.56 – 1.40 (2H, m, $PhCH_2CH_2$), 1.23 (12H, s, $C(CH_3)_2$), 0.92 (1H, dd, *J* = 15.6, 3.2 Hz, BC*H*H'), 0.68 (1H, dd, *J* = 15.6, 10.4 Hz, BCH*H*'); $\delta_C$ (100 MHz, $CDCl_3$) (rotamer mixture) 185.7 (C=S), 142.3 (*i*-Ph), 128.5 (*m*-Ph), 128.4 (*o*-Ph), 125.9 (*p*-Ph), 85.1 ($C(CH_3)_3$), 83.3 ($C(CH_3)_2$), 67.9 (67.0) (NCH), 49.8 ($NCH_2$), 35.3 (NCH*C*H), 34.6 ($PhCH_2CH_2$), 33.9 ($PhCH_2$), 28.5 (28.6) ($C(CH_3)_3$), 25.2 ($C(CH_3)_2$), 24.9 ($C(CH_3)_2$), 15.8 ($NCH*C*H_2$). BCH carbon not observed due to quadrupolar relaxation. $\delta_B$ (128 MHz, $CDCl_3$) 34; HRMS (FTMS) calcd for [M+H] $C_{24}H_{39}O_3N^{11}B^{32}S$ 432.2740, found 431.2741.

**O-(*t*-Butyl) (*R**)-2-((*R**)-1-(furan-2-yl)-3-phenylpropyl)azetidine-1-carbothioate (*R**,*R**)-242a**

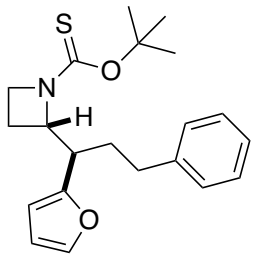


A solution of furan (18 µL, 0.23 mmol) in THF (0.76 mL) under $N_2$ was cooled to –78 °C. *n*-BuLi (0.11 mL, 2.1 M in hexanes, 0.23 mmol) was added dropwise and the reaction mixture was then warmed to rt. The mixture was stirred at rt for 1 h, then cooled to –78 °C. A solution of boronic ester (*R**,*R**)-**223b** (0.38 mL, 0.5 M in THF, 0.19 mmol) was added dropwise and the mixture was stirred at –78 °C for 1 h. DDQ (0.96 mL, 0.3 M in THF, 0.29 mmol) was then added dropwise and the reaction mixture was stirred at –78 °C for 1 h. The reaction mixture was then quenched with sat. aq $Na_2S_2O_3$ (2 mL) at –78 °C, and the mixture was warmed to rt. To the mixture was added $Et_2O$ (2 mL) and $H_2O$ (2 mL), the layers were separated and the aq layer was extracted with $Et_2O$ (3 x 2 mL). The combined organic layers were washed with brine (1 x 3 mL), dried ($MgSO_4$) and concentrated under reduced pressure to give a brown oil. This residue was purified by column chromatography (5% $Et_2O$/petroleum ether). First eluted a colourless oil, furan (*R**,*R**)-**242a** (38 mg, 55%). Second eluted a colourless oil, alkene (*Z*)-**232a** (16 mg, 28%).

$R_f$ 0.55 (25% $Et_2O$/petroleum ether); IR (neat/$cm^{-1}$) 3025 (w), 2927 (w), 1476 (m), 1437 (s), 1390 (w), 1364 (w), 1279 (s), 1141 (s); $\delta_H$ (400 MHz, $CDCl_3$) (3.9:1 rotamer mixture by analysis of the NCH signals in the 4.76 – 4.46 region) 7.38 (1H, d, *J* = 1.9 Hz, OCH=), 7.32 – 7.24 (2H, m, *m*-Ph), 7.22 – 7.09 (3H, m, *o*-Ph & *p*-Ph), 6.35 (1H, dd, *J* = 3.2, 1.9 Hz, OCH=C*H*), 6.12 (1H, d, *J* = 3.2 Hz, OCq=CH), 4.50 (4.76 – 4.64) (1H, dt, *J* = 9.6, 4.2 Hz, (m), NCH), 3.98 (1H, td, *J* = 9.7, 6.1 Hz, NC*H*H'), 3.88 (1H, td, *J* = 9.7, 6.1 Hz, NCH*H'*), 3.42 (4.21 – 4.07) (1H, dt, *J* = 11.9, 4.2 Hz, (m), NCHC*H*), 2.70 (2.63 – 2.54) (1H, ddd, *J* = 13.6, 8.7, 4.8 Hz, (m), PhC*H*H'), 2.44 (1H, dt, *J* = 13.6, 8.4 Hz, PHCH*H'*), 2.29 – 1.92 (4H, m, NCHC$H_2$ & $PhCH_2CH_2$), 1.53 (1.64) (9H, s, $C(CH_3)_3$); $\delta_C$ (100 MHz, $CDCl_3$) (rotamer mixture) 186.0 (C=S), 154.4 (OCq=), 142.0 (OCH=), 141.7 (*i*-Ph), 128.7 (*o*-Ph), 128.6 (128.5) (*m*-Ph), 126.1 (125.9) (*p*-Ph), 110.3 (OCH=*C*H), 107.0 (OCq=*C*H), 85.3 (*C*$(CH_3)_3$), 66.4 (NCH), 49.88 (49.93) ($NCH_2$), 40.0

(NCH*C*H), 33.6 ($PhCH_2$), 28.5 (28.6) ($C(CH_3)_3$ & $PhCH_2CH_2$), 17.1 ($NCHCH_2$); HRMS (FTMS) calcd for [M+Na] $C_{21}H_{27}O_2N^{32}SNa$ 380.1655, found 380.1654.

**O-(*t*-Butyl) (*R**)-2-((*S**)-1-(furan-2-yl)-3-phenylpropyl)azetidine-1-carbothioate (*R**,*S**)-242a'**

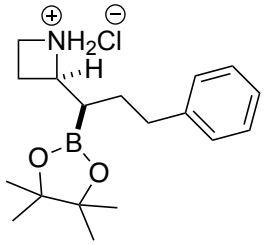



A solution of furan (18 µL, 0.23 mmol) in THF (0.76 mL) under $N_2$ was cooled down to –78 °C. *n*-BuLi (0.11 mL, 2.1 M in hexanes, 0.23 mmol) was added dropwise and the reaction mixture was then warmed to rt. The mixture was stirred at rt for 1 h, then cooled to –78 °C. A solution of boronic ester (*R**,*S**)-**223b'** (0.38 mL, 0.5 M in THF, 0.19 mmol) was added dropwise and the mixture was stirred at –78 °C for 1 h. A solution of DDQ (0.96 mL, 0.3 M in THF, 0.29 mmol) was added dropwise and the reaction mixture was stirred at –78 °C for 1 h. The reaction mixture was quenched with sat. aq $Na_2S_2O_3$ (2 mL) at –78 °C, and the mixture was warmed to rt. To the mixture was added $Et_2O$ (2 mL) and $H_2O$ (2 mL), the layers were separated and the aq layer was extracted with $Et_2O$ (3 x 2 mL). The combined organic layers were washed with brine (1 x 3 mL), dried ($MgSO_4$) and concentrated under reduced pressure to give a brown oil. The residue was purified by column chromatography (5% $Et_2O$/petroleum ether) to give a colourless oil, furan (*R**,*S**)-**242a'** (33 mg, 49%).

$R_f$ 0.58 (25% $Et_2O$/petroleum ether); IR (neat/$cm^3$) 3025 (w), 2967 (w), 1479 (s), 1464 (m), 1439 (s), 1390 (m), 1365 (m), 1280 (s), 1144 (s); $\delta_H$ (400 MHz, $CDCl_3$) (2.8:1 rotamer mixture

by analysis of the NCH signals in the 4.63 – 4.34 region) 7.41 (1H, d, *J* = 1.8 Hz, OCH=), 7.30 – 7.24 (2H, m, *m*-Ph), 7.20 – 7.09 (3H, m, *o*-Ph & *p*-Ph), 6.37 (1H, dd, *J* = 3.2, 1.8 Hz, OCH=C*H*), 6.13 (6.24) (1H, d, *J* = 3.2 Hz, (d, *J* = 3.2 Hz), OCq=C*H*), 4.37 (4.60) (1H, dt, *J* = 9.2, 5.1 Hz, (dt, *J* = 8.8, 4.6 Hz), NCH), 3.83 (3.69) (1H, td, *J* = 9.8, 5.6 Hz, (td, *J* = 9.7, 5.2 Hz) NC*H*H'), 3.50 – 3.40 (4.32 – 4.20 & 3.30 – 3.15) (2H, m, NCH*H'* & NCHC*H*), 2.74 – 2.55 (1H, m, PhC*H*H'), 2.48 (1H, dt, *J* = 13.8, 8.2 Hz, PhCH*H'*), 2.24 – 1.94 (3H, m, NCHC$H_2$ & $PhCH_2CH$H'), 1.87 – 1.72 (1H, m, $PhCH_2CH$*H'*), 1.57 (1.60) (9H, s, $OC(CH_3)_3$); $\delta_C$ (100 MHz, $CDCl_3$) (rotamer mixture) 185.3 (C=S), 153.6 (OCq=), 142.1 (O*C*H=), 141.6 (*i*-Ph), 128.6 (128.5) (*o*-Ph & *m*-Ph), 126.2 (128.5) (*p*-Ph), 110.5 (OCH=*C*H), 108.2 (OCq=*C*H), 85.1 ($C(CH_3)_3$), 66.5 (67.3) (NCH), 49.5 (49.2) ($NCH_2$), 40.0 (NCH*C*H), 33.6 (34.0) ($PhCH_2$), 30.7 (30.6) ($PhCH_2CH_2$), 28.6 (28.7) ($C(CH_3)_3$), 17.5 (17.7) ($NCHCH_2$); HRMS (FTMS) calcd for [M+Na] $C_{21}H_{27}O_2N^{32}SNa$ 380.1655, found 380.1654.

**(*R**)-2-((*R**)-3-Phenyl-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propyl)azetidin-1-ium (*R**,*R**)-243a**

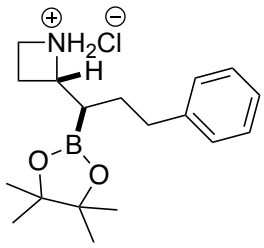



HCl (0.20 mL, 2 M in $Et_2O$, 0.40 mmol) was added to boronic ester (*R**,*R**)-**223b** (20 mg, 0.05 mmol) at rt. The mixture was stirred for 1 h at rt, then concentrated under reduced pressure to give a white solid, azetidinium chloride (*R**,*R**)-**243a** (16 mg, quant).

mp 131–132 °C; IR (neat/$cm^{-1}$) 3394 (br), 2924 (w), 2858 (w), 1453 (w), 1372 (m), 1328 (m), 1141 (s); $\delta_H$ (400 MHz, $CD_3OD$) 7.36 – 7.11 (5H, m, Ph), 4.53 (1H, q, *J* = 9.2 Hz, NCH), 4.03

(1H, q, *J* = 9.8 Hz, NC*H*H'), 3.76 (1H, td, *J* = 9.8, 4.0 Hz, NCH*H'*), 2.79 (1H, ddd, *J* = 14.3, 8.8, 5.8 Hz, PhC*H*H'), 2.70 – 2.51 (2H, m, PhCH*H'* & NCHC*H*H'), 2.38 – 2.25 (1H, m, NCHCH*H'*), 1.79 – 1.59 (3H, m, BCH & $PhCH_2CH_2$), 1.35 (12H, s, $C(CH_3)_2$); $\delta_C$ (100 MHz, $CD_3OD$) 143.0 (*i*-Ph), 129.5 (*m*-Ph), 129.4 (*o*-Ph), 127.1 (*p*-Ph), 85.6 ($OC(CH_3)_2$), 63.5 (NCH), 43.5 ($NCH_2$), 35.3 ($PhCH_2$), 29.0 ($PhCH_2CH_2$), 27.3 ($NCHCH_2$), 25.3 ($OC(CH_3)_2$), 25.1 ($OC(CH_3)_2$). BCH carbon not observed due to quadrupolar relaxation. $\delta_B$ (128 MHz, $CD_3OD$) 33; HRMS (FTMS) calcd for [M-Cl] $C_{18}H_{29}O_2N^{11}B$ 302.2286, found 302.2288.

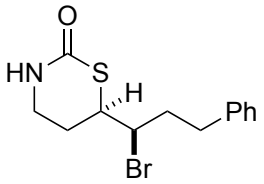
**(*S**)-2-((*R**)-3-phenyl-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propyl)azetidin-1-ium chloride 243a'**




HCl (0.20 mL, 2 M in $Et_2O$, 0.40 mmol) was added to boronic ester (*R**,*S**)-**223b'** (20 mg, 0.05 mmol) at rt. The mixture was stirred for 1 h at rt, then concentrated under reduced pressure to give a yellow oil, azetidinium chloride (*R**,*S**)-**243a'** (16 mg, quant).

IR (neat/$cm^{-1}$) 1344 (m), 908 (m), 729 (s); $\delta_H$ (400 MHz, $CD_3OD$) 7.33 – 7.21 (5H, m, Ph), 4.56 (1H, q, *J* = 9.3 Hz, NCH), 4.06 (1H, q, *J* = 9.9 Hz, NCH*H*'), 3.78 (1H, td, *J* = 9.9, 4.4 Hz, NC*H*H'), 2.86 – 2.67 (1H, m, PhCH*H*'), 2.66 – 2.51 (2H, m, PhC*H*H' & NCHCH*H*'), 2.49 – 2.27 (1H, m, NCHC*H*H'), 1.81 – 1.69 (3H, m, BCH & $PhCH_2CH_2$), 1.31 (12H, s, $C(CH_3)_2$); $\delta_C$ (100 MHz, $CD_3OD$) 142.9 (*i*-Ph), 129.4 (*m*-Ph), 129.3 (*o*-Ph), 127.1(*p*-Ph), 85.4 ($OC(CH_3)_2$), 64.7 (NCH), 43.4 ($NCH_2$), 35.5 ($PhCH_2$), 30.4 ($PhCH_2CH_2$), 27.0 ($NCHCH_2$), 25.2($OC(CH_3)_2$) , 25.1($OC(CH_3)_2$). BCH carbon not observed due to quadrupolar relaxation. $\delta_B$ (128 MHz, $CD_3OD$) 33; HRMS (FTMS) calcd for [M-Cl] $C_{18}H_{29}O_2N^{11}B$ 302.2286, found 302.2288.

**(*R**)-6-((*R**)-1-Bromo-3-phenylpropyl)-1,3-thiazinan-2-one 238a**

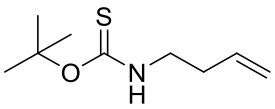



Prepared following lit.[203] procedure. To a solution of 1,3-bis(trifluoromethyl)-5-bromobenzene (0.26 mL, 0.15 mmol) in THF (1.3 mL) under $N_2$ was cooled to –78 °C. *n*-BuLi (0.07 mL, 2.1 M in hexanes, 0.15 mmol) was added dropwise and the reaction mixture was stirred for 1 h at –78 °C. A solution of boronic ester **223b** (50 mg, 0. 12 mmol) in THF (0.6 mL) was added dropwise and the mixture was stirred at –78 °C for a further 30 min. The mixture was warmed to rt and stirred for 30 mins before a solution of NBS (27 mg, 0.15 mmol) in THF (1.5 mL) was added dropwise. The mixture was stirred at rt for a 1 h before the reaction mixture was quenched with $Na_2S_2O_3$ (3 mL) and the layers separated. The aqueous layer was extracted with $Et_2O$ (3 x 3 mL), the combined organic layers were washed brine (3 x 3 mL), dried ($MgSO_4$) and concentrated under reduced pressure to give a pale yellow oil. This crude material was purified flash chromatography (50-100% EtOAc/petroleum ether) to give a white solid, 1-3-thiazinan-2-one **238a** (11 mg, 28%).

$R_f$ 0.13 (100% EtOAc/ petroleum ether); mp 85–86 °C; IR (neat/$cm^{-1}$) 3208 (br), 2924 (w), 1707 (w), 1647 (s); $\delta_H$ (400 MHz, $CDCl_3$) 7.35 – 7.15 (5H, m, Ph), 6.38 (1H,br s, NH), 3.97 (1H, ddd, *J* = 11.0, 4.0, 2.9 Hz, CHBr), 3.80 (1H, dt, *J* = 11.0, 4.0 Hz, SCH), 3.47 (1H, ddt, *J* = 13.0, 5.2, 4.0 Hz NC$H_{eq}$H), 3.36 (1H, ddd, *J* = 13.0, 11.5, 2.6 Hz, NCH$H_{ax}$), 2.97 (1H, ddd, *J* = 13.4, 8.4, 4.7 Hz, PhC*H*H'), 2.82 – 2.67 (1H, m, PhCH*H*'), 2.38 – 2.25 (2H, m, $PhCH_2CHH'$ & $NCH_2CH_{eq}H$), 2.17 – 2.06 (1H, m, $PhCH_2CHH'$), 1.98 (1H, dtd, *J* = 13.8, 11.5, 4.0 Hz, $NCH_2CHH_{ax}$); $\delta_C$ (100 MHz, $CDCl_3$) 167.3 (C=O), 140.1 (*i*-Ph), 128.8 (*o*-Ph), 128.7 (*m*-Ph),

126.6 (*p*-Ph), 57.0 (CHBr), 49.7 (SCH), 41.7 ($NCH_2$), 36.2 ($CHBrCH_2$), 33.7 ($PhCH_2$), 27.3 ($NCH_2CH_2$); HRMS (FTMS) calcd for [M+H] $C_{13}H_{17}NOBrS$ 314.0209, found 314.0210.

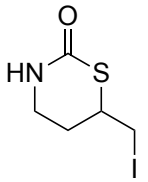
**O-(t-Butyl) but-3-en-1-ylcarbamothioate 232c**



To a solution of xanthate **100** (1.10 g, 6.5 mmol) in pentane (1.8 mL) at 0 °C was added 3-buten-1-amine (0.54 mL, 1.66 mmol). The reaction mixture was stirred at 0 °C for 1.5 h, then stirred at rt for 1 h, then concentrated under reduced pressure. Purification of the resulting pale yellow oil by flash chromatography (5% Et2O/petroleum ether) gave a pale yellow oil, thiocarbamate **232c** (429 mg, 39%).

$R_f$ 0.60 (25% $Et_2O$/petroleum ether); IR (neat/$cm^{-1}$) 3248 (br), 2965 (w), 2928 (w), 1506 (m), 1146 (s); $\delta_H$ (400 MHz, $CDCl_3$) (1.3:1 rotamer mixture by analysis of $C(CH_3)_3$ signals in the 1.67 – 1.62 region) 6.14 (6.50) (1H, br s, NH), 5.82 – 5.66 (1H, m, $CH=CH_2$), 5.15 – 5.07 (2H, m, $CH=CH_2$), 3.54 (3.24) (2H, td, *J* = 6.8, 5.4 Hz, (td, *J* = 6.9, 5.7 Hz), $NCH_2$), 2.33 (2.24) (2H, qt, *J* = 6.8, 1.3 Hz, (*J* = 6.8, 1.3 Hz), $NCH_2CH_2$), 1.62 (1.67) (9H, s, $C(CH_3)_3$); $\delta_C$ (100 MHz, $CDCl_3$) (rotamers) 188.4 (188.1) (C=S), 135.2 (134.6) ($CH=CH_2$), 117.6 (117.9) ($CH=CH_2$), 85.0 (86.4) ($C(CH_3)_3$), 43.5 (42.7) ($NCH_2$), 32.8 (33.3) ($NCH_2CH_2$), 28.6 (28.4) ($C(CH_3)_3$; HRMS (FTMS) calcd for [M+H] $C_9H_{18}ONS$ 188.1104, found 188.1105.

**6-(Iodomethyl)-1,3-thiazinan-2-one 238b**

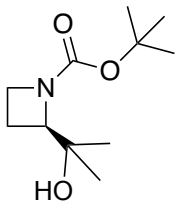


To a solution of *O*-(*t*-butyl) but-3-en-1-ylcarbamothioate **232c** (19 mg, 0.1 mmol) in $CHCl_3$ (1 mL) at rt, was added iodine (77mg, 0.3 mmol). The mixture was stirred overnight at rt and quenched with aq. $Na_2S_2O_3$ (1 mL), extracted with EtOAc (3 x 1 mL), washed with brine (1 mL), dried ($MgSO_4$) and concentrated under reduced pressure to give a yellow solid. The crude solid was purified by column chromatography (EtOAc) to give a white solid, thiazinan-2-one **238b** (4 mg, 16%).

$R_f$ 0.51 (100% EtOAc); mp 109–110 °C; IR (neat/$cm^{-1}$) 3196 (w), 3068 (w), 1646 (s), 1472 (w), 1391 (w), 1325 (w), 1299 (m); $\delta_H$ (400 MHz, $CDCl_3$) 6.15 (1H, br s, NH), 3.59 (1H, dddd, *J* = 10.5, 8.4, 4.7, 3.8 Hz, SCH), 3.52 – 3.36 (3H, m, $NCH_2$ and IC*H*H'), 3.30 (1H, t, *J* = 10.5 Hz, ICH*H*'), 2.44 (1H, ddt, *J* = 14.2, 7.3, 3.8 Hz, $NCH_2CH$H'), 2.04 (1H, dtd, *J* = 14.2, 8.4, 3.6 Hz, $NCH_2CHH$'); $\delta_C$ (100 MHz, $CDCl_3$) 166.5 (C=O), 43.3 (SCH), 40.3 ($NCH_2$), 29.4 ($NCH_2CH_2$), 7.8 ($ICH_2$); HRMS (FTMS) calcd for [M+H] $C_5H_9ONIS$ 257.9444, found 257.9444.

### 5.3.9 Compounds for determination of absolute configuration for acetone/benzaldehyde trapped azetidines

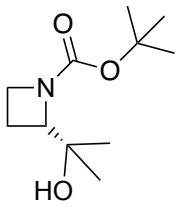
**t-Butyl (*R*)-2-(tribut-2-yl)azetidine-1-carboxylate (*R*)-220d**




The alcohol was prepared following general procedure **F**, using *N*-Botc alcohol (*R*)-**104c** (50 mg, 0.22 mmol, 89:11 er). The crude material was purified by column chromatography (10% EtOAc/petroleum ether) to give a colourless oil, alcohol (*R*)-**220d** (22 mg, 46%, 89:11 er by HPLC: AD-H column; eluent; *n*-hexane/*i*-PrOH (95:5); flow rate = 1 mL $min^{-1}$; $\tau_R$ ((*R*) major) = 9.4 min, $\tau_R$ ((*S*) minor) = 15.8 min).

$[\alpha]_D^{25}$ +45.8 (*c* 0.62, $CHCl_3$); all other data as described for racemate in lit.[56]

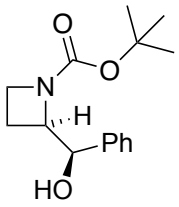
**_t_-Butyl (_S_)-2-(2-hydroxypropan-2-yl)azetidine-1-carboxylate (_S_)-220d**




A solution of ester (*S*)-**253** (50 mg, 0.23 mmol) in THF (2.3 mL) was cooled to 0 °C. To the solution was added MeMgBr (3 M in $Et_2O$, 0.17 mL, 0.51 mmol) dropwise and the mixture was stirred at 0 °C for 1 h. The reaction mixture was quenched with sat. aq $NH_4Cl$ (5 mL) and the organic layer was concentrated under a stream of $N_2$. The solution was extracted with $CH_2Cl_2$ (3 x 5 mL), combined organic layers were washed with brine (5 mL), dried ($Na_2SO_4$) and concentrated under reduced pressure to give the crude as a colourless oil. The crude was purified by column chromatography (10% EtOAc/petroleum ether) to give a colourless oil, alcohol (*S*)-**220d** (33 mg, 67%, 97.5:2.5 er by HPLC: AD-H column; eluent; *n*-hexane/*i*-PrOH (95:5); flow rate = 1 mL $min^{-1}$; $\tau_R$ ((*R*) minor) = 9.0 min, $\tau_R$ ((*S*) major) = 15.7 min).

$[\alpha]_D^{25}$ –49.3 (*c* 0.82, $CHCl_3$); all other data as described for racemate in lit.[56]

**_t_-Butyl (_R_)-2-((_R_)-hydroxy(phenyl)methyl)azetidine-1-carboxylate (_R_,_R_)-220e**

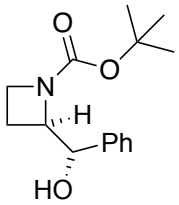



The alcohol was prepared following general procedure **F**, using *N*-Botc alcohol (*R*,*R*)-**104b** (27 mg, 0.10 mmol, 86:14 er). The crude material was purified by column chromatography (10% EtOAc/petroleum ether) to give a colourless oil, alcohol (*R*,*R*)-**220e** (14 mg, 53%,

85:15 er by HPLC: AD-H column; eluent; *n*-hexane/*i*-PrOH (95:5); flow rate = 1 mL $min^{-1}$; $\tau_R$ ((*R*, *R*) major) = 19.8 min, $\tau_R$ ((*S*, *S*) minor) = 45.9 min).

$[\alpha]_D^{25}$ –0.80 (*c* 0.89, $CHCl_3$); all other data as described for in lit.[96]

**t-Butyl (*R*)-2-((*S*)-hydroxy(phenyl)methyl)azetidine-1-carboxylate (*R*,*S*)-220e'**

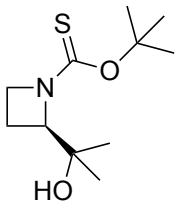



Alcohol **220e'** was prepared following general procedure **F**, using *N*-Botc alcohol (*R*,*S*)-**104b'**[1] (18 mg, 0.06 mmol, 85:15 er). The crude material was purified by column chromatography (10% EtOAc/petroleum ether) to give a colourless oil, alcohol (*R*,*S*)-**220e'** (11 mg, 70%, 85:15 er by HPLC: AD-H column; eluent; *n*-hexane/*i*-PrOH (95:5); flow rate = 1 mL $min^{-1}$; $\tau_R$ ((*R*, *S*) major) = 12.3 min, $\tau_R$ ((*S*, *R*) minor) = 13.8 min).

