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Lithiation and Borylation of Secondary *O*- and *S*- Substituted Hindered Benzoates

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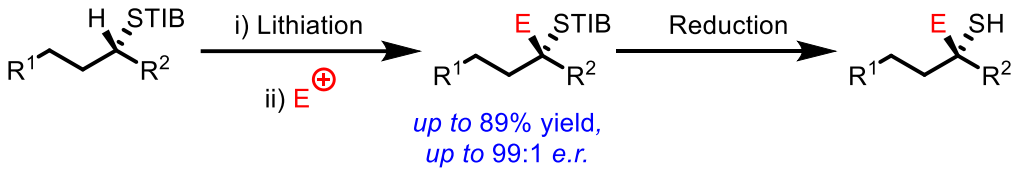
Abstract

The work described in this thesis is divided into two chapters; of which the first chapter explores the asymmetric synthesis of tertiary thiols by lithiation-electrophilic trapping of secondary dialkyl thiobenzoates and the second chapter investigates the lithiation-borylation chemistry of cyclobutyl benzoates.

Chapter 1: The lithiation-electrophilic trapping of secondary dialkyl thiobenzoates

The synthesis of enantioenriched tertiary thiols remains a challenging, under-developed area in the field of organic synthesis. In addition, the prevalence of enantioenriched thiols in nature and biologically active molecules warrants further development in this field. Previous work has shown dialkyl thiobenzoates to undergo facile deprotonation and subsequent reaction with an electrophile to furnish a tertiary thiobenzoate, followed by reduction of the thiobenzoate group to produce a tertiary thiol centre. However, the thiobenzoate carbenoid was shown to be configurationally labile, thus limiting the application in asymmetric synthesis. In this work, we have identified conditions for the lithiation-electrophilic trapping of enantioenriched secondary dialkyl thiobenzoates (Scheme A).

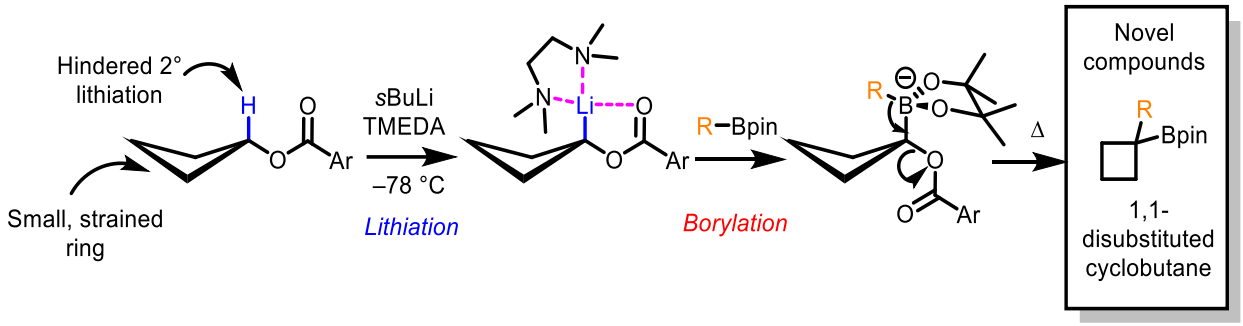


Scheme A: Synthesis of enantioenriched tertiary thiols.

Having established suitable reaction conditions, a range of substrates was screened and lithiation-electrophile trapping reactions were conducted *via in-situ* IR spectroscopy to understand the course of the reaction and the fate of the reactants. Finally, a kinetic study was conducted to quantify the barrier to racemisation.

Chapter 2: The lithiation-borylation chemistry of cyclobutyl benzoates

The well-established lithiation-borylation methodology using secondary dialkyl benzoates provides a powerful tool for the synthesis of enantioenriched tertiary boronic esters. However, studies into the lithiation-borylation of small ring benzoates, such as cyclobutanes remains underdeveloped. As cyclobutyl scaffolds offer a rigid, sp^3 bioisostere analogous to aromatic rings that are found in biologically active natural products with antibacterial, anticancer and antimicrobial properties, such scaffolds are synthetically relevant and medicinally valuable (Scheme B).



Scheme B: Studies into the lithiation-borylation of cyclobutyl benzoates for the synthesis of 1,1-disubstituted cyclobutanes.

Herein, we report the lithiation-borylation of cyclobutyl benzoates for the synthesis of 1,1 disubstituted cyclobutanes. We have reported a wide functional group tolerance, for both primary, secondary and sp^2 boronic esters, with homologated products isolated in low to high yields (29-72%). Application to biologically relevant molecules, such as a lithocholic acid derivate and enantioenriched boronic esters, showed that this reaction has a broad substrate tolerance. In addition, various substituted cyclobutyl and oxetanyl and azetdinyl benzoate derivatives were tested in the lithiation-borylation methodology. Finally, functional group interconversion of the homologated boronic ester products provided access to a library of diverse compounds.

Acknowledgements

I am heavily indebted to Varinder, more so than most PhD students. Over the course of my PhD Varinder has been patient, provided guidance and support not only as a supervisor, but also in his capacity as a friend. I am unreservedly grateful to Varinder for being a great role model.

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Finally, to my parents, I am grateful for the sacrifices you have made and the support that you have given me to this day to help me reach my dreams. I hope I can make you proud!

असतो मा सद्गमय ।
तमसो मा ज्योतिर्गमय ।
मृत्योर्माऽमृतं गमय ॥

Bṛhadāraṇyaka Upaniṣhad (1.3.28.)

Author's Declaration

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

SIGNED: .....  ..... DATE: .....07-03-2021.....

Abbreviations

acac	acetylacetone
aq.	aqueous
Ar	aryl
ax.	axial
Bn	benzyl
b.p.	boiling point
br.	broad
°C	Celsius degree
c-	cyclo-
cat.	catalyst
Cb	carbamate
COD	1,5-Cyclooctadiene
CPME	cyclopentyl methyl ether
d	doublet
dba	dibenzylideneacetone
DCM	dichloromethane
DCME	dichloromethyl methy ether
DFT	density functional theory
DIAD	diisopropyl azodicarboxylate
dippf	1,1′-bis(diisopropylphosphino)ferrocene
DMAP	4-dimethylaminopyridine
DME	1,2-dimethoxyethane
DMF	dimethylformamide
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidone
DMSO	dimethyl sulfoxide
dppb	1,4-bis(diphenylphosphino)butane
d.r.	diastereomeric ratio
E	electrophile
e.r.	enantiomeric ratio
e.e.	enantiomeric excess
eq.	equivalent
e.s.	enantiospecificity
ESI	electronspray ionisation
Et_2O	diethyl ether
g	gram
GC	gas chromatography
GCMS	gas chromatography-mass spectrometry
gly	ethylene glycol
GP	general procedure
hept.	heptet (otherwise known as septet)
hr(s)	hour(s)
HPLC	high performance liquid chromatography

HRMS	high resolution mass spectrometry
IR	infrared
J	coupling constant
KHMDS	potassium bis(trimethylsilyl)amide
LDA	lithium diisoprpylamide
LG	leaving group
LiHMDS	lithium bis(trimethylsilyl)amide
$LiNCy_2$	lithium Dicyclohexylamide
lit.	literature
LiTMP	lithium tetramethylpiperidine
M	molar
m-	*meta*-
*m*CPBA	*meta*-chloroperoxybenzoic acid
M.P.	melting point
Mes	2,4,6-mesityl
2-MeTHF	2-methyltetrahydrofuran
mg	milligram
MHz	Megahertz
min(s)	minute(s)
mL	millilitre
mmol	millimole
mol	mole
MS	mass spectrometry
N_2	nitrogen gas
n.d.	not determined
neo	neopentyl glycol
NMR	nuclear magnetic resonance
Nu	nucleophile
o-	*ortho*-
o/n	overnight
OTf	triflate
p-	*para*-
PE	petroleum ether (40-60 ºC)
Pent.	pentet
Ph	phenyl
pin	pinacol
PMDTA	*N*,*N*,*N'*,*N''*,*N''*-pentamethyldiethylenetriamine
PMB	*para*-methoxybenzyl
PMP	*para*-methoxyphenyl
ppm	parts per million
rac	racemic
R_f	retention factor
rt	room temperature
s	singlet

sec(s)	second(s)
sext.	sextet
t	triplet
tt	triplet of triplet
TBAF	tetra-*n*-butylammonium fluoride
TBME	*tert*-butyl methyl ether
*t*BuLi	*tert*-butyllithium
Tf	trifluoromethanesulfonyl
THF	tetrahydrofuran
THP	tetrahydropyranyl
TIB	2,4,6-triisopropyl benzoate
TIBCl	2,4,6-triisopropyl benzoyl chloride
TIBOH	2,4,6-triisopropyl benzoic acid
TIBSH	2,4,6-triisopropylbenzothioic *S*-acid
TLC	thin layer chromatography
TMEDA	*N*,*N*,*N'*,*N'*-tetramethylethylenediamine
T_R	retention time
µW	microwave

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1. The Asymmetric Synthesis of Tertiary Thiols by Lithiation-Electrophilic Trapping of Secondary Dialkyl Thiobenzoates

1.1. Introduction

1.1.1. Importance of Thiol Derivatives

In 2011, organosulfur containing molecules represented a quarter of the top 200 selling pharmaceutical compounds worldwide (Scheme 1).[1] Similarly, more than 30% of fungicides, herbicides and insecticides produced by the agrochemical industry contained an organosulfur-based functional group.[2,3] Furthermore, sulfur-containing motifs are present in cysteine and methionine, both proteinogenic amino acids, and natural products (such as 3-methyl-3-sulfanylhexan-1-ol (onion-like smell, found in human sweat), thioterpineol (responsible for the taste of grapefruit) and glutathione) (Scheme 1).

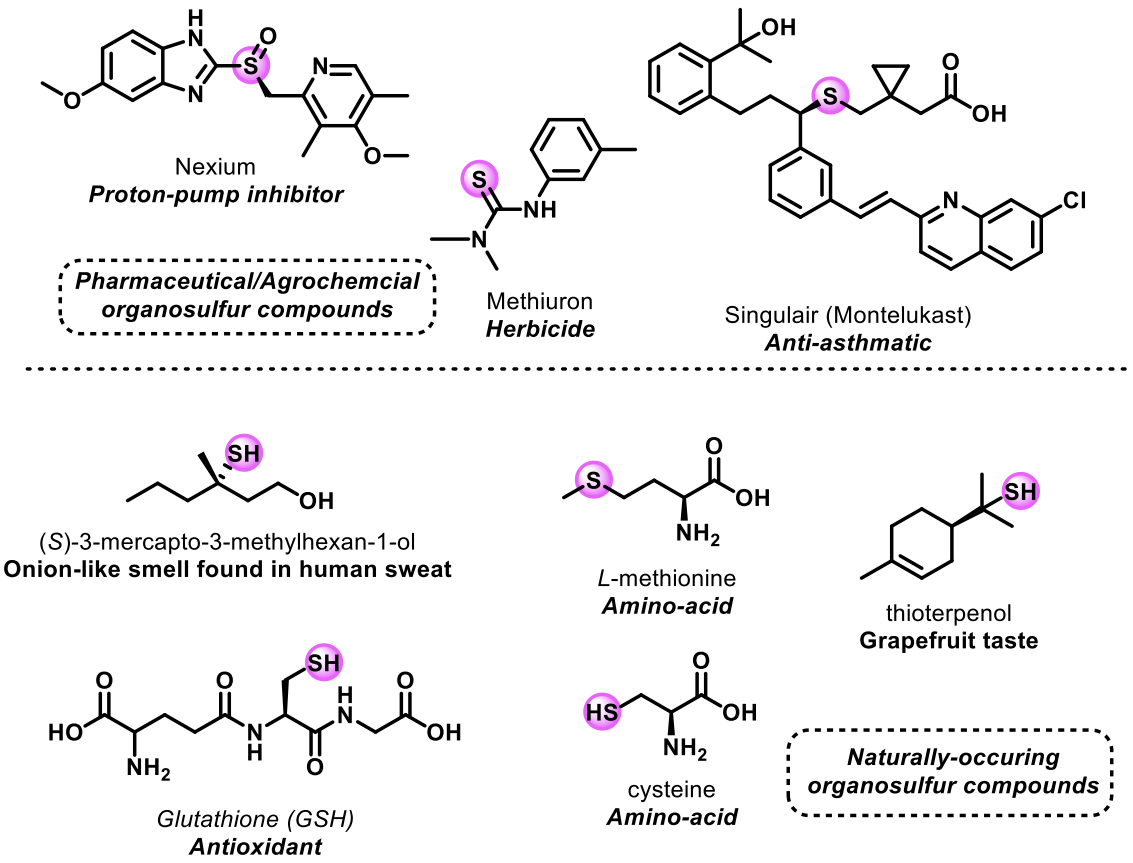


Figure 1: Examples of organosulfur containing molecules found in natural products, agrochemicals, and pharmaceuticals.

Despite the prevalence of organosulfur compounds in nature, biological and agrochemical/ medicinal chemistry, a lack of synthetic methodology limits the manipulation of such molecules, which in turn hampers further scientific developments. There are growing pressures on the commercial R&D sector,[4] such as in the pharmaceutical industry, to produce more efficacious medicines. In addition, there is an apparent need to "escape from flatland" by shifting from the high-throughput synthetic methodologies ideal for creating achiral, aromatic molecules (sp^2-hybridised), to other methods to access chiral, sp^3-hybridised molecules with more spatial diversity, ideal for probing biological receptors. For example, as shown in Figure 2, dimethylpiperidine is a superior substituent for exploring 3D chemical space than the analogous sp^2-hybridised dimethylpyridine; there are more structural isomers possible in the former (5 *vs* 34) to facilitate such exploration in a controlled manner. This emphasises the need for advancements in asymmetric synthesis to allow access to such molecules with high stereocontrol.[5]

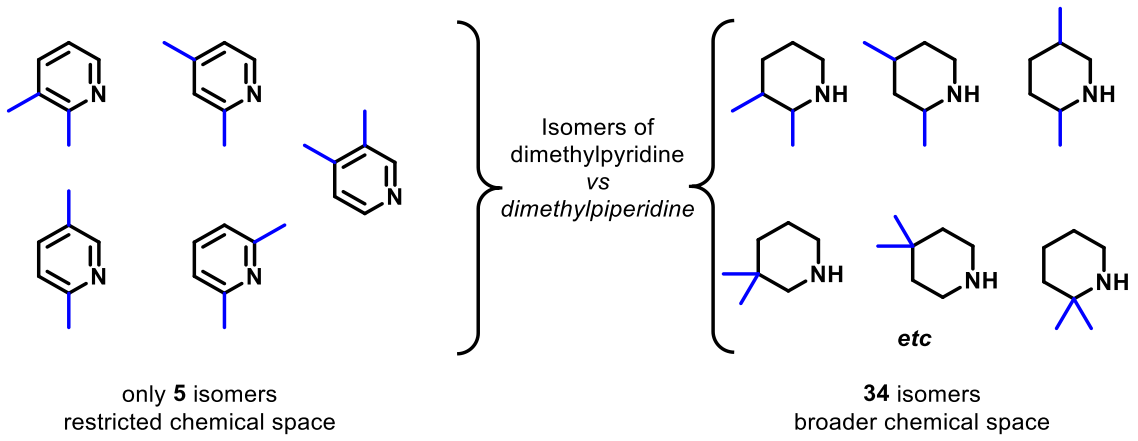


Figure 2: Isomer count comparison for sp^2 to sp^3 hybridised heterocyclic analogues.

Sulfur is an exceptionally versatile element due to the wide range of oxidation states it can access: -2, -1, 0, +2, +3, +4, +5 and +6. This allows sulfur to bond with most elements (using single or double bonds) in the periodic table, excluding noble gases.[6]

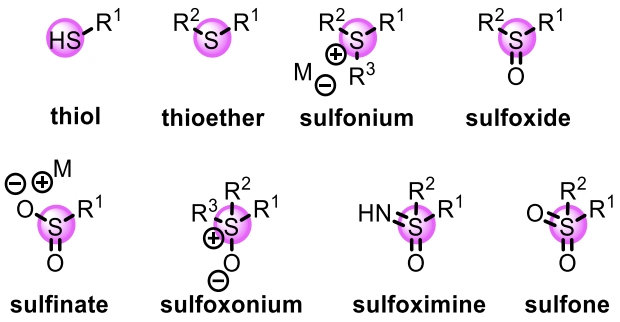
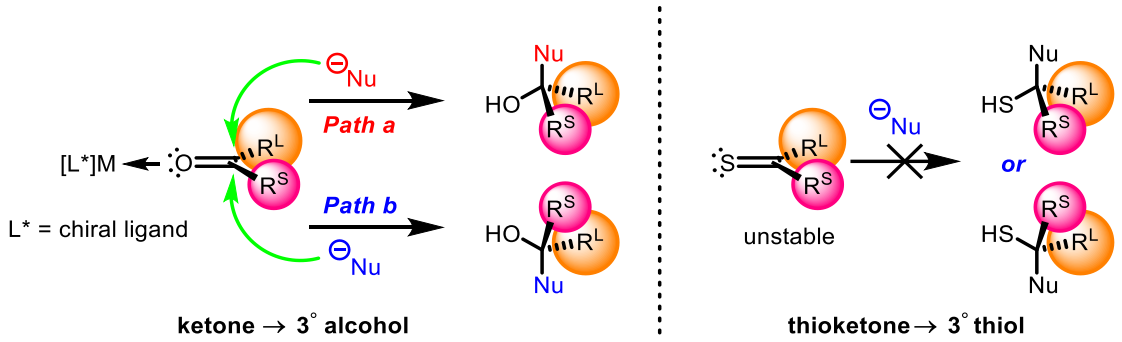


Figure 3: Common organosulfur compounds.

There are a vast range of sulfur-containing functional groups, including thiols[II]7, thioethers[II]8, sulfonium salts[III]9, sulfoxides[IV]9, sulfinate salts[IV]9, sulfoxonium[V]10, sulfilimines[VI]11 and sulfates[VI]11,12 (Figure 3). Many named reactions in literature are based upon the manipulation of such organosulfur compounds, or use organosulfur-derived reagents: Pummerer rearrangement,[13,14] Corey-Chaykovsky reaction, Stevens rearrangement,[15] Herz reaction,[16] Swern oxidation,[17] aza-Mislow-Evans reaction,[18–20] retro-Michael[21,22] and Morin rearrangements[23], for example.

In recent years, further developments into the synthesis of enantiopure organosulfur compounds have been explored, with chirality residing on either the carbon (thiols and thioethers[8]) or sulfur (sulfonium[14], sulfoxide[24], sulfoxonium[25]) atoms. Owing to a lack of literature protocols, most syntheses of enantiopure thiols focus on secondary thiols (or thioethers), with methods for the synthesis of enantioenriched tertiary thiols few and far between.