$[\alpha]_D^{25}$ +74.6 (*c* 0.70, $CHCl_3$); all other data as described for in lit.[96]

### 5.3.10 Compounds from mechanistic studies

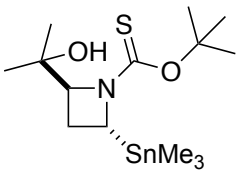
***O*-(*tert*-butyl) (*R*)-2-(2-hydroxypropan-2-yl)azetidine-1-carbothioate (*R*)-104c**




*N*-Botc alcohol (*R*)-**104c** was prepared following general procedure **G**, using stannane (±)-**104f** (84 mg, 0.25 mmol) and DIANANE (*S*)-**105**, with a −78 °C lithiation temp (1 h). Acetone (60 µL, 0.75 mmol) was then added with a −78 °C trapping temp (1 h). The crude material was purified by column chromatography (1%-10% $Et_2O$/petroleum ether) to first give a

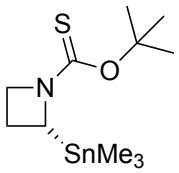
colourless oil, 2-stannyl azetidine **104f** (3 mg, 4%). Second eluted a colourless oil, *N*-Botc azetidine **101a** (13 mg, 30%). Third eluted a colourless oil, 2,4-disubstituted azetidine **108e** (5 mg, 5%, 95:5 dr *trans*:*cis*). Fourth eluted a colourless oil, *N*-Botc alcohol (*R*)-**104c** (33 mg, 56%, 90:10 er by HPLC: AD-H column; eluent: *n*-hexane/*i*-PrOH (95:5); flow rate = 1 mL $min^{-1}$; $\tau_R$ (*R*) = 12.5 min, $\tau_R$ (*S*) = 14.3 min); all other data as described in lit.[93]

***O*-(*t*-Butyl) (*R*)-2-(2-hydroxypropan-2-yl)-4-(trimethylstannyl)azetidine-1-carbothioate 108e**



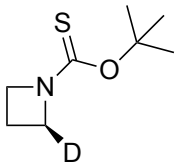

$R_f$ 0.28 (20% EtOAc/petroleum ether); IR (neat/$cm^{-1}$) 3323 (br), 2974 (m), 2916 (m), 1472 (s), 1446 (s), 1367 (s), 1270 (s), 1148 (s); $\delta_H$ (400 MHz, $CDCl_3$) (mixture of diastereomers and rotamers) 6.09 (3.59) (1H, s, OH), 4.37 (4.58) (1H, ddd, *J* = 8.5, 6.2, 1.9 Hz (*J* = 8.8, 7.3, 1.9 Hz) NC*H*), 4.25 – 4.15 (1H, m, $Me_3SnCH$), 2.25 – 2.00 (2H, m, $NCHCH_2$), 1.68 (1.64) (9H, s, $C(CH_3)_3$), 1.25 (1.31) (3H, s, $C(CH_3)_2$), 1.12 (1.08) (3H, s, $C(CH_3)_2$), 0.18 (0.20) (9H, s, $^2J_{119Sn\ H}$ = 27 Hz, $^2J_{117Sn-H}$ = 26 Hz, $Sn(CH_3)_3$)); $\delta_C$ (125 MHz, $CDCl_3$) (mixture of diastereomers and rotamers) 182.5 (183.3) (C=S), 86.8 (86.1) ($C(CH_3)_3$), 74.5 (74.9) (NCH), 72.6 (72.3) ($C(CH_3)_2$), 53.2 (52.8) ($Me_3SnCH$), 28.6 (29.0) ($C(CH_3)_3$), 24.7 (25.0) ($C(CH_3)_2$), 23.2 (22.8) ($C(CH_3)_2$), 22.0 ($NCHCH_2$), -7.6 (-8.7) ($SnMe_3$); HRMS (FTMS) calcd for $[M+H]^+$ $C_{14}H_{30}O_2NS^{120}Sn$ 396.1011, found 396.1014.

***O*-(*t*-Butyl) (*R*)-2-(trimethylstannyl)azetidine-1-carbothioate (*R*)-104f**



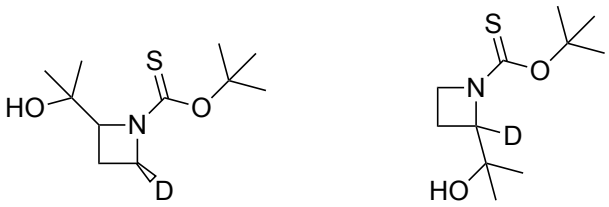

The stannane was prepared following general procedure **B**, using *N*-Botc azetidine **101a** (430 mg, 2.50 mmol) and DIANANE (*R*)-**105**, with a –78 °C lithiation temp (1 h). $Me_3SnCl$ (4.5 mL, 1.0 M in pentane, 4.5 mmol) was then added dropwise at –78 °C (1 h). The crude material was purified by column chromatography (1% $Et_2O$/petroleum ether) to first give a colourless oil, stannane (*R*)-**104f** (764 mg, 91%, 67:33 er by HPLC: OD-H column; eluent: *n*-hexane/*i*-PrOH (99.9:0.01); flow rate = 1 mL $min^{-1}$; $\tau_R$ ((*S*) minor) = 6.09 min, $\tau_R$ ((*R*) major) = 7.44 min); $[\alpha]_D^{25}$–97.9 (*c* 1.03, $CHCl_3$); all other data as described in lit.[94] Second eluted a colourless oil, recovered *N*-Botc azetidine **101a** (23 mg, 5%).

***O*-(*t*-Butyl) (*S*)-azetidine-1-carbothioate-2-*d* ($d_1$)-104n**




*N*-Botc-($d_1$)-azetidine ($d_1$)-**101a** was prepared following general procedure **B**, using *N*-Botc-azetidine **101a** (380 mg, 2.20 mmol) and DIANANE (*S*)-**105**, with a lithiation temp of −78 °C (1 h). To which $CD_3OD$ (0.90 mL, 22.2 mmol) was added with a trapping temp −78 °C (1 h). Crude material was purified by column chromatography (1%-5% $Et_2O$/petroleum ether) to give colourless oil, ($d_1$)-azetidine ($d_1$)-**104n** (353 mg, 91%, 99% D by NMR). $[\alpha]_D^{25}$–0.35 (*c* 10.9, $CHCl_3$) All data described in lit.[93]

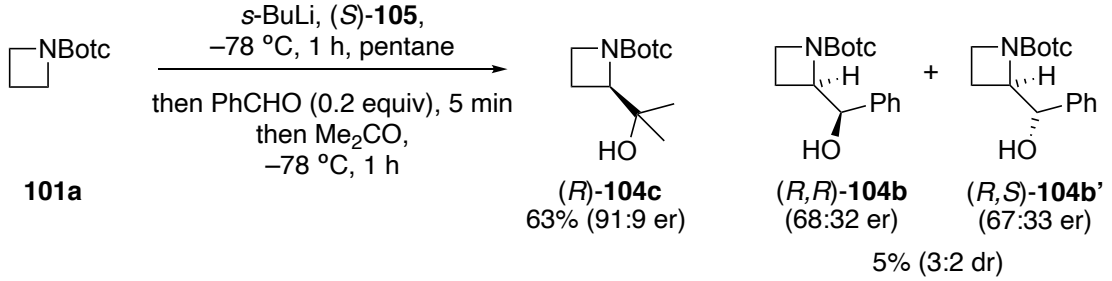
**_O_-(_t_-Butyl) (4_S_)-2-(2-hydroxypropan-2-yl)azetidine-1-carbothioate-4-_d_ and _O_-(_t_-butyl) 2-(2-hydroxypropan-2-yl)azetidine-1-carbothioate-2-_d_ ($d_1$)-104c**



The alcohol was prepared following general procedure **B**, using ($d_1$)-azetidine ($d_1$)-**104n** (43 mg, 0.25 mmol, 99% D) and racemic DIANANE (±)-**105**, with a lithiation temp of −78 °C (1 h). To which acetone (55 μL, 0.75 mmol) was added with a trapping temp −78 °C (1 h). Crude material was purified by column chromatography (10%-20% $Et_2O$/petroleum ether) to first give colourless oil, ($d_1$)-azetidine ($d_1$)-**104n** (21 mg, 49%, 99% D). Second eluted a colourless oil, deuterated alcohols ($d_1$)-**104c** (23 mg, 40%, 99% D NMR, 51:49 er by HPLC: AD-H column; eluent; *n*-hexane/*i*-PrOH (95:5); flow rate = 1 mL $min^{-1}$; $\tau_R$ ((*R*) major) = 12.18 min, $\tau_R$ ((*S*) minor) = 14.17 min).

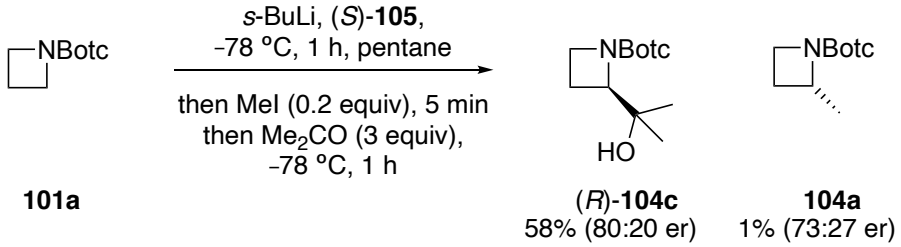
$R_f$ 0.22 (20% EtOAc/petroleum ether); IR (neat/$cm^{-1}$) 3325 (br), 2973 (w), 1437 (s), 1365 (m), 1270 (s), 1143 (s); $\delta_H$ (400 MHz, $CDCl_3$) (1.7:1 rotamer mixture by analysis of NCH signals in the 4.57–4.31 region and 1:1 mixture of regioisomers) 5.50 (3.06) (1H, br s, OH), 4.54 (4.32) (0.5H, d, *J* = 9.2, 6.2 Hz, (*J* = 9.0, 5.8 Hz), NCH), 4.10–3.80 (1.5H, m, $NCH_2$), 2.32–1.76 (2H, m, $NCH_2C\mathit{H}_2$), 1.62 (1.68) (9H, s, $C(CH_3)_3$), 1.29 (1.22) (3H, s, $C\mathit{H}_3COH$), 1.09 (1.15) (3H, s, $C\mathit{H}_3COH$); $\delta_C$ (125 MHz, $CDCl_3$) (rotamer and regioisomer mixture) 187.0 (186.3) (C=S), 86.0 (87.3) ($\mathit{C}(CH_3)_3$), 74.8 (74.1) (NCH), 74.4 (T, *J* = 22.9 Hz, NCD), 72.64 (72.57) (COH), 49.4 (50.6) ($NCH_2$), 49.1 (50.3) (T, *J* = 22.8 Hz, (*J* = 22.8 Hz), NCDH), 28.55 (28.59) ($C(\mathit{C}H_3)_3$), 25.1 (25.4) ($\mathit{C}H_3COH$), 23.1 (23.6) ($\mathit{C}H_3COH$), 18.7 (18.1) ($NCH_2\mathit{C}H_2$); HRMS ($ESI^+$) calcd for [M+H] $C_{11}H_{21}{}^2HNO_2S$: 233.1429, found 233.1430.

**Sacrificial electrophile benzaldehyde**



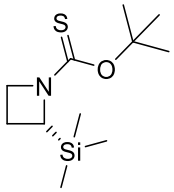

The alcohol was prepared following general procedure **B**, using *N*-Botc-azetidine **101a** (43 mg, 0.25 mmol) and DIANANE (*S*)-**105**, with a lithiation temp of −78 °C (1 h). To which benzaldehyde (5 µL, 0.05 mmol) was added, mixture was stirred for 5 min at −78 °C before acetone (55 µL, 0.75 mmol) was added with a trapping temp −78 °C (1 h). Crude material was purified by column chromatography (1%-20% $Et_2O$/petroleum ether) to first give colourless oil, *N*-Botc-azetidine **101a** (12 mg, 29%). Second eluted a colourless oil, mixture of diastereomeric alcohols minor (*R,S*)-**104b'** (2 mg, 2%, 67:33 er by HPLC: AD-H column; eluent; *n*-hexane/*i*-PrOH (96:4); flow rate = 1 mL $min^{-1}$; $\tau_R$ ((*S*,*R*) minor) = 10.54 min, $\tau_R$ ((*R*,*S*) major) = 11.31 min) and (*R,R*)-**104b** (3 mg, 3%, 68:32 er by HPLC: AD-H column; eluent; *n*-hexane/*i*-PrOH (96:4); flow rate = 1 mL $min^{-1}$; $\tau_R$ ((*S*,*S*) minor) = 23.41 min, $\tau_R$ ((*R*,*R*) major) = 33.10 min). Third eluted a colourless oil, alcohol (*R*)-**104** (36 mg, 63%, 91:9 er by HPLC: AD-H column; eluent; *n*-hexane/*i*-PrOH (95:5); flow rate = 1 mL $min^{-1}$; $\tau_R$ ((*R*) major) = 12.18 min, $\tau_R$ ((*S*) minor) = 14.17 min). All other data described in Lit.[93]

**Methyl Iodide as a sacrificial electrophile**



The alcohol was prepared following general procedure **B**, using *N*-Botc-azetidine **101a** (43 mg, 0.25 mmol) and DIANANE (*S*)-**105**, with a lithiation temp of −78 °C (1 h). To which MeI (3 µL, 0.05 mmol) was added, mixture was stirred for 5 min at −78 °C before acetone (55 µL, 0.75 mmol) was added with a trapping temp −78 °C (1 h). Crude material was purified by column chromatography (1%-20% $Et_2O$/petroleum ether) to first give colourless oil, 2-methylazetidine (*R*)-**104a** (0.5 mg, 1%, 73:27 er by HPLC: IC column; eluent; *n*-hexane/*i*-PrOH (99:1); flow rate = 1 mL $min^{-1}$; $\tau_R$ ((*S*) minor) = 17.03 min, $\tau_R$ ((*R* major) = 19.34 min). All other data described in Lit.[3] Second eluted a colourless oil, *N*-Botc-azetidine **5** (9 mg, 21% RSM). Third eluted a colourless oil, alcohol (*R*)-**104c** (33 mg, 58%, 80:20 er by HPLC: AD-H column; eluent; *n*-hexane/*i*-PrOH (95:5); flow rate = 1 mL $min^{-1}$; $\tau_R$ ((*R*) major) = 12.20 min, $\tau_R$ ((*S*) minor) = 14.34 min). All other data described in lit.[93]

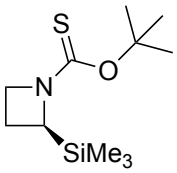
**Internal trapping with TMSCl**
***O*-(*t*-Butyl) 2-(trimethylsilyl)azetidine-1-carbothioate (*R*)-104e**




A solution of DIANANE (*S*)-**105** (60 mg, 0.33 mmol), *N*-Botc azetidine **101a** (43 mg, 0.25 mmol) and TMSCl (0.32 mL, 2.5 mmol) in pentane (2 mL) was cooled to −78 °C. *s*-BuLi (0.25 mL, 1.3 M in cyclohexane/hexane, 0.33 mmol) was added dropwise (~1 min). The reaction mixture was stirred for 1 h at −78 °C, then quenched with sat. aq $NH_4Cl$ (5 mL), and extracted with $Et_2O$ (3 × 5 mL). The combined organic extracts were washed with water (5 mL), then brine (5 mL), dried ($MgSO_4$) and concentrated under reduced pressure to give a yellow oil. The crude material was purified by column chromatography (1% $Et_2O$/petroleum ether) to first give a colourless oil, disilane **119a** (24 mg, 30%). Second eluted a colourless oil, silane (*R*)-**104e** (18 mg, 29%, 70:30 er by HPLC: OD-H column; eluent:

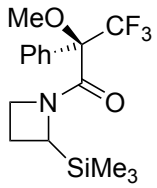
*n*-hexane/*i*-PrOH (99.9:0.01); flow rate = 1 mL min$^{-1}$; $\tau_R$ ((*S*) minor) = 5.97 min, $\tau_R$ ((*R*) major) = 6.51 min); $[\alpha]_D^{25}$ –60.0 (*c* 1.01, $CHCl_3$); all other data as described in lit.[93] Third eluted a colourless oil, recovered *N*-Botc azetidine **101a** (16 mg, 37%).

**O-(*t*-butyl) 2-(trimethylsilyl)azetidine-1-carbothioate (*S*)-104e**




Silane **104e** was prepared following general procedure **B**, using *N*-Botc azetidine **101a** (43 mg, 0.25 mmol) and DIANANE (*S*)-**105**, with a −78 °C lithiation temp (1 h). TMSOTf (0.14 mL, 0.75 mmol) was then added with a −78 °C trapping temp (1 h). The crude material was purified by column chromatography (1% $Et_2O$/petroleum ether) to give eluted a colourless oil, silane (*S*)-**104e** (17 mg, 28 %, 58:42 er by HPLC: OD-H column; eluent: *n*-hexane/*i*-PrOH (99.9:0.01); flow rate = 1 mL min$^{-1}$; $\tau_R$ ((*S*) major) = 5.44 min, $\tau_R$ ((*R*) minor) = 5.82 min); $[\alpha]_D^{25}$+25.5 (*c* 0.86, $CHCl_3$); all other data as described in lit.[93]

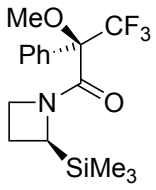
**(2*R*)-3,3,3-Trifluoro-2-methoxy-2-phenyl-1-(2-(trimethylsilyl)azetidin-1-yl)propan-1-one (*R*,*S*)-253a and (*R*,*R*)-253a'**




Silyl Mosher amides (*R*,*S*)-**253a** and (*R*,*R*)-**253a'** were prepared following general procedure **H**, using silane **104e** (10 mg, 0.04 mmol). The crude material was purified by column chromatography (10%-20% $Et_2O$/petroleum ether) to first give a colourless oil, silyl Mosher amide (*R*,*S*)-**253a** (3 mg, 22%). Second eluted a colourless oil, silyl Mosher amide (*R*,*R*)-

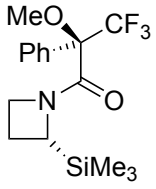
**253a'** (4 mg, 30%).

**(*R*)-3,3,3-Trifluoro-2-methoxy-2-phenyl-1-((*S*)-2-(trimethylsilyl)azetidin-1-yl)propan-1-one (*R*,*S*)-253a**




$R_f$ 0.57 (50% $Et_2O$/petroleum ether); $[\alpha]_D^{25}$ +46.0 (*c* 0.05, $CHCl_3$); IR (neat/$cm^{-1}$) 2955 (w), 1656 (s), 1266 (m), 1251 (m), 1180 (s), 1165 (s), 841 (m); $\delta_H$ (500 MHz, $CDCl_3$) 7.60 – 7.53 (2H, m, *m*-Ph), 7.42 – 7.33 (3H, m, *o*-Ph & *p*-Ph), 4.18 (1H, ddd, *J* = 9.6, 7.4, 1.3 Hz, NCH), 3.98 (1H, dddd, *J* = 10.1, 9.2, 6.2, 1.3 Hz, NCH*H*'), 3.67 (3H, q, *J* = 1.9 Hz, OMe), 3.44 (1H, td, *J* = 10.1, 6.3 Hz, NC*H*H'), 2.14 (1H, dddd, *J* = 11.0, 10.1, 9.6, 6.2 Hz, NCHCH*H*'), 1.97 (1H, dddd, *J* = 11.0, 9.2, 7.4, 6.3, NCHC*H*H'), 0.16 (9H, s, $SiMe_3$); $\delta_C$ (125 MHz, $CDCl_3$) 164.5 (C=O), 133.6 (*i*-Ph), 129.3 (*p*-Ph), 128.4 (*o*-Ph), 127.1 (*m*-Ph), 123.5 (Q, *J* = 290 Hz, $CF_3$), 84.1 (q, *J* = 26 Hz *C*$CF_3$), 55.2 (NCH), 55.1 (q, *J* = 2 Hz, OMe), 52.6 ($NCH_2$), 18.2 (NCH*C*$H_2$), –3.1 ($SiMe_3$); $\delta_F$ (377 MHz, $CDCl_3$) –69.9 (s); HRMS ($ESI^+$) calcd for [M+H] $C_{16}H_{23}O_2NF_3{}^{28}Si$ 346.1445, found 346.1445.

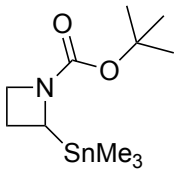
**(*R*)-3,3,3-Trifluoro-2-methoxy-2-phenyl-1-((*R*)-2-(trimethylsilyl)azetidin-1-yl)propan-1-one (*R*,*R*)-253a'**




$R_f$ 0.46 (50% $Et_2O$/petroleum ether); $[\alpha]_D^{25}$–13.8 (*c* 0.09, $CHCl_3$) IR (neat/$cm^{-1}$) 2981 (w), 1655 (s), 1268 (m), 1250 (m), 1178 (s), 1166 (s), 841 (m); $\delta_H$ (500 MHz, $CDCl_3$) 7.60 – 7.53

(2H, m, *m*-Ph), 7.40 – 7.35 (3H, m, *o*-Ph & *p*-Ph), 4.17 (1H, ddd, *J* = 11.0, 7.4, 1.6 Hz, NCH), 4.10 (1H, ddd, *J* = 10.3, 9.5, 6.3 Hz, NCH*H*'), 3.67 (3H, q, *J* = 1.7 Hz, OMe), 3.25 (1H, dddd, *J* = 10.3, 9.3, 6.1, 1.6 Hz, NC*H*H'), 2.25 (1H, tdd, *J* = 11.0, 9.5, 6.1 Hz, NCHCH*H*'), 1.85 (1H, dddd, *J* = 11.0, 9.3, 7.4, 6.3 Hz, NCHC*H*H'), 0.11 (9H, s, $SiMe_3$); $\delta_C$ (125 MHz, $CDCl_3$) 164.2 (C=O), 133.7 (*i*-Ph), 129.3 (*p*-Ph), 128.1 (*o*-Ph), 127.2 (*m*-Ph), 123.8 (Q, *J* = 289 Hz, $CF_3$), 83.9 (q, *J* = 26 Hz *C*$CF_3$), 55.2 (q, *J* = 3 Hz, OMe), 54.8 (NCH), 52.1 ($NCH_2$), 18.2 (NCH*C*$H_2$), –3.0 ($SiMe_3$); $\delta_F$ (377 MHz, $CDCl_3$) –70.6 (s); HRMS ($ESI^+$) calcd for [M+H] $C_{16}H_{23}O_2NF_3{}^{28}Si$ 346.1445, found 346.1445.

**_t_-Butyl 2-(trimethylstannyl)azetidine-1-carboxylate (±)-254**

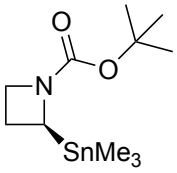



To a solution of stannane (±)-**104f** (173 mg, 0.51 mmol) in $CH_2Cl_2$ (3 mL) was added TMSI (0.10 mL, 0.66 mmol) at rt. The mixture was stirred for 30 min and then concentrated under a stream of nitrogen. The residue was dissolved in $CH_2Cl_2$ (5 mL), then $NEt_3$ (0.1 mL, 0.77 mmol), DMAP (5 mg, 0.05 mmol) and $Boc_2O$ (120 mg, 0.56 mmol) was added and the mixture was stirred overnight. The reaction mixture was then concentrated under reduced pressure and to the residue was added sat. aq $NH_4Cl$ (10 mL), and the mixture extracted with $CH_2Cl_2$ (10 × 2 mL). The combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure to give a pale yellow oil. This crude material was purified by column chromatography (5% $Et_2O$/petroleum ether) to give a colourless oil, stannane (±)-**254** (108 mg, 66%).

$R_f$ 0.44 (20% $Et_2O$/petroleum ether); IR (neat/$cm^{-1}$) 2976 (w), 1687 (s), 1399 (s), 1365 (m), 1152 (m); $\delta_H$ (500 MHz, $CDCl_3$) 4.33 (1H, br, NCH), 4.14 – 4.02 (1H, m, NCH*H*'), 3.96 (1H, td,

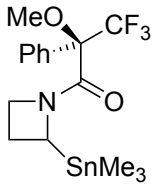
*J* = 9.0, 6.3 Hz, NC*H*H'), 2.47 (1H, qd, *J* = 10.0, 6.3 Hz, NCHCH*H'*), 2.18 – 2.08 (1H, m, NCHC*H*H'), 1.42 (9H, s, $C(CH_3)_3$), 0.14 (9H, s, $^2J_{119Sn-H}$ = 53 Hz, $^2J_{117Sn-H}$ = 51 Hz, $SnMe_3$); $\delta_C$ (125 MHz, $CDCl_3$) (rotamers) 156.5 (155.9) (C=O), 79.3 (78.8) ($C(CH_3)_3$), 52.8 (51.2) (NCH), 50.8 (49.6) ($NCH_2$), 28.7 ($C(CH_3)_3$), 19.7 ($NCHCH_2$), –10.1 ($J_{119Sn-C}$ = 325 Hz, $J_{117Sn-C}$ = 312 Hz, $SnMe_3$); HRMS (FTMS) calcd for [M+Na] $C_{11}H_{23}O_2NNa^{120}Sn$ 344.0644, found 344.0644.

**_t_-Butyl (*S*)-2-(trimethylstannyl)azetidine-1-carboxylate (*S*)-254**




Stannane (*S*)-**254** was prepared following the same procedure for racemic **254** (see above), but using stannane (*S*)-**104f** (173 mg, 0.51 mmol, 63:37 er) to give stannane (*S*)-**254** (104 mg, 63%, 66:34 er by HPLC: OD-H column; eluent: *n*-hexane/*i*-PrOH (99:1); flow rate = 1 mL $min^{-1}$; $\tau_R$ ((*S*) major) = 4.16 min, $\tau_R$ ((*R*) minor) = 4.53 min); $[\alpha]_D^{25}$ +57.9 (*c* 0.38, $CHCl_3$); all other data as described above.

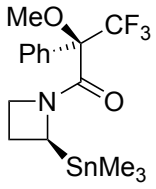
**(2*R*)-3,3,3-Trifluoro-2-methoxy-2-phenyl-1-(2-(trimethylstannyl)azetidin-1-yl)propan-1-one (*R*,*S*)-253b and (*R*,*R*)-253b'**




To a solution of stannane **104f** (34 mg, 0.1 mmol) in $CH_2Cl_2$ (0.6 mL) was added TMSI (20 µL, 0.13 mmol) dropwise at rt. The mixture was stirred for 30 min and then concentrated under a stream of nitrogen. The crude was dissolved in $CH_2Cl_2$ (1.0 mL), then DIPEA (38 µL, 0.22 mmol) and (*S*)-MTPA-Cl (22 µL, 0.12 mmol) was added and the mixture was stirred overnight. The reaction mixture was then concentrated under reduced pressure and to the

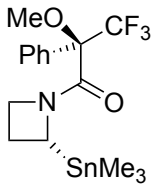
residue was added sat. aq $NH_4Cl$ (2 mL), and extracted with $CH_2Cl_2$ (3 × 2 mL). The combined organic extracts were washed with brine (2 mL), dried ($MgSO_4$) and concentrated under reduced pressure to give a pale yellow oil. This was purified by column chromatography (5%-10% $Et_2O$/petroleum ether) to first give crystalline solid, stannyl Mosher amide (*R*,*S*)-**253b** (6 mg, 14%).[8] Second eluted a colourless oil stannyl Mosher amide (*R*,*R*)-**253b'** (6 mg, 14%).