By comparison, asymmetric syntheses of tertiary alcohols are more prevalent in the literature, partially due to the ease of synthesis of such molecules in comparison to the analogous tertiary thiols.[26–29] For example, nucleophilic addition to a prochiral ketone can be achieved through selective enantiofacial addition to generate an enantioenriched tertiary alcohol (Scheme 1).

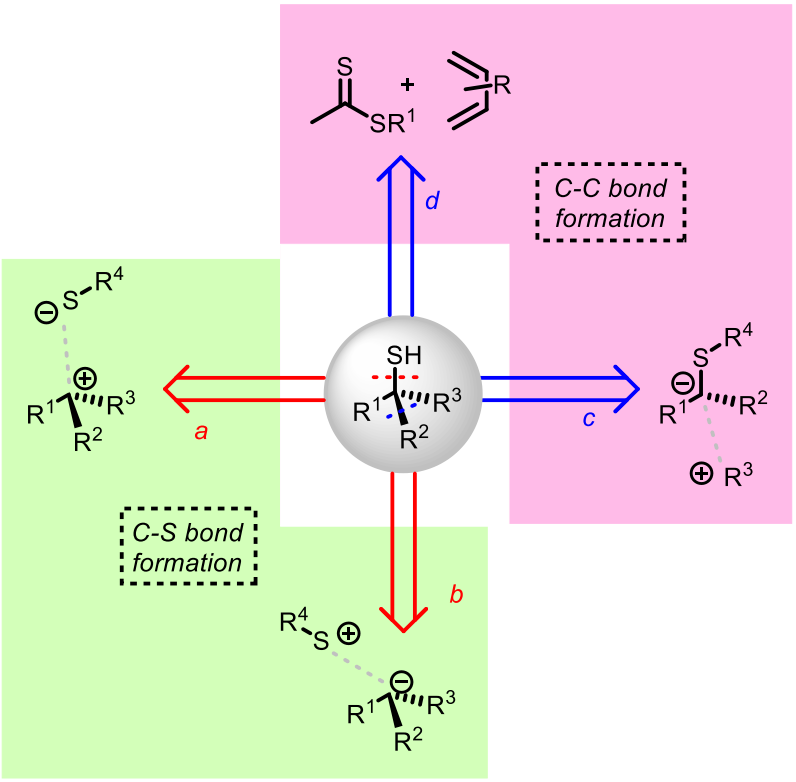


Scheme 1: Tertiary alcohol synthesis *via* nucleophilic addition to a ketone by asymmetric induction.

Unfortunately, the analogous reaction with a thioketone is challenging due to its instability and the preferential nucleophilic reaction at the sulfur heteroatom rather than the carbon centre.[30] The lack of synthetic protocols to access enantiopure tertiary thiols renders any developments to access such molecules highly beneficial for the advancement of synthesis in chemistry.[7]

1.1.2. Disconnections in the Synthesis of Tertiary Thiols

The majority of literature surrounding the synthesis of asymmetric tertiary thiols considers one of four retrosynthetic disconnections: (a) C-S bond formation by thio-nucleophile addition to a tertiary carbon centre, (b) C-S bond formation by electrophilic sulfenylation,[31–35] (c) C-C bond formation by electrophilic addition to a secondary thiol derivative, or (d) C-C bond formation by addition to a C=S bond[36] (Scheme 2). Many of the above routes utilise organo- or metal-based catalysts. Whilst disconnections (a), (b) and (c) have been plenty explored, (d) is a lesser-developed method for the synthesis of tertiary organosulfur molecules. This chapter will discuss literature methods based upon disconnections (a) and (c), as these are the most relevant to this chapter.



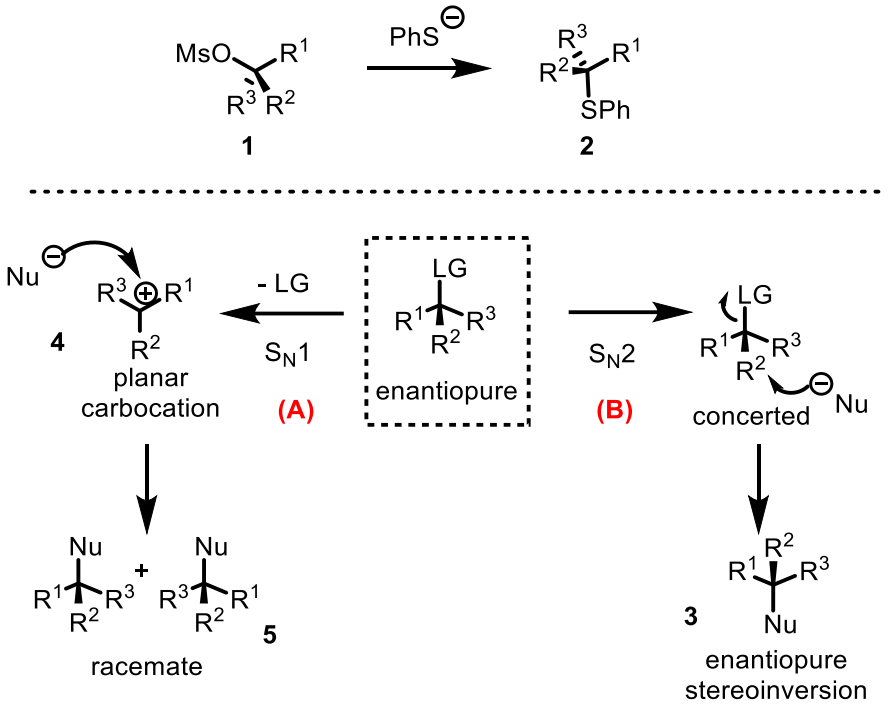
Scheme 2: Retrosynthetic analysis of tertiary thiols.

1.1.3. Tertiary Thiols *via* Carbon-Sulfur Bond Formation (a)

The vast majority of methods for the asymmetric formation of carbon-sulfur bonds produce only secondary stereocentres, despite great advances in the field over the last decade.[37] For comprehensive reviews on this topic please refer to the referenced articles.[38] The processes for carbon-sulfur bond formation in the synthesis of tertiary thiols can be simplified into two reaction types: **S_N2 reaction** and **conjugate addition.**

1.1.3.1 S_N2 Sisplacement by Thiol Derivatives

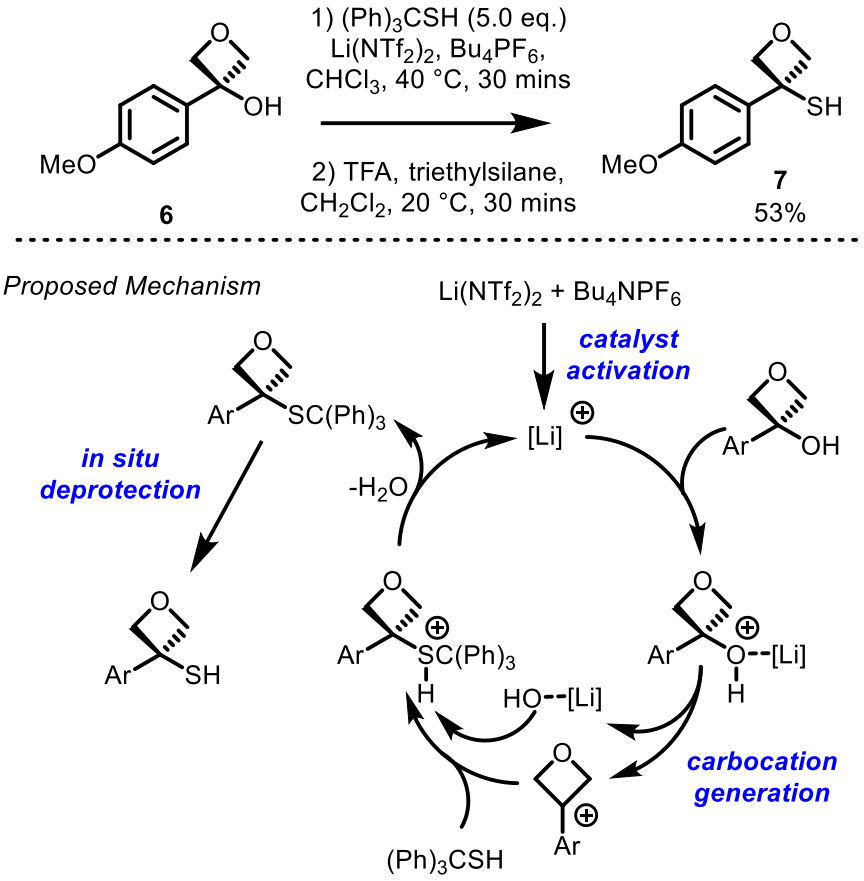
It could be envisaged that a thiol nucleophile, such as phenyl thiolate, could stereospecifically attack a quaternary carbon centre **1** with the explusion of a mesyl group (a good leaving group), resulting in inversion of stereochemistry to give product **2** (Scheme 3).



Scheme 3: S_N2 reaction pathway vs S_N1.

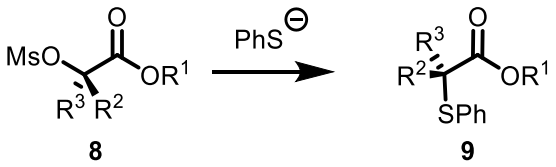
This type of S_N2 reaction pathway (B) would provide a facile way to construct enantiopure tertiary stereocentres **3**. Typically, steric congestion hinders nucleophilic attack at quaternary centres and the tendency for such carbon centres to form carbocations would facilitate a S_N1 reaction pathway (A) over S_N2 (B). In turn the generation of a formal (planar) carbocation **4** would destroy the carbon stereogenic centre, therefore giving rise to racemic product **5** (Scheme 3).

Consequently, there have been reports that utilise this S_N1 pathway to access tertiary thiols from tertiary alcohols **6**, albeit achirally, through the abstraction of the hydroxy group. The lithium-catalyzed alkylation of thiol **7** for the synthesis of 3-sulfanyl-oxetanes reported by Bull and co-workers is an example of such a process (Scheme 4).[39,40]



Scheme 4: Bull's synthesis of tertiary thiols using tertiary carbocations.

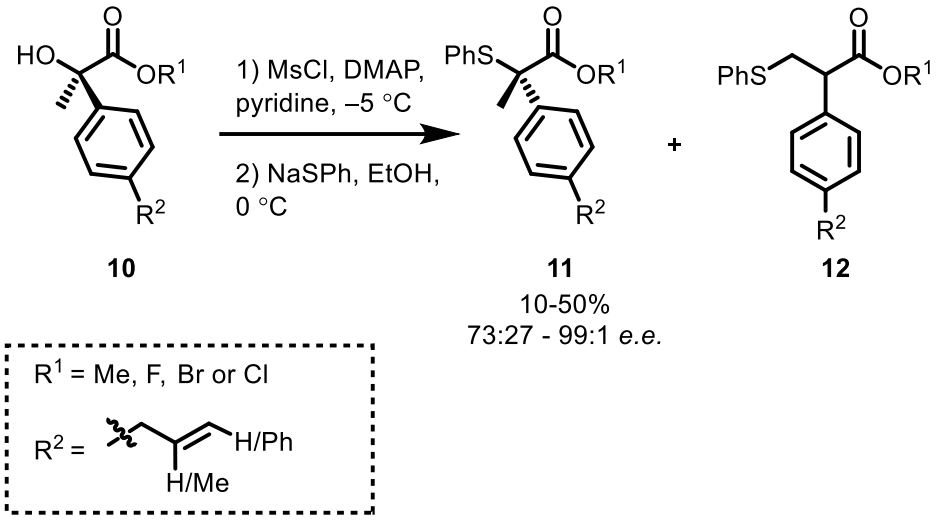
There have been reports of successful S_N2 reactions at quaternary stereocentres, such as the reaction of thiophenol with α-mesylate esters **8** with displacement of the mesyl group to give **9** (Scheme 5).[41] The presence of the electron-withdrawing ester group prevents the competing S_N1 pathway by destabilising carbocation formation. In addition, the lack of steric congestion in these molecules, owing to the adjacent sp^2 centre, promotes S_N2 attack by the thiophenolate nucleophile.



Scheme 5: α-mesylate esters in S_N2 reactions for the synthesis of quaternary stereocentres.

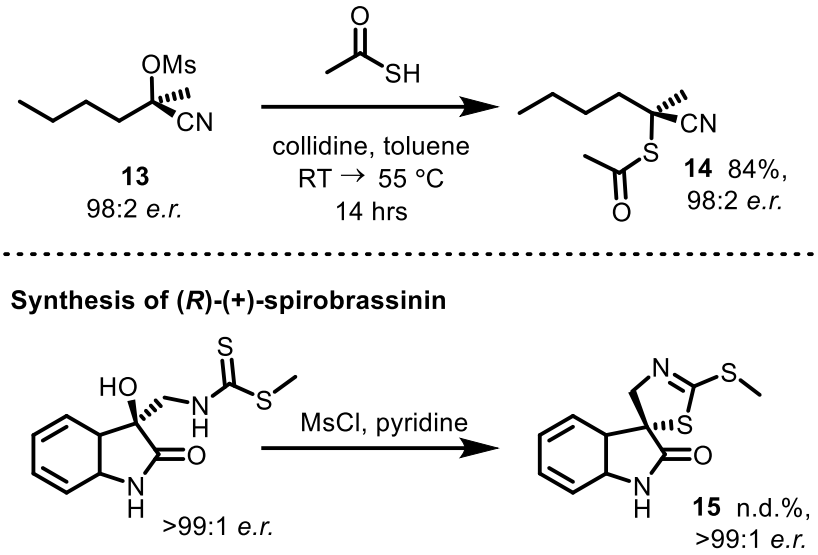
Unfortunately, Tunge and co-workers found that this approach was not applicable to all substrates.[41] In the case of α-aryl-α-hydroxy esters **10**, this reaction gave products **11** in poor yield and poor to high enantioselectivities (Scheme 6). A mixture of competing β-thioether **12**

side-product was also obtained, resulting from the elimination of the thiophenolate to form the α,β-unsaturated ester, which underwent conjugate addition. The activated alcohol intermediate is also prone to S_N1 dissociation, which accounted for the poor enantiomeric ratio obtained in the desired product. Better results were achieved by exchanging *α*-aryl-*α*-hydroxy for *α,α*-dialkyl hydroxy esters.



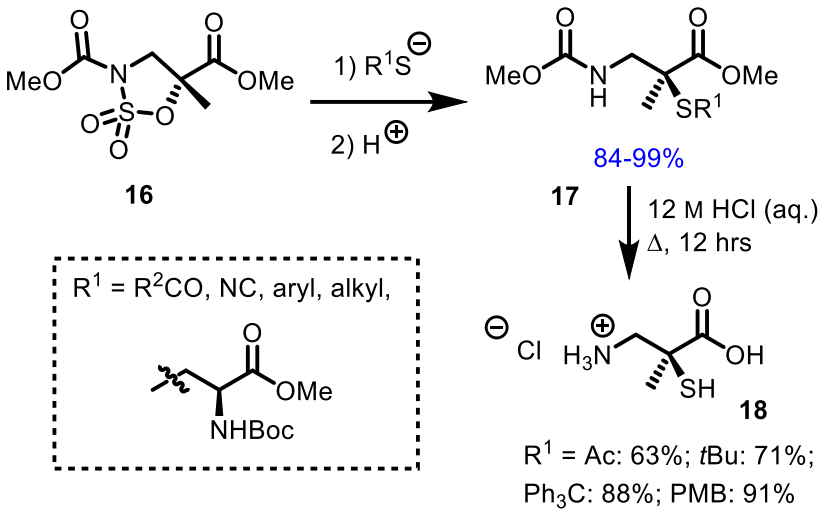
Scheme 6: *α*-mesylate esters in S_N2 reactions with competing product formation.

Similarly, *α*-(sulfonyloxy)nitriles **13** can also undergo a S_N2 reaction with thioacetic acid, with displacement of the mesyl group, in good yield and enantioselectivities to produce acetyl protected **14** (Scheme 7).[42] However, some of these reactions were very slow; using potassium thioacetate/DMF after 72 hours gave 35% conversion. This was circumvented by conducting the reaction in toluene at 55 °C. This methodology was successfully applied to the enantioselective synthesis of the natural product spirobrassinin[43] **15** (Scheme 7), which contains an enantioenriched thioether motif.



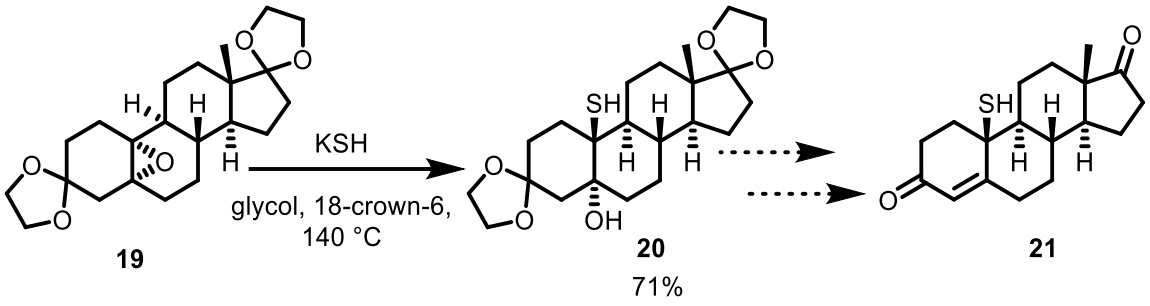
Scheme 7: Displacement of a mesyl group in tertiary cyanohydrin **13** and total synthesis of (*R*)-(+)-spirobrassinin **15**.

Peregrina *et al.* redeveloped this methodology for the synthesis of functionalised *β*-amino acids (Scheme 8).[44–46] Here the intramolecular ring opening of sulfamidate **16** by nucleophilic S_N2 displacement used a range of thiolate nucleophiles, acid-cleavage of the sulfonamide bond furnished enantioenriched thioether **17**. Subsequent carbamate hydrolysis by reflux under acidic conditions gave thioether *β*-amino acid **18**. In cases where the thiolate R group was acid-labile, such as with an acetate, *t*butyl, trityl or PMB group, the use of acid reflux furnished the thiol derivative.



Scheme 8: Peregrina's synthesis of *β*-amino acids.