**(*R*)-3,3,3-Trifluoro-2-methoxy-2-phenyl-1-((*S*)-2-(trimethylstannyl)azetidin-1-yl)propan-1-one (*R*,*S*)-253b**



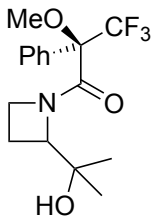

$R_f$ 0.33 (5% $Et_2O$/petroleum ether); $[\alpha]_D^{25}$ +192.2 (*c* 0.25, $CHCl_3$); mp 115–116 °C; IR (neat/$cm^{-1}$) 2954 (w), 1813 (m), 1643 (m), 1165 (s); $\delta_H$ (400 MHz, $CDCl_3$) 7.58 – 7.52 (2H, m, *m*-Ph), 7.45 – 7.36 (3H, m, *o*-Ph & *p*-Ph), 4.50 – 4.37 (1H, m, NCH), 4.12 (1H, dddd, *J* = 10.5, 9.1, 5.8, 1.6 Hz, NCH*H*'), 3.67 – 3.60 (1H, m, NC*H*H'), 3.63 (3H, q, *J* = 1.9, OMe), 2.31 (1H, dddd, *J* = 11.2, 10.0, 9.3, 5.8 Hz, NCHCH*H*'), 2.20 (1H, dddd, *J* = 11.2, 9.1, 7.7, 6.5 Hz, NCHC*H*H'), 0.21 (9H, s, $^2J_{119Sn-H}$ = 54 Hz, $^2J_{117Sn-H}$ = 52 Hz, $SnMe_3$); $\delta_C$ (100 MHz, $CDCl_3$) 163.7 (C=O), 133.6 (*i*-Ph), 129.3 (*p*-Ph), 128.3 (*o*-Ph), 127.2 (*m*-Ph), 123.7 (Q, *J* = 290 Hz, $CF_3$), 84.2 (q, *J* = 26 Hz, *C*$CF_3$), 55.1 (q, *J* = 3 Hz, OMe), 53.3 ($NCH_2$), 52.5 (NCH), 20.6 (NCH*C*$H_2$), –9.76 ($J_{119Sn-C}$ = 331 Hz, $J_{117Sn-C}$ = 317 Hz, $SnMe_3$); $\delta_F$ (377 MHz, $CDCl_3$) –69.8 (s); HRMS ($ESI^+$) calcd for [M+H] $C_{16}H_{23}O_2NF_3{}^{120}Sn$ 438.0699, found 438.0691.

**(*R*)-3,3,3-Trifluoro-2-methoxy-2-phenyl-1-((*R*)-2-(trimethylstannyl)azetidin-1-yl)propan-1-one (*R*,*R*)-253b'**




$R_f$ 0.26 (5% $Et_2O$/petroleum ether); $[\alpha]_D^{25}$ –44.0 (*c* 0.13, $CHCl_3$); IR (neat/$cm^{-1}$) 2954 (w), 1814 (m), 1643 (m), 1230 (m), 1166 (s); $\delta_H$ (400 MHz, $CDCl_3$) 7.67 – 7.48 (2H, m, *m*-Ph), 7.46 – 7.28 (3H, m, *o*-Ph & *p*-Ph), 4.41 (1H, dddd, *J* = 10.1, 7.4, 1.5, 0.9 Hz, NCH), 4.21 (1H, dddd, *J* = 10.2, 9.3, 6.4, 0.9 Hz, NCH*H*'), 3.65 (3H, q, *J* = 1.8 Hz, OMe), 3.50 – 3.36 (1H, m, NC*H*H'), 2.41 (1H, dddd, *J* = 11.2, 10.1, 9.3, 5.9 Hz, NCHCH*H*'), 2.04 (1H, dddd, *J* = 11.2, 9.2, 7.4, 6.4 Hz, NCHC*H*H'), 0.17 (9H, s, $^2J_{119Sn-H}$ = 54 Hz, $^2J_{117Sn-H}$ = 52 Hz, $SnMe_3$); $\delta_C$ (100 MHz, $CDCl_3$) 163.9 (C=O), 133.6 (*i*-Ph), 129.3 (*p*-Ph), 128.2 (*o*-Ph), 127.2 (*m*-Ph), 124.0 (Q, *J* = 290 Hz, $CF_3$), 83.7 (q, *J* = 28 Hz, *C*$CF_3$), 55.1 (q, *J* = 2 Hz, OMe), 53.2 ($NCH_2$), 51.8 (NCH), 20.6 (NCH*C*$H_2$), –9.5 ($J_{119Sn-C}$ = 332 Hz, $J_{117Sn-C}$ = 318 Hz, $SnMe_3$); $\delta_F$ (377 MHz, $CDCl_3$) –70.2 (s); HRMS ($ESI^+$) calcd for [M+H] $C_{16}H_{23}O_2NF_3{}^{120}Sn$ 438.0699, found 438.0694.

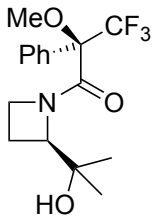
**(2*R*)-3,3,3-Trifluoro-1-(2-(2-hydroxypropan-2-yl)azetidin-1-yl)-2-methoxy-2-phenylpropan-1-one (*R*,*R*)-253c' and (*R*,*S*)-253c**




Alcohol Mosher amides (*R*,*R*)-**253c** and (*R*,*S*)-**253c'** were prepared following general procedure **H**, using alcohol **104c** (10 mg, 0.04 mmol). The crude material was purified by column chromatography (40%-80% $Et_2O$/petroleum ether) to first give a crystalline solid,

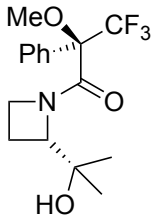
alcohol Mosher amide (*R*,*R*)-**253c'** (1 mg, 8%). Second eluted a crystalline solid alcohol Mosher amide (*R*,*S*)-**253c** (1 mg, 8%).

**(*R*)-3,3,3-Trifluoro-1-((*R*)-2-(2-hydroxypropan-2-yl)azetidin-1-yl)-2-methoxy-2-phenylpropan-1-one (*R*,*R*)-253c'**



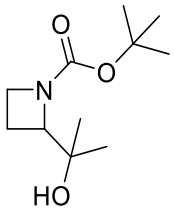

$R_f$ 0.59 (100% $Et_2O$); $[\alpha]_D^{25}$ +136.5 (*c* 0.13, $CHCl_3$); mp 94 °C; IR (neat/$cm^{-1}$) 3363 (br), 2924 (m), 1639 (m), 1167 (m); $\delta_H$ (400 MHz, $CDCl_3$) 7.60 – 7.52 (2H, m, *m*-Ph), 7.45 – 7.39 (3H, m, *o*-Ph & *p*-Ph), 4.45 (1H, pseudo t, *J* = 8.2 Hz, NCH), 3.88 (1H, tdd, *J* = 9.9, 5.2, 1.3 Hz, NCH*H*'), 3.71 (3H, q, *J* = 1.9 Hz, OMe), 3.33 (1H, dddd, *J* = 9.9, 9.1, 7.2, 0.8, NC*H*H'), 2.08 (1H, dtd, *J* = 11.7, 9.1, 5.2 Hz, NCHCH*H*'), 1.87 (1 H, ddt, *J* = 11.7, 9.9, 7.2 Hz, NCHC*H*H'), 1.58 (1H, br s, OH), 1.31 (3H, s, $CH_3$), 1.09 (3H, s, $CH_3$); $\delta_C$ (100 MHz, $CDCl_3$) 167.8 (C=O), 132.9 (*i*-Ph), 129.7 (*p*-Ph), 128.6 (*o*-Ph), 127.0 (*m*-Ph), 123.4 (Q, *J* = 289 Hz, $CF_3$), 84.2 (q, *J* = 26 Hz, *C*$CF_3$), 73.8 (NCH), 71.3 (COH), 55.4 (q, *J* = 3 Hz, OMe), 49.8 ($NCH_2$), 24.2 ($CH_3$), 23.4 ($CH_3$), 20.4 (NCH*C*$H_2$); $\delta_F$ (377 MHz, $CDCl_3$) –69.9 (s); HRMS ($ESI^+$) calcd for [M+Na] $C_{16}H_{20}O_3NF_3Na$ 354.1287, found 354.1287.

**(*R*)-3,3,3-Trifluoro-1-((*S*)-2-(2-hydroxypropan-2-yl)azetidin-1-yl)-2-methoxy-2-phenylpropan-1-one (*R*,*S*)-253c**



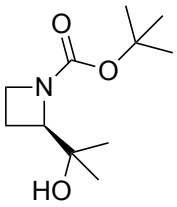
$R_f$ 0.32 (100% $Et_2O$); $[\alpha]_D^{25}$ +32.6 (*c* 0.06, $CHCl_3$); mp 118–119 °C; IR (neat/$cm^{-1}$) 3362 (br), 2925 (m), 1635 (s), 1432 (m), 1168 (s); $\delta_H$ (500 MHz, $CDCl_3$ 7.61 – 7.57 (2H, m, *m*-Ph), 7.43 – 7.37 (3H, m, *o*-Ph & *p*-Ph), 4.55 (1H, pseudo t, *J* = 7.9 Hz, NCH), 4.01 (1H, dddd, *J* = 10.1, 9.2, 6.9, 0.8 Hz, NCH*H*'), 3.69 (3H, q, *J* = 1.7 Hz, OMe), 3.15 (1H, dddd, *J* = 10.1, 9.8, 5.6, 1.4 Hz, NC*H*H'), 2.22 (1H, dtd, *J* = 11.9, 9.2, 5.6 Hz, NCHCH*H*'), 1.71 (1H, ddt, *J* = 11.9, 9.8, 6.9 Hz, NCHC*H*H'), 1.16 (3H, s, $CH_3$), 1.05 (3H, s, $CH_3$); $\delta_C$ (125 MHz, $CDCl_3$) 167.2 (C=O), 132.7 (*i*-Ph), 129.7 (*p*-Ph), 128.4 (*o*-Ph), 127.1 (*m*-Ph), 123.5 (Q, *J* = 290 Hz, $CF_3$), 84.1 (q, *J* = 26 Hz, *C*$CF_3$), 73.7 (NCH), 71.4 (COH), 55.4 (q, *J* = 3 Hz, OMe), 49.6 ($NCH_2$), 24.2 ($CH_3$), 22.8 ($CH_3$), 20.3 (NCH*C*$H_2$); $\delta_F$ (377 MHz, $CDCl_3$) –70.5 (s); HRMS ($ESI^+$) calcd for [M+Na] $C_{16}H_{20}O_3NF_3Na$ 354.1287, found 354.1287.

**_t_-Butyl 2-(2-hydroxypropan-2-yl)azetidine-1-carboxylate (±)-220d**



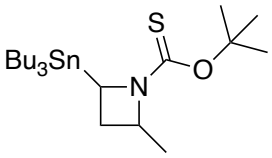

*N*-Boc alcohol (±)-**220d** was prepared following general procedure **G**, using stannane (±)-**254** (80 mg, 0.25 mmol) and DIANANE (*S*)-**105**, with a −78 °C lithiation temp (1 h). Acetone (60 µL, 0.75 mmol) was then added with a −78 °C trapping temp (1 h). The crude material was purified by column chromatography (1%-10% $Et_2O$/petroleum ether) to first give a colourless oil, *N*-Boc azetidine (6 mg, 16%). Second eluted a colourless oil, *N*-Boc alcohol **220d** (25 mg, 47%, 50:50 er by HPLC: AD-H column; eluent: *n*-hexane/*i*-PrOH (95:5); flow rate = 1 mL $min^{-1}$; $\tau_R$ (*R*) = 9.42 min, $\tau_R$ (*S*) = 15.10 min); all other data as described in lit.[56]

**_t_-Butyl (_R_)-2-(2-hydroxypropan-2-yl)azetidine-1-carboxylate (_R_)-220d**




*N*-Boc alcohol (*R*)-**220d** was prepared following general procedure **G**, using stannane (*S*)-**254** (80 mg, 0.25 mmol, 66:34 er) and racemic DIANANE (±)-**105**, with a −78 °C lithiation temp (1 h). Acetone (60 μL, 0.75 mmol) was then added with a −78 °C trapping temp (1 h). The crude material was purified by column chromatography (1%-10% $Et_2O$/petroleum ether) to first give a colourless oil, *N*-Boc-azetidine **65a** (6 mg, 16%). Second eluted a colourless oil, *N*-Boc alcohol (*R*)-**220d** (22 mg, 40%, 67:33 er by HPLC: AD-H column; eluent: *n*-hexane/*i*-PrOH (95:5); flow rate = 1 mL $min^{-1}$; $\tau_R$ (*R*) major = 9.38 min, $\tau_R$, (*S*) minor = 15.09 min); $[\alpha]_D^{25}$+14.6 (*c* 0.13, $CHCl_3$); all other data as described in lit.[56]

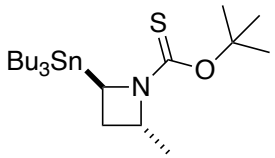
**_O_-(_t_-Butyl)-2-methyl-4-(tributylstannyl)azetidine-1-carbothioate 108f**




2,4-disubstituted azetidine **108f** was prepared following general procedure **A**, using 2-methyl-azetidine **104a** (220 mg, 1.20 mmol) and TMEDA (0.23 mL, 1.56 mmol), with a –78 °C lithiation temp (30 min). $Bu_3SnCl$ (0.42 mL, 1.56 mmol) was then added dropwise at – 78 °C (30 min). The crude material was purified by column chromatography (1% $Et_2O$/petroleum ether) to first give a colourless oil, stannane **108f** (320 mg, 55%, ~1:1 dr) as a mixture of inseparable diastereomers. Second eluted a colourless oil, 2-methyl-

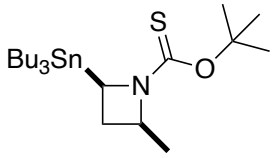
azetidine **104a** (98 mg, 45%). Analytically pure samples of seperated diastereomers were obtained by prep-TLC (1% $Et_2O$/petroleum ether).

**_O_-(_t_-Butyl) (2_R_*,4_R_*)-2-methyl-4-(tributylstannyl)azetidine-1-carbothioate _trans_-108f**




$R_f$ 0.60 (2% $Et_2O$/petroleum ether); IR (neat/$cm^{-1}$) 2956 (m), 2922 (m), 1483 (s), 1450 (m), 1274 (s), 1255 (m), 1152 (s), 1135 (s); $\delta_H$ (400 MHz, $CDCl_3$) (14.7:1 rotamer mixture by analysis of NCH signals in the 1.66 – 1.60 region) 4.43 – 4.12 (2H, m, NC*H*$CH_3$ & NC*H*Sn), 2.31 (1H, ddd, *J* = 11.0, 8.0, 6.7 Hz, NCHC*H*H'), 2.00 (1H, td, *J* = 11.0, 5.7 Hz, NCHCH*H*'), 1.61 (1.66) (9H, s, $C(CH_3)_3$), 1.55 – 1.46 (6H, m, $CH_2CH_3$), 1.42 (3H, d, *J* = 6.4 Hz, $CHCH_3$), 1.34 – 1.25 (6H, m, $SnCH_2CH_2$), 0.94 (6H, t, *J* = 8.2 Hz, $SnCH_2$), 0.89 (9H, t, *J* = 7.3 Hz, $CH_2CH_3$); $\delta_C$ (125 MHz, $CDCl_3$) (mixture of rotamers) 181.7 (C=S), 83.7 ($C(CH_3)_3$), 60.1 (NCHCH$_3$), 51.7 (NCHSn), 29.3 ($CH_2CH_3$), 28.8 (29.1) ($C(CH_3)_3$), 27.7 ($SnCH_2CH_2$), 26.9 ($NCHCH_2$), 20.4 ($NCHCH_3$), 13.9 ($CH_2CH_3$), 11.4 ($SnCH_2$); HRMS (FTMS) calcd for [M+H] $C_{21}H_{44}NOSSn$ 478.2160, found 478.2158.

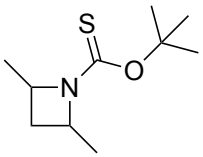
**_O_-(_t_-Butyl) (2R*,4S*)-2-methyl-4-(tributylstannyl)azetidine-1-carbothioate _cis_-108f**




$R_f$ 0.56 (2% $Et_2O$/petroleum ether); IR (neat/$cm^{-1}$) 2956 (m), 2925 (m), 1317 (s), 1273 (m), 1258 (m), 1151 (s); $\delta_H$ (400 MHz, $CDCl_3$) (5.6:1 rotamer mixture by analysis of NCH signals in the 4.67 – 4.42 region) 4.54 – 4.42 (4.67 – 4.57) (1H, m, NC*H*$CH_3$), 4.31 (4.37) (1H, dd, *J*

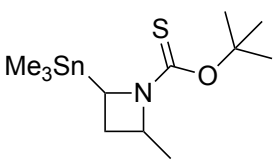
= 10.0, 7.4 Hz, (*J* = 10.5, 6.6 Hz) NCHSn), (1H), 2.55 (2.69) (1H, ddd, *J* = 11.1, 10.1, 8.4 Hz,(td, *J* = 10.7, 8.7 Hz), NCHC*H*$_{trans}$H$_{cis}$) 1.81 – 1.72 (1H, m, NCHCH$_{trans}$*H*$_{cis}$), 1.61 (1.65) (9H, s, C(CH$_3$)$_3$), 1.55 – 1.46 (6H, m, C*H*$_2$CH$_3$), 1.42 (3H, d, *J* = 6.4 Hz, CHC*H*$_3$), 1.35 – 1.23 (6H, m, SnCH$_2$C*H*$_2$), 0.98 – 0.93 (6H, m, SnCH$_2$), 0.89 (9H, t, *J* = 7.3 Hz, CH$_2$CH$_3$); $\delta_C$ (125 MHz, CDCl$_3$) (mixture of rotamers) 181.5 (182.3) (C=S), 83.7 (84.5) (*C*(CH$_3$)$_3$), 60.3 (62.3) (N*C*HCH$_3$), 52.1 (52.8) (N*C*HSn), 29.3 (29.2) (*C*H$_2$CH$_3$), 28.8 (29.0) (C(*C*H$_3$)$_3$), 27.7 (27.6) (SnCH$_2$*C*H$_2$), 27.0 (NCH*C*H$_2$), 20.9 (20.0) (NCH*C*H$_3$), 13.9 (13.8) (CH$_2$*C*H$_3$), 11.4 (10.9) (SnCH$_2$); HRMS (FTMS) calcd for [M+H] $C_{21}H_{44}NOSSn$ 478.2160, found 478.2158.

**_O_-(_t_-Butyl) 2,4-dimethylazetidine-1-carbothioate 108a**




2,4-Dimethyl-azetidine **108a** was prepared following general procedure **B**, using 2-methyl-azetidine (±)-**104a** (47 mg, 0.25 mmol) and racemic DIANANE (±)-**105**, with a lithiation temp of −78 °C (1 h). To which MeI (50 µL, 0.75 mmol) was added with a trapping temp −78 °C (1 h). Crude material was purified by column chromatography (1%-5% Et$_2$O/petroleum ether) to first give colourless oil, a mixture of diastereomers 2,4-dimethyl-azetidine **108a** (7 mg, 15%, 57:43 dr). Second eluted a colourless oil 2-methyl-azetidine **104a** (19 mg, 40%).

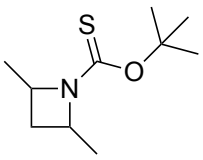
**_O_-(_t_-Butyl) 2-methyl-4-(trimethylstannyl)azetidine-1-carbothioate 108g**



2,4-disubstituted azetidine **108g** was prepared following general procedure **A**, using 2-methyl-azetidine **104a** (240 mg, 1.30 mmol) and TMEDA (0.46 mL, 1.56 mmol), with a –78 °C lithiation temp (30 min). $Me_3SnCl$ (2.40 mL, 1 M in pentane, 2.40 mmol) was then added dropwise at – 78 °C (30 min). The crude material was purified by column chromatography (1% $Et_2O$/petroleum ether) to first give a colourless oil, stannane **108g** (270 mg, 59%, ~1:1 dr) as a mixture of inseparable diastereomers. Second eluted a colourless oil, 2-methyl-azetidine **104a** (84 mg, 41%).

$R_f$ 0.86 (5% $Et_2O$/petroleum ether); IR (neat/$cm^{-1}$) 2975 (w), 1793 (m), 1490 (m), 1228 (s), 1144 (s); $\delta_H$ (400 MHz, $CDCl_3$) (mixture of diastereomers and rotamers) 4.70 – 4.24 (4H, m, NCH), 2.56 (2.70) (1H, ddd, *J* = 11.1, 10.1, 8.4 Hz,(td, *J* = 10.8, 8.6 Hz), NCHC*H*H' (*cis*)), 2.26 (1H, ddd, *J* = 11.0, 8.0, 6.3 Hz, NCHC*H*H' (*trans*)), 2.01 (1H, ddd, *J* = 11.0, 10.1, 5.9 Hz, NCHCH*H*' (*trans*)), 1.78 – 1.68 (1H, m, NCHCH*H*' (*cis*)), 1.61 (1.61) (1.65) (1.64) (18H, s, $C(CH_3)_3$), 1.26 (6H, pseudo t, *J* = 6.7 Hz, $CHCH_3$), 0.02 (0.00) (18H, s, $^2J_{119Sn\ H}$ = 27 Hz, $^2J_{117Sn\text{-}H}$ = 26 Hz, $Sn(CH_3)_3$); $\delta_C$ (100 MHz, $CDCl_3$) (mixture of diastereomers and rotamers)) 181.8 (C=S), 83.92 (83.86) ($C(CH_3)_3$), 60.14 (60.11) ($NCHCH_3$), 52.3 (51.80) ($NCHSnMe_3$), 28.74 (28.72) (28.9) ($C(CH_3)_3$), 26.5 (26.4) ($NCHCH_2$), 20.7 (20.4) ($NCHCH_3$), -7.87 (-8.25) ($SnMe_3$); HRMS not found.

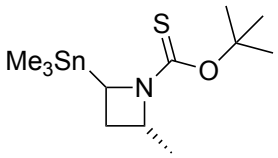
**_O_-(_t_-Butyl) 2,4-dimethylazetidine-1-carbothioate 108a**




2,4-Dimethyl-azetidine **108a** was prepared following general procedure **G**, using stannane (±)-**108g** (88 mg, 0.25 mmol) and racemic DIANANE (±)-**105**, with a lithiation temp of −78 °C (1 h). To which MeI (50 µL, 0.75 mmol) was added with a trapping temp −78 °C (1 h).

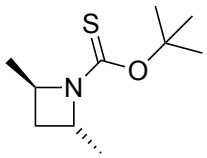
Crude material was purified by column chromatography (1%-5% $Et_2O$/petroleum ether) to first give colourless oil, a mixture of diastereomers 2,4-dimethyl-azetidine **108a** (32 mg, 63%, 75:25 dr). Second eluted a colourless oil 2-methyl-azetidine **104a** (5 mg, 11%).

***O*-(*t*-Butyl) (2*R*)-2-methyl-4-(trimethylstannyl)azetidine-1-carbothioate (2*R*)-108g**




2,4-disubstituted azetidine **108g** was prepared following general procedure **A**, using (*R*)-2-methyl-azetidine (*R*)-**104a** (290 mg, 1.50 mmol, 80:20 er) and TMEDA (0.55 mL, 3.70 mmol), with a –78 °C lithiation temp (30 min). $Me_3SnCl$ (2.90 mL, 1 M in pentane, 2.90 mmol) was then added dropwise at – 78 °C (30 min). The crude material was purified by column chromatography (1% $Et_2O$/petroleum ether) to first give a colourless oil, stannane **108g** (340 mg, 63%, 1:1 dr) as a mixture of inseparable diastereomers. Second eluted a colourless oil, 2-methyl-azetidine (*R*)-**104a** (90 mg, 31%, 76:24 er by HPLC: IC column; eluent; *n*-hexane/*i*-PrOH (99:1); flow rate = 1 mL $min^{-1}$; $\tau_R$ ((*S*) minor) = 17.06 min, $\tau_R$ ((*R*) minor) = 20.23 min). All other data described in lit.[93]

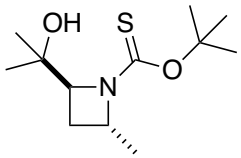
***O*-(*t*-Butyl) (2*R*,4*R*)-2,4-dimethylazetidine-1-carbothioate (*R*,*R*)-108a**




2,4-Dimethyl-azetidine (*R*,*R*)-**108a** was prepared following general procedure **G**, using enantioenriched stannanes (2*R*)-**108g** (70 mg, 0.20 mmol) and DIANANE (*S*)-**105**, with a lithiation temp of −78 °C (1 h). To which MeI (40 µL, 0.60 mmol) was added with a trapping temp −78 °C (1 h). Crude material was purified by column chromatography (1%-5%

$Et_2O$/petroleum ether) to first give colourless oil, a mixture of diastereomers 2,4-dimethyl-azetidine (*R*,*R*)-**108a** (18 mg, 45%, 74:26 dr, 82:18 er by HPLC: Chiralcel I-C column, Solvent: *n*-hexane/*i*-PrOH (99:1), flow rate = 1 mL/min$^{-1}$; $\tau_R$ ((*R*,*R*) major) = 11.8 min, $\tau_R$ (meso) = 13.0 min, $\tau_R$ ((*S*,*S*) minor) = 21.3 min) as a mixture of inseparable diastereomers. Second eluted a colourless oil 2-methyl-azetidine (*R*)-**104a** (5 mg, 13%, 74:26 er by HPLC: IC column; eluent; *n*-hexane/*i*-PrOH (99:1); flow rate = 1 mL min$^{-1}$; $\tau_R$ ((*S*) minor) = 17.09 min, $\tau_R$ ((*R*) major) = 20.75 min). All other data described in lit.[93]

**_O_-(_t_-Butyl) (2_R_*,4_S_*)-2-(2-hydroxypropan-2-yl)-4-methylazetidine-1-carbothioate 108h**




Alcohol **108h** was prepared following general procedure **G**, using stannane (±)-**108g** (88 mg, 0.25 mmol) and racemic DIANANE (±)-**105**, with a lithiation temp of −78 °C (1 h). To which acetone (40 µL, 0.6 mmol) was added with a trapping temp −78 °C (1 h). Crude material was purified by column chromatography (5-20% $Et_2O$/petroleum ether) to first give colourless oil, a 2-methyl-azetidine **104a** (16 mg, 33%). Second eluted a white crystalline solid alcohol **108h** (27 mg, 45%, dr 93:7).