A similar S_N2 epoxide ring opening strategy was explored by Nelson and co-workers, for the synthesis of tertiary thiols, in their synthesis of 10*β*-thiol analogue of androstenedione **21** (Scheme 9).[47] Here, a strained epoxide **19** in a steroidal system under basic conditions facilitated nucleophilic potassium hydrosulfide addition to furnish tertiary enantiopure thiol **20**, which was then further manipulated to access the desired natural product **21**.

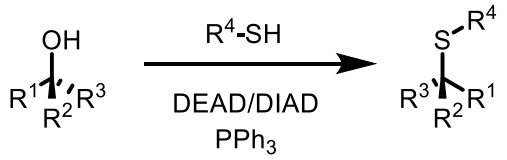


Scheme 9: Nelson's androstenedione synthesis.

Similar ring opening strategies have also been reported by other groups.[48–52] The methods discussed so far cannot be used generally for the synthesis of simple enantioenriched tertiary thiols. The substrate functional group pre-requisite, such as an adjacent electron-withdrawing group or strained system, means that only a certain class of sulfur-containing molecules can be synthesised through these protocols.

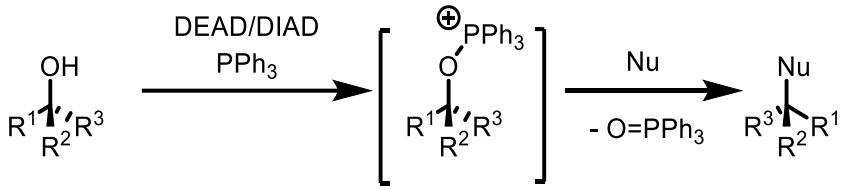
1.1.3.2. The Mitsunobu Reaction

In 1967, Mitsunobu and co-workers reported a method to convert primary and secondary alcohols into different functional groups. By activating the alcohol group to inversive S_N2 displacement using DIAD/DEAD and triphenylphosphine, simple, non-activated alcohols can be functionalised through this protocol (Scheme 10).[53]



Scheme 10: Mitsunobu reaction employing thiol nucelophiles.

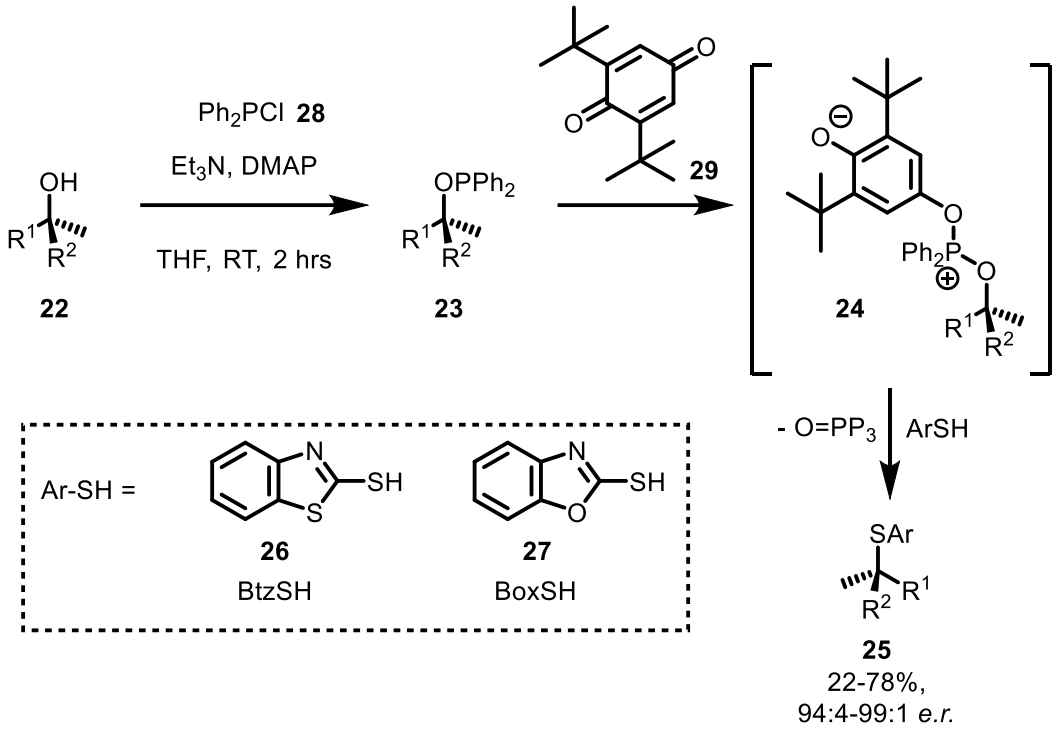
This reaction provides a powerful tool to create carbon-heteroatom stereocentres and, as a result, many ethers, azides, amines and thioethers have been prepared using this approach (Scheme 11).[54,55] The mild reaction conditions and wide substrate scope tolerance makes the Mitsunobu reaction versatile.



Scheme 11: Mitsunobu reaction to convert tertiary alcohols.

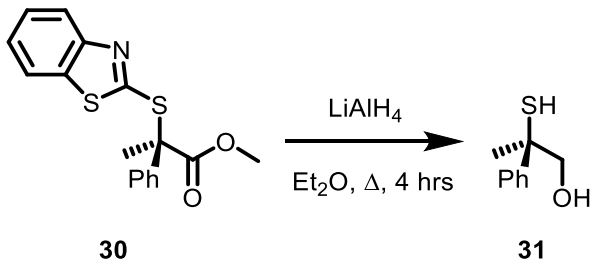
The ease in synthesis of enantioenriched alcohols and their abundance in natural products makes their conversion to tertiary thiols a viable synthetic route. However, the reaction is sensitive to steric crowding thus the synthesis of tertiary thiols *via* this route is often not feasible.

More recently, the Mukaiyama group has reported several modified Mitsunobu reactions, expanding the substrate scope and allowing access to tertiary thiol derivates, with inversion of stereochemistry with respect to the starting alcohol.[56,57] In this modified procedure, DIAD and triphenylphosphine are replaced by benzoquinone derivate **29** and chlorodiphenylphosphine **28** respectively. A stereodefined tertiary alcohol **22** is reacted with chlorodiphenylphosphine, using DMAP and trimethylamine to generate phosphinite **23** (Scheme 12). Subsequent oxidation of phosphinite **23** by **29** gives intermediate **24**, followed by nucleophilic S_N2 substitution by the thiol derivate **26/27** to give product **25** in high enantioselectivity.



Scheme 12: Mukaiyama-modified Mitsunobu reaction.

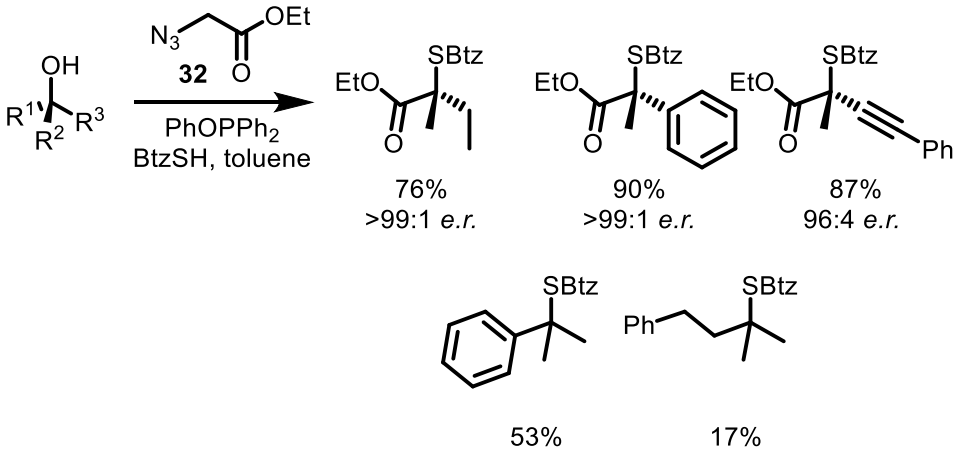
The Mukaiyama protocol provides a route for stereodefined hindered tertiary alcohols to be converted to the corresponding thiol derivatives with stereoinversion. A range of alcohol substituents (alkyl, alkenyl, aryl and esters) are tolerated, producing corresponding thioethers in excellent yields. The reaction of simple alkyl alcohols, however, is less successful, as this chemistry requires an α-ester group for the reaction to produce positive results. Usefully, the BtzSH **26** group can be reduced using lithium aluminium hydride and so, thioether **30** can be unmasked to give the free thiol **31** (Scheme 13).[57]



Scheme 13: Reduction of a BtzSH group to unmask a thiol.

This methodology was further simplified to a one-pot methodology to access tertiary thiols, by using phenoxydiphenylphosphine to prepare the intermediate phosphinite.[58] Both azide **32** and

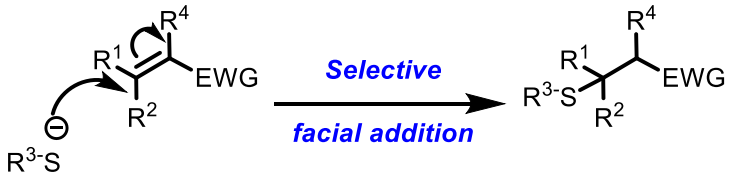
benzoquinones DBBQ, DMBQ and DMOBQ were used as oxidising agents in this protocol (Scheme 14). The reaction mechanism is analogous to that discussed before. A range of tertiary alcohols was successfully employed in the substrate scope of this protocol.



Scheme 14: One-pot optimised Mitsunobu (Mukaiyama).

1.1.3.3. Michael Addition

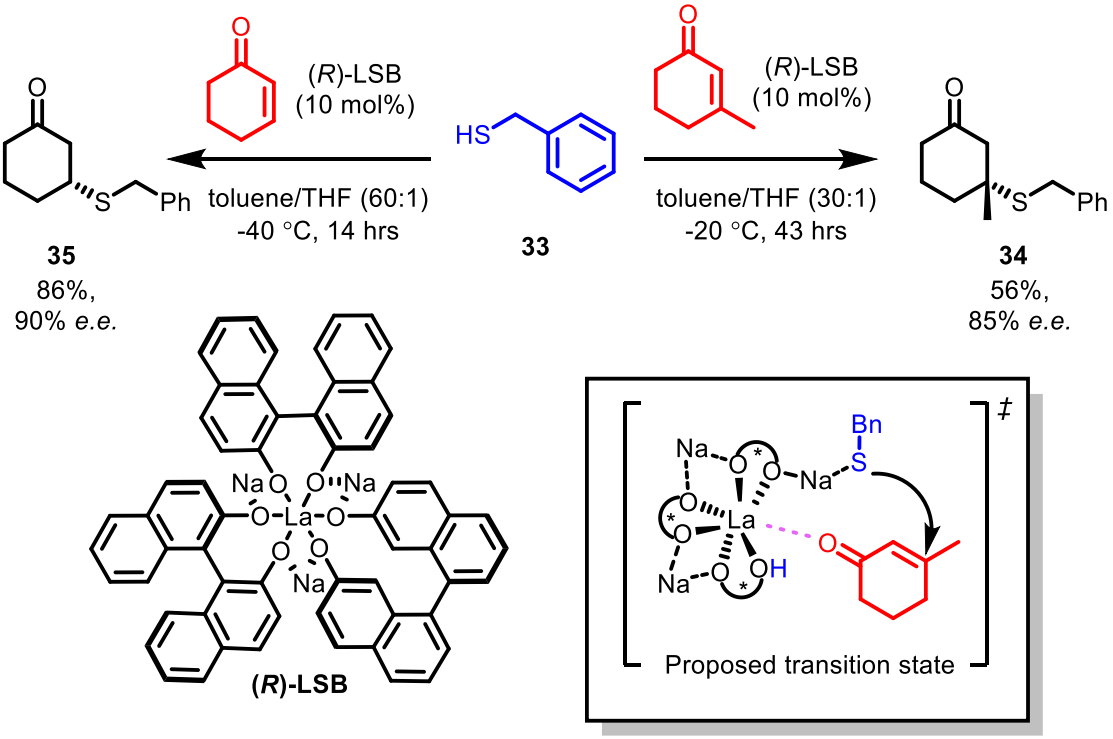
Another route to access tertiary thiols is through conjugate addition (Michael reaction) of a thiol nucleophile to a *β,β*-disubstituted olefin, pending an electron withdrawing substituent, through facially selective nucleophilic addition (Scheme 15). The facial selectivity can be achieved through intra or intermolecular control (substrate control) or using a chiral auxiliary.[59]



EWG	$R^{1/2}$	R^3	R^4
NO_2, CF_3, O^tBu, Aryl, Oxazolone, Imidazole	Aryl, Alkyl, TBSO, NHBoc,	Aryl, Alkyl, Ester, Amide,	H, Me, Ph

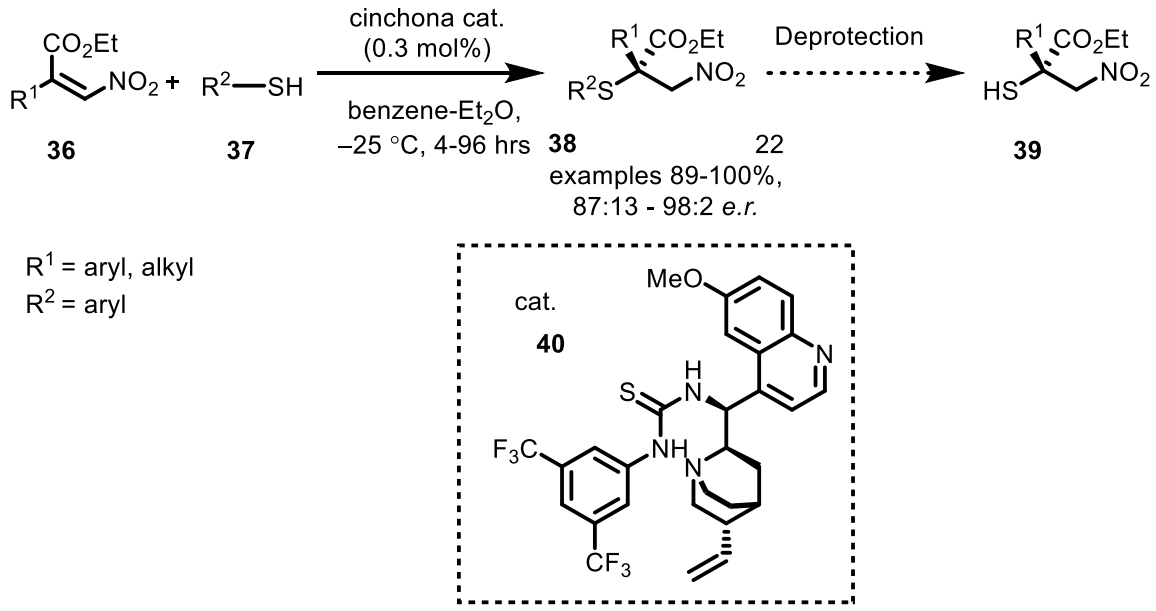
Scheme 15: Michael Addition of a thiol nucleophile to an electron deficient alkene.

However, the limited literature precedent of asymmetric tertiary thiols synthesised by this method can be attributed to the challenges in controlling the stereoselective addition and the poor reactivity of *β,β*-disubstituted olefins to nucleophilic addition.[59,60] This results in both poor product yield and *e.r.* Additionally, a competing addition-elimination pathway produces a mixture of stereoisomers. These issues were exemplified by Shibasaki and co-workers when exploring the conjugate nucleophilic addition of thiols **33** to cyclic enones. With *β*-methylated substrate the product yield and *e.r.* of **34** were lower than when non-*β*-substituted enone was used to synthesise **35** (Scheme 16).[61]



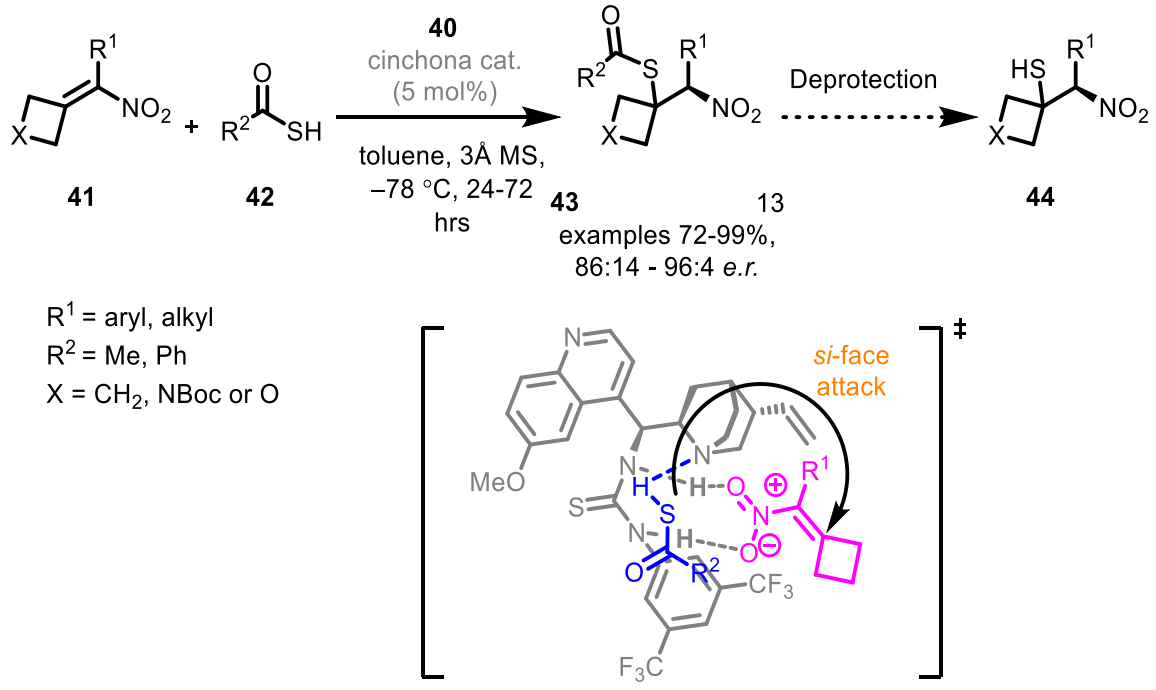
Scheme 16: Shibasaki's Michael Addition of a thiol nucleophile to an alkene.

Subsequently, in 2009 Xiao and co-workers reported the organocatalytic enantioselective sulfa-Michael addition reaction of thiols **37** to *β,β*-disubstituted nitroacrylate **36** to generate tertiary *α*-ester *β*-nitrosulfides **38** in near quantitative yields with high *e.r.* (Scheme 17).[60] The reaction utilised a bifunctional cinchona-derived thiourea organocatalyst **40**. The products from these reactions were carried forward towards the synthesis of *α*-thio-*β*-2,2-amino-acids **39**, which are biologically important molecules.[44,45]



Scheme 17: Xiao's enantioselective Michael Addition of a thiol nucleophile to a *β,β*-disubstituted nitroalkene.