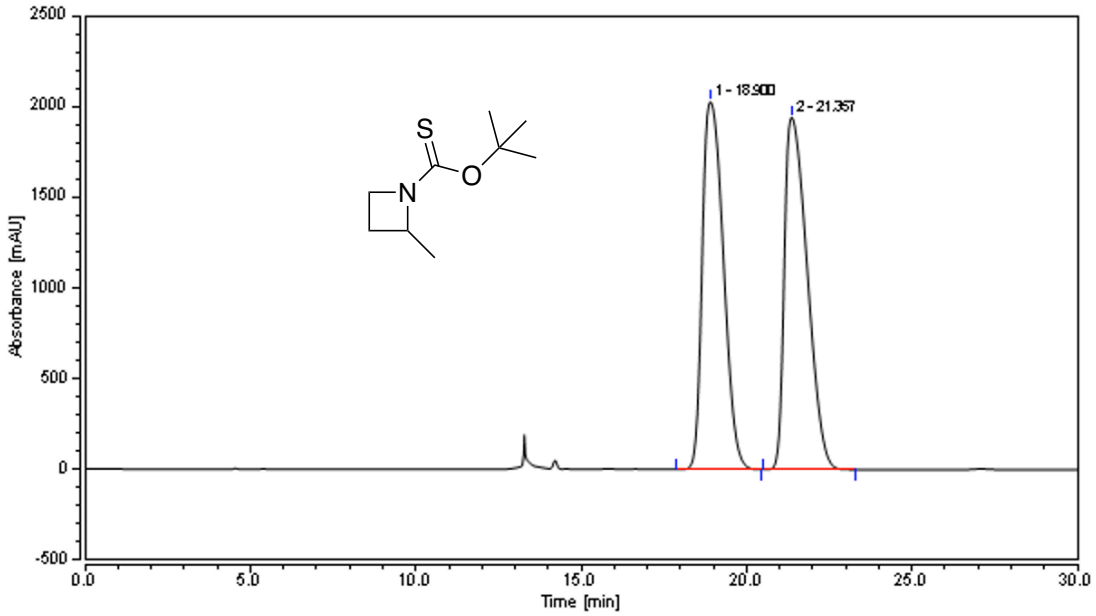
$R_f$ 0.25 ($Et_2O$/petroleum ether); mp 82 °C; IR (neat/cm$^{-1}$) 3331 (br), 2972 (m), 2928 (w), 1469 (m), 1438 (m), 1276 (m), 1145 (s); $\delta_H$ (400 MHz, $CDCl_3$) (diastereomer) 4.59 (1H, ddd, *J* = 9.3, 6.4, 1.3 Hz, NCH), (4.47) (0.1H, ddd, *J* = 8.8, 6.4, 1.3 Hz, NCH), 4.41 – 4.32 (0.1H, m, NC*H*$CH_3$), 4.26 (1H, dqdd, *J* = 8.7, 6.3, 5.2, 1.3 Hz, NC*H*$CH_3$), (2.39) (0.1H, dt, *J* = 11.6, 8.8 Hz, NCHCH*H*'), 1.97 (1H, ddd, *J* = 11.7, 8.7, 6.4 Hz, NCHCH*H*'), 1.84 (1H, ddd, *J* = 11.7, 9.3, 5.2 Hz, NCH*H*H'), (1.71) (0.9H, s, $C(CH_3)_3$), 1.64 (9H, s, $C(CH_3)_3$), (1.60) (0.3H, d, *J* = 6.2 Hz, NCHC*H*$_3$), 1.43 (3H d, *J* = 6.3 Hz, NCHC*H*$_3$), 1.28 (3H, s, $COH(CH_3)_2$), 1.07 (3H, s, $COH(CH_3)_2$);

$\delta_C$ (100 MHz, $CDCl_3$) 186.1 (C=S), 86.0 ($C(CH_3)_3$), 73.0 (COH), 72.9 (73.1) (NCH), 58.5 (58.1) ($NCHCH_3$), 28.7 (28.8) ($C(CH_3)_3$), 27.2 (27.0) ($NCHCH_2$), 25.3 (24.6) ($COH(CH_3)_2$), 23.0 ($COH(CH_3)_2$), 20.5 (19.2) ($NCHCH_3$); HRMS (FTMS) calcd for [M+Na] $C_{12}H_{23}O_2NNa^{32}S$ 268.1342, found 268.1340.

## 6. Appendix- HPLC traces

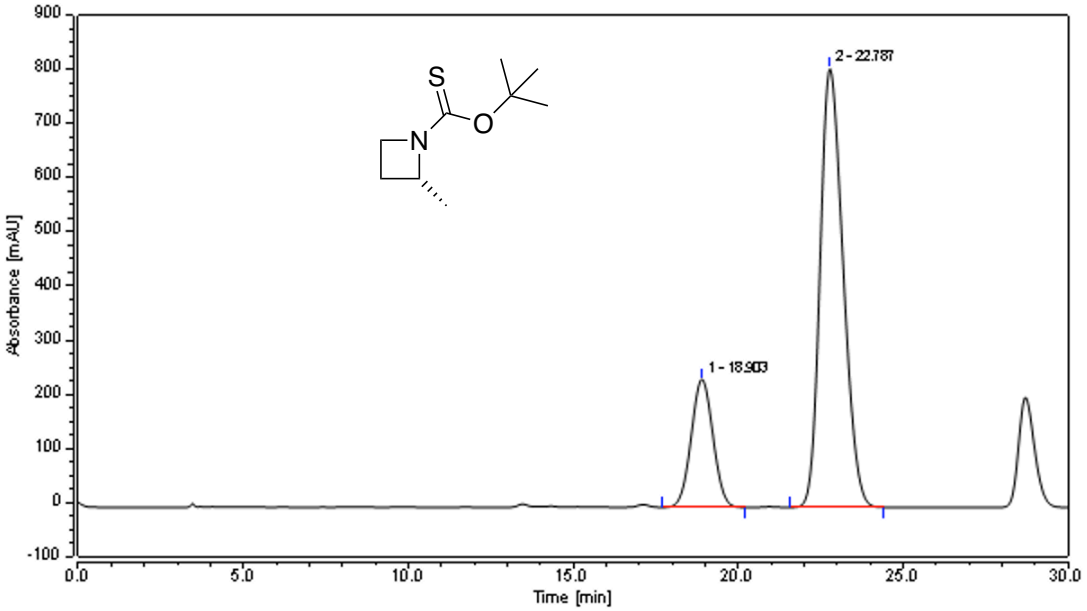
**Racemic (±)-104a**

**Chiral HPLC for 2-methylazetidine 104a:** (Chiralpak IC, 1% $^{i}$PrOH, 99% hexane, 1.0 mL min$^{-1}$, $\lambda$ = 258 nm, 50 µL injection) $\tau_R$ = 18.9 min, $\tau_R$ = 21.4 min.




| No. | Peak Name | Retention Time | Area | Height | Relative Area |
|---|---|---|---|---|---|
| | | min | mAU*min | mAU | % |
| 1 | | 18.900 | 1498.102 | 2030.911 | 49.13 |
| 2 | | 21.357 | 1551.000 | 1945.040 | 50.87 |
| **Total:** | | | 3049.101 | 3975.951 | 100.00 |

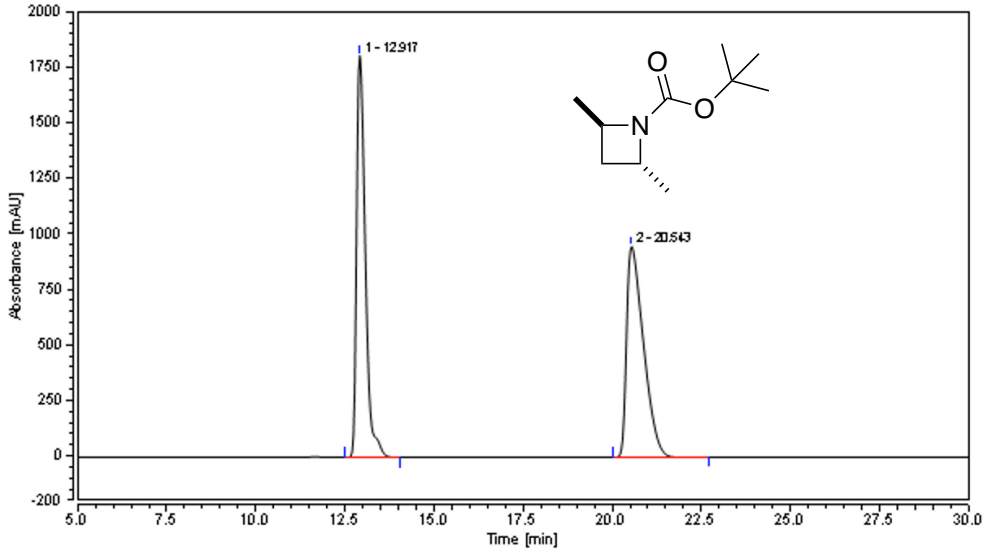
**Enantioenriched (*R*)-104a**




| No. | Peak Name | Retention Time | Area | Height | Relative Area |
|---|---|---|---|---|---|
| | | min | mAU*min | mAU | % |
| 1 | | 18.903 | 181.113 | 236.890 | 21.67 |
| 2 | | 22.787 | 654.624 | 810.985 | 78.33 |
| **Total:** | | | 835.738 | 1047.875 | 100.00 |

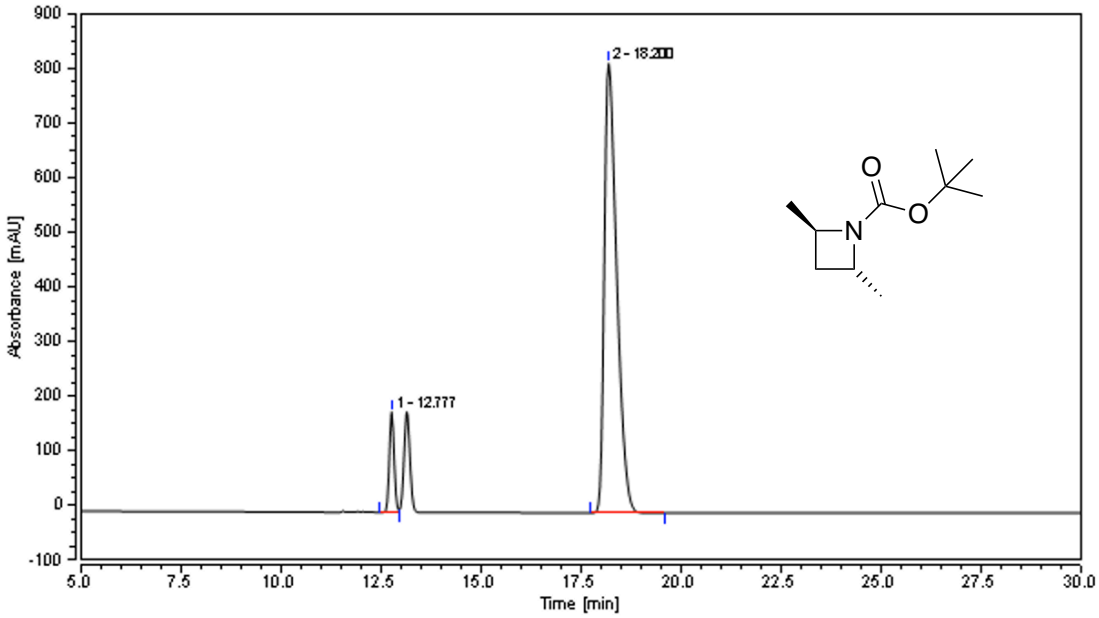
**Racemic (*R**,*R**)-108a**

**Chiral HPLC for 2,4-dimethylazetidine 108a:** (Chiralpak IC, 1% $^{i}$PrOH, 99% hexane, 1.0 mL min$^{-1}$, $\lambda$ = 260 nm, 20 μL injection) $\tau_R$ = 12.9 min, $\tau_R$ = 20.5 min.




| No. | Peak Name | Retention Time | Area | Height | Relative Area |
|---|---|---|---|---|---|
| | | min | mAU*min | mAU | % |
| 1 | | 12.917 | 513.135 | 1808.372 | 49.62 |
| 2 | | 20.543 | 521.055 | 950.119 | 50.38 |
| **Total:** | | | 1034.190 | 2758.491 | 100.00 |

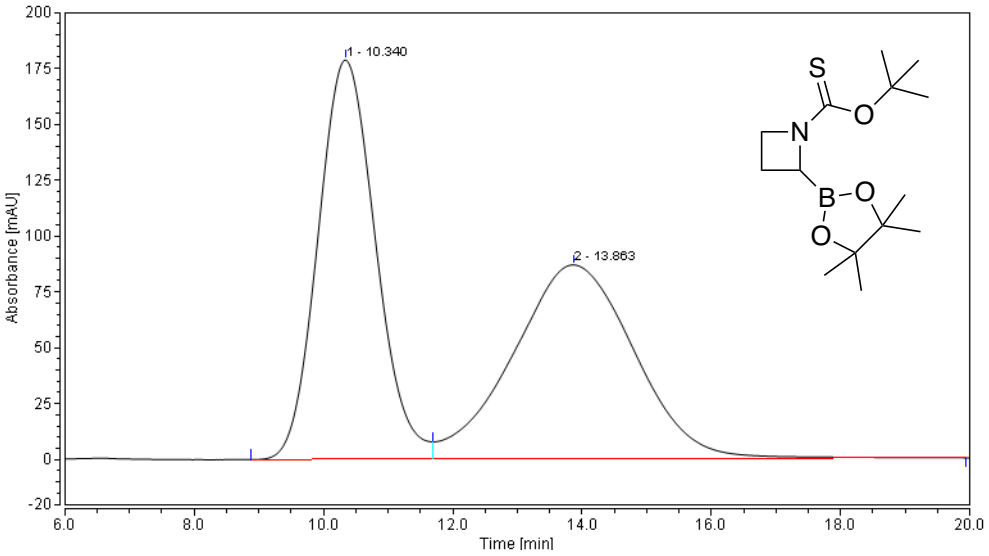
**Enantioenriched (*R*,*R*)-108a**




| No. | Peak Name | Retention Time | Area | Height | Relative Area |
|---|---|---|---|---|---|
| | | min | mAU*min | mAU | % |
| 1 | | 12.777 | 25.689 | 183.715 | 8.00 |
| 2 | | 18.200 | 295.403 | 822.491 | 92.00 |
| **Total:** | | | 321.092 | 1006.206 | 100.00 |

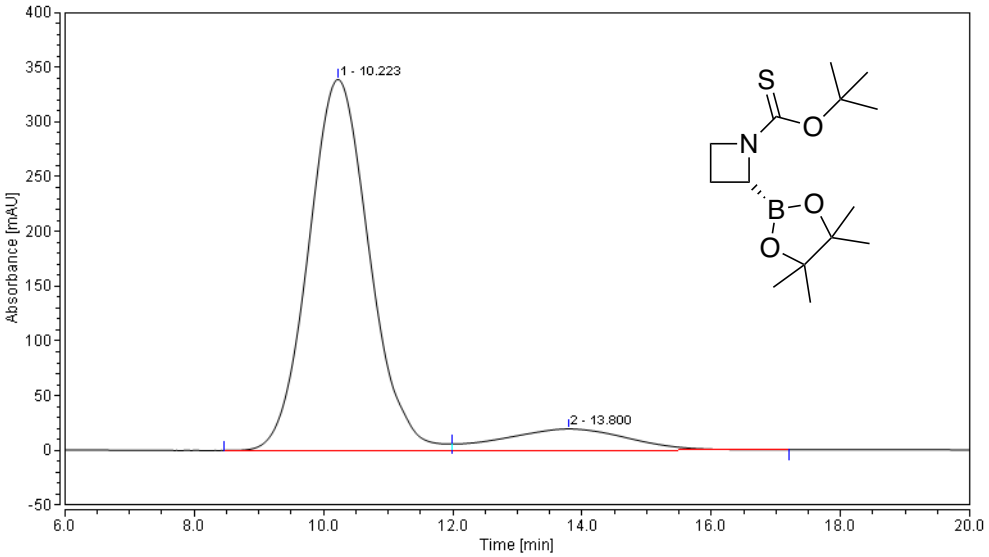
**Racemic-104g**

**Chiral HPLC for 104g:** (Chiralpak AD-H, 1% *i*-PrOH, 99% hexane, 1.0 mL $min^{-1}$, $\lambda$ = 260 nm) $\tau_R$ (major) = 13.9 min, $\tau_R$ (minor) = 10.3 min.



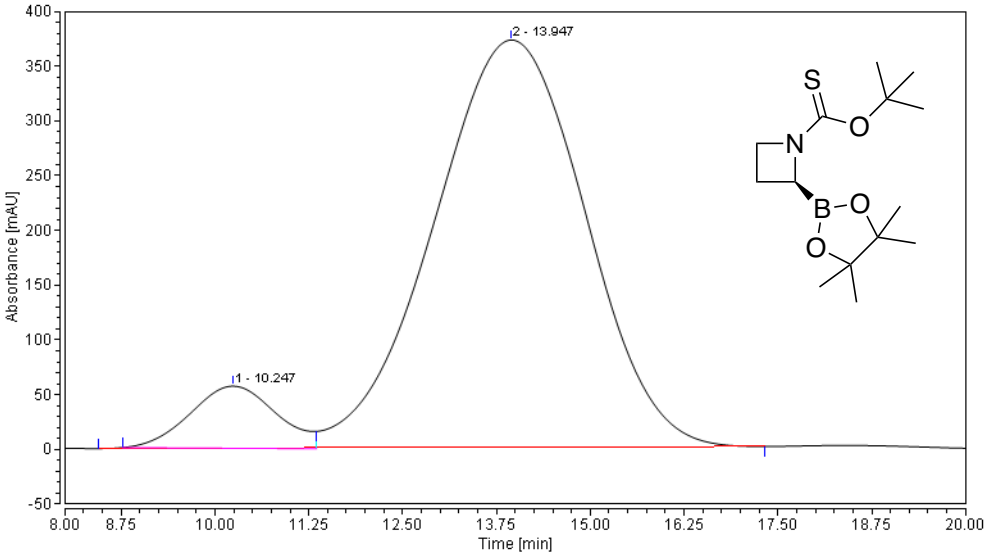

| No. | Peak Name | Retention Time | Area | Height | Relative Area |
|---|---|---|---|---|---|
| | | min | mAU*min | mAU | % |
| 1 | | 10.340 | 183.857 | 178.600 | 49.42 |
| 2 | | 13.863 | 188.154 | 86.722 | 50.58 |
| Total: | | | 372.011 | 265.322 | 100.00 |

**Enantioenriched (*R*)-104g**



| No. | Peak Name | Retention Time | Area | Height | Relative Area |
|---|---|---|---|---|---|
| | | min | mAU*min | mAU | % |
| 1 | | 10.223 | 368.089 | 338.749 | 89.40 |
| 2 | | 13.800 | 43.662 | 19.511 | 10.60 |
| Total: | | | 411.751 | 358.260 | 100.00 |

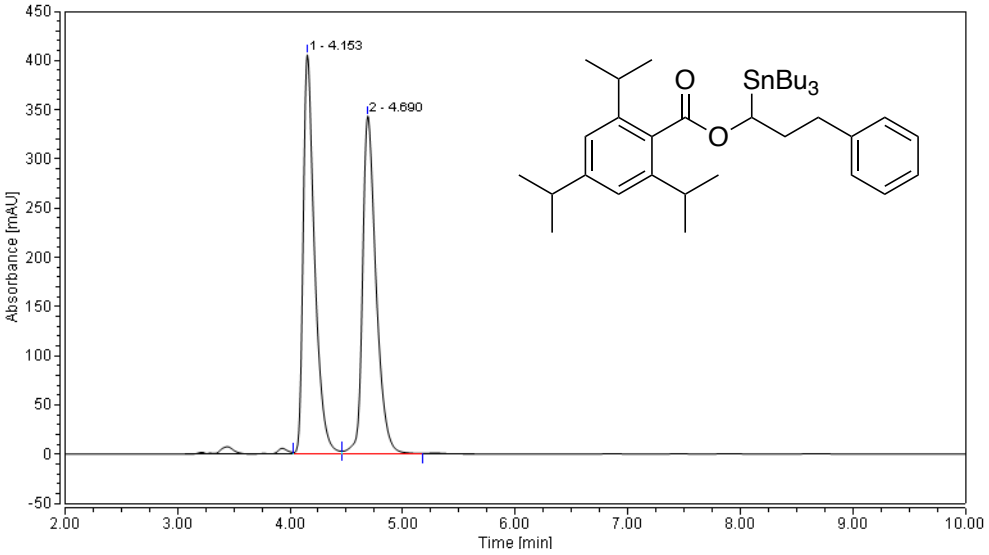
**Enantioenriched (*S*)-104g**




| No. | Peak Name | Retention Time | Area | Height | Relative Area |
|---|---|---|---|---|---|
| | | min | mAU*min | mAU | % |
| 1 | | 10.247 | 75.596 | 56.736 | 8.02 |
| 2 | | 13.947 | 867.108 | 371.947 | 91.98 |
| Total: | | | 942.704 | 428.684 | 100.00 |

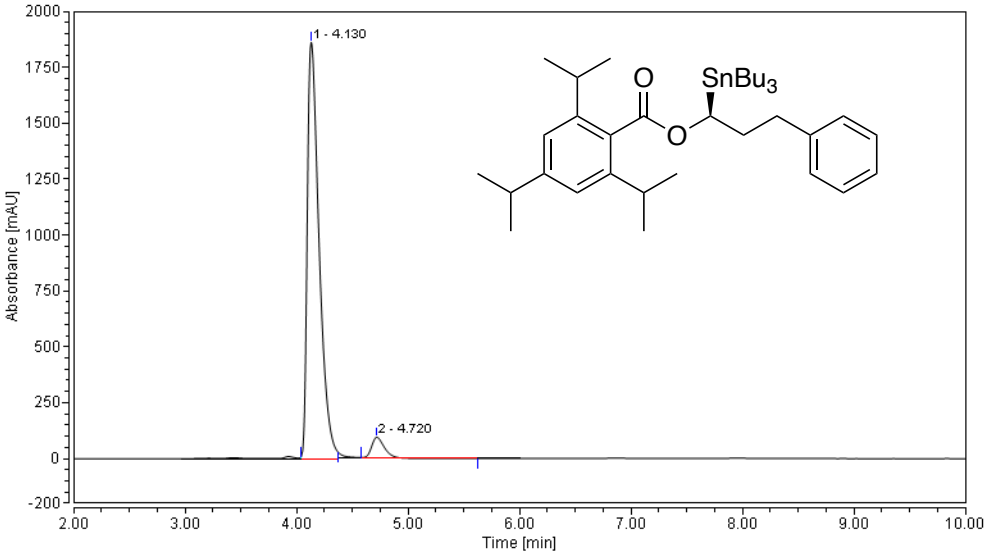
## Racemic 230a

**Chiral HPLC for 230a:** (Chiralpak OD-H, 100% hexane, 1.0 mL $min^{-1}$, $\lambda$ = 242 nm) $\tau_R$ (major) = 4.1 min, $\tau_R$ (minor) = 4.7 min.




| No. | Peak Name | Retention Time | Area | Height | Relative Area |
|---|---|---|---|---|---|
| | | min | mAU*min | mAU | % |
| 1 | | 4.153 | 47.720 | 405.879 | 49.94 |
| 2 | | 4.690 | 47.837 | 343.624 | 50.06 |
| Total: | | | 95.557 | 749.503 | 100.00 |

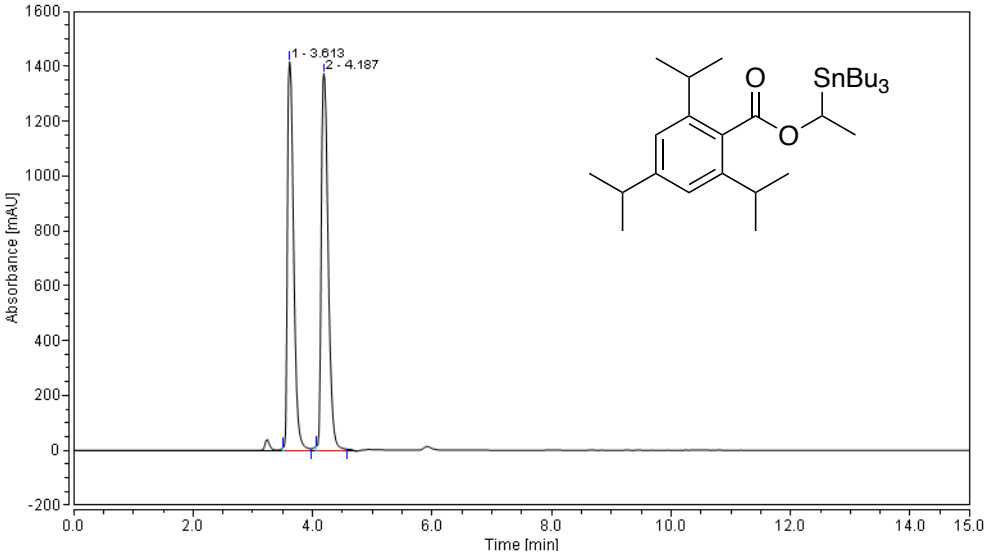
## Enantioenriched (*S*)-230a



| No. | Peak Name | Retention Time | Area | Height | Relative Area |
|---|---|---|---|---|---|
| | | min | mAU*min | mAU | % |
| 1 | | 4.130 | 228.240 | 1861.960 | 94.39 |
| 2 | | 4.720 | 13.568 | 95.950 | 5.61 |
| Total: | | | 241.809 | 1957.910 | 100.00 |