More recently, Ellman and co-workers reported a catalytic enantioselective Michael Addition of a thiol **42** to a trisubstituted nitroalkene **41** using the same cinchona-derived catalyst **40**, giving rise to 1,1-disubstituted cyclobutanes, azetidines and oxetanes **43** in excellent enantioselectivity. In this case, the chiral centre resides on the nitro group carbon (Scheme 18).[62]



Scheme 18: Ellman's Michael Addition of a thiol nucleophile to a trisubstituted nitroalkene.

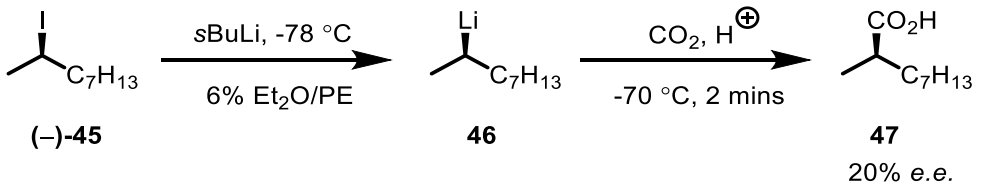
1.1.4. Tertiary Thiols *via* Carbon-Carbon Bond Formation (c)

Previous advancements in carbon-carbon bond formation in organic synthesis have led to the awarding of the Nobel Prize in Chemistry, in 2010.[63] However, carbon-carbon bond formation with absolute control of stereochemistry still remains remains a challenging theme and it has not been fully solved.

Carbon-carbon bond formation requires a difference in electron density between the bonding atoms, such that one of the two carbon atoms is relatively more electron-rich and the other more electron-deficient by comparison, which can be influenced by the presence of functional groups on the carbon atoms.

Developments in organometallic chemistry, starting with Grignard reagents in 1900, have provided a novel source of carbon nucleophiles suitable for synthesising carbon-carbon bonds. This field has since expanded to accommodate the enantiospecific construction of carbon bonds at stereogenic carbon centres.[64]

Organolithium reagents, with a carbon-lithium bond, have played a key role in this field. In 1950, Letsinger and co-workers reported the first enantioenriched organolithium, and established a new era of chiral organometallic reagents for use in organic synthesis.[65] Here, they reported an enantioenriched organolithium reagent **46**, generated by lithium-iodine exchange of (–)-2-iodononane **45** at –70 °C in petroleum ether/diethyl ether mixture (Scheme 19). The subsequent electrophile trapping with carbon dioxide afforded (–)-2-methylnonanoic acid **47** in 20% *e.e.*[65] The use of polar solvents or higher reaction temperatures reduced the optical activity of the product due to enhanced racemisation of the organolithium intermediates.

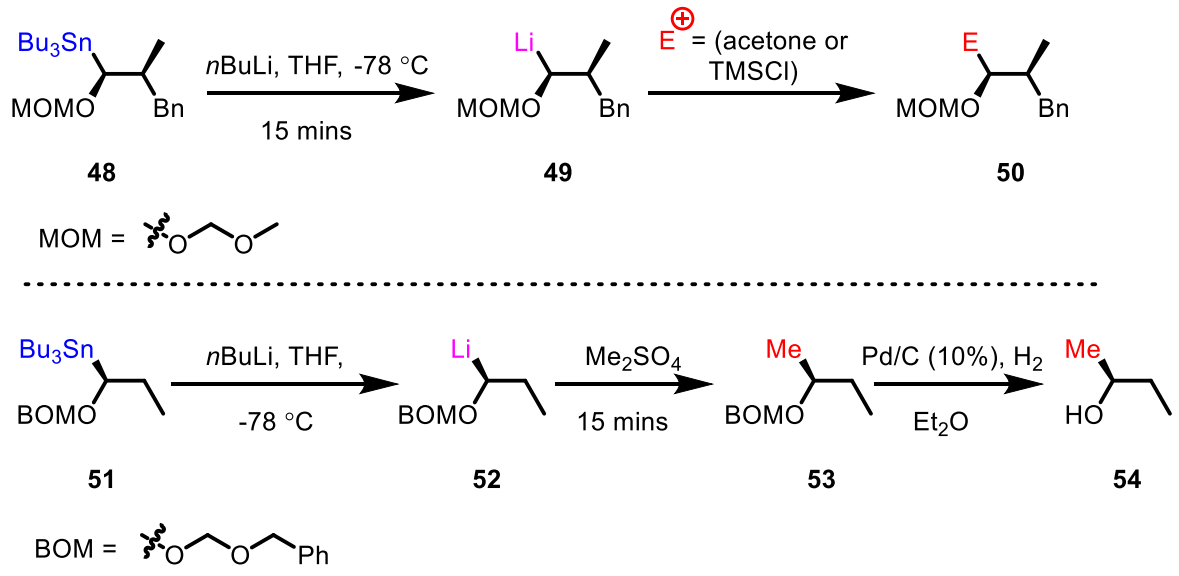


(–)-45 **46** **47** 20% *e.e.*

Scheme 19: Letsinger's synthesis of the first enantioenriched organolithium.

Subsequent studies by Nozaki and co-workers showed that deprotonation of ethylbenzenes in the presence of *n*BuLi/(–)-sparteine followed by electrophilic trapping furnished enantioenriched products, albeit with poor selectivities.[66] A Hoffmann test of this substrate showed the intermediate organolithium to be configurationally labile (see § 1.1.4.4.).[67]

It was not until the 1980s when the first configurationally stable *α*-alkoxyorganolithiums **49** were reported by Still and co-workers (Scheme 20).[68] Here, dipole- and *α*-heteroatom-stabilised lithium carbenoids were generated from tin-lithium transmetalation of **48** and were shown to retain stereochemical information for several minutes at -78 °C, followed by trapping with acetone or trimethylchlorosilane, to give the corresponding enantioenriched product **50**. In addition, the stereoretentive methylation of *α*-alkoxyorganolithium **52** (derived from **51**) with dimethyl sulfate to generate enantiopure 2-butanol **54** (referenced with (*R*)-2-butanol) through the deprotection of **53** was also reported.

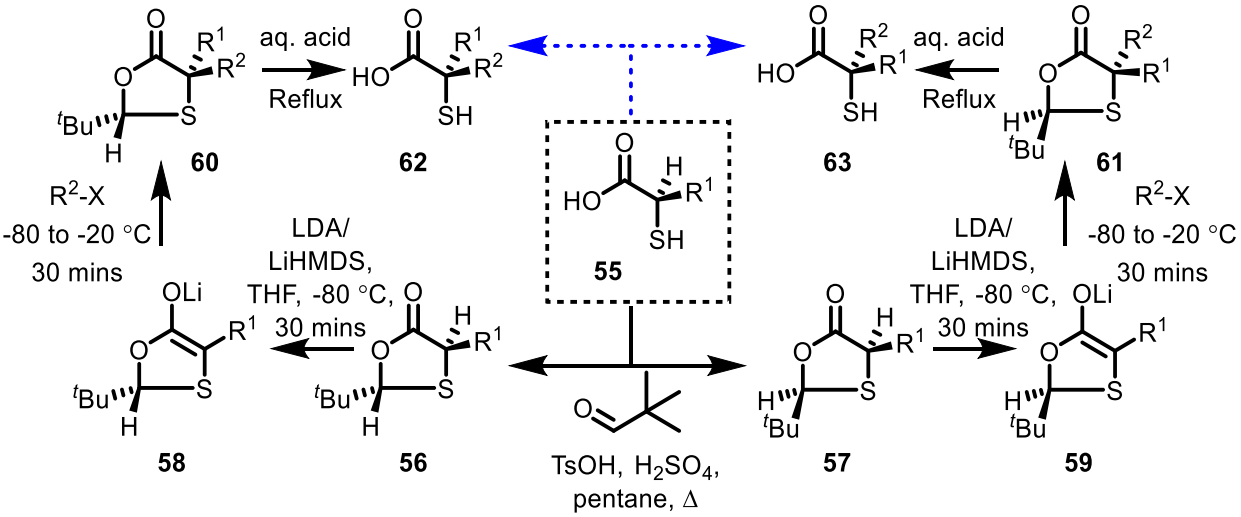


Scheme 20: *α*-Alkoxyorganolithiums in stereospecific alkylation reactions.

In recent years, the development of chiral *α*-heteroorganolithium reagents (*α*-O, *α*-S, *α*-N and *α*-Se) has provided a powerful tool for the stereospecific synthesis of enantioenriched alcohols, thiols, amines and selenides.[69,70] For these reactions to be successful, the enantioenriched organolithium reagent must be configurationally stable.

1.1.4.1. Electrophilic Trapping of *α*-Thioenolates

Kellogg and co-workers explored the alkylation of *α*-thioenolates *via* diastereoselective control to access enantioenriched thioethers, which were subsequently cleaved by acid hydrolysis to produce the first general method for the synthesis of enantiopure tertiary thiols **62** and **63** (Scheme 21).[71]

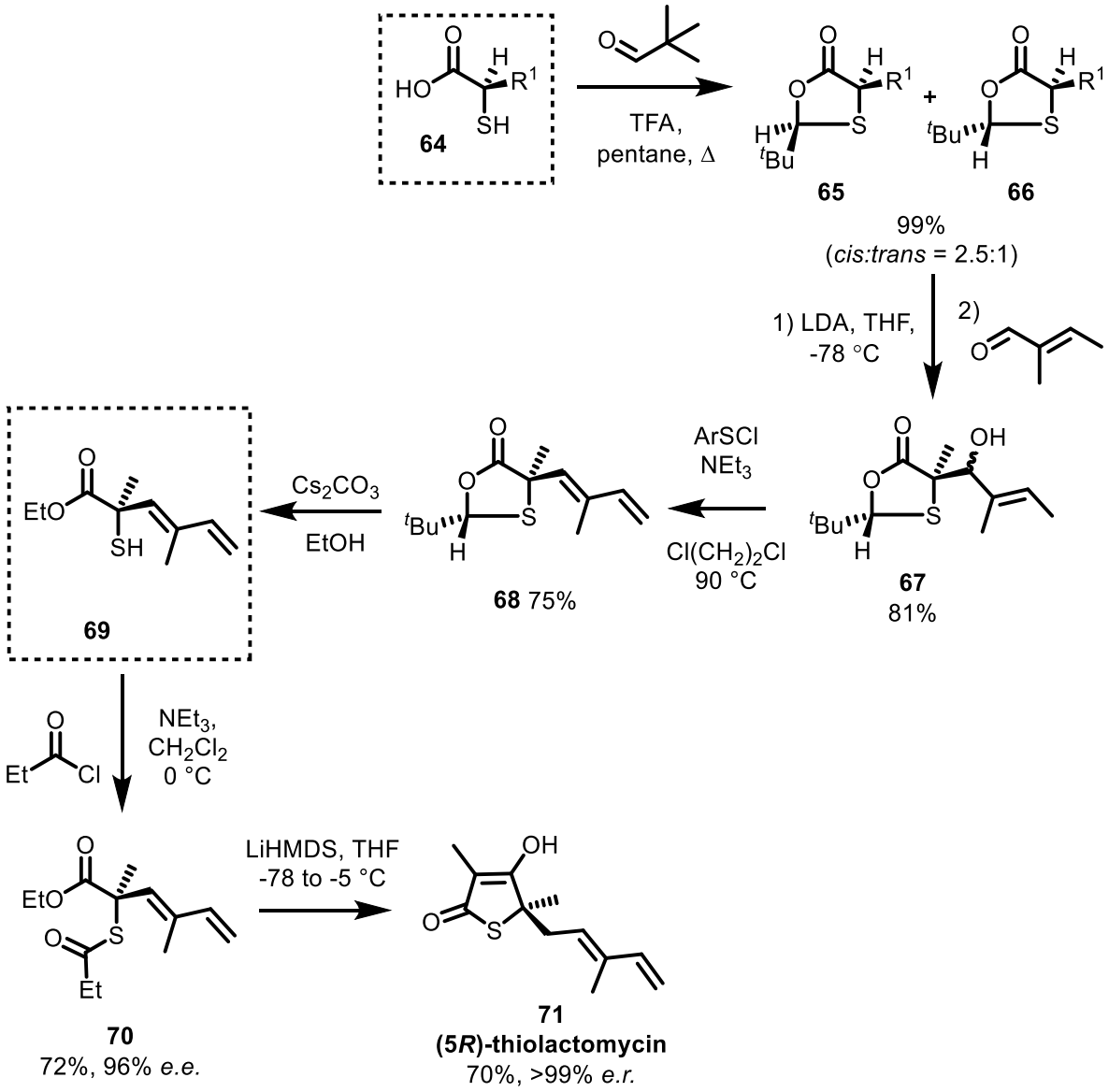


Scheme 21: Kellogg's diastereoselective alkylation of *α*-thioenolates.

Using conditions reported by Seebach, the authors synthesised 1,3-oxathiolan-4-one diastereomers *trans*-**56** and *cis*-**57** (50-92%), through a condensation reaction between pivaldehyde and *α*-thiocarboxylic acid **55**.[71] The reaction proceeded with preferential diastereoselectivity for the *cis*-**57** isomer (2:1 to 8:1 *cis:trans* selectivity), and the product could be further enriched by recrystallisation to exclusively obtain the *cis* product. Subsequent deprotonation, using a lithium base (LDA or LiHMDS) at -80 ˚C, of the *trans*-**56** and *cis*-**57** diastereomers gave enolates **58** and **59**, respectively. Based on Seebach's theme of "self-regeneration of chirality" in which producing the enolate destroys the *α*-stereocentre, this stereocentre is regenerated upon alkylation of enolates **58** and **59** to furnish product **60** and **61** in excellent diastereoselectivity 60-92%, *d.r.* 80:20 to >99:1).[72] The diastereoselectivity in this reaction is controlled by steric bias of the distil *t*butyl stereocentre, which forces the incoming addition to take place on the opposite face to the *t*butyl group. It should be noted that enolates **58** and **59** are sensitive intermediates and therefore limit the electrophile scope; whilst alkyl and benzyl halides were competent electrophiles giving the desired product in high yields and diastereoselectivity, aldehydes and unsymmetrical ketones proved more challenging, with

lower yields and diastereoselectivity. Finally, acid hydrolysis of alkylated oxathiolanones **60** and **61** produced enantioenriched chiral tertiary α-mercaptocarboxylic acids **62** and **63** (≥78% *e.e.*).

Townsend *et al.* utilised this methodology by for the synthesis of (5*R*)-thiolactomycin **71** with >99:1 *e.r.* (Scheme 22),[73] a naturally occurring antibiotic active against mycobacteria. Condensation of thiol **64** with pivaldehyde produced *cis/trans* diastereomers **65** and **66** respectively, then diastereoselective addition of (*E*)-2-methylbut-2-enal to the *cis*-diastereomer **65** produced to produce allylic alcohol **67**.

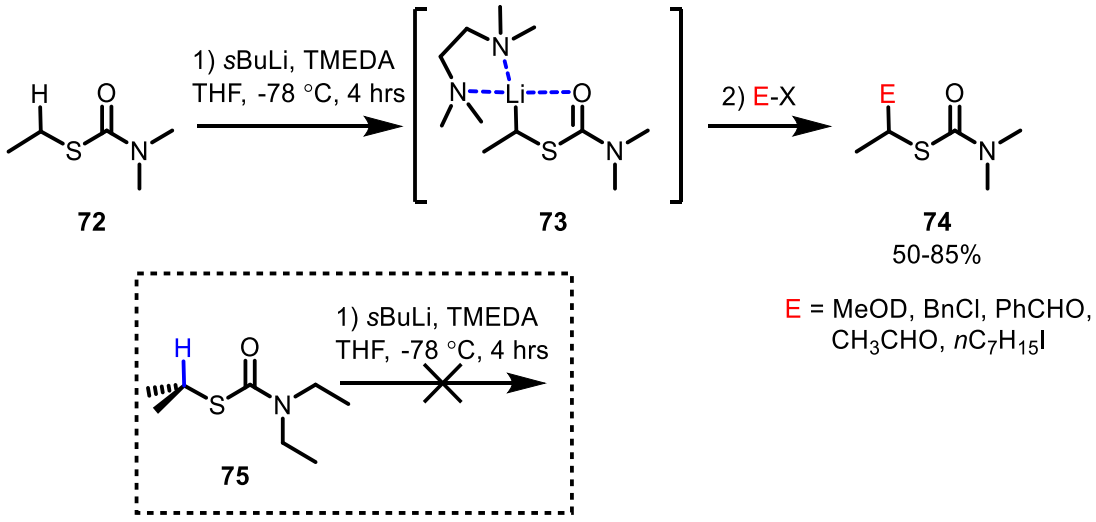


Scheme 22: Synthesis of (5*R*)-thiolactomycin.

The 1,4 dehydration of allylic alcohol **67** was achieved by using 2,4-dinitrobenzenesulfenyl chloride to generate a sulfenate ester intermediate which underwent a [2,3]-sigmatropic rearrangement to the allylic sulfoxide. Subsequently, a syn-elimination of the sulfoxide was achieved by heating the reaction mixture to produce 1,3-diene **68** in 75% yield. Finally, ring opening of oxathiolanone **68** generated thiol derivative **69**, which was not isolated due to issues with the stability of the thiol molecule. Instead, protection of thiol **69** as the acyl derivative **70** allowed isolation of the thioester, which was converted to the desired natural product (5*R*)-thiolacomycin **71** *via* a thio-Dieckman condensation reaction.

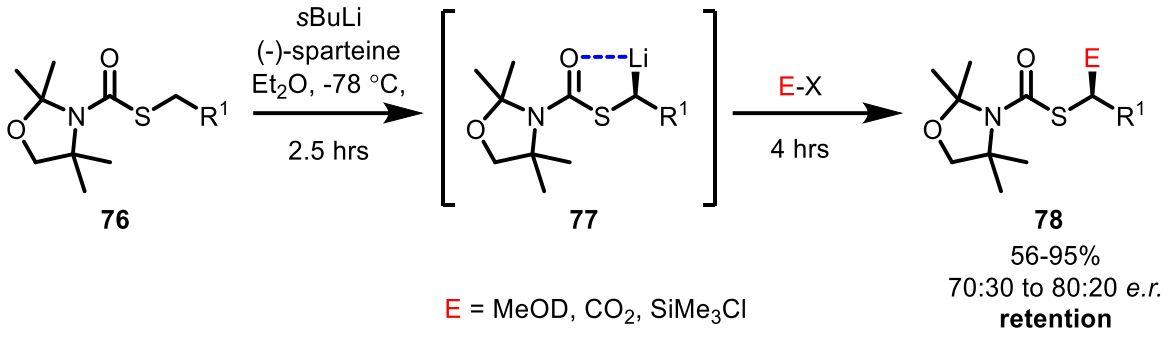
1.1.4.2. Lithiation of α-Thiocarbamates

Beak reported the first achiral deprotonation of primary alkyl thiocarbamate **72**, employing *s*BuLi/TMEDA, which generated lithiated species **73**, that were then trapped with various electrophiles to produce **74** in good to excellent yields (Scheme 23).[74] Beak also reported an attempt at deprotonating *S*-isopropyl *N,N*-diethylthiocarbamate **75** at –98 °C, but this proved unsuccessful. No further conditions were reported for this substrate.