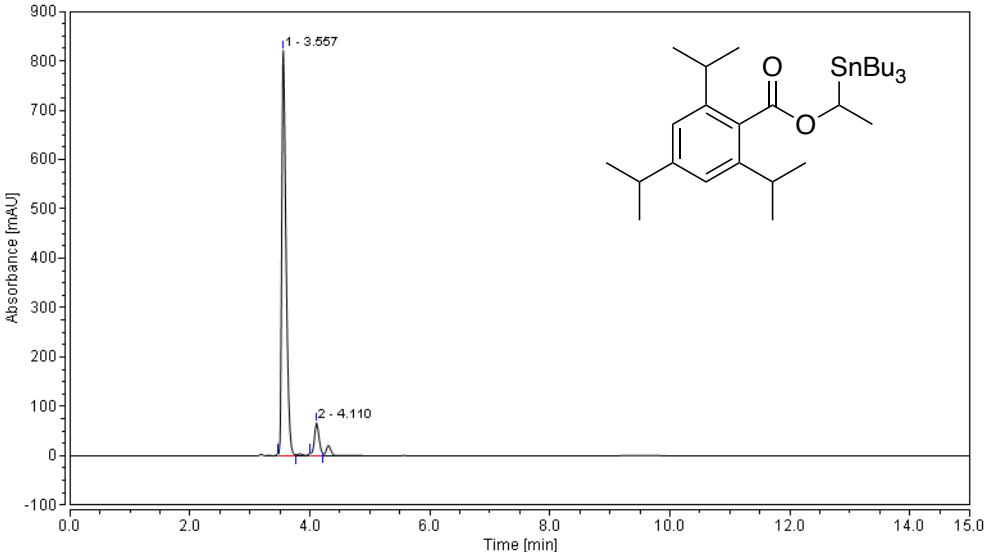
**Racemic 230b**

**Chiral HPLC for 230b:** (Chiralpak OD-H, 100% hexane, 1.0 mL $min^{-1}$, $\lambda$ = 267nm, 25 µL injection) $\tau_R$ (major) = 3.557 min, $\tau_R$ (minor) = 4.110 min.




| No. | Peak Name | Retention Time | Area | Height | Relative Area |
|---|---|---|---|---|---|
| | | min | mAU*min | mAU | % |
| 1 | 3.613 | 172.537 | 1419.342 | 48.27 | 50.75 |
| 2 | 4.187 | 184.878 | 1377.335 | 51.73 | 49.25 |
| Total: | | | 357.414 | 2796.677 | 100.00 |

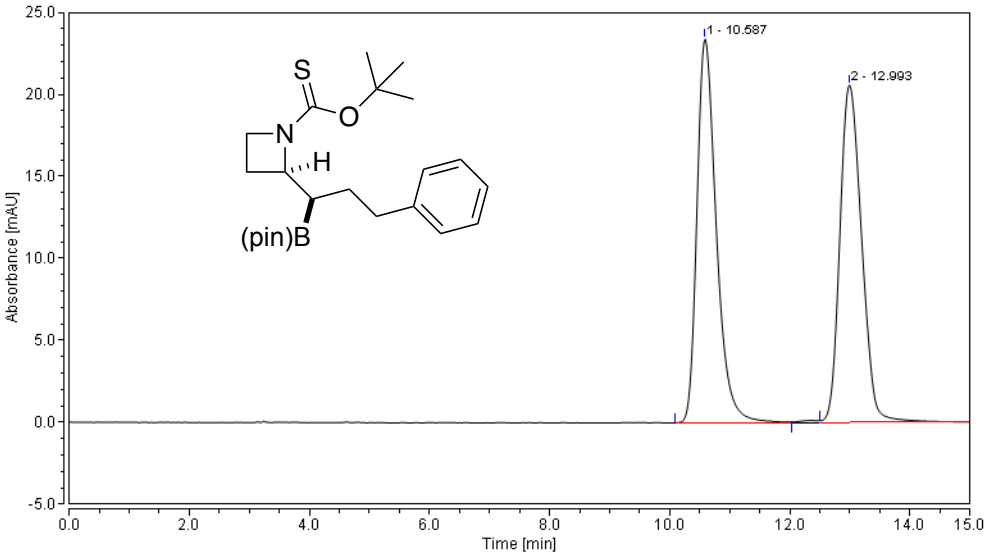
**Enantioenriched (*S*)-230b**




| No. | Peak Name | Retention Time | Area | Height | Relative Area |
|---|---|---|---|---|---|
| | | min | mAU*min | mAU | % |
| 1 | | 3.557 | 67.660 | 821.349 | 91.78 |
| 2 | | 4.110 | 6.063 | 66.913 | 8.22 |
| Total: | | | 73.722 | 888.262 | 100.00 |

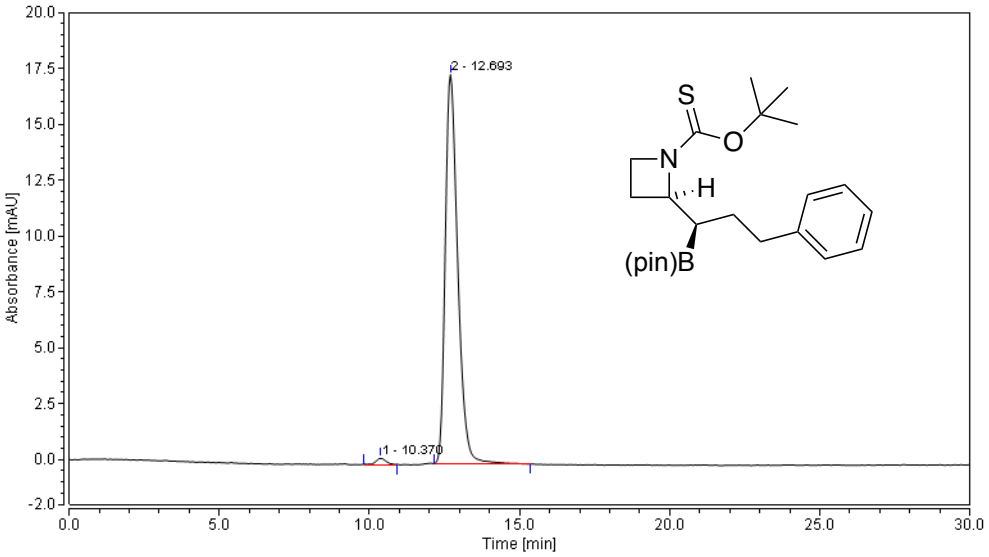
**Racemic (*R**,*R**)-223b**

**Chiral HPLC for 223b:** (Chiralpak OD-H, 0.2% *i*-PrOH, 99.8% hexane, 1.0 mL $min^{-1}$, $\lambda$ = 266nm, 2 μL injection) $\tau_R$ (minor) = 10.587 min, $\tau_R$ (major) = 12.993 min.



| No. | Peak Name | Retention Time | Area | Height | Relative Area |
|---|---|---|---|---|---|
| | | min | mAU*min | mAU | % |
| 1 | | 10.590 | 10.246 | 27.518 | 50.64 |
| 2 | | 12.993 | 9.985 | 24.079 | 49.36 |
| Total: | | | 20.231 | 51.597 | 100.00 |

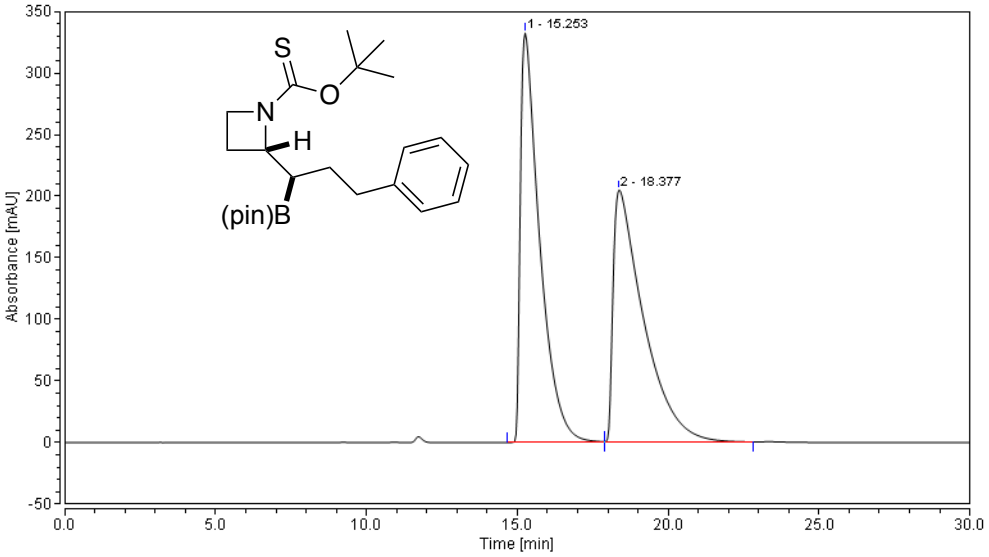
**Enantioenriched (*R*,*R*)-223b**




| No. | Peak Name | Retention Time | Area | Height | Relative Area |
|---|---|---|---|---|---|
| | | min | mAU*min | mAU | % |
| 1 | | 10.370 | 0.124 | 0.340 | 1.25 |
| 2 | | 12.690 | 9.800 | 20.444 | 98.75 |
| Total: | | | 9.924 | 20.783 | 100.00 |

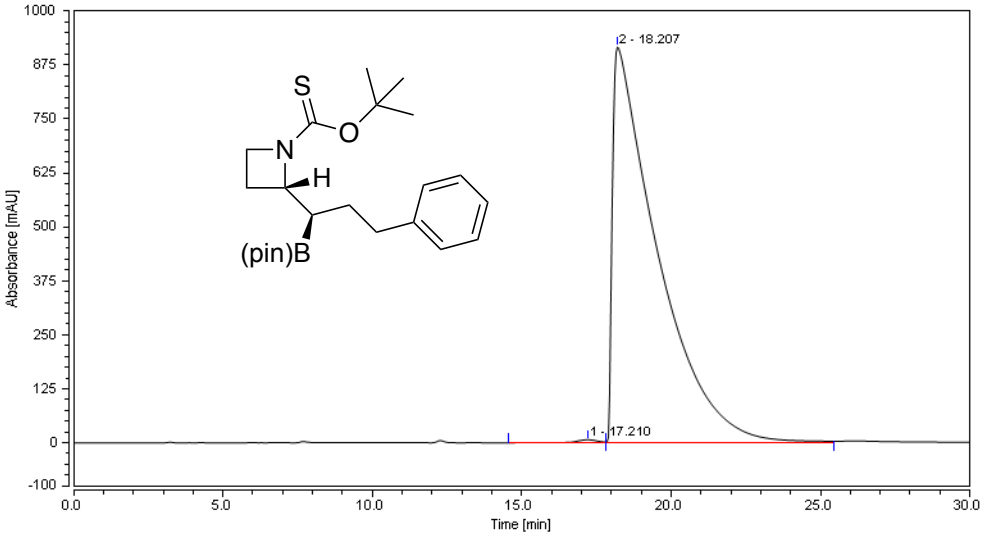
**Racemic (*R**,*S**)-223b'**

**Chiral HPLC for 223b':** (Chiralpak OD-H, 0.1% *i*-PrOH, 99.9% hexane, 1.0 mL $min^{-1}$, $\lambda$ = 266 nm, 50 μL injection) $\tau_R$ (minor) = 15.253 min, $\tau_R$ (major) = 18.377 min.




| No. | Peak Name | Retention Time | Area | Height | Relative Area |
|---|---|---|---|---|---|
| | | min | mAU*min | mAU | % |
| 1 | | 15.253 | 246.885 | 332.492 | 50.63 |
| 2 | | 18.377 | 240.752 | 205.072 | 49.37 |
| Total: | | | 487.637 | 537.564 | 100.00 |

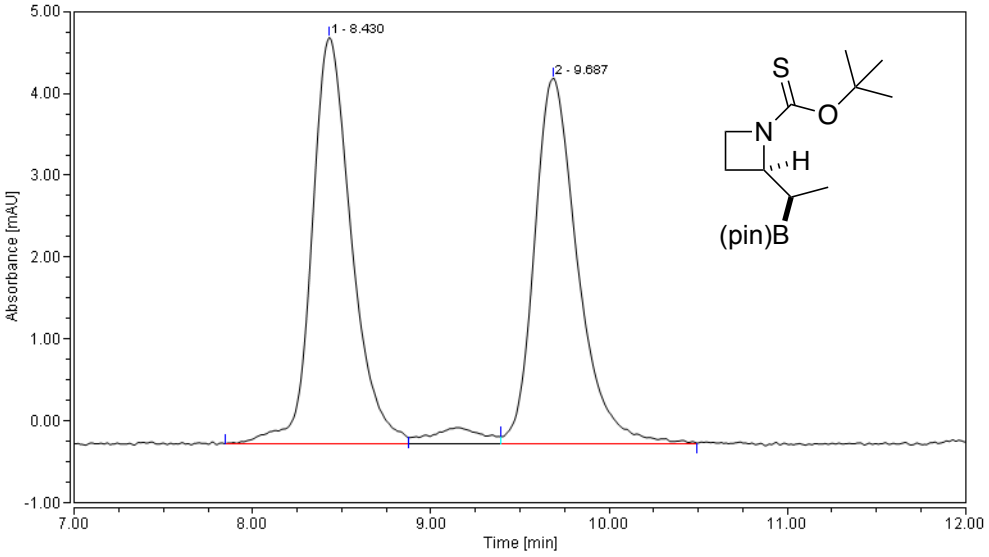
**Enantioenriched (*R*,*S*)-223b'**



| No. | Peak Name | Retention Time | Area | Height | Relative Area |
|---|---|---|---|---|---|
| | | min | mAU*min | mAU | % |
| 1 | | 17.210 | 5.596 | 6.872 | 0.35 |
| 2 | | 18.207 | 1591.452 | 916.535 | 99.65 |
| Total: | | | 1597.048 | 923.407 | 100.00 |

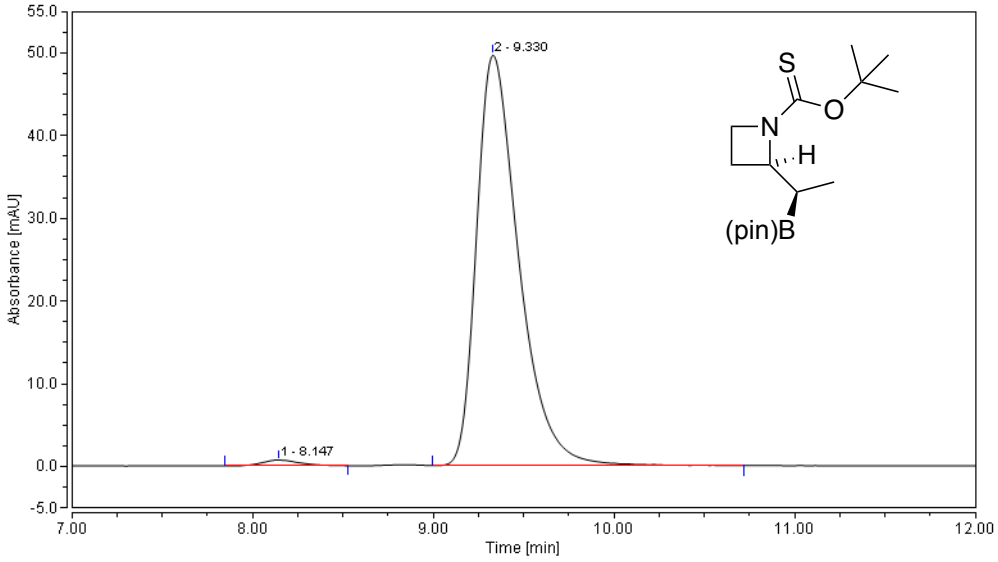
**Racemic (*R*,R**)-223c**

**Chiral HPLC 223c:** (Chiralpak OD-H, 0.1% *i*-PrOH, 99.9% hexane, 1.0 mL $min^{-1}$, $\lambda$ = 250m, 5 $\mu$L injection) $\tau_R$ (major) = 9.687 min, $\tau_R$ (minor) = 8.430 min.




| No. | Peak Name | Retention Time | Area | Height | Relative Area |
|---|---|---|---|---|---|
| | | min | mAU*min | mAU | % |
| 1 | | 8.430 | 1.273 | 4.957 | 50.53 |
| 2 | | 9.687 | 1.246 | 4.455 | 49.47 |
| Total: | | | 2.518 | 9.413 | 100.00 |

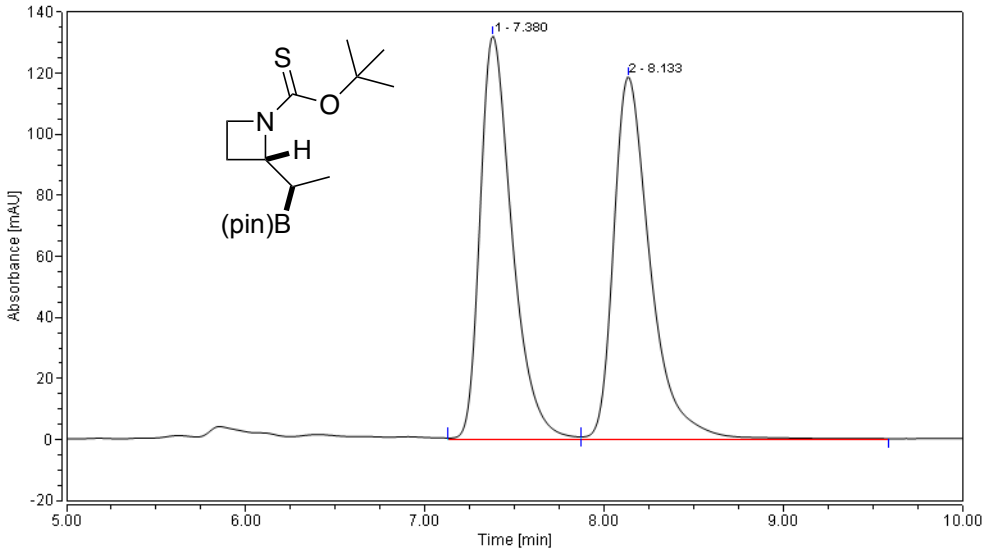
**Enantioenriched (*R*,*R*)-223c**




| No. | Peak Name | Retention Time | Area | Height | Relative Area |
|---|---|---|---|---|---|
| | | min | mAU*min | mAU | % |
| 1 | | 8.147 | 0.168 | 0.696 | 1.24 |
| 2 | | 9.330 | 13.431 | 49.613 | 98.76 |
| Total: | | | 13.599 | 50.309 | 100.00 |

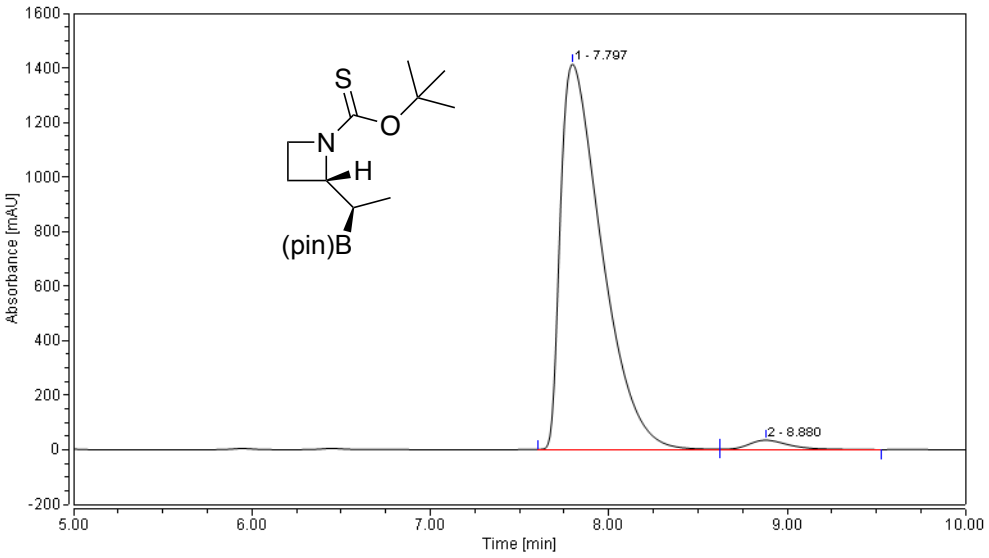
**Racemic (*R**,*S**)-223c'**

**Chiral HPLC for 223c':** (Chiralpak OD-H, 0.1% *i*-PrOH, 99.9% hexane, 1.0 mL $min^{-1}$, $\lambda$ = 250 nm, 50 µL injection) $\tau_R$ (major) = 7.360 min, $\tau_R$ (minor) = 8.133 min.



| No. | Peak Name | Retention Time | Area | Height | Relative Area |
|---|---|---|---|---|---|
| | | min | mAU*min | mAU | % |
| 1 | | 7.380 | 27.308 | 132.035 | 49.33 |
| 2 | | 8.133 | 28.047 | 118.694 | 50.67 |
| Total: | | | 55.355 | 250.729 | 100.00 |

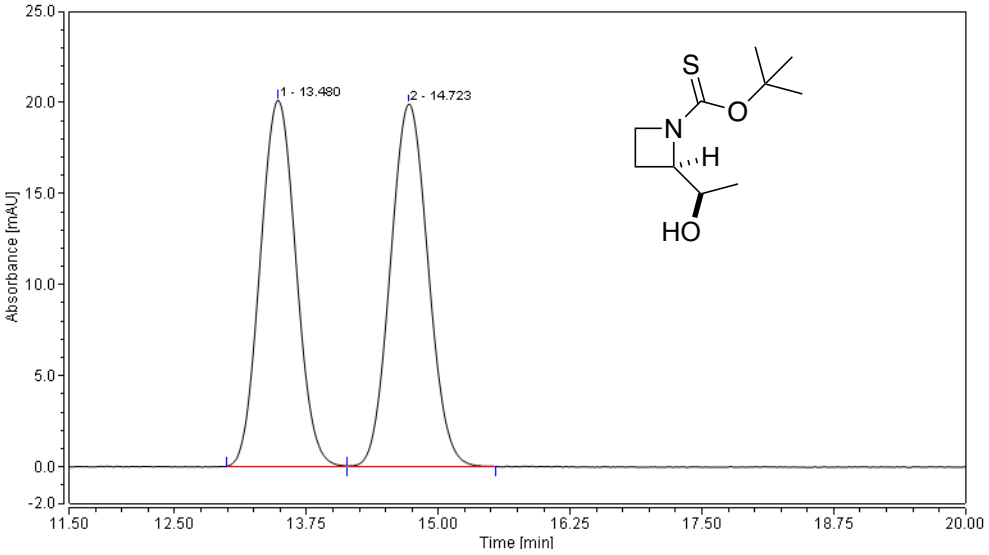
**Enantioenriched (*R*,*S*)-223c'**




| No. | Peak Name | Retention Time | Area | Height | Relative Area |
|---|---|---|---|---|---|
| | | min | mAU*min | mAU | % |
| 1 | | 7.797 | 379.821 | 1413.818 | 97.51 |
| 2 | | 8.880 | 9.717 | 35.201 | 2.49 |
| Total: | | | 389.539 | 1449.020 | 100.00 |

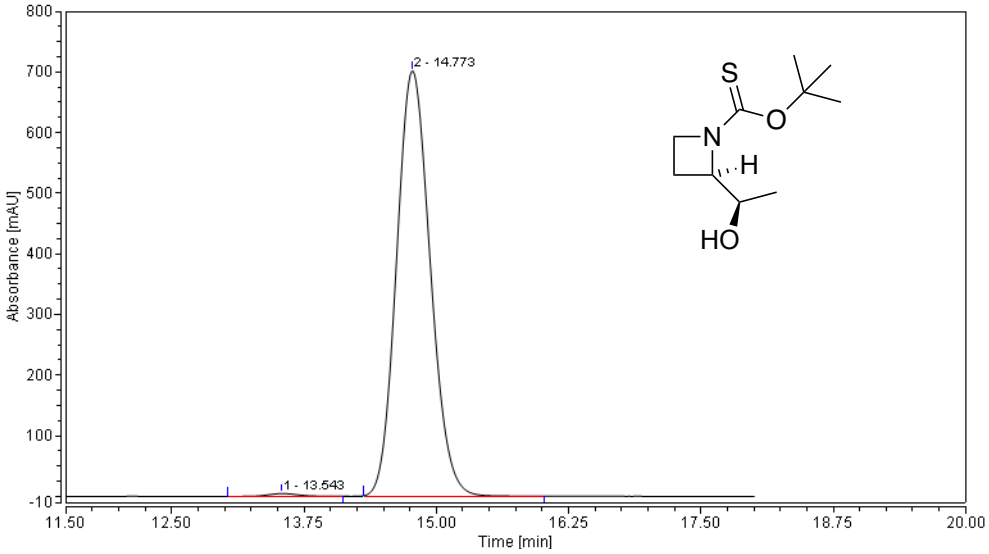
**Racemic (*R**,*R**)-219c**

**Chiral HPLC for 219c:** (Chiralpak AD-H, 3% *i*-PrOH, 97% hexane, 1.0 mL $min^{-1}$, $\lambda$ = 260 nm) $\tau_R$ (major) = 14.7 min, $\tau_R$ (minor) = 13.5 min.




| No. | Peak Name | Retention Time | Area | Height | Relative Area |
|---|---|---|---|---|---|
| | | min | mAU*min | mAU | % |
| 1 | | 13.480 | 7.889 | 20.117 | 48.92 |
| 2 | | 14.723 | 8.236 | 19.899 | 51.08 |
| Total: | | | 16.126 | 40.016 | 100.00 |

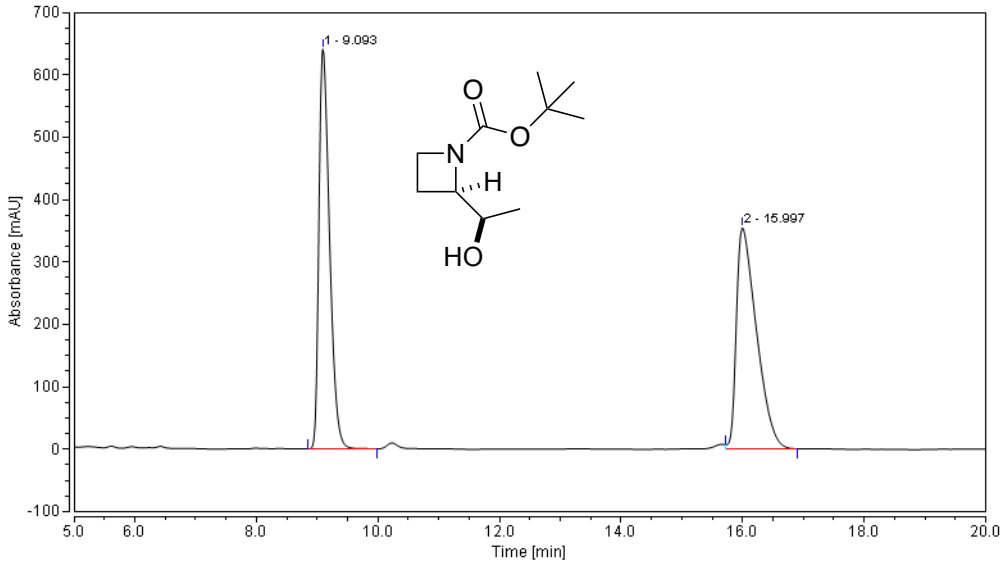
**Enantioenriched (*R*,*R*)-219c**



| No. | Peak Name | Retention Time | Area | Height | Relative Area |
|---|---|---|---|---|---|
| | | min | mAU*min | mAU | % |
| 1 | | 13.543 | 1.534 | 4.539 | 0.59 |
| 2 | | 14.773 | 258.857 | 701.866 | 99.41 |
| Total: | | | 260.391 | 706.405 | 100.00 |

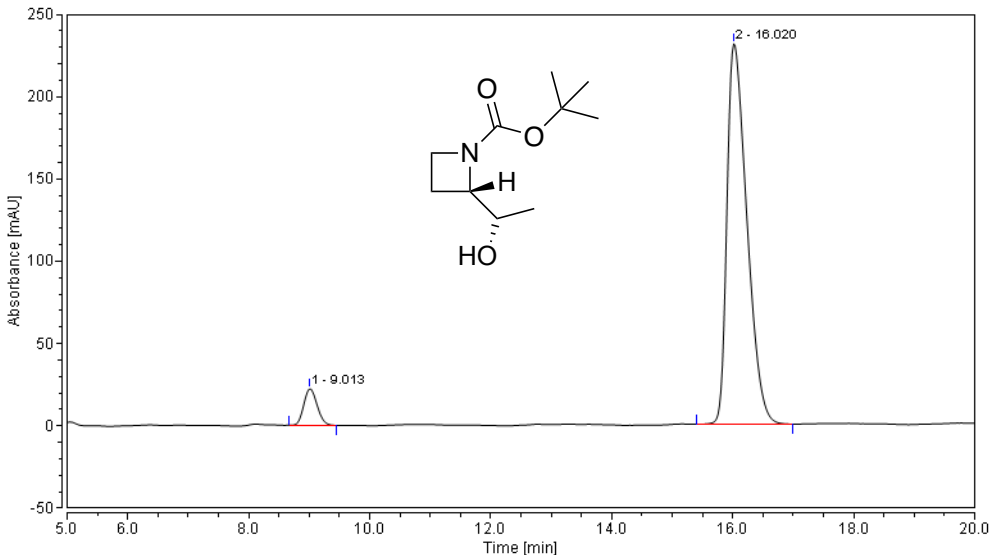
**Racemic (*R**,*R**)-220c**

**Chiral HPLC for 220c:** (Chiralpak AD-H, 5% *i*-PrOH, 95% hexane, 1.0 mL min$^{-1}$, λ = 210nm, 25 μL injection) $\tau_R$ (major) = 9.0 min, $\tau_R$ (minor) = 16.0 min.