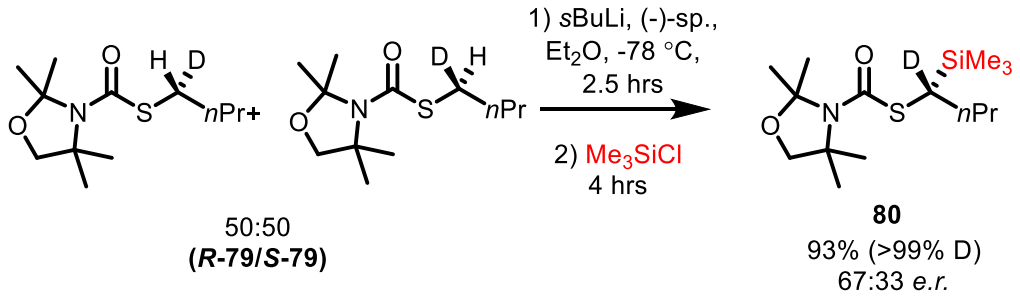
Scheme 23: Beak's study into primary α-lithiothiocarbamate **72**.

Subsequently, Hoppe and co-workers reported the first primary α-lithiothiocarbamate **77**, *via* the stereoselective deprotonation of thiocarbamate **76** using *s*BuLi/(–)-sparteine (Scheme 24).[75] The α-lithiothiocarbamate **77** was trapped with various electrophiles to furnish secondary α-thiocarbamates **78** in poor to moderate enantioselectivity. Further studies to establish the cause of poor enantioselectivity found that the α-lithiothiocarbamate **77** was configurationally labile.



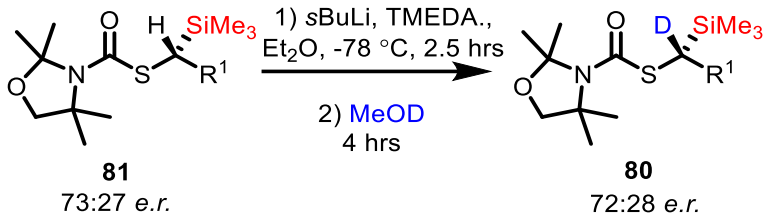
Scheme 24: Hoppe's study into lithiation-electrophile trapping of primary α-lithiothiocarbamate **77**.

To address this issue, Hoppe investigated the configurational stability of **77**. This was achieved through a kinetic H/D isotope labelling study, which had been previously reported on similar compounds.[76] A racemic mixture of **(*R*)-79** and **(*S*)-79** was lithiated with *s*BuLi/(–)-sp. and trapped with trimethylsilyl chloride (Scheme 25). The high deuterium incorporation yield (>99%) suggested that both enantiomers were lithiated, but the reaction outcome is non-racemic (**80** in 67:33 *e.r.*), confirming that lithiated thiocarbamate **77** was configurationally unstable.



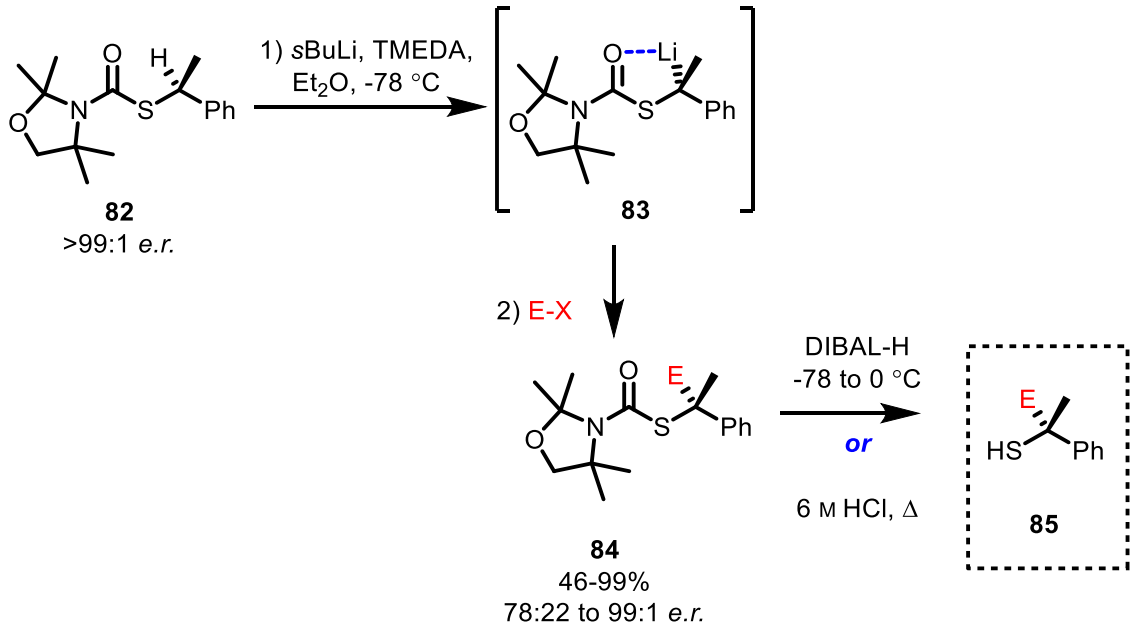
Scheme 25: Hoppe's study into the configurational stability of α-lithiothiocarbamate **77**.

To induce stability in the organolithium, the bulkier, secondary α-trimethylsilyl thiocarbamate **81** was prepared according to the above methodology in 73:27 *e.r.* and studies into the lithiation-deuteration of these species were conducted (Scheme 26). Due to a lack of enantiotopic protons, (–)-sparteine was not required and substituted for achiral TMEDA. After lithiation (2.5 hours) at -78 °C and deuteration, α-trimethylsilyl thiocarbamate **80** was obtained in 72:28 *e.r.*, with retention of configuration. This suggested that the intermediate organolithium was configurationally stable.



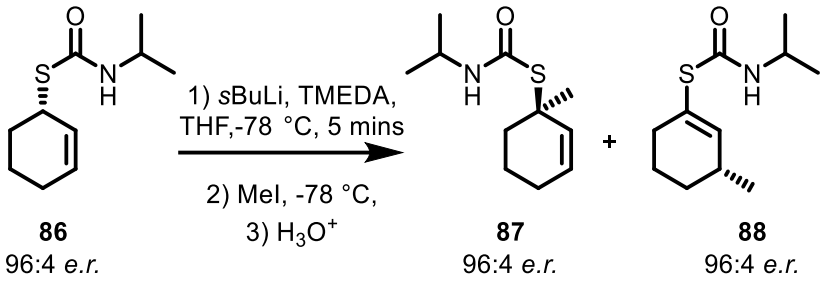
Scheme 26: Hoppe's study into secondary α-trimethylsilyl thiocarbamate **81**.

Successive lithiation-electrophile trapping studies of benzylic thiocarbamate **82** found that the corresponding thioorganolithium **83** exhibited exceptional macroscopic configurational stability and was successfully trapped with a range of electrophiles (Scheme 27).[77–79] The electrophile addition to produce **84** proceeded with retention of stereochemistry. Subsequent, DIBAL-H reduction or acid hydrolysis of the carbamate provided enantiomerically pure tertiary thiol **85**.



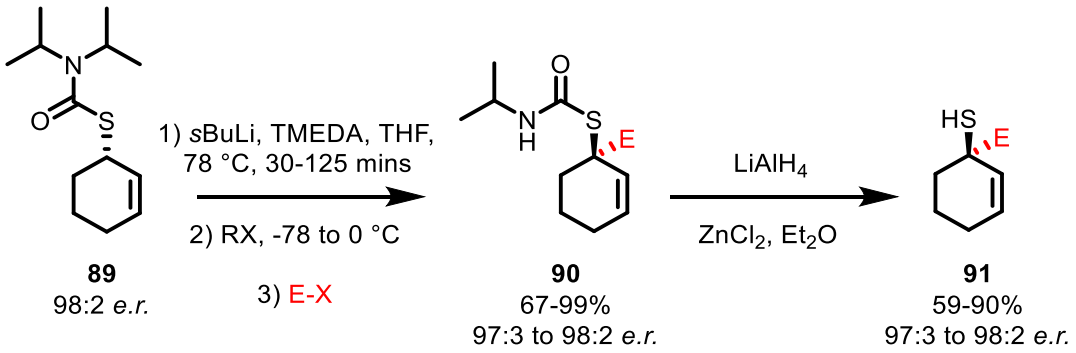
Scheme 27: Lithiation-electrophile trapping studies of benzylic thiocarbamate **82**.

Expanding upon this theme, Hoppe investigated cyclohexenyl thiocarbamate **86**.[80,81] Here cyclohexenyl organolithium was found to be configurationally stable at -78 °C in THF (not Et_2O as used before) and underwent reaction with methyl iodide to produce regioisomers **87** (21%) and **88** (41%) (Scheme 28). Interestingly, the reaction favoured γ-substituted product over α-substituted product. The α-substituted **87** product resulted in inversion of configuration.



Scheme 28: Lithiation-electrophile trapping studies of cyclohexenyl thiocarbamate **86**.

The regioselectivity issue was addressed by substituting the secondary amide for a tertiary amide. Here, it was found that a diisopropyl protecting group on **89** gave solely α-substituted **90** in excellent yield and *e.r.* (Scheme 29). The reaction proceeded with inversion of stereochemistry and the reaction scope tolerated a range of organohalides. Finally, reduction of **90** with lithium aluminium hydride furnished the desired tertiary thiols **91** in high *e.r.*

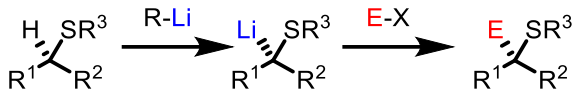


E = MeI, nC$_6$H$_{13}$I, BnBr, allyl bromide, (*E*)-(3-bromoprop-1-en-1-yl)benzene

Scheme 29: Modified lithiation-electrophile trapping studies of cyclohexenyl thiocarbamate **89**.

1.1.4.3. Lithiation of α-Thiolithiums and α-Thiobenzoates

In the previously discussed carbamate examples, the α-thioenolates required an α-carboxylic acid or ester moiety to be present for the reaction to procced. However, there have been studies into the lithiation of enantioenriched secondary thiol derivatives (Scheme 30), which provides a versatile route to stereodefined tertiary thiols.

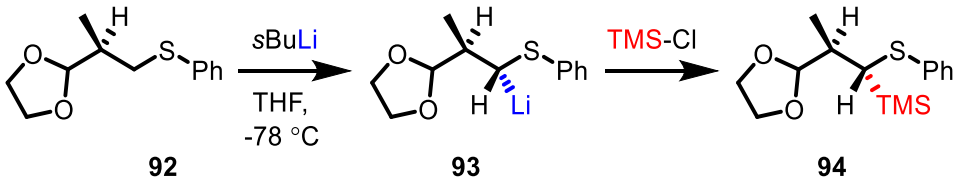


Scheme 30: Lithiation of enantioenriched secondary thiol derivatives.

Studies into the lithiation of α-oxylithium and α-aminolithium compounds by Hoppe and Beak, showed these class of molecules to be "macroscopically configurationally stable", ie. these organolithiums were stable after 10 mins.[82,83] As a result, there have been numerous studies into the lithiation of configurationally stable α-oxy-alkyl-[84], -allyl-[85–90], -cinnamyl-[91] and -benzyl-lithium[92] species, alongside α-lithiocyclohexylamine[93,94], α-amino-cinnamyl[93,95–97] and various other -allyl-lithium[98] species.

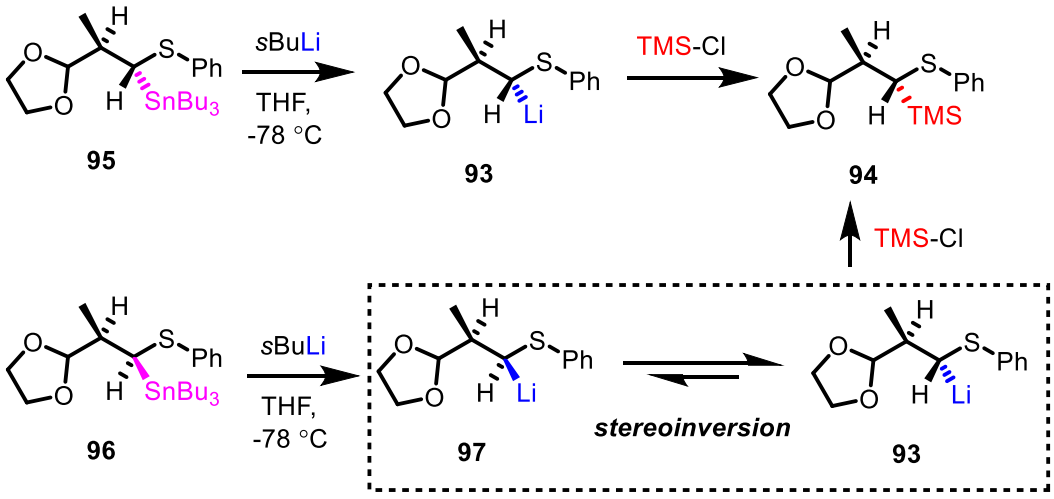
In comparison, studies into α-thioorganolithium species have been challenging, due to their configurational instability, even at temperatures as low as –80 °C. Therefore, these organolithium species are microscopically configurationally stable.

Studies by McDougal and co-workers showed that thioether **92** could be lithiated using *s*BuLi to form organolithium **93**, and then trapped by trimethylsilyl chloride in 98:2 *d.r.* to produce **94** (Scheme 31).[99]



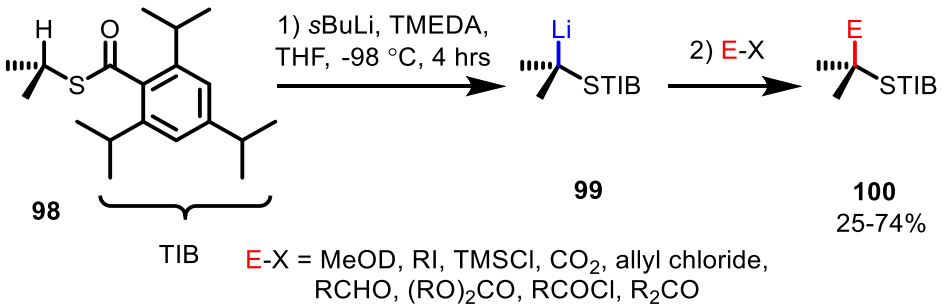
Scheme 31: McDougal's study into the lithiation-electrophile trapping of thioether **92**.

Interestingly, as shown in Scheme 32, when either diastereomer of enantioenriched thioether **95** and **96** underwent tin-lithium exchange at –78 °C to produce lithiated intermediates **93** and **97**, which underwent electrophilic trapping with TMSCl, only one diastereomer product **94** was obtained through either reaction. McDougal rationalised the difference in diastereomeric ratio between starting materials **95**/**96** and the product **94** was due to a thermodynamic equilibrium that leads to interconversion of diastereomer **97** into diastereomer **93**.[99]



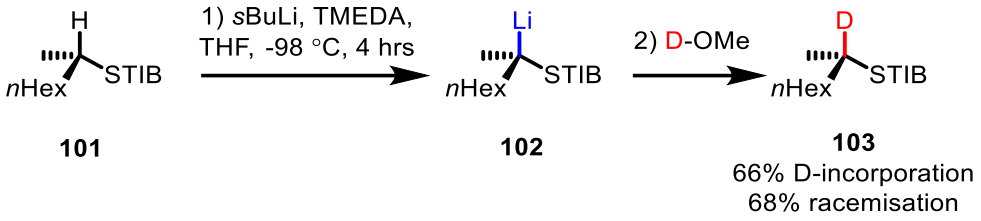
Scheme 32: McDougal's study of **94**.

Studies by Beak in the 1980's into the lithiation-electrophilic trapping of lithiated *α*-thiobenzoates proved somewhat challenging due to their configurational lability, unlike the *α*-thiocarbamate substrates discussed previously.[74] Though Beak studied the lithiation of *S*-methyl 2,4,6-trialkylthiobenzoate and *S*-ethyl 2,4,6-triethylthiobenzoate, but no asymmetric deprotonations have been reported for the latter. An interesting observation was the facile deprotonation of *S*-isopropyl 2,4,6-triisopropylthiobenzoate **98** (Scheme 33), in comparison to the analogous *S*-isopropyl *N,N*-diethylcarbamate.[74] The lithiated thiobenzoates **99** were successfully trapped with various electrophiles to give **100** in poor to good yields.



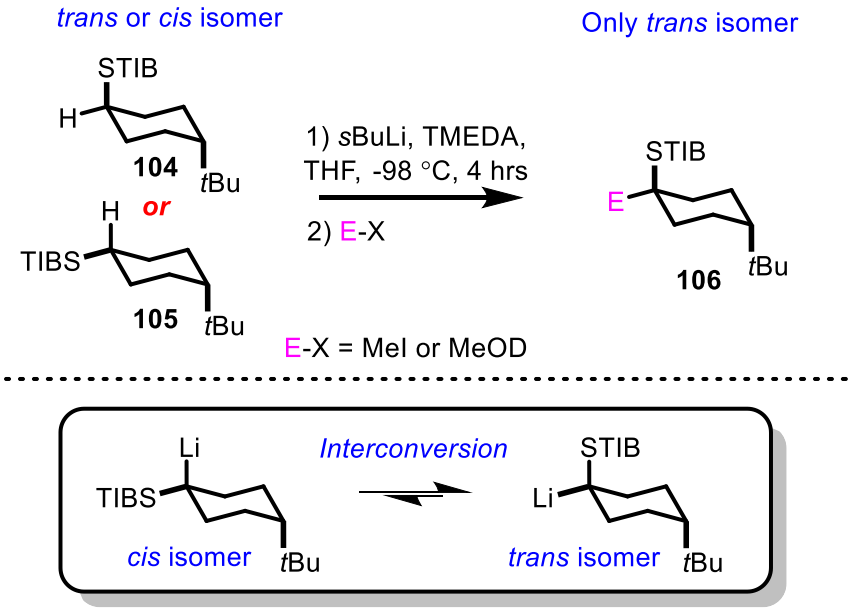
Scheme 33: Lithiation-electrophilic trapping of enantioenriched *S*-isopropy 2,4,6-triisopropylthiobenzoate **98**.

Attempts to render this reaction asymmetric were less fruitful (Scheme 34). Compound **101** was successfully deprotonated to give **102** and quenched with MeOD to give **103** with 66% deuterium incorporation and 68% racemisation (quantified using optical rotation). The authors did not explicitly state the exact enantiomeric ratios of the starting material or product.



Scheme 34: Reaction of enantioenriched S-thiobenzoate **101**.

Similar issues were encountered in the lithiation of *cis*- and *trans*- diastereoisomers of 4-*t*butyl--cyclohexyl 2,4,6-triisopropylbenzoates **104** and **105**, in which trapping with either MeOD or MeI gave only the trans product **106** (Scheme 35).[74] Based on these findings, Beak concluded that "*α*-lithio thioesters are configurationally equilibrated either in the formation of the lithiated species, in the intermediate organometallic, or in quenching the reaction."[74]



Scheme 35: Configurational lability of cyclohexyl *S*-thiobenzoates *cis*-**104** and *trans*-**105**.

However, many of Beak's conclusions in this study were based on incomplete results. For example, THF, the only solvent reported in this study, is known to decrease configurational stability of *α*-thioorganolithiums.[79] This is a reflection on the lack of reaction conditions explored in this study. In addition, by drawing on conclusions from primary *α*-oxo and *α*-amino organolithium studies, Beak assumed that the electrophile trapping step proceeds with retention

of configuration.[79] However, it has since been discovered that whether the trapping is invertive or retentive depends on the choice of electrophile.

These findings prompted further study into the configurational stability of *α*-thioorganolithiums to help understand the mechanism of epimerisation, as shown in the works of Reich and Hoffmann.[69,70]

1.1.4.4. Configurational Stability of α-Thioorganolithiums

The configurational stability of an enantioenriched organometallic species can be studied through the rate of inversion under specific conditions. This term is generally applied to a system under a specific temperature and timescale (microscopic and macroscopic), however other factors such as additives and solvents can affect the configurational stability of an organolithium species.[100] The microscopic stability of an organolithium species can be assessed by the time taken for the organometallic species to react with an electrophile. The Hoffmann test provides a practical method to assess the configurational stability of an organolithium.

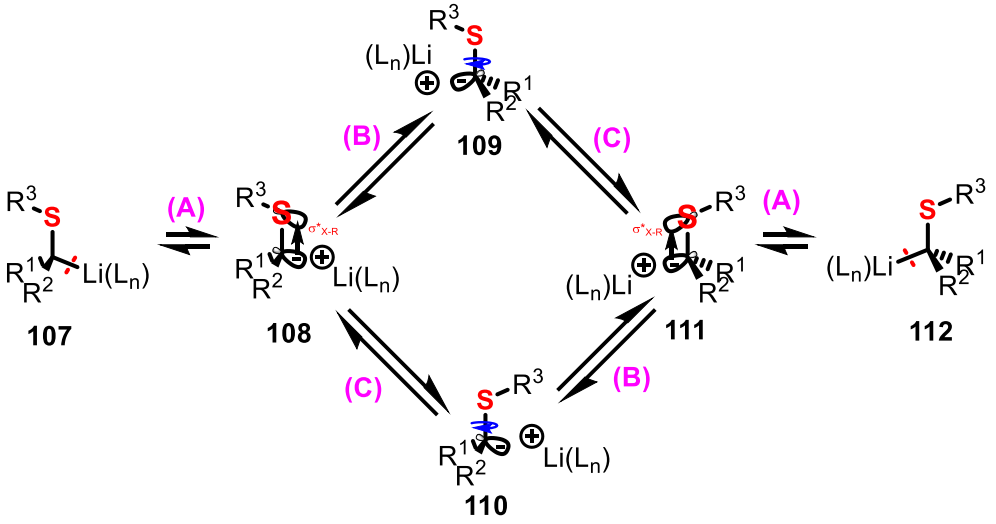
The Hoffmann test requires two separate experiments to evaluate the organolithium species. In the first experiment a racemic organolithium is reacted with an achiral electrophile to produce diastereomers, from which the kinetic resolution selectivity factor is ascertained. In the second experiment of this study, the same racemic organolithium is reacted with an enantiopure electrophile, ensuring that the reaction can reach completion. In the case of configurationally stable organolithium species the reaction outcome from the second experiment will result in a product with 50:50 *d.r.* However, if a non-identical product *d.r.* is obtained from the two experiments (i.e. not 50:50), then the organolithium species are deemed configurationally unstable, since the organolithium species have been kinetically resolved. If a distinct *d.r.* is obtained in both experiments then the organolithium is configurationally stable. These outcomes are relative to the timescale on which the reaction been conducted.

Understanding the mechanism of racemisation is difficult due to the multicomponent aspect of an apparently simple, single step process. Previous studies into the epimerisation of *α*-heterobenzyllithiums took into consideration the following factors: i) the nature of the heteroatom substituent, ii) the presence of intramolecular chelation stabilisation, iii) whether

carbanionic centre was secondary or tertiary, iv) the degree of carbanionic centre pyramidalisation, and v) the solvent.

However, subsequent work by Hoffman into the mechanism of enantiomerisation of *α*-thio (and *α*-seleno and *α*-telluroorganolithium) **107** and **112** suggested that the mechanism of racemisation can be broken down into three distinct steps:

A. Dissociation into solvent separated ion pair (**108** and **111**).
B. Inversion of the stereogenic carbanionic centre and rotation of the hyperconjugated sulfur–carbon bond at the carbanionic centre (**109** and **110**).
C. Recombination of the ion pair to give opposite enantiomer (**108** and **111**).



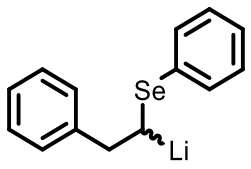
Scheme 36: Mechanism of racemisation of *α*-thioorganolithiums **107** and **112**.

As several groups reported, negative hyperconjugation also plays an important role in the racemisation of *α*-thioorganolithiums. It is necessary for the carbanionic centre lone pair to be *anti*-periplanar to the S-R bond, as shown in Scheme 36. This ensures the lone pair is delocalised into the $\sigma^*_{X\text{-}R}$-orbital. Therefore, during step B, where the carbanionic centre undergoes inversion, the C-S bond must rotate to ensure the *anti*-periplanar relationship is maintained.

The proposed mechanism outlined above was probed with further studies. Initially, *α*-selenoorganolithium **113** was used to elucidate the effects of solvent on the activation barrier

for racemisation. It was understood that co-ordinating solvents (such as THF) would stabilise the solvent separated ion pair and establish an equilibrium between the separated and contact ion pairs (Table 1).

Table 1: The energy barrier to racemisation of *α*-selenorganolithium **113** in various solvent systems.

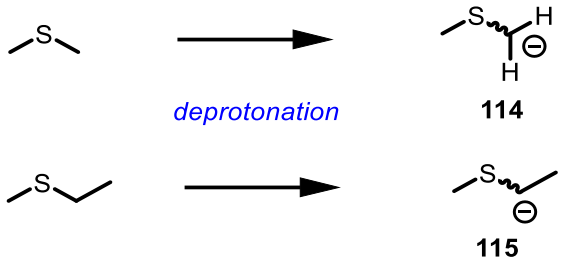


113

Solvent	$\Delta G^{\ddagger}$ (kcal/mol)
Et_2O	12.6
THF	12.5
Toluene + THF (1.0 eq.)	12.2
Toluene + THF (2.0 eq.)	11.8
Toluene + THF (3.0 eq.)	11.9

The energy barrier to racemisation ($\Delta G^{\ddagger}$) was calculated from the coalescence of the diastereotopic benzylic protons (^{1}H NMR) upon enantiomerisation. The authors screened ethereal solvents, such THF or Et_2O, and toluene:THF solvent mixtures (with 1.0-3.0 eq. THF) (Table 1). However, it was found that the choice of solvent had minimal effect upon the barrier to racemisation. These results led the authors to conclude that the rate-determining step was either carbanionic inversion or rotation about the C-Se bond.

Subsequent studies by various groups found the barriers to inversion of *α*-thiocarbanions to be low, with values for the carbanion of dimethyl sulfide[69] **114** and ethylmethyl sulfide[101] **115** measured at 0.5 and 1.1 kcalmol^{-1} respectively (Scheme 37). This led to the assumption that barrier to inversion was not the rate limiting step for racemisation.

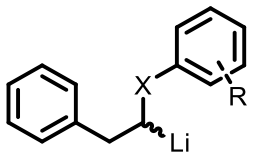


Scheme 37: Hoffman's study on α-thiocarbanions **114** and **115**.

As a result, further studies into the barrier to rotation about the C-S bond were explored. It was understood that if C-X (X = S, Se or Te) rotation was rate limiting, then the presence of bulky substituents on the heteroatom would further increase the barrier to enantiomerisation. Modelling studies of the minimum-energy conformation of phenylthio methyllithium suggested that the thiolithium had a planar geometry to allow for negative hyperconjugation (C-S) and sulfur lone pair delocalisation into the π^*-orbital of the phenyl group, rendering the molecule completely planar. During rotation about the C-S bond, the phenyl group is forced to rotate past either the carbanion hydrogen or the methyl group. However, in the latter, the *syn*-pentane interaction between the methyl and aryl group forces rotation about the *S*-phenyl bond. This disrupts the n-π^* delocalisation and raising the barrier to rotation. On this basis, a substituted aryl ring would further raise the barrier to rotation and therefore increase the barrier to racemisation.

To probe this hypothesis, various α-thio, α-seleno and α-telluroorganolithium derivatives **116** bearing aryl group that possessed various steric substitutions were prepared (Table 2).

Table 2: The energy barrier to racemisation for *α*-(S, Se or Te)organolithium species **116** with differing steric substitution.

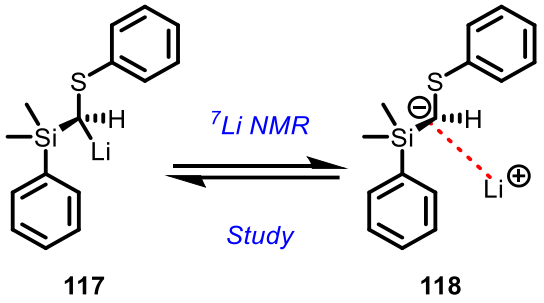


116

Where X = S, Se or Te

X	R	$\Delta G^{\ddagger}$ (kcal mol^{-1})
S	H	11.3
S	3-CF_3	11.4
S	4-OMe	11.4
S	2,3,5,6-Me_4	>13.9
Se	H	12.4
Se	2-Me	12.7
Se	4-Me	12.3
Se	2,4,6-Me_3	>14.3
Se	2,3,5,6-Me_4	>14.5
Te	H	11.8
Te	2,3,5,6-Me_4	13.9

The results suggest that as the steric bulk increased on the aryl ring, the barrier to racemisation increased. This implied that the rotation about the C-X bond was rate determining in the racemisation of these configurationally labile organolithiums.



117 118

Scheme 38: Reich's ^{7}Li NMR spectroscopy to explore solvent effect on barrier to enantiomerisation of **117**.

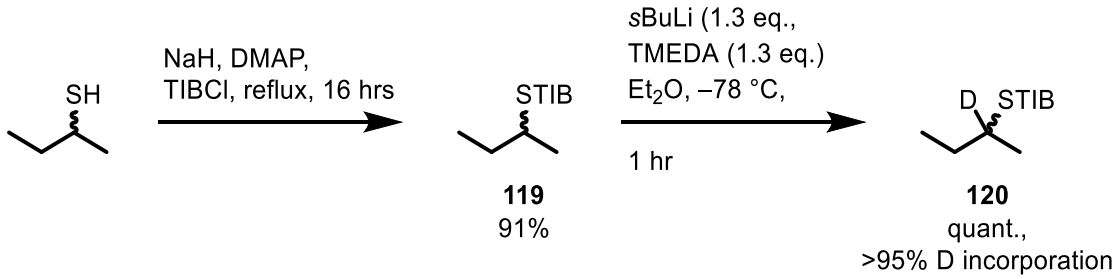
Subsequent ^{7}Li NMR studies by Reich[70] aimed to underpin the concentration of HMPA needed to produce solvent separated ion pairs for α-silyl, α-thioorganolithiums **117** (Scheme 38). It was found that 3.0 eq. HMPA were sufficient to achieve this. The presence of HMPA decreased racemisation by a factor of 20 when compared to the control reaction (with no HMPA), due to stabilisation of the solvent separated ion pairs **118**. This verified Hoffman's finding that the rotation about the C-X bond was rate limiting in the racemisation of these organolithium species.

1.2. Previous Work

All previous work reported in this section on the lithiation-electrophile trapping of **122** was conducted by Dr. Alex Pulis (AP), and the contents of this work were reported in his Ph.D thesis.[102]

Dr. Pulis re-investigated the work reported by Beak and co-workers on α-thio organolithiums[74], since a single test condition was used to draw conclusions on the stability/ reactivity of an entire class of carbenoid. Given the facile deprotonation of *S*-2,4,6-triisopropyl thiobenzoates and configurational stability of secondary *S*-thiocarbamates, dialkyl α-thio organolithiums may provide synthetically useful carbenoid intermediates. Additional interest in enantioenriched thiobenzoates came from wanting to explore a different source of chiral lithium carbenoid for application in lithiation-borylation methodology (see Chapter 2.1 for further information on lithiation-borylation methodology).

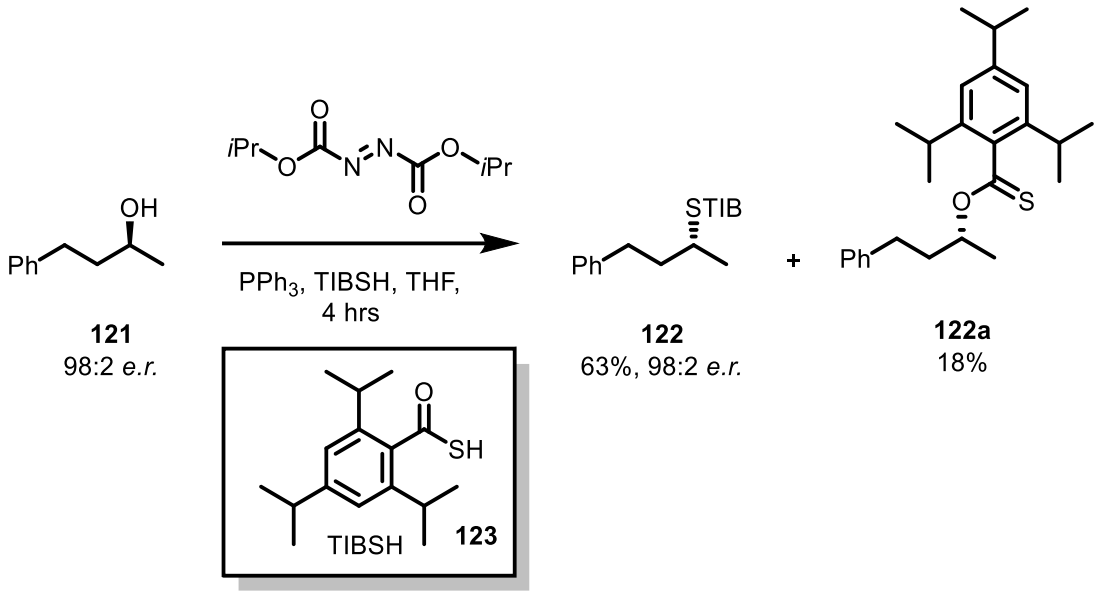
Initially, Dr. Pulis tested lithiation-deuteration conditions on racemic thiobenzoate **119** (Scheme 39), which was synthesised by esterification of butane-2-thiol in 91% yield. Next, thiobenzoate **119** was lithiated in the presence of *s*BuLi and TMEDA in Et_2O at -78 °C for 1 hour, after which MeOD was added to the reaction mixture. Pleasingly, this reaction furnished D-incorporated thiobenzoate **120** quantitatively with >95% D incorporation.



Scheme 39: Synthesis and lithiation-deuteration of dialkyl *S*-thiobenzoate **119**.

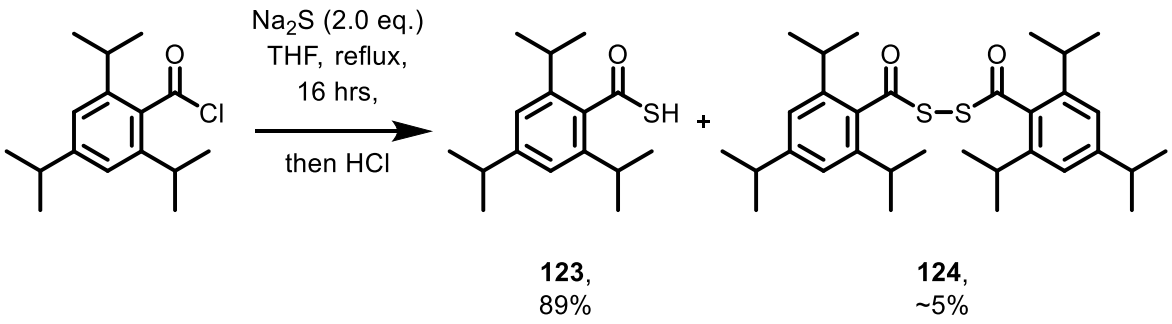
Having established lithiation and deuteration of the chiral racemic carbenoid, Dr. Pulis sought to test the enantioenriched *S*-thiobenzoate **122** in the same reaction. This would provide insight into the configurational stability of the carbenoid generated. However, the synthesis of the enantioenriched secondary thiobenzoate **122** (Scheme 40) required a different synthetic approach to the route shown in Scheme 40, *via* a Mitsunobu reaction of alcohol **121** and 2,4,6-

triisopropylbenzothioic acid (TIBSH) **123**, with full stereoinversion. The *O*-substituted thiobenzoate **122a** was also isolated in 18% yield.