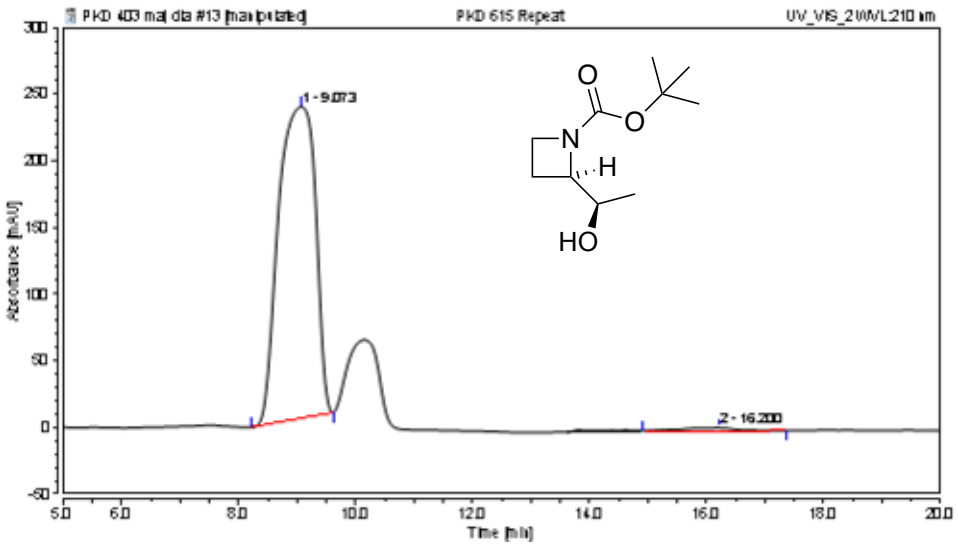

| No. | Peak Name | Retention Time | Area | Height | Relative Area |
|---|---|---|---|---|---|
| | | min | mAU*min | mAU | % |
| 1 | | 9.093 | 129.860 | 641.077 | 48.98 |
| 2 | | 15.997 | 135.286 | 354.724 | 51.02 |
| Total: | | | 265.146 | 995.802 | 100.00 |

**Enantioenriched (*S*,*S*)-220c**




| No. | Peak Name | Retention Time | Area | Height | Relative Area |
|---|---|---|---|---|---|
| | | min | mAU*min | mAU | % |
| 1 | | 9.013 | 5.684 | 22.238 | 6.05 |
| 2 | | 16.020 | 88.332 | 231.758 | 93.95 |
| Total: | | | 94.015 | 253.996 | 100.00 |

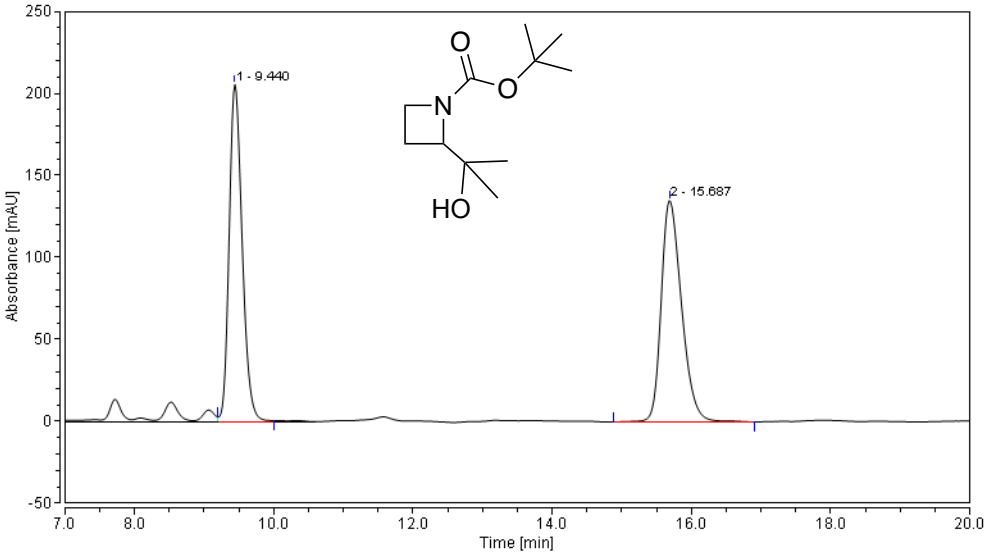
**Enantioenriched (*R*,*R*)-220c**



| No. | Peak Name | Retention Time | Area | Height | Relative Area |
|---|---|---|---|---|---|
| | | min | mAU*min | mAU | % |
| 1 | 9.073 | 170.410 | 233.504 | 98.19 | 98.97 |
| 2 | 16.200 | 3.142 | 2.437 | 1.81 | 1.03 |
| Total: | | 173.552 | 235.941 | 100.00 | 100.00 |

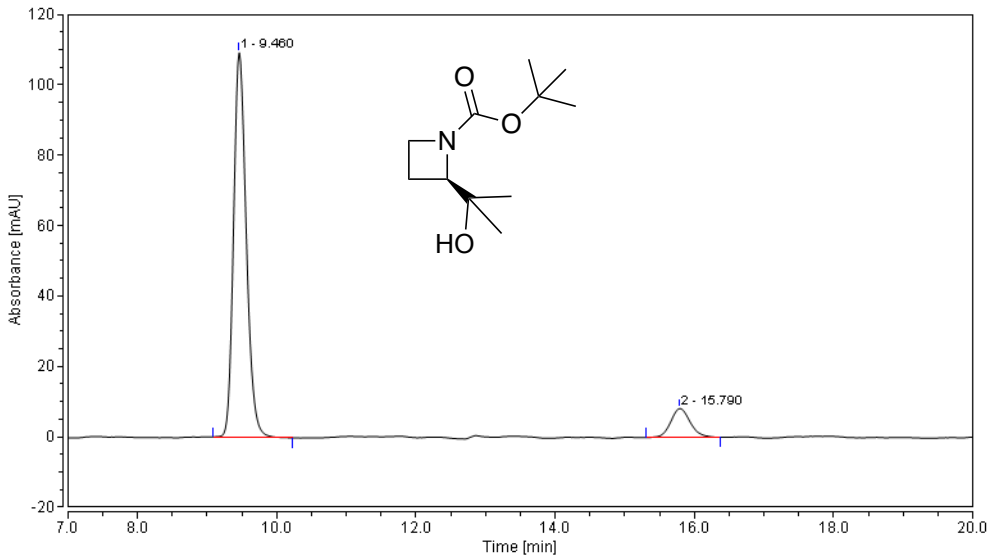
**Racemic 220d**

**Chiral HPLC for 220d:** (Chiralpak AD-H, 5% *i*-PrOH, 95% hexane, 1.0 mL $min^{-1}$, $\lambda$ = 205 nm) $\tau_R$ (*R*) = 9.4 min, $\tau_R$ (*S*) = 15.7 min.



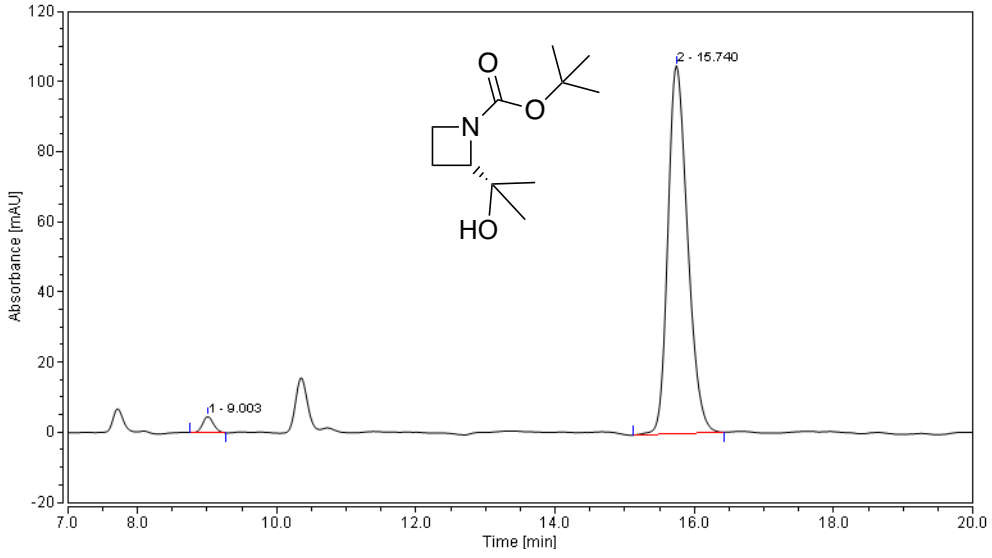

| No. | Retention Time | Area | Height | Relative Area |
|---|---|---|---|---|
| | min | mAU*min | mAU | % |
| 1 | 9.443 | 80.502 | 365.413 | 48.22 |
| 2 | 15.683 | 86.429 | 248.290 | 51.78 |
| Total: | | 166.931 | 613.703 | 100.00 |

**Enantioenriched (*R*)-220d**




| No. | Peak Name | Retention Time | Area | Height | Relative Area |
|---|---|---|---|---|---|
| | | min | mAU*min | mAU | % |
| 1 | | 9.460 | 23.115 | 109.226 | 89.59 |
| 2 | | 15.790 | 2.686 | 8.251 | 10.41 |
| Total: | | | 25.801 | 117.477 | 100.00 |

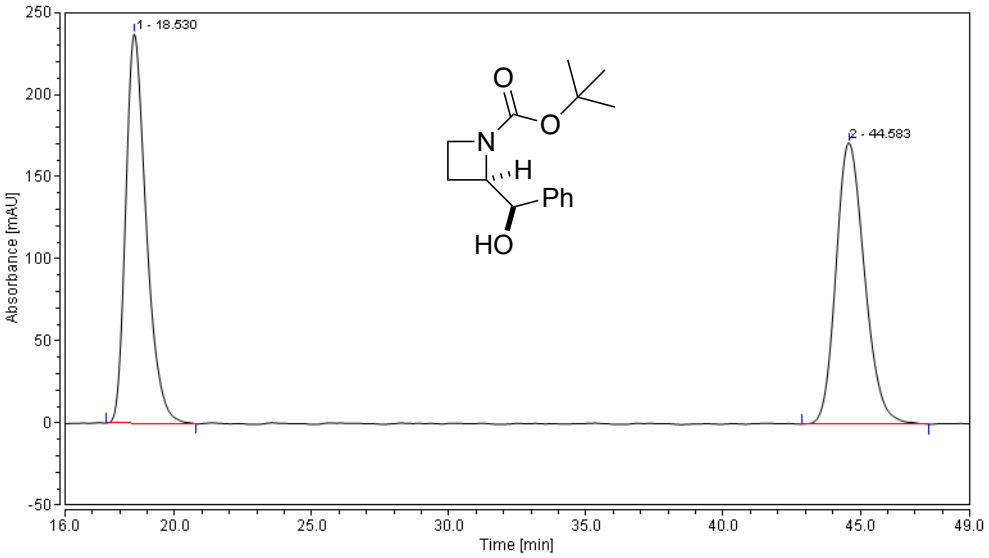
**Enantioenriched (*S*)-220d**



| No. | Peak Name | Retention Time | Area | Height | Relative Area |
|---|---|---|---|---|---|
| | | min | mAU*min | mAU | % |
| 1 | | 9.003 | 0.834 | 4.538 | 2.37 |
| 2 | | 15.740 | 34.402 | 104.997 | 97.63 |
| Total: | | | 35.236 | 109.535 | 100.00 |

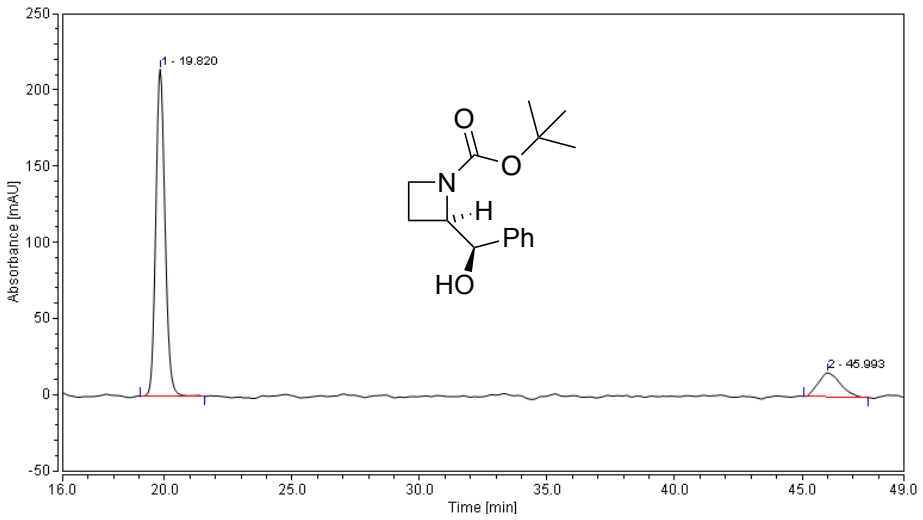
**Racemic (*R**,*R**)-220e**

**Chiral HPLC for 220e:** (Chiralpak AD-H, 5% *i*-PrOH, 95% hexane, 1.0 mL min$^{-1}$, $\lambda$ = 203 nm, 5 μL injection) $\tau_R$ (major) = 19.8 min, $\tau_R$ (minor) = 46.0 min.




| No. | Peak Name | Retention Time | Area | Height | Relative Area |
|---|---|---|---|---|---|
| | | min | mAU*min | mAU | % |
| 1 | | 18.533 | 243.132 | 277.402 | 50.30 |
| 2 | | 44.580 | 240.244 | 200.625 | 49.70 |
| Total: | | | 483.376 | 478.027 | 100.00 |

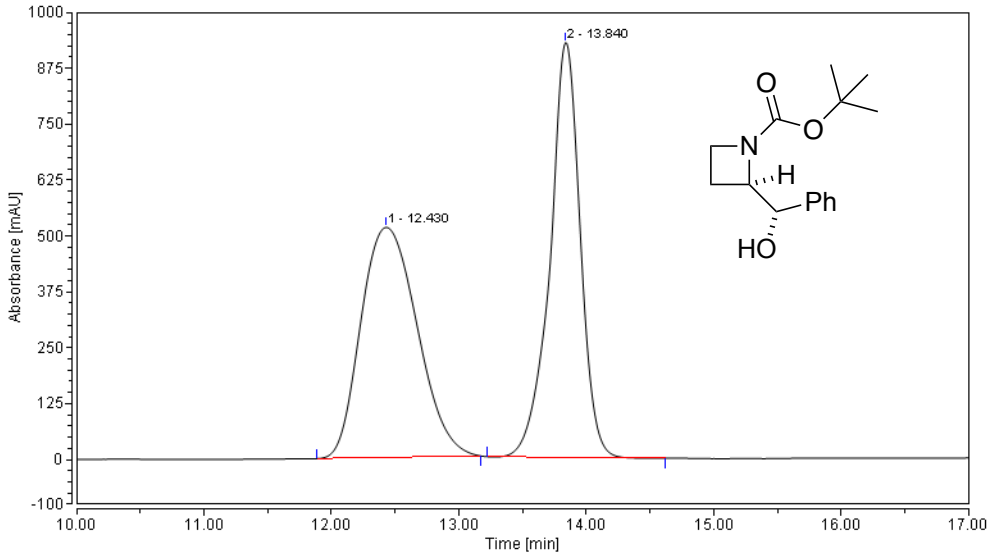
**Enantioenriched- (*R*,*R*)-220e**




| No. | Peak Name | Retention Time | Area | Height | Relative Area |
|---|---|---|---|---|---|
| | | min | mAU*min | mAU | % |
| 1 | | 19.823 | 90.883 | 216.159 | 84.67 |
| 2 | | 45.987 | 16.454 | 16.139 | 15.33 |
| Total: | | | 107.337 | 232.298 | 100.00 |

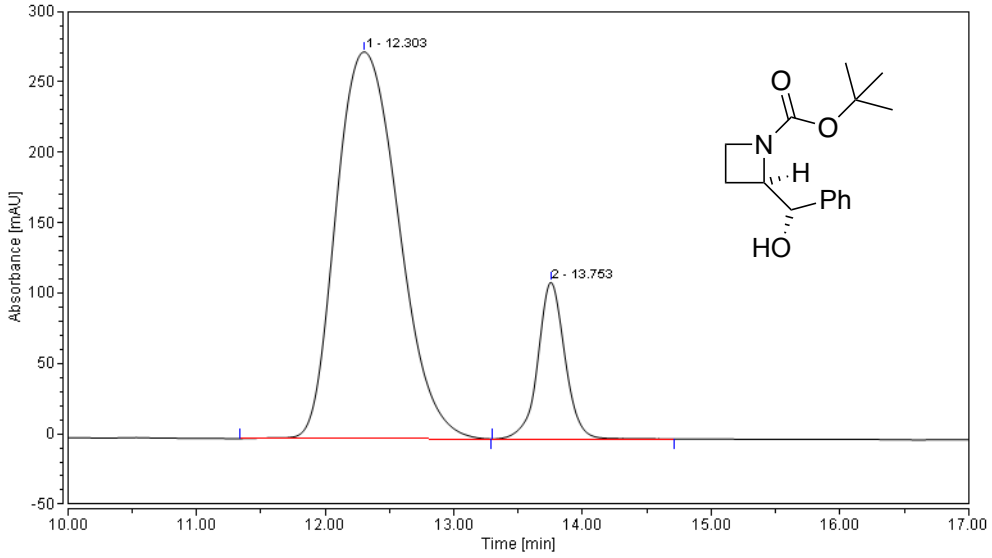
**Racemic (*R**,*S**)-220e'**

**Chiral HPLC for 220e':** (Chiralpak AD-H, 5% *i*-PrOH, 95% hexane, 1.0 mL min$^{-1}$, $\lambda$ = 206 nm, 15 µL injection) $\tau_R$ (major) = 12.3 min, $\tau_R$ (minor) = 13.8 min.



| No. | Peak Name | Retention Time | Area | Height | Relative Area |
|---|---|---|---|---|---|
| | | min | mAU*min | mAU | % |
| 1 | | 12.430 | 263.034 | 518.432 | 50.64 |
| 2 | | 13.840 | 256.353 | 926.301 | 49.36 |
| Total: | | | 519.387 | 1444.733 | 100.00 |

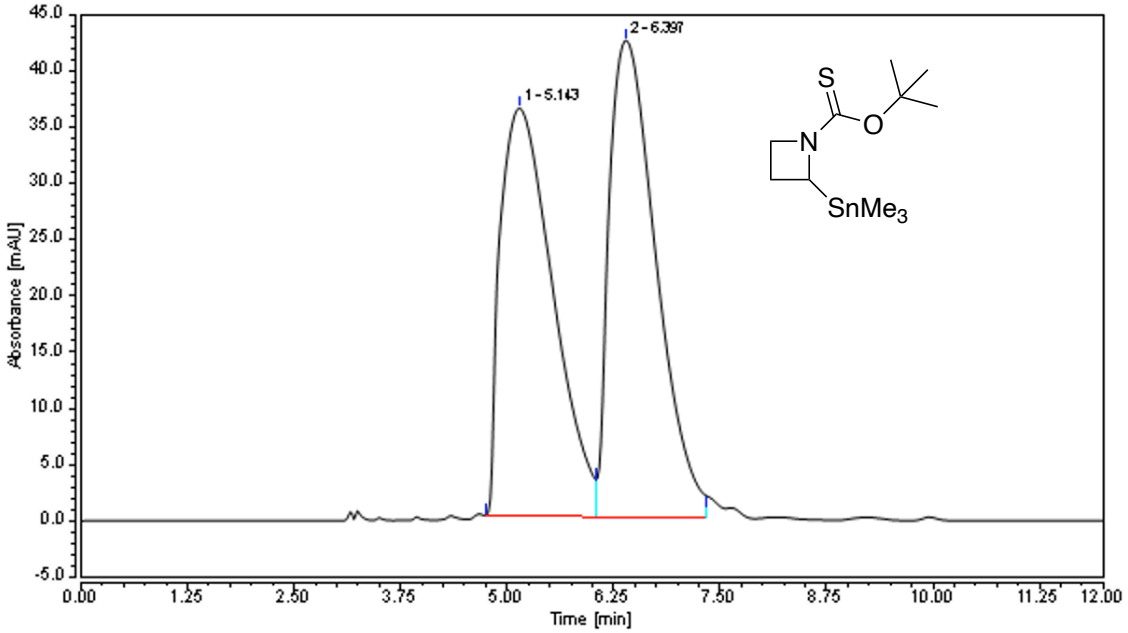
**Enantioenriched (*R*,*S*)-220e'**




| No. | Peak Name | Retention Time | Area | Height | Relative Area |
|---|---|---|---|---|---|
| | | min | mAU*min | mAU | % |
| 1 | | 12.303 | 154.644 | 274.793 | 85.09 |
| 2 | | 13.753 | 27.103 | 111.267 | 14.91 |
| Total: | | | 181.747 | 386.061 | 100.00 |

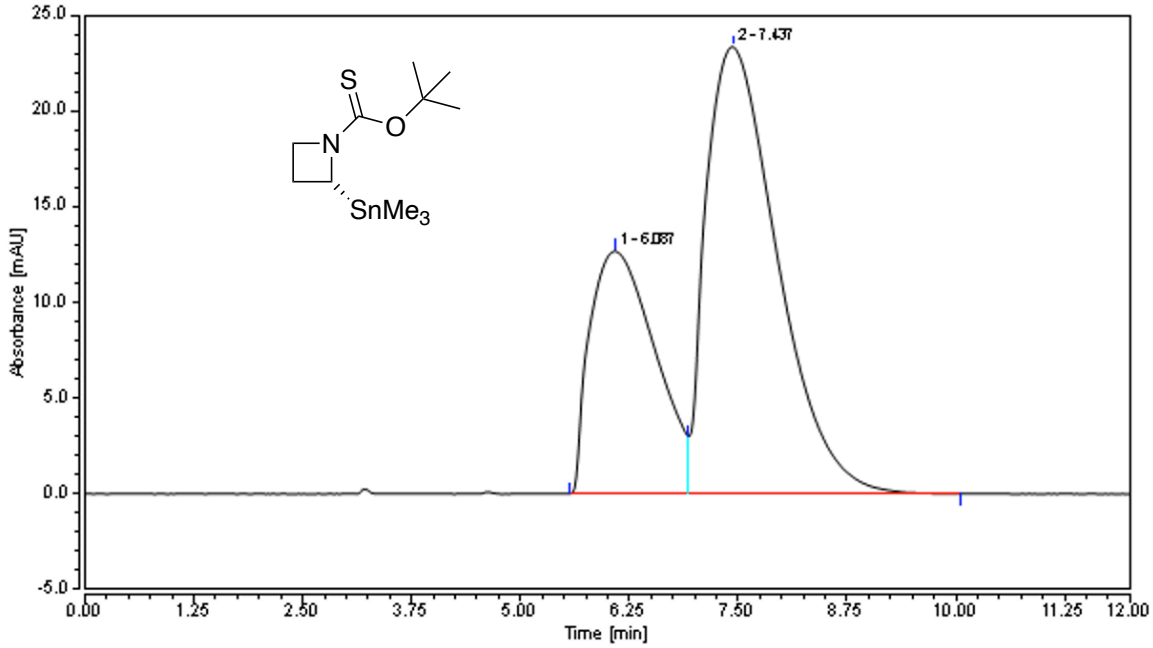
**Racemic (±)-104f**

**Chiral HPLC for stannane 104f:** (Chiralpak ODH, 0.1% $^{i}$PrOH, 99.9% hexane, 1.0 mL min$^{-1}$, $\lambda$ = 254 nm, 10 μL injection) $\tau_R$ = 5.1 min, $\tau_R$ = 6.4 min.