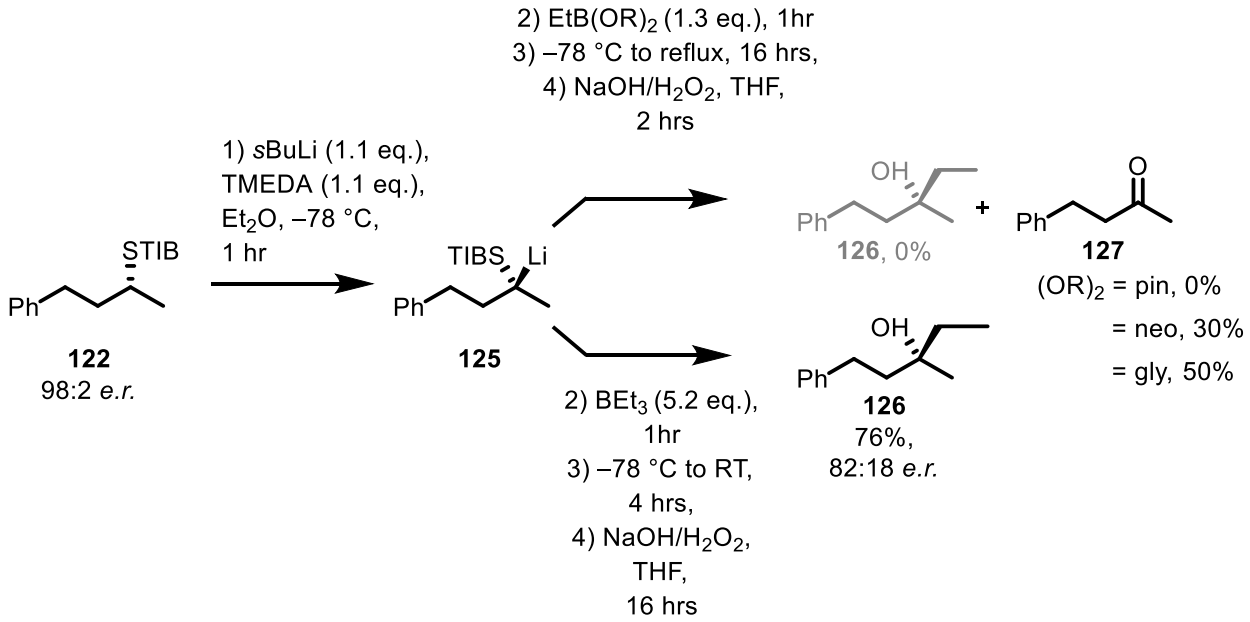
Scheme 40: Synthesis of secondary thiobenzoate **122** *via* Mitsunobu reaction**.**

However, the TIBSH **123** is not commercially available and was synthesised in house by reacting the corresponding 2,4,6-triisopropylbenzoyl chloride (TIBCl) and sodium sulfide under anhydrous anaerobic conditions. It was crucial to maintain anaerobic conditions to minimise disulfide **124** formation, which was still present in the isolated product (5%) (Scheme 41). The presence of disulfide **124** did not affect the subsequent Mitsunobu reaction. Furthermore, the excess sodium sulfide generated toxic H_2S gas when the reaction was quenched with HCl, which was a safety issue when synthesising this material in large scale.



Scheme 41: Synthesis of TIBSH **123.**

Subsequently, enantioenriched *S*-2,4,6-triisopropyl dialkyl thiobenzoate **122** was fully deprotonated using *s*BuLi/TMEDA in Et_2O at –78 °C after 1 hour. However, reaction of the deprotonated *α*-thio organolithium **125** with EtB(pin), EtB(neo) or EtB(gly), followed by heating under reflux, failed to give tertiary alcohol **126** after oxidation (Scheme 42), instead ketone **127** was isolated in various yields (0-50%). The addition of Lewis acid, $MgBr_2{\bullet}OEt_2$, did not remedy the reaction outcome. In contrast, reaction of *α*-thio organolithium **125** with triethyl borane furnished tertiary alcohol **126** following oxidation of crude reaction mixture, with a high yield (76%), but poor enantiospecificity (82:18 *e.r.,* 64% *e.s.*). The change in enantiomeric ratio raised concerns over the configurational stability of the carbenoid generated in this reaction. Further optimisations were required to address this issue, such as variation in temperature, solvent and reagent additives. However, no further optimisations were reported in Dr. Pulis's thesis.



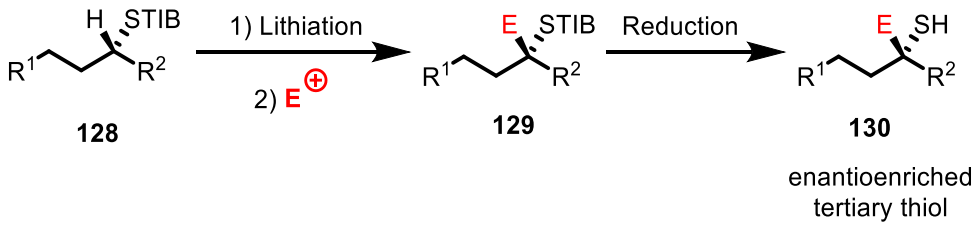
Scheme 42: Lithiation-borylation of secondary thiobenzoate **122**.

Due to thiobenzoate **122** only reacting with boranes in lithiation-borylation reactions and the poor enantiospecificity observed in these reactions, all further studies into the use of a thiobenzoate carbenoid in lithiation-borylation methodology were stopped at this stage.

Carbenoids formed by lithiation of *O*-benzoates have been found to display much higher macroscopic configuration stability than the corresponding thiobenzoate. Therefore, the *O*-benzoate is preferred for enantiospecific lithiation-borylation reactions.

1.3. Project Aims

Having shown that thiobenzoate **122** could be lithiated, it was confirmed that the carbenoid was configurationally unstable, leading to loss of enantiomeric excess over time. For this reason, thiobenzoate **122** was deemed unsuitable for lithiation-borylation methodology. Based on the lithiation-deuteration study for thiobenzoate **122**, it was envisaged that optimising lithiation conditions for thiobenzoate **128**, to improve configuration stability of the lithiated species could enable the carbenoid to react with a range of electrophiles to produce **129** with high *e.r.* if the electrophile trapping process were to proceed in a rapid and irreversible manner. Therefore, such a process would give access to enantioenriched tertiary thiobenzoates **129**, which could be reduced to generate enantioenriched tertiary thiols **130**, as shown in Scheme 43.



Scheme 43: Synthesis of enantioenriched tertiary thiols **130.**

First, we will establish optimal conditions for the lithiation-deuteration on a model thiobenzoate substrate and then test this with a range of suitable electrophiles. This methodology will be expanded to analogous thiobenzoate substrates by varying the R group. Similarly, a range of thiobenzoate-containing natural products will be tested using this methodology to showcase broader application.

Subsequently, *in-situ* IR spectroscopy will be employed to monitor and understand the reaction profile for various electrophiles used in this methodology. Furthermore, Excitation-Sculptured Indirect-Detection Experiment (EXSIDE) NMR spectroscopy[103] will be conducted to elucidate the stereochemistry of the lithiation-electrophile trapping product. Finally, a study to determine the thermodynamic parameters of racemisation ($\Delta H^{\neq}$, $\Delta S^{\neq}$ and $\Delta G^{\neq}$) will be undertaken.

1.4. Results and Discussion

1.4.1 Collaboration Disclaimer

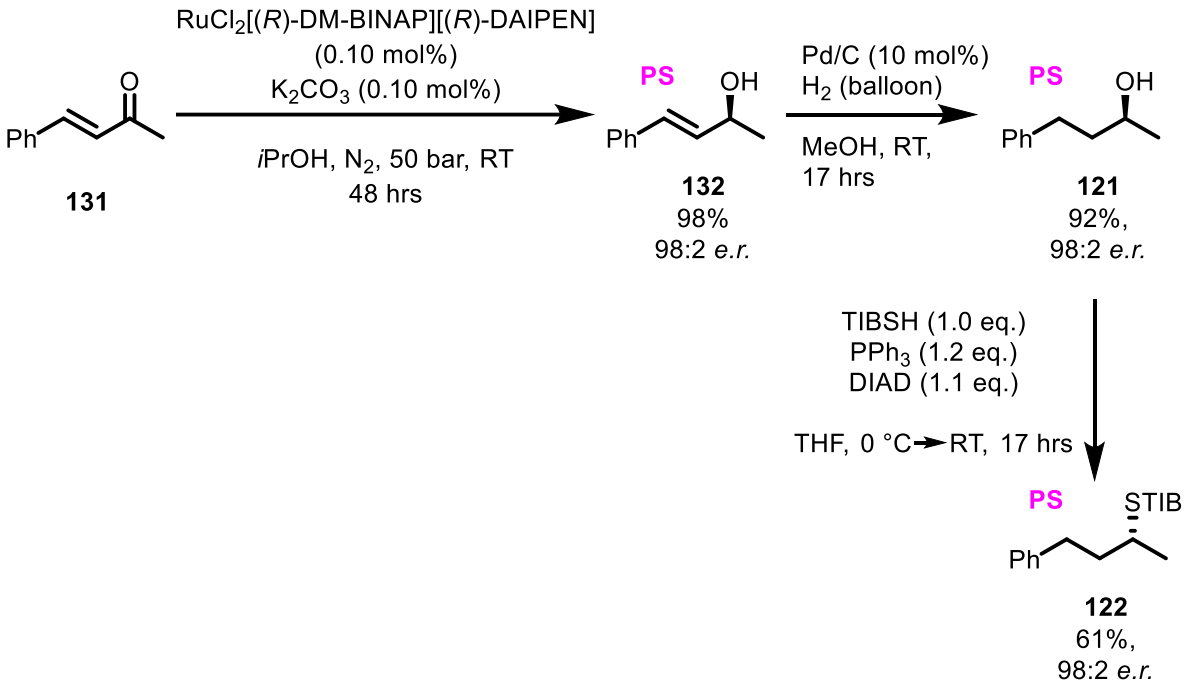
Parts of this project have been completed in collaboration with Dr. Alex Pulis (AP), Dr. Ana Varela (AV) and Dr. Cinzia Citti (CC) which form the basis of the publication.[104] The work of the above collaborators has been included to provide a complete story for this chapter. All work completed by myself has been marked with my initials PS. Only the molecules synthesised by myself (PS) have been reported in the Experimental Chapter.

1.4.2. Synthesis of Starting Materials

1.4.2.1. Synthesis of Thiobenzoates

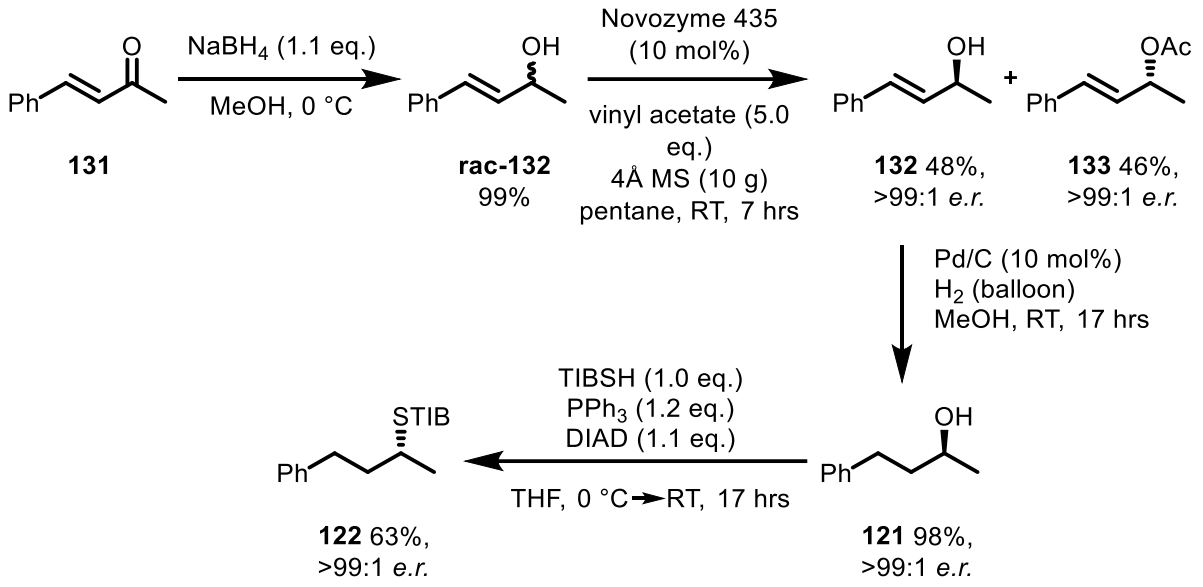
Initially, focus was turned to improving enantiomeric ratio of the secondary thiobenzoate, which for thiobenzoate **122**, was 98:2 *e.r.* as reported by Dr. Pulis (Scheme 44). In the original synthesis of thiobenzoate **122**, a Noyori asymmetric hydrogenation ruthenium catalyst ($RuCl_2$[(*R*)-DM-BINAP][(*R*)-DAIPEN] was used to convert (E)-4-phenylbut-3-en-2-one **131** to enantioenriched alcohol **132** in 98% yield and 98:2 *e.r*, as shown in Scheme 44. Then alcohol **132** was converted by hydrogenation to alcohol **121**, using palladium on charcoal and hydrogen gas in 92% yield. The saturated enantioenriched secondary alcohol **121** was then reacted *via* Mitsunobu to furnished secondary thiobenzoate **122** in 61% yield and 98:2 *e.r.*

Unfortunately, attempts to recrystallize enantioenriched thiobenzoate **122** to improve enantiomeric ratio of this material were unsuccessful. A combination of solvent systems were screened to this extent, however due to solubility issues, thiobenzoate **122** failed to dissolve or precipitated as an oil. Subsequently, recrystallisation of alcohol **121**, was utilised to overcome this issue.



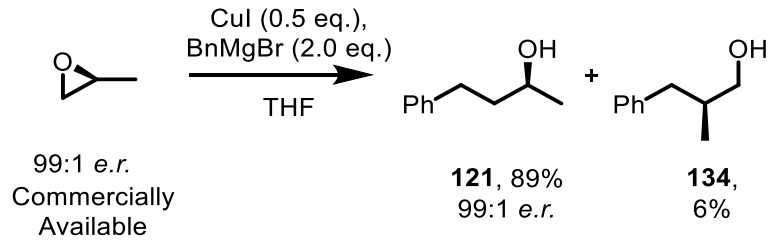
Scheme 44: Original synthesis of thiobenzoate **122**, using Noyori hydrogenation catalyst**.**

An alternate route to thiobenzoate **122**, in high *e.r.*, without the need for recrystallisation was also explored (Scheme 45). In this route, (E)-4-phenylbut-3-en-2-one **131** was reduced with $NaBH_4$ to afford the racemic alcohol **rac-132**. Then lipase-catalysed enzymatic resolution of this alcohol generated **132** and **133** both of which were isolated in >99:1 *e.r.* Subsequent hydrogenation reaction afforded **121** and then Mitsunobu reaction yielded desired thiobenzoate **122** in 63% yield and >99:1 *e.r.* The only concern with this route is that the $NaBH_4$ reduction results in a racemic mixture of alcohol **rac-132**, which ultimately means at least half the material is lost during the enzymatic resolution.



Scheme 45: Using enzymatic resolution for the synthesis of secondary alcohol **121**.

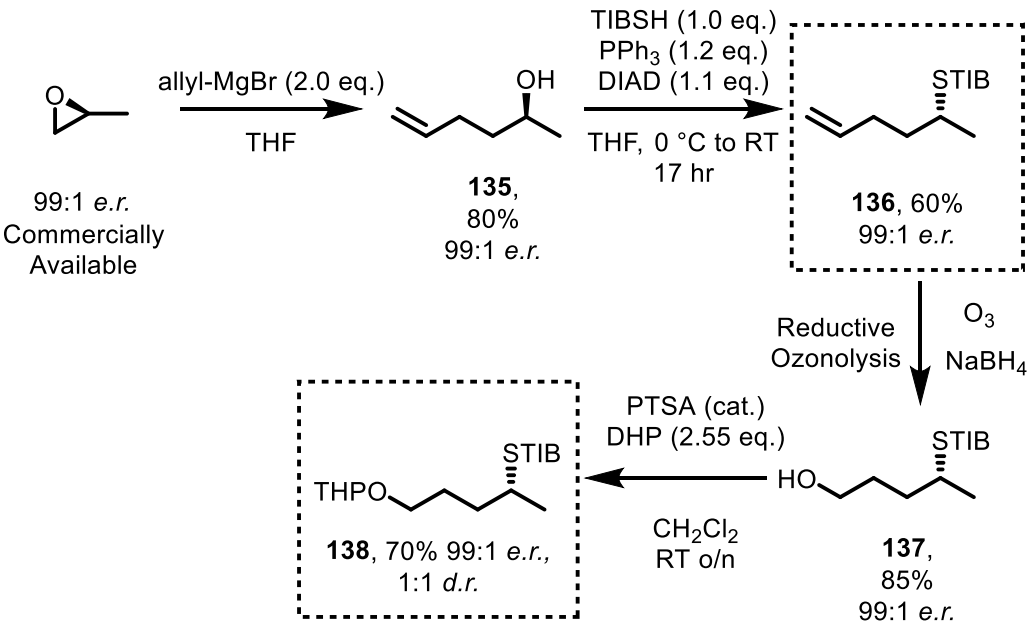
Finally, the synthesis of desired secondary alcohol **121**, was simplified to a single step, by adding benzyl magnesium bromide (Grignard reagent) to (*S*)-2-methyloxirane in the presence of CuI (Scheme 46). Though this route simplified the route to synthesise enantioenriched alcohol **121** without compensating the enantiomeric excess (99:1 *e.r.*), the Grignard reagent addition led to the formation of regioisomer **134**, due to competing ring-opening of the epoxide. This side product was inseparable by column chromatography and distillation. The production of regioisomers **134** was circumvented by adding a diluted solution of Grignard reagent in a drop-wise manner (~1 drop per 2 seconds using a syringe pump) to a cooled solution of epoxide and copper iodide. Similarly, preparing a fresh batch of the Grignard reagent rather than using commercially available material improved the reaction yield.



Scheme 46: Epoxide ring-opening strategy for the synthesis of secondary enantioenriched alcohol **121**.