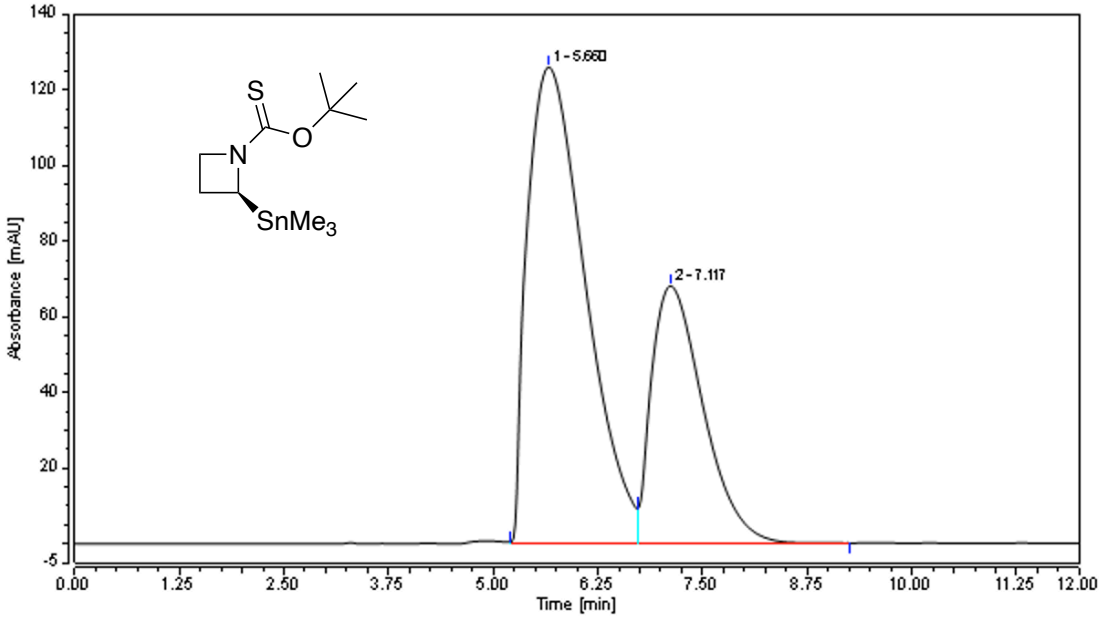

| No. | Peak Name | Retention Time | Area | Height | Relative Area |
|---|---|---|---|---|---|
| | | min | mAU*min | mAU | % |
| 1 | | 5.143 | 25.902 | 36.336 | 48.79 |
| 2 | | 6.397 | 27.187 | 42.529 | 51.21 |
| **Total:** | | | 53.089 | 78.865 | 100.00 |

**Enantioenriched (*R*)-104f**




| No. | Peak Name | Retention Time | Area | Height | Relative Area |
|---|---|---|---|---|---|
| | | min | mAU*min | mAU | % |
| 1 | | 6.087 | 10.974 | 12.699 | 33.07 |
| 2 | | 7.437 | 22.210 | 23.386 | 66.93 |
| **Total:** | | | 33.184 | 36.085 | 100.00 |

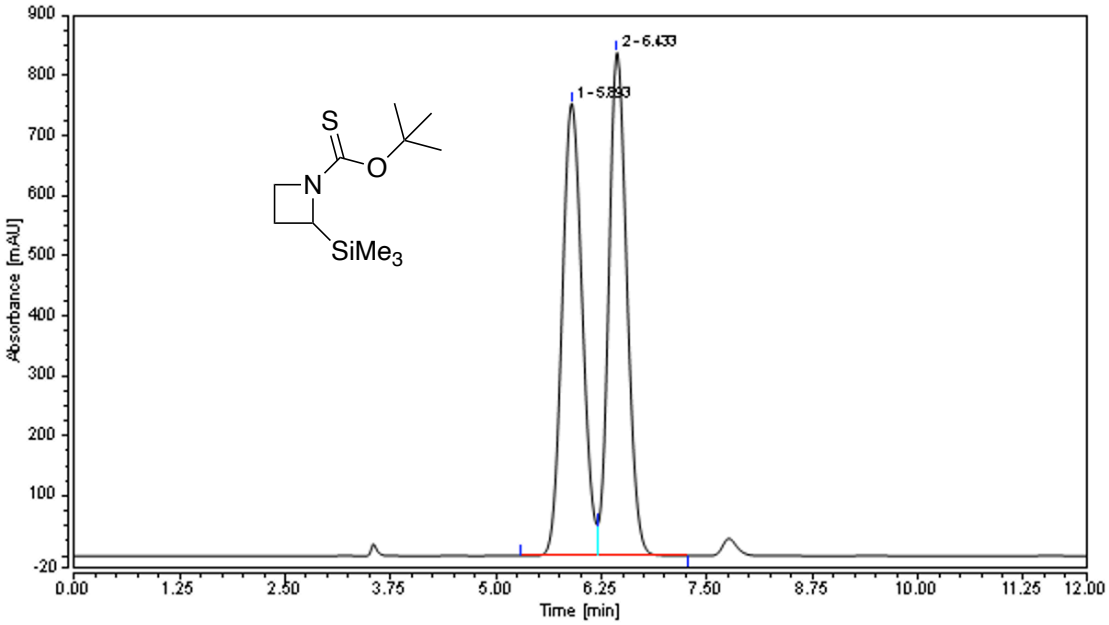
**Enantioenriched (*S*)-104f**



| No. | Peak Name | Retention Time | Area | Height | Relative Area |
|---|---|---|---|---|---|
| | | min | mAU*min | mAU | % |
| 1 | | 5.660 | 100.736 | 125.963 | 67.42 |
| 2 | | 7.117 | 48.683 | 68.077 | 32.58 |
| **Total:** | | | 149.420 | 194.040 | 100.00 |

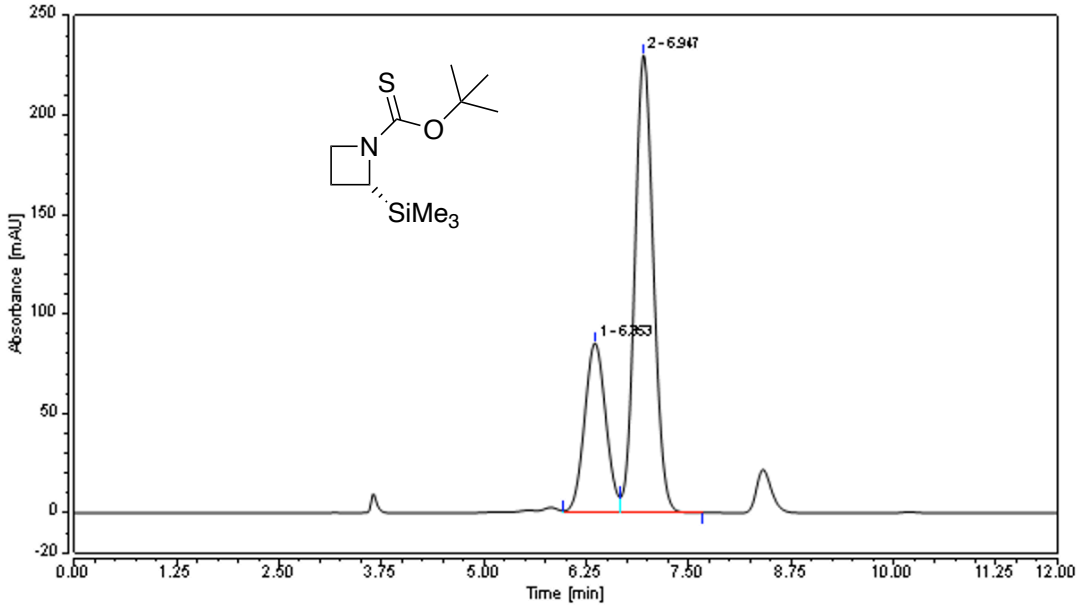
**Racemic (±)-104e**

**Chiral HPLC for silane 104e:** (Chiralpak ODH, 0.1% $^{i}$PrOH, 99.9% hexane, 1.0 mL min$^{-1}$, $\lambda$ = 254 nm, 10 μL injection) $\tau_R$ = 5.9 min, $\tau_R$ = 6.4 min.



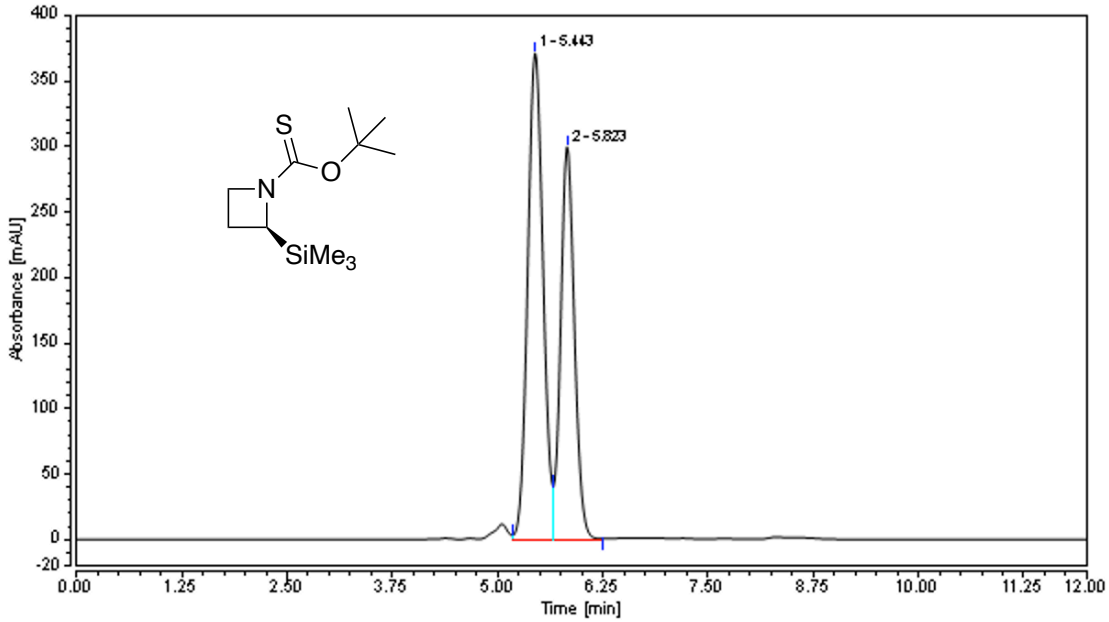

| No. | Peak Name | Retention Time | Area | Height | Relative Area |
|---|---|---|---|---|---|
| | | min | mAU*min | mAU | % |
| 1 | | 5.893 | 207.092 | 753.880 | 49.85 |
| 2 | | 6.433 | 208.340 | 838.482 | 50.15 |
| **Total:** | | | 415.433 | 1592.362 | 100.00 |

**Enantioenriched (*R*)-104e**




| No. | Peak Name | Retention Time | Area | Height | Relative Area |
|---|---|---|---|---|---|
| | | min | mAU*min | mAU | % |
| 1 | | 6.353 | 25.771 | 85.502 | 29.80 |
| 2 | | 6.947 | 60.721 | 230.218 | 70.20 |
| **Total:** | | | 86.492 | 315.721 | 100.00 |

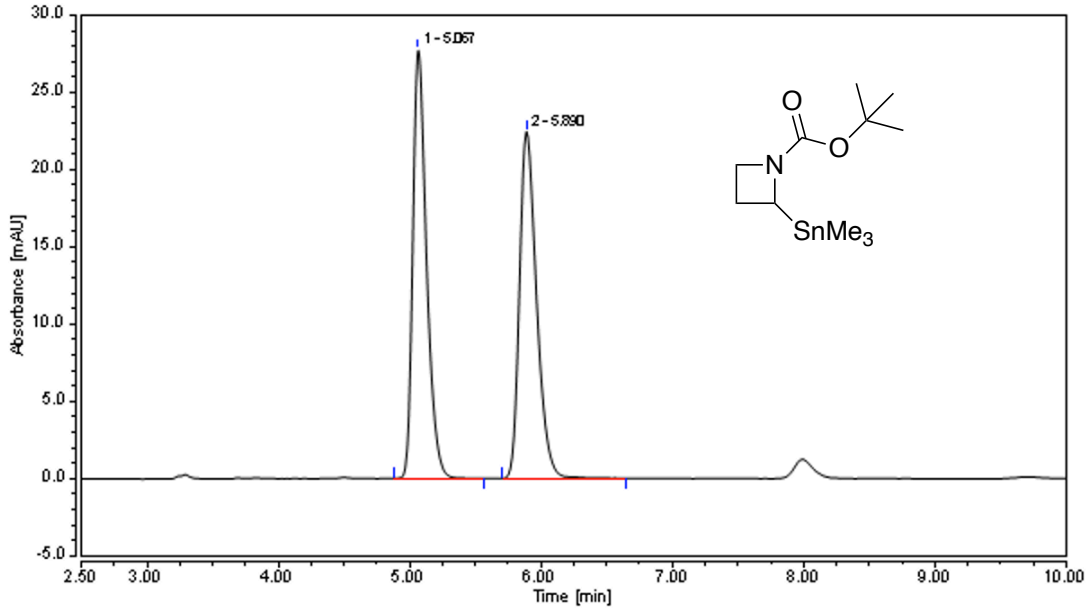
**Enantioenriched (*S*)-104e**



| No. | Peak Name | Retention Time | Area | Height | Relative Area |
|---|---|---|---|---|---|
| | | min | mAU*min | mAU | % |
| 1 | | 5.443 | 78.373 | 371.110 | 57.94 |
| 2 | | 5.823 | 56.903 | 299.682 | 42.06 |
| **Total:** | | | 135.276 | 670.792 | 100.00 |

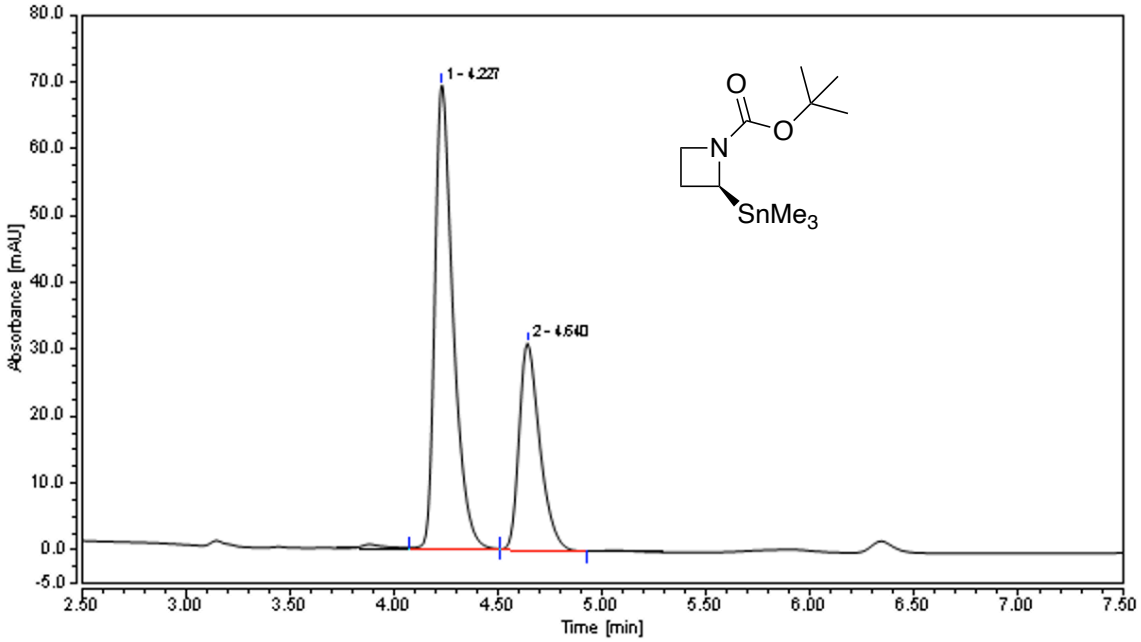
**Racemic (±)-254**

**Chiral HPLC for stannane 254:** (Chiralpak ODH, 1% $^{i}$PrOH, 99% hexane, 1.0 mL min$^{-1}$, $\lambda$ = 254 nm, 10 μL injection) $\tau_R$ = 5.1 min, $\tau_R$ = 5.9 min.




| No. | Peak Name | Retention Time | Area | Height | Relative Area |
|---|---|---|---|---|---|
| | | min | mAU*min | mAU | % |
| 1 | | 5.067 | 3.356 | 27.726 | 49.80 |
| 2 | | 5.890 | 3.383 | 22.475 | 50.20 |
| **Total:** | | | 6.739 | 50.200 | 100.00 |

**Enantioenriched (*S*)-254**




| No. | Peak Name | Retention Time | Area | Height | Relative Area |
|---|---|---|---|---|---|
| | | min | mAU*min | mAU | % |
| 1 | | 4.227 | 7.107 | 69.434 | 66.49 |
| 2 | | 4.640 | 3.582 | 31.038 | 33.51 |
| **Total:** | | | 10.689 | 100.472 | 100.00 |

## 7. References

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[4] (a) Hoppe, D.; Hense, T. *Angew. Chem. Int. Ed.* **1997**, *36*, 2282–2316.
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[234] A single crystal suitable for X-ray crystallographic analysis of (*R*,*S*)-**253b** was grown by slow evaporation of an $Et_2O$ solution. 2027137 CCDC contains the supplementary crystallographic data for (*R*,*S*)-**253b**, which confirms the configuration assigned by NMR. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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## 8. Publications

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# Synthesis and Homologation of an Azetidin-2-yl Boronic Ester with α-Lithioalkyl Triisopropylbenzoates

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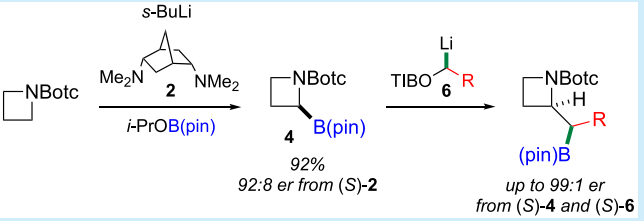
Supporting Information

**ABSTRACT:** An α-boryl azetidine, obtained by α-lithiation−borylation of *N*-Botc azetidine, undergoes reaction with α-triisopropylbenzoyloxy organolithiums to give homologated boronic esters that can be further oxidized, homologated, arylated, and deprotected to give a range of α-substituted azetidines. Scalemic α-boryl azetidine−α-triisopropylbenzoyloxy organolithium pairings show stereospecific reagent control, providing access to either diastereomeric series of homologated boronic esters with very high er's.



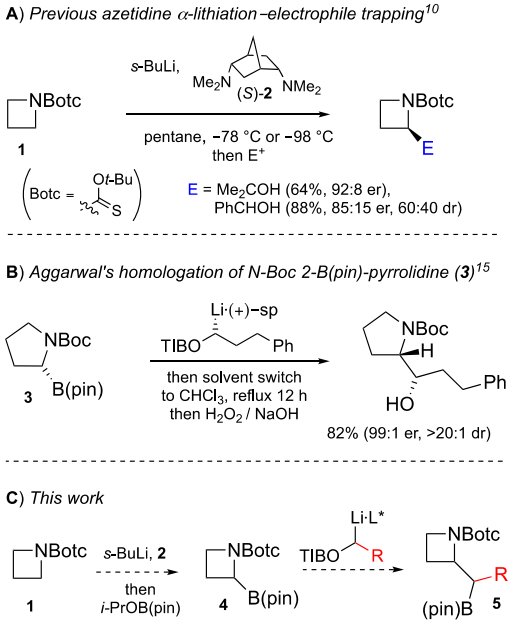

Saturated azacycles are ubiquitous structural motifs in natural products,[1] drug designs,[2] and organocatalysts.[3] Synthetic studies on pyrrolidines[4] and piperidines[5] have been extensive and aziridines[6] have also seen more attention compared with azetidines. However, with azetidine moieties increasingly emerging as constituents of highly bioactive compounds,[7] developing effective syntheses of substituted azetidines has become an important and growing field of chemistry.[8]

Our previous research on azetidine α-lithiation−electrophile trapping gave 2-substituted azetidines through the use of a thiopivaloyl or *tert*-butoxythiocarbonyl (Botc) *N*-protecting/activating group (Scheme 1, A).[9−11] The methodology enables direct diversifying α-functionalization of the azetidine moiety. Good enantioselectivities can be achieved by α-lithiation of *N*-Botc azetidine **1** in the presence of the chiral DIANANE ligand **2**[12] and trapping with certain electrophiles (e.g., Scheme 1, A).[10,13] However, reactions with aldehydes typically suffered from poor diastereoselectivity and enolizable aldehydes, such as hydrocinnamaldehyde, gave no conversion.

Boronic esters are established as highly versatile functional groups, known to undergo many stereospecific transformations.[14] In a recent synthesis of (−)-stemaphylline, Aggarwal, Leonori, and co-workers reported the preparation and some C−C bond-forming reactions of 2-B(pin)-pyrrolidine **3** (e.g., Scheme 1, B).[15] We considered that if access to 2-B(pin)-azetidine **4** was achievable (Scheme 1, C), then this could lead on to providing a broader range of α-functionalized azetidines than previously possible through direct α-lithiation−electrophile trapping. Here we communicate progress on these areas, in both racemic and asymmetric variants.

We began by applying our azetidine α-lithiation chemistry in a racemic sense with *N*-Botc azetidine **1** and TMEDA in THF[10] using *i*-PrOB(pin) as the electrophile; this gave boronic ester **4** in moderate yield (53%, Scheme 2). A factor contributing to the modest yield was likely product loss during purification by column chromatography. Despite testing a variety of different deactivated silica gels, chromatographed boronic ester **4** proved impossible to isolate without partial decomposition.[16] $^1$H NMR analysis of the crude material indicated pinacol as a major impurity, which could not be easily removed via aqueous wash. It was reasoned that running the reaction in a more hydrophobic solvent than THF, such as pentane, could enable easier removal of impurities such as pinacol during aqueous workup. Conditions for lithiation/

**Scheme 1. α-Substitution of Azetidines and Pyrrolidines through Organolithium Chemistry**

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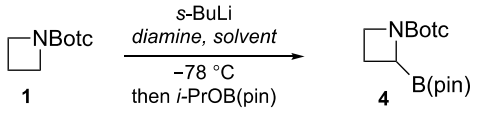
**Scheme 2. Racemic and Asymmetric α-Lithiation–Borylation of *N*-Botc Azetidine 1**



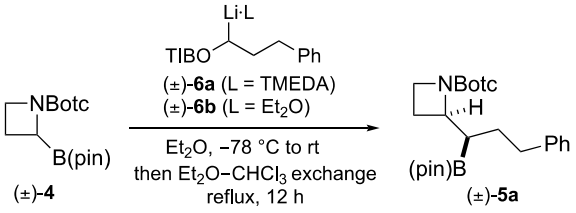

53% (using TMEDA in THF)
89% (using (±)-**2** in pentane)
92%, 92:8 er (using (*S*)-**2** in pentane)

electrophile trapping in pentane using (*S*)-**2** as a ligand (Scheme 1, A)[10] were applied with (±)-**2**, to give 2-B(pin)-azetidine **4** in excellent yield (89%) and sufficiently high purity to negate the need for chromatographic purification. Following acid/base extraction, the diamine ligand could also be efficiently recovered (88%) and recycled.

Applying the above conditions using (*S*)-**2** gave the enantioenriched boronic ester (+)-**4** also in excellent yield (92%) and high enantioenrichment (92:8 er). The absolute configuration of boronic ester (+)-**4** was determined to be *S* by derivatization to an alcohol enantiomeric to that derived from (*S*)-azetidine-2-carboxylic acid.[16] The sense of asymmetric induction is opposite to that previously seen with MeI,[10] but the same as found for acetone and benzaldehyde.[13] These findings parallel observations by O'Brien and co-workers, who noted that the sense of asymmetric induction following lithiation of *N*-thiopivaloyl azetidine in the presence of (−)-sparteine is dependent on the nature of the electrophile.[17]

An attractive functionalization of boronic ester **4** would be homologation via ate complex formation with an α-triisopropylbenzoyloxy (TIBO) organolithium and subsequent 1,2-metalate rearrangement (cf. Scheme 1, B and C).[18] This should in principle allow assembly of two contiguous stereocenters with, ultimately, control arising from choice of reactant configurations. Homologations of α-to-nitrogen boronic esters have often been found to be difficult,[15,19] although such transformations can benefit from a solvent exchange to chloroform following ate complex formation to facilitate the migration step.[15,20] Following such a protocol, 2-B(pin)-azetidine (±)-**4** was reacted with α-lithiobenzoate (±)-**6a** (1.3 equiv) to give homologated boronic ester **5a** in moderate yield (45%, Scheme 3) as a readily separable mixture

**Scheme 3. Homologation of 2-B(pin)-azetidine (±)-4**

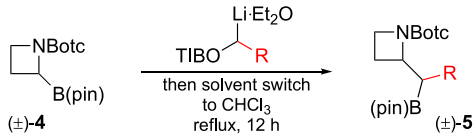


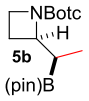
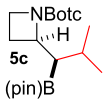
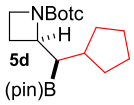
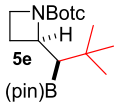
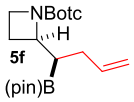
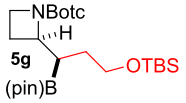
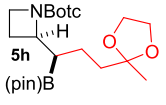

45%, 74:26 dr (from **4**:**6a**, 1:1.3)
71%, 83:17 dr (from **4**:**6a**, 1.5:1)
69%, 72:28 dr (from **4**:**6b**, 1:1.3)

of diastereomers (74:26 dr, major diastereomer shown[16]). Using boronic ester **4** in slight excess (1.5 equiv) significantly improved the yield of **5a** (71%, 83:17 dr, Scheme 3). While these latter conditions would be appropriate when the benzoate is the more precious material, studies to establish an efficient method for homologation with boronic ester **4** as the limiting reagent were also undertaken. Aggarwal and co-workers previously employed stannanes in a diamine-free tin–lithium exchange approach to α-lithiated benzoates and carbamates.[21] This latter method has the benefit of reduced steric hindrance around α-TIBO organolithiums such as **6b**, as the only coordinating species on their generation is solvent ($Et_2O$). Pleasingly, following this strategy with 1.3 equiv of tributylstannyl-derived organolithium (±)-**6b** gave the homologated boronic ester **5a** in good yield (69%, 72:28 dr, Scheme 3).

Having established conditions for homologation of azetidine boronic ester **4** where it could be used as the limiting reagent, a study of substrate scope with respect to the stannyl-derived α-TIBO organolithium was carried out to examine reaction tolerance toward steric hindrance and functional groups. Reaction using a smaller α-TIBO ethyl stannane proceeded smoothly; a shorter reflux time of 3 h was sufficient to give

**Table 1. Homologation Scope of 2-B(pin)-azetidine 4 with Stannane-Derived α-TIBO Organolithiums**




| Entry[a] | Homologated boronate **5**[b] | Yield | dr |
|---|---|---|---|
| 1[c] |  **5b** | 68% | 56:44 |
| 2 |  **5c** | 65% | 86:14 |
| 3 |  **5d** | 55% | 72:28 |
| 4 |  **5e** | 0%[d] | n/a |
| 5 |  **5f** | 50% | 71:29 |
| 6[e] |  **5g** | 65% | 58:42 |
| 7[f] |  **5h** | 56% | 67:33 |

[a]Unless otherwise noted, (i) reactions used 2-B(pin)-azetidine **4** (0.42 mmol), stannane (0.55 mmol), 12 h reflux in $CHCl_3$ and (ii) amount of individual diastereomers isolated after chromatography used to give dr's and combined yields. [b]Major diastereomer shown (**5c,d,f–h** assigned by analogy to **5a,b**).[16] [c]3 h reflux. [d]Tin–B(pin) exchange observed (71%).[16] [e]Using 2-B(pin)-azetidine **4** (0.21 mmol) and stannane (0.28 mmol). [f]Yield for inseparable diastereomeric mixture and dr from $^1$H NMR analysis.



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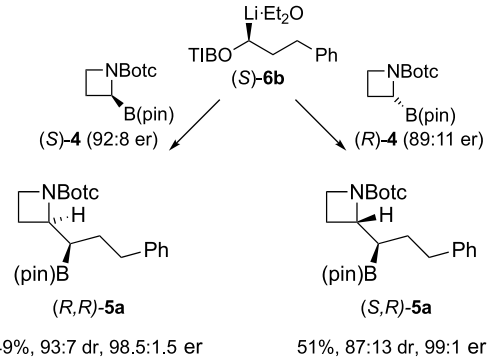
homologated boronic ester **5b** in 68% yield (Table 1, entry 1). Applying this shorter reflux time with $\alpha$-TIBO organolithium **6b** also gave **5a** in 65% yield and unchanged dr. More sterically demanding $\beta$-branched stannanes remained effective, giving homologated isobutyl and methylcyclopentyl boronic esters **5c** and **5d** in good yields (Table 1, entries 2 and 3). However, further increase of the steric bulk at the $\beta$-position, using an $\alpha$-TIBO neopentyl stannane, failed to give any of the desired homologated product **5e** (entry 4). In this last case, isolation of the B(pin) neopentyl benzoate (71%)[16] from overall tributyltin−B(pin) exchange suggests generation of the intermediate ate complex proceeded, but its collapse occurred without 1,2-metalate rearrangement. Homologations performed using stannanes bearing alkenyl, silyloxy and ketal functionality all proved viable (entries 5−7).

The observation of diastereoselectivity in the above boronate homologations suggests possible matched/mismatched effects depending on reactants configurations.[22] This could potentially render the asymmetric approach less effective in enabling access to the enantiomers of both diastereomers. To examine this aspect, separate reactions were carried out (Scheme 4) of *S* and *R* boronic ester **4** with $\alpha$-

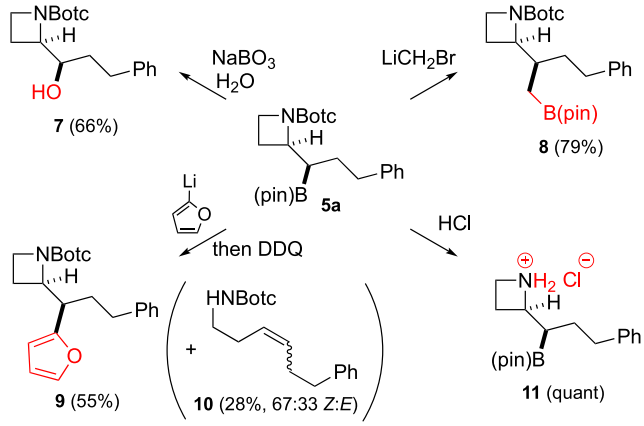
**Scheme 4. Asymmetric Homologation of *S* and *R* Boronic Ester 4**




lithiobenzoate (*S*)-**6b** [generated by stereoretentive Sn−Li exchange[23] from the corresponding *S* stannane (95:5 er)].[18] Pleasingly, both reactions proceeded to give homologated boronic esters (*R*,*R*)- and (*S*,*R*)-**5a**, respectively, in high diastereoselectivities and excellent enantioselectivities (up to 99:1 er), albeit with slightly lower yields compared with the racemic homologation. Similar selectivities (up to 99:1 er) and yields were also achieved for **5b**.[16]

To demonstrate synthetic versatility of the homologated boronic esters, further transformations of boronic ester **5a** were performed [Scheme 5, shown for (*R**,*R**)-**5a**; separately examined (*R**,*S**)-**5a** behaved similarly].[16] Oxidation of boronic ester **5a** to alcohol **7** was achieved using sodium perborate in good yield (66%). Matteson homologation, using dibromomethane, successfully gave the one-carbon homologated boronic ester **8** in high yield (79%). Arylation was achieved using DDQ as the activating electrophile[24] to give the furanylated product **9** in moderate yield (55%). This reaction also resulted in the formation of homoallylic amine **10** (28%). The latter likely arises from a competitive 1,2-elimination/ring-opening pathway, indicating that these C−B derivatizations, on a system with a $\beta$-electron withdrawing functional group incorporated within a strained ring, are not always straightforward. Finally, Botc deprotection of **5a** in ethereal HCl gave the

**Scheme 5. Transformations of Homologated Boronic Ester (*R**,*R**)-5a**




azetidinium chloride salt **11** (quant), which further demonstrates the utility/lability of this recently introduced protecting/activating group.[10] Whiting and co-workers have shown homoboroprolines to be effective organocatalysts for asymmetric aldol reactions,[19] and the current formation of a similar azetidinium boronic ester could lead to applications in this area.

In conclusion, we have developed a synthetic route to enantioenriched 2-B(pin)-azetidine **4**, and the latter has been converted to homologated azetidine boronic esters, by boronate formation with $\alpha$-lithiobenzoates and subsequent 1,2-metalate rearrangement. This process can be performed with high diastereo- and enantioselectivity. The homologated boronic esters can be further transformed into $\alpha$-substituted azetidines which cannot be accessed through direct $\alpha$-lithiation−electrophile trapping chemistry.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.9b03901.

Full experimental procedures and characterization data (PDF)

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### Notes

The authors declare no competing financial interest.

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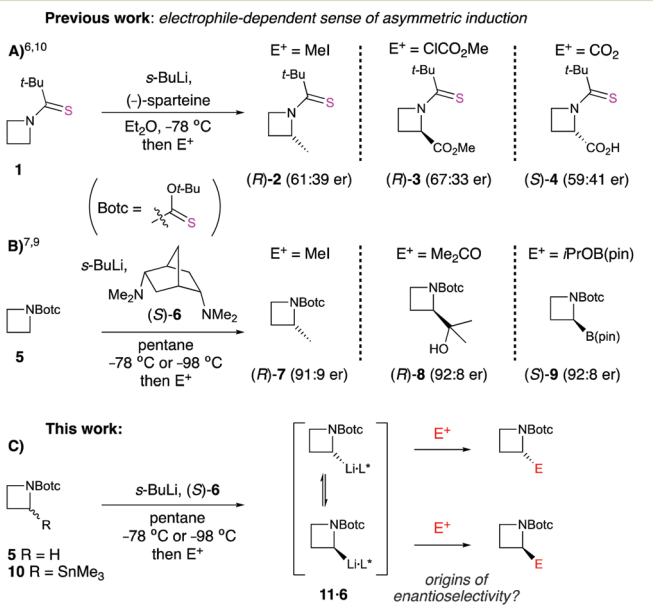
# Electrophile dependent mechanisms in the asymmetric trapping of α-lithio-*N*-(*tert*-butoxythiocarbonyl)azetidine†

Pascal K. Delany, Claire L. Mortimer and David M. Hodgson *

**Sn–Li exchange and 'poor man's Hoffmann tests' establish asymmetric trapping of α-lithio-*N*-(*tert*-butoxythiocarbonyl) (Botc) azetidine to be controlled by dynamic thermodynamic resolution or dynamic kinetic resolution, depending on the electrophile. Unusually, different configurational stability is seen for the anion generated by lithiation compared to transmetallation. Configurational stability of α-lithio-*N*-Boc azetidine indicates instability with the *N*-Botc system is due to the C═S group.**

Saturated azacycles are pervasive motifs in pharmaceutically active compounds;[1] consequently, advances in their asymmetric synthesis are of significant interest.[2] Directed deprotonative lithiation—electrophile trapping sequences are synthetically powerful approaches in enantioselective synthesis,[3] especially for α-functionalisation of saturated azacycles.[4] Azetidines have recently received increased attention due to their desirable physiochemical properties and the emergence of highly bioactive azetidine containing compounds.[5] We have developed asymmetric α-lithiation—electrophile trapping of azetidines, enabled by a *N*-thiopivaloyl or -*tert*-butoxythiocarbonyl (Botc) directing group (Scheme 1A and B);[6–9] the latter being preferred owing to greater levels of asymmetric induction, ease of deprotection and accessibility to 2,4-disubstituted azetidines.[7,8] Knowledge of pathways for enantioinduction provides insight and rationalisation of previous observations and serves as valuable understanding to underpin future studies. O'Brien and co-workers reported the sense of asymmetric induction in α-lithiation—electrophile trapping of *N*-(thiopivaloyl)azetidine (**1**) was electrophile dependent (Scheme 1A),[10] a phenomenon rarely observed for non-benzylic $sp^3$ lithiated species.[11] On previous evaluation of our DIANANE (*S*)-**6**-mediated asymmetric α-lithiation—electrophile trapping of *N*-Botc azetidine **5**,[9] we also observed the sense of enantioinduction was electrophile dependent (Scheme 1B). This has prompted us to investigate the origins of asymmetric substitution of *N*-Botc azetidine through α-lithiation, with emphasis on how the process proceeds with respect to different electrophiles (Scheme 1C).




Scheme 1 Investigations of α-lithiated azetidines.

Enantioselectivity can originate from three distinct pathways (Scheme 2).[12] An organolithium base coordinated with a chiral ligand could preferentially remove the *pro-R* or *pro-S* hydrogen to give a configurationally stable anion; if an introduced electrophile reacts stereospecifically then asymmetric induction is controlled by the lithiation rate difference (*e.g.*, $k_{HS} \gg k_{HR}$). Enantioselectivity can also arise post-deprotonation when a configurationally unstable anion is formed (Scheme 2). Dynamic thermodynamic resolution (DTR) occurs if the lithiated complexes (*e.g.*, (*R*)-**11·6** and (*S*)-**11·6**) equilibrate to a thermodynamically controlled ratio and substitute with an electrophile at a rate faster

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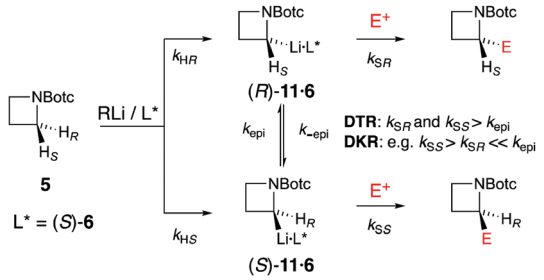
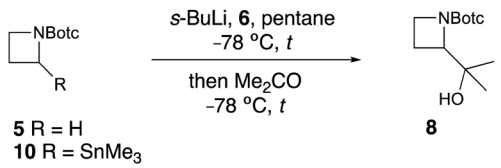
† Electronic supplementary information (ESI) available: Additional configurational stability studies, experimental procedures and $^1$H and $^{13}$C NMR spectra. CCDC 2027137. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/d0cc05396a




Scheme 2 Possible enantiodetermining steps.

than epimerisation ($k_{SR}$ and $k_{SS} > k_{epi}$).[12] Alternatively, dynamic kinetic resolution (DKR) could operate, where the rate of epimerisation between diastereomeric complexes is faster than reaction with the electrophile (*e.g.*, $k_{SR} > k_{SS} \ll k_{epi}$, Scheme 2); enantioselectivity is now determined by the difference in rate of reaction of the two diastereomeric complexes with the electrophile (*i.e.*, $\Delta\Delta G^{\ddagger}$).

We first examined the configurational stability of *N*-Botc azetidine complexes ((*R*)-**11·6** and (*S*)-**11·6**) with chiral diamine ligand DIANANE (*S*)-**6**,[13] when generated through α-deprotonation and Sn–Li exchange (Scheme 3). A control reaction using previously optimised conditions for lithiation (deuteration studies) and for enantioselectivity (pentane, 1 h, −78 °C) with acetone as the electrophile (3 equiv.),[7] gave alcohol (*R*)-**8** (61%) in 89 : 11 er (*cf.*, Scheme 1B). Sn–Li exchange, a process with considerable precedent for occurring in a stereoretentive manner,[14] with stannane (±)-**10** in the presence of (*S*)-**6** (1 h, −78 °C, then acetone) gave alcohol (*R*)-**8** in 90 : 10 er (57%). Matching levels of enantioenrichment from these two experiments show the intermediate organolithium complexes are configurationally unstable at −78 °C and enantioselectivity originates after anion formation. If DTR is occurring, then altering incubation time may influence enantioselectivity. Following Sn–Li exchange, decreasing incubation to 5 min gave alcohol (*R*)-**8** in essentially unchanged er (85 : 15, 64%), indicating either anion equilibration following transmetallation is effectively complete after 5 min at −78 °C, or a DKR process.




Scheme 3 Studies on the synthesis of alcohol **8** from deprotonation or Sn–Li exchange.

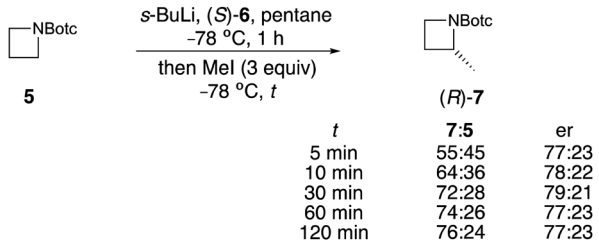
Although the enantiodetermining step occurs post-deprotonation, asymmetric deprotonation could still be occurring.[15] 1 min lithiation at −78 °C of azetidine **5** in the presence of DIANANE (*S*)-**6** before acetone trapping, gave alcohol (*R*)-**8** in 58 : 42 er (28%). The reduced er after 1 min indicates the lithiated diastereomeric complexes have not fully equilibrated (unlike after 1 h), and there is no favourable initial formation of one organolithium complex by asymmetric deprotonation that is then reduced on equilibration. Sn–Li exchange with enantioenriched stannane (*R*)-**10** (67 : 33 er) in the presence of racemic DIANANE (±)-**6** at −98 °C for 1 min before acetone trapping, resulted in essentially racemic alcohol **8** (51 : 49 er, 39%). Assuming stereoretentive Sn–Li exchange (although see below), this demonstrates configurational instability of the organolithium complexes even at −98 °C when the anion is formed by transmetallation. However, in contrast to anion generation through Sn–Li exchange, partial configurational stability was demonstrated in deprotonations with different incubation temperatures and times. Lithiation of azetidine **5** in the presence of DIANANE (*S*)-**6** and incubation for 1 h at −98 °C before trapping gave alcohol (*R*)-**8** with moderate enantioselectivity (65 : 35 er, 38%), showing incomplete equilibration. But when deprotonation and incubation were performed at −78 °C for 1 h, then cooling to −98 °C before trapping, this gave alcohol (*R*)-**8** with good enantioselectivity (88 : 12 er, 55%), indicating that high enantioselectivity can be achieved with trapping at −98 °C. Deprotonation and incubation at −98 °C for 3 h before trapping gave alcohol (*R*)-**8** in 86 : 14 er (51%), with the high er suggesting equilibration is almost complete at −98 °C after 3 h. These time dependent enantioselectivities imply DTR, with acetone (for a full table of acetone trapping studies and similar results obtained with aromatic aldehydes, see the ESI†), and indicate the organolithium complexes possess greater configurational stability at −98 °C when formed through deprotonation.

Remarkably, compared to 65 : 35 er obtained from deprotonation for 1 h at −98 °C, increased enantioselectivity was observed through Sn–Li exchange of stannane (±)-**10** when carried out under the same conditions in the presence of DIANANE (*S*)-**6**, giving alcohol (*R*)-**8** in 84 : 16 er (41%). This difference at −98 °C can be rationalised by 'unproductive' kinetic deprotonation (preferential generation of the thermodynamically less stable lithiated complex) and a longer equilibration time, relative to transmetallation. Alternatively, Sn–Li exchange with stananne (±)-**10** could be occurring non-stereospecifically in the presence of DIANANE (*S*)-**6**, although precedent for non-retentive Sn–Li exchange is very limited;[16] no transmetallation occurred without the ligand present. Non-retentive Sn–Li exchange could explain the rapid racemisation observed at −98 °C after 1 min with enantioenriched stannane (*R*)-**10**. The possibility of non-stereospecific Sn–Li exchange was probed using stannane (±)-**10** with DIANANE (*S*)-**6** and *in situ* acetone. This gave trace amounts (1%) of essentially racemic alcohol **8** (52 : 48 er), indicating Sn–Li exchange is occurring stereospecifically with some degree of 'microscopic'[17] configurational stability, relative to the rate of acetone trapping.

In a 'poor man's Hoffmann test',[12] azetidine **5** was deprotonated (1 h, −78 °C) and reacted with sub-stoichiometric acetone (0.5 and 0.1 equiv.) to give alcohol (*R*)-**8** in 61 : 39 er (29%) and 60 : 40 er (2%), respectively. Decreased enantioselectivity (compared with 89 : 11 er using 3 equiv. earlier) suggest the minor lithiated complex reacts marginally faster than the major complex[15] ((*R*)-**11·6** faster than (*S*)-**11·6**, assuming retentive substitution, $S_E2$ret, with acetone[11]). The difference in enantioselectivity shows epimerisation

is not occurring on the timescale of acetone trapping at −78 °C, confirming a DTR process.

A sacrificial electrophile has been previously used to improve enantioselectivity in a reaction where DTR operates.[18] Generation of α-lithio-*N*-Botc azetidine in the presence of DIANANE (*S*)-**6** at −78 °C, then reaction with MeI (0.2 equiv.) for 5 min before addition of acetone (3 equiv.) only led to alcohol (*R*)-**8** (58%) with a slight reduction in er (80 : 20). However, the enantioenrichment of the traces (1%) of isolated methylated azetidine (*S*)-**7** (73 : 27 er) is similar to that found at this temperature for (*S*)-**7** (77 : 23 er) using only MeI (3 equiv.), sampled as the reaction progressed (5–120 min, Scheme 4). While these results do not strictly discriminate between DTR and DKR (as potentially $k_{SR} \approx k_{SS}$, *cf.*, Scheme 2), enantioselectivity independent of reaction conversion and (also in contrast to acetone) improved enantioenrichment at −98 °C after 1 h (91 : 9 er),[7] support a DKR process with this slower reacting[19] electrophile.



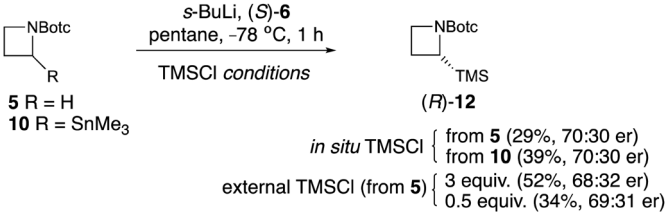

| *t* | **7**:**5** | er |
|---|---|---|
| 5 min | 55:45 | 77:23 |
| 10 min | 64:36 | 78:22 |
| 30 min | 72:28 | 79:21 |
| 60 min | 74:26 | 77:23 |
| 120 min | 76:24 | 77:23 |

Scheme 4 Unchanging er during the methylation of *N*-Botc azetidine **5**.

With $Me_3SnCl$ as the electrophile, both variation in reaction time and temperature altered asymmetric induction (Table 1).

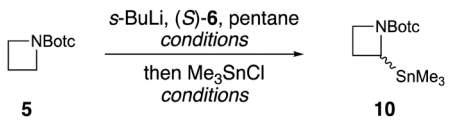
Lithiation of *N*-Botc azetidine **5** in the presence of DIANANE (*S*)-**6** at −78 °C for 1 h led to stannane (*S*)-**10** in 67 : 33 er (90%, Table 1, entry 1). An otherwise identical reaction, but without warming to rt following $Me_3SnCl$ addition, resulted in stannane (*S*)-**10** in similar enantioselectivity (61 : 39 er, entry 2) in 80% yield. However, reducing the lithiation time to 5 min before stannylation inverted the sense of asymmetric induction, to give stannane (*R*)-**10** in 54 : 46 er (62%). Decreasing the lithiation temperature to −98 °C for 3 h before trapping at the same temperature gave stannane (*S*)-**10** in 64 : 36 er (77%, entry 4). However, reducing the lithiation time to 1 h at −98 °C again resulted in a change in the sense of asymmetric induction to 54 : 46 er (entry 5). The dependence of asymmetric induction on lithiation time at −78 °C and −98 °C indicates DTR in stannylation, similar to trapping with acetone. These results also suggest deprotonation-derived organolithium complex equilibration is incomplete after 5 min at −78 °C and reinforces the earlier observation with acetone of increased time required for complex equilibration at −98 °C, due to a less configurationally labile anion at this lower temperature. The reduced overall levels of enantioselectivity compared with optimised conditions for acetone trapping suggests either an interfering DKR mechanism in which the thermodynamically less stable complex reacts with at a faster rate with $Me_3SnCl$, or possible competing non-stereospecific electrophile trapping ($S_E2$ret and $S_E2$inv).[11]

Use of an internal electrophile such as TMSCl has been previously used to ascertain the degree of an asymmetric deprotonation.[15] Two parallel '*in situ*' trapping experiments were performed at −78 °C using *N*-Botc azetidine **5** and stannane (±)-**10** substrates (Scheme 5). These reactions gave silane (*R*)-**12** in identical enantioenrichment (70 : 30 er), showing the level of asymmetric induction with this electrophile is independent of the method of anion generation. TMSCl is a slower reacting electrophile[19] and the matching enantioselectivity could therefore be due to DKR. A deprotonation reaction with a 1 h incubation period at −78 °C before external addition of TMSCl gave silane (*R*)-**12** in 52% yield and essentially the same enantioselectivity (68 : 32 er). A 'poor man's Hoffmann test' with 0.5 equiv. of TMSCl, gave silane (*R*)-**12** in 69 : 31 er (34%), providing further evidence for DKR. With TMSOTf, a more reactive silylating agent, a change in the sense of asymmetric induction was observed, giving (*S*)-**12** in 58 : 42 er (28%); this is most likely a result of diminished influence of a DKR mechanism.




Scheme 5 Silylation studies.

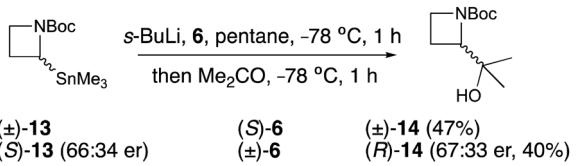
Table 1 Asymmetric stannylation of *N*-Botc azetidine **5**




| Entry | Lithiation temp (time) | Stannylation temp (time) | Yield **10** | er (*R* : *S*) | Recovered **5** |
|---|---|---|---|---|---|
| 1 | −78 °C (1 h) | −78 °C (30 min) then rt (30 min) | 90% | 33 : 67 | 0% |
| 2 | −78 °C (1 h) | −78 °C (30 min) | 80% | 39 : 61 | 0% |
| 3 | −78 °C (5 min) | −78 °C (30 min) then rt (30 min) | 62% | 54 : 46 | 38% |
| 4 | −98 °C (3 h) | −98 °C (30 min) | 77% | 36 : 64 | 21% |
| 5 | −98 °C (1 h) | −98 °C (30 min) | 70% | 54 : 46 | 24% |

For the two electrophiles which trap through DKR (MeI and TMSCl), the predominant sense of asymmetric induction is opposite to those electrophiles which proceed through DTR (acetone, benzaldehyde† and $Me_3SnCl$). This could be due either to preferential invertive $S_E2inv$ trapping, not uncommon for mesomerically stabilised organolithiums reacting with alkyl halides,[15] or to retentive trapping in which the minor diastereomeric organolithium complex is the faster reacting species, as was observed earlier in the 'poor man's Hoffmann test' with acetone.

O'Brien and co-workers previously established with *N*-thiopivaloyl azetidine that asymmetric induction occurs post deprotonation; however, no distinction between DTR or DKR was made.[10] They also speculated the origin of configurational instability may due to the longer C═S bond leading to a weaker C–Li bond. To discriminate between the C═S group or azacycle size being responsible for the configurational instability of *N*-Botc azetidine lithiated complexes ((*R*)-**11**·**6** and (*S*)-**11**·**6**), we sought to access the lithiated *N*-Boc azetidine equivalents. We previously found that direct α-lithiation of *N*-Boc azetidine is problematic,[6] but access to α-lithiated *N*-Boc azetidine is achievable by Sn–Li exchange from *N*-Boc stannane **13** (Scheme 6). Stannane **13** was accessed by deprotection/reprotection of *N*-Botc stannane **10**, using TMSI for deprotection (66%). Under identical transmetallation conditions used for stannane **10** in the presence of DIANANE (*S*)-**6**, stannane (±)-**13** underwent Sn–Li exchange and trapping with acetone to give racemic *N*-Boc alcohol (±)-**14** (47%). Transmetallation of enantioenriched *N*-Boc stannane (*S*)-**13** (66 : 34 er) using *s*-BuLi with racemic DIANANE (±)-**6**, led to enantioenriched alcohol (*R*)-**14** in 67 : 33 er (40%). These results demonstrate, for the first time, access to a configurationally stable α-lithiated azetidine and indicate the C═S group is responsible for the configurational instability of α-lithio *N*-Botc azetidine.




Scheme 6 Transmetallation of *N*-Boc stannane **13**.

In summary, the present studies show configurational instability of α-lithiated *N*-Botc azetidine complexes ((*R*)-**11**·**6** and (*S*)-**11**·**6**). These diastereomeric complexes reach thermodynamic equilibrium after 1 h at −78 °C (3 h at −98 °C). They react with a fast trapping electrophile such as acetone *via* DTR, producing α-substituted azetidines with enantioselectivities (~90 : 10) that reflect the complexes dr. Slower trapping electrophiles (MeI and TMSCl) react by DKR; this provides an explanation as to why different enantioselectivities are observed when conditions for optimal DTR are used with these electrophiles and also rationalises the different sense of enantioinduction. This change in mechanism could also be occurring with *N*-thiopivaloyl azetidine. In the current work, an intriguing difference in configurational stability of the anion formed by lithiation *versus* transmetallation was also observed (further discussed in the ESI†). Finally, the origin of configurational instability was determined to be the presence of C═S group, as demonstrated by the configurational stability of α-lithiated *N*-Boc azetidine. The stereochemical lability may be due to the longer C═S bond and/or the greater polarisability of S, compared to O, allowing greater charge transfer from N to S.[8,20]

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## Conflicts of interest

There are no conflicts to declare.

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