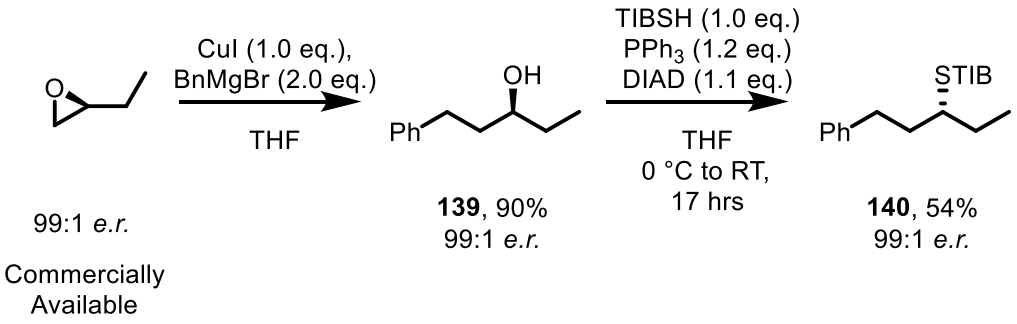
1.4.2.2. Synthesis of Thiobenzoate Analogues

Using the epoxide ring-opening protocol towards the synthesis of enantioenriched secondary alcohols provided a more facile and versatile route towards the synthesis of analogous secondary thiobenzoates, as shown in scheme 47. Using allyl magnesium bromide in this protocol generated the allylic alcohol **135** *via* ring-opening of (*S*)-2-methyloxirane, which was converted to thiobenzoate **136** *via* Mitsunobu esterification. Subsequently, reductive ozonolysis of thiobenzoate **136** cleaved the terminal alkene to produce primary alcohol **137**. Finally, primary alcohol **137** was protected using 3,4-Dihydropyran (DHP), to give THPO-thiobenzoate analogue **138** in good yield and high *e.r.* The synthesis and electrophile trapping of these substrates was reported by Dr. Varela (AV).



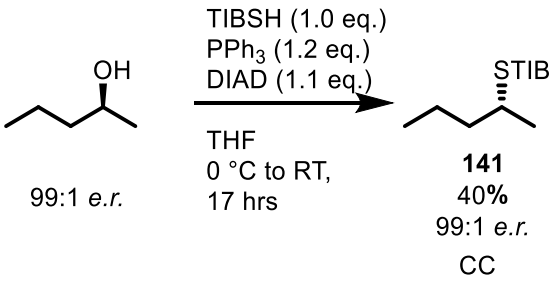
Scheme 47: Synthesis of allylic secondary thiobenzoate **136** and THPO thiobenzoate **138**.

In addition, commercially available (*S*)-2-ethyloxirane (99:1 *e.r.*), Scheme 48, was reacted with benzylmagnesium bromide to produce alcohol **139** in high *e.r.* and yield, which was taken through into a Mitsunobu esterification to produce ethyl branched thiobenzoate **140** in moderate yield and high *e.r.*



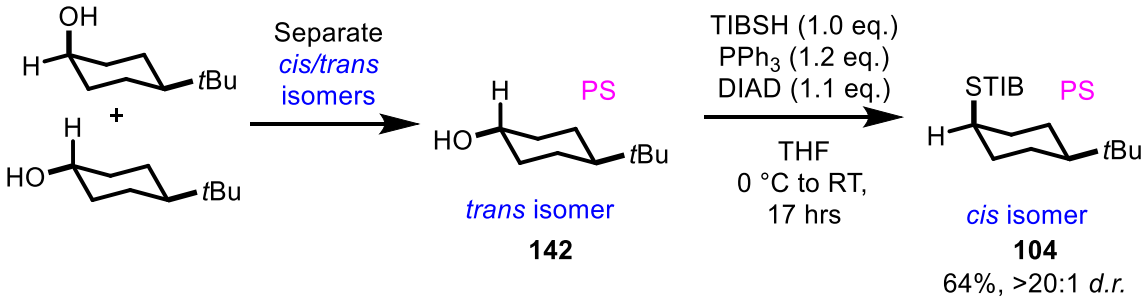
Scheme 48: Synthesis of ethyl branched secondary thiobenzoate **140**.

Furthermore, commercially available (*S*)-(+)-2-pentanol was also subjected to Mitsunobu esterification to furnish thiobenzoate **141**, as shown in Scheme 49. The absence of a functional group tether in this analogue should be highlighted in this thiobenzoate. The synthesis and electrophile trapping of this substrate was carried out by Dr. Citti (CC).



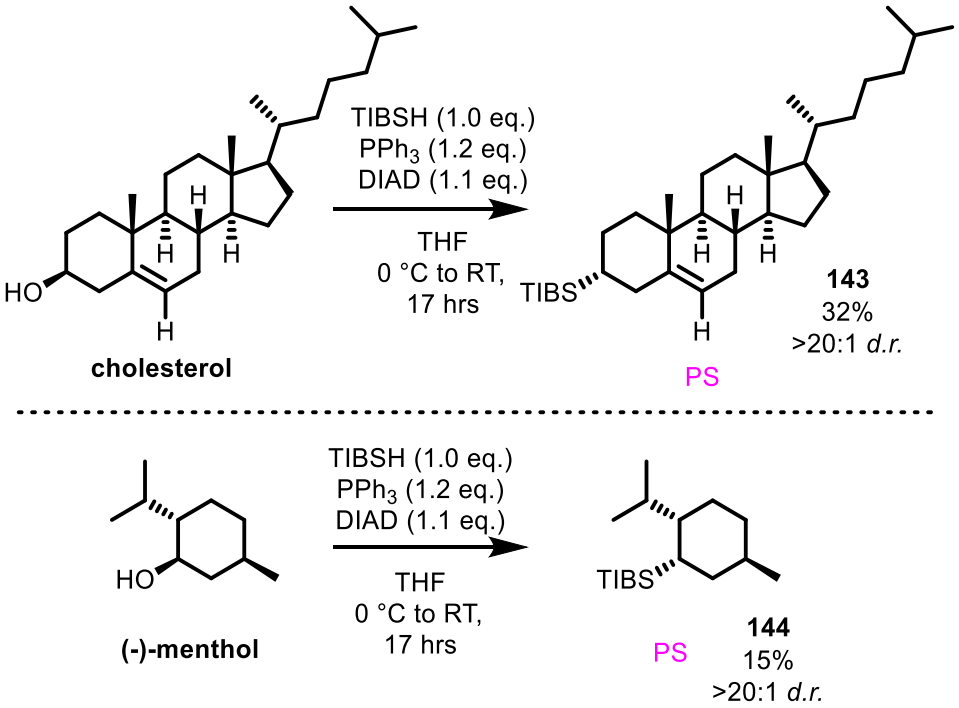
Scheme 49: Mitsunobu esterification of (*S*)-(+)-2-pentanol **141**.

Similarly, *S*-((*cis*)-4-(*tert*-Butyl)cyclohexyl) 2,4,6-triisopropylbenzothioate **104**, which has been previously shown by Beak[74] to undergo thermodynamic equilibration to the more stable *trans*-organolithium when lithiated, was re-evaluated using our modified conditions. It was envisaged that the shorter lithiation times would reduce thermodynamic equilibration, thus gaining access to the previous unobtainable *cis*-isomer product. The mixture of *cis*- and *trans*-**142** diastereoisomers were separated by column chromatography and the *trans*-**142** isomer was carried through to a Mitsunobu esterification to obtain the *cis*-thiobenzoate **104**, as shown in Scheme 50.



Scheme 50: Synthesis of *S*-((*cis*)-4-(*tert*-butyl)cyclohexyl) 2,4,6-triisopropylbenzothioate **104**.

To broaden the thiobenzoate scope, natural product containing carbocycles, such as cholesterol and (–)-menthol were utilised. In a similar manner to the example above, the alcohol functional groups on cholesterol and (–)-menthol were successfully reacted with thioic acid **123** in a Mitsunobu esterification to furnished cholesterol-derived thiobenzoate **143** and (–)-menthol-derived thiobenzoate **144** in high yield and diastereoselectivity (Scheme 51). The poor yield observed in the menthol Mitsunobu reaction is due to steric hindrance from the adjacent isopropyl group, which is on the same face as the TIBS group in the product **144**.

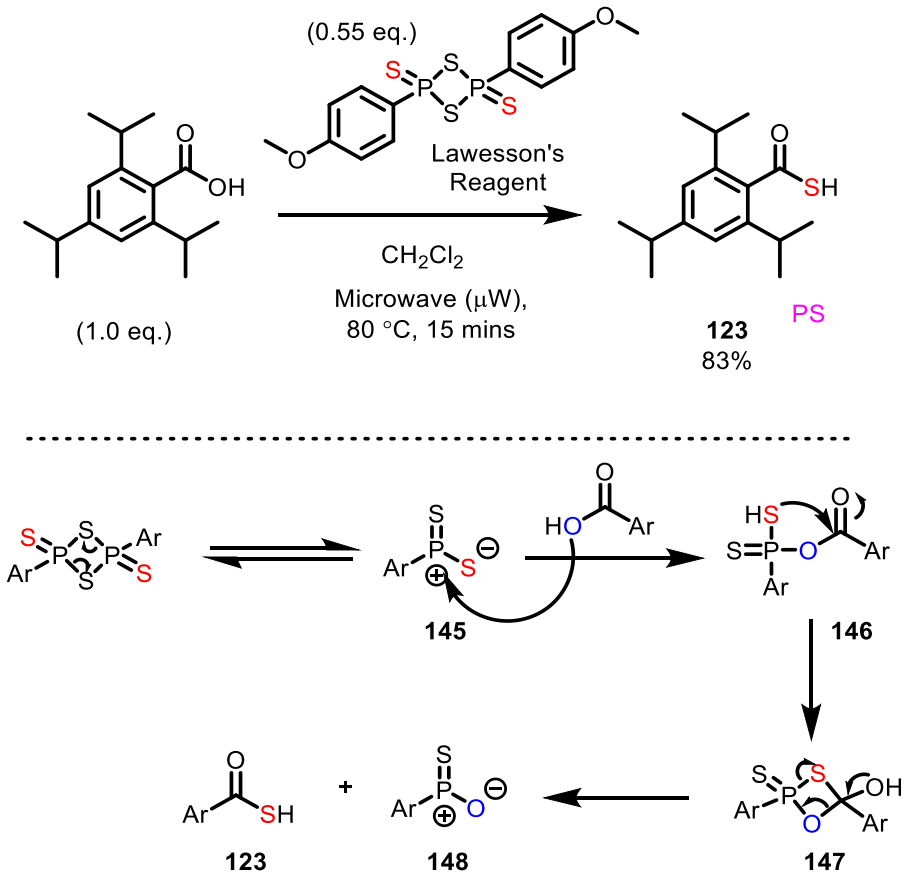


Scheme 51: Synthesis cholesterol-derived thiobenzoate **143** and (–)-menthol-derived thiobenzoate **144**.

1.4.2.3. Exploring an Alternate Strategy in the Synthesis of TIBSH

The route to synthesise TIBSH **123** was developed by Dr. Pulis using TIBCl and sodium sulfide, however, during this project TIBCl became difficult to obtain from suppliers. With a lack of TIBCl an alternate route to synthesise this in-house material was warranted. Given that we had access to 2,4,6-triisopropyl benzoic acid (TIBOH), we attempted to access TIBCl from TIBOH using thionyl chloride. However, only a difficult to purify, gummy oil was obtained from this route.

Ideally, a protocol to convert the carboxylic acid directly into the thioic acid could solve two issues. Firstly, the corresponding thioic acid should be accessible in one-step and secondly, it would circumvent the use of Na_2S, which posed a safety issue when working on scale. Previous work by Danishefsky and co-workers[105], reported a protocol for the conversion of carboxylic acids to the analogous thioic acid with Lawesson's reagent, using a microwave reactor, as shown in Scheme 52.



Scheme 52: Synthesis of TIBSH **123** and mechanism.

Table 3 shows conditions screened to find optimal reaction temperature (°C) and time (mins). Given that the aryl C-H shift (^{1}H NMR spectra) of the TIBOH (7.00 ppm), TIBSH (7.02 ppm) and disulfide (7.08 ppm) are similar, this reaction could only be monitored *via* GCMS or change in the quaternary carbonyl signal seen in the ^{13}C NMR spectrum. The initial reaction (Entry 1) using literature conditions, showed conversion of the carboxylic acid to desired product (95 % conversion by ^{13}C NMR). Attempts to improve conversion were achieved by heating the reaction for prolonged time (15 (Entry 2) and 20 mins (Entry 3)), however prolonged heating led to a difficult to purify crude mixture, possibly due to competing side reactions. Unfortunately, the impurities could not be separated and isolated nor were the impurities identified. It was found that heating for 15 mins at 80 °C showed complete consumption of TIBOH without the pink impurity being generated (Entry 4). Following purification (under N_2 to avoid disulfide formation) an isolated yield of 83 % was obtained. For the scale-up reaction it was found that to ensure full conversion, reaction mixtures had to be kept below 0.25 M, otherwise stirring was inefficient in the microwave reactor. It is also crucial to purify the crude reaction mixture under nitrogen to avoid formation of disulfide. As expected, leaving the crude reaction mixture over a prolonged period in the presence of air resulted in quantitative disulfide formation.

Table 3: Optimisation of conditions for the synthesis of thiobenzoate **123** using Lawesson's reagent.

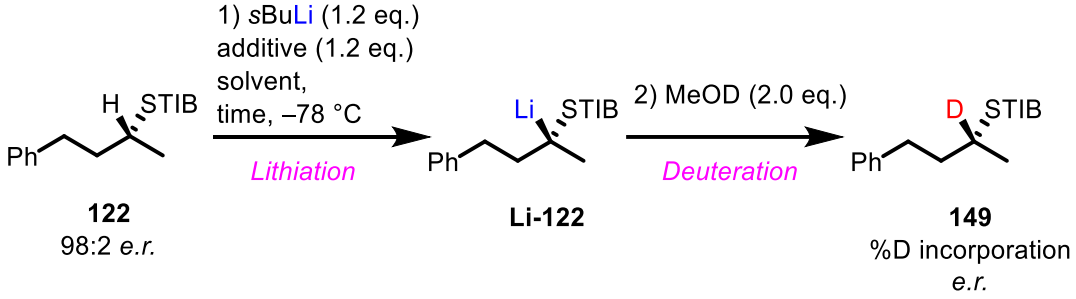
Entry	Reaction time (mins)	Temperature (°C)	Product: SM ratio	Isolated Yield (%)
1	10	100	>95:5	62
2	20	100	100:0	ND
3	15	100	100:0	ND
4	15	80	100:0	83
5	10	60	50:50	37

Danishefsky and co-workers[105] postulated a mechanism for this reaction, as shown in Scheme 52, which requires the generation of ylide **145**, derived from Lawesson's reagent. Subsequently, the carboxylic acid undergoes nucleophilic addition onto the phosphorus heteroatom of ylide **145** to give intermediate **146**. Then intramolecular cyclisation facilitated through the sulfur atom, furnished intermediate **147**, which then undergoes a "Wittig-like" rearrangement to give thioic acid **123** and (thioxo)phosphine oxide **148**.

1.4.3. Optimising Reaction Conditions

This work was jointly carried out by Dr. Citti (CC) and myself (PS). We investigated both the lithiation efficiency and configurational stability of Li-**122** *via* a lithiation-deuteration experiment (Table 4). This optimisation was achieved using thiobenzoate **122** with 98:2 *e.r.*

Table 4: Optimisation of lithiation conditions for thiobenzoate **122**.

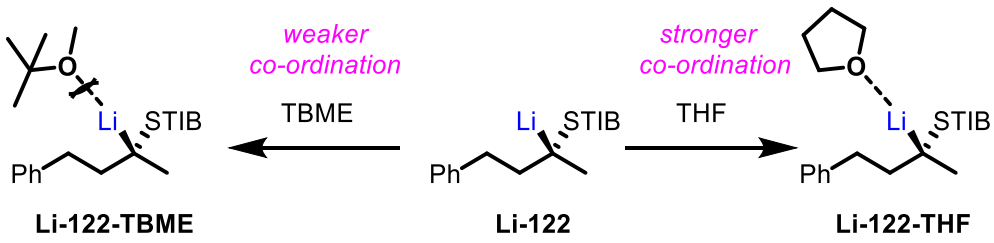


Entry	Solvent	Lithiation time (mins)	Additive	D-incorporation (%)[a]	*e.r.*[b]
1	THF	15[c]	TMEDA	88	56:44
2	Et_2O	60[c]	TMEDA	100	84:16
3	Et_2O	15[c]	TMEDA	100	90:10
4	Et_2O	15[c]	-	11	97:3
5	CPME	60[c]	TMEDA	100	92:8
6	CPME	15[c]	TMEDA	100	94:6
7	TBME	60[d]	TMEDA	100	93:7
8	TBME	15[d]	TMEDA	100	96:4
9	TBME	5[d]	TMEDA	100	97:3
10	TBME	15[c]	(−)-sparteine	7	98:2
11	TBME	15[c]	TMCDA	58	97:3
12	TBME	15[c]	PMDTA	6	ND
13	TBME	15[c]	DME	14	93:7
14	Toluene	60[c]	TMEDA	85	95:5
15	Toluene	15[c]	TMEDA	78	94:6
16	Et_2O/hexane (1:10)	60[c]	TMEDA	100	92:8
17	Et_2O/hexane (1:10)	15[c]	TMEDA	100	94:6

Yield of **122** and **149** was ≥90% in all cases. [a]Determined by ^{1}H NMR. [b]Determined by HPLC on the crude mixture of **122** and **149**. TMEDA = *N,N,N',N'*-tetramethylethylene diamine; TMCDA = (*rac,trans*) *N,N,N',N'*- tetramethylcyclohexane-1,2-diamine; PMDTA = *N,N,N',N',N''*- pentamethyldiethylenetriamine; DME = dimethoxyethane. [c] Experiment conducted by Dr. Citti. [d] Experiment conducted by Pradip Songara.

As shown in Table 4, it was found that reducing the lithiation time for the conditions reported by Beak and co-workers (Entry 1) gave good levels of D-incorporation (88%), but poor enantiospecificity (near racemic product). Since both solvents and additives effect lithiation, we studied this by modifying these parameters to maximise both efficiency and configurational stability. In Entry 2, exchanging THF solvent for Et_2O aided the configurational stability of **Li-122**, with quantitative D-incorporation and 84:16 *e.r.* after 60 mins lithiation. Similarly, under the same conditions, reducing lithiation time to 15 mins (Entry 3), improved the product enantiomeric ratio (90:10 *e.r.*), with no detriment to product yield. It was evident that shorter lithiation periods were crucial to the stability of the **Li-122** generated in the reaction. Attempts to repeat the reaction in the absence of additive (Entry 4) further improved the enantiomeric ratio (97:3 *e.r.*), however resulted in poor D-incorporation (11%), suggesting that the ligand played an important role in facilitating lithiation.

Having seen improvements in the configurational stability of **Li-122** when switching from THF to Et_2O, we suspected that controlling the solvent oxygen lone-pair availability could control the reaction outcome. We envisaged that using bulkier groups on the ethereal solvent would shield the oxygen lone-pair from interacting with the **Li-122** (Scheme 53).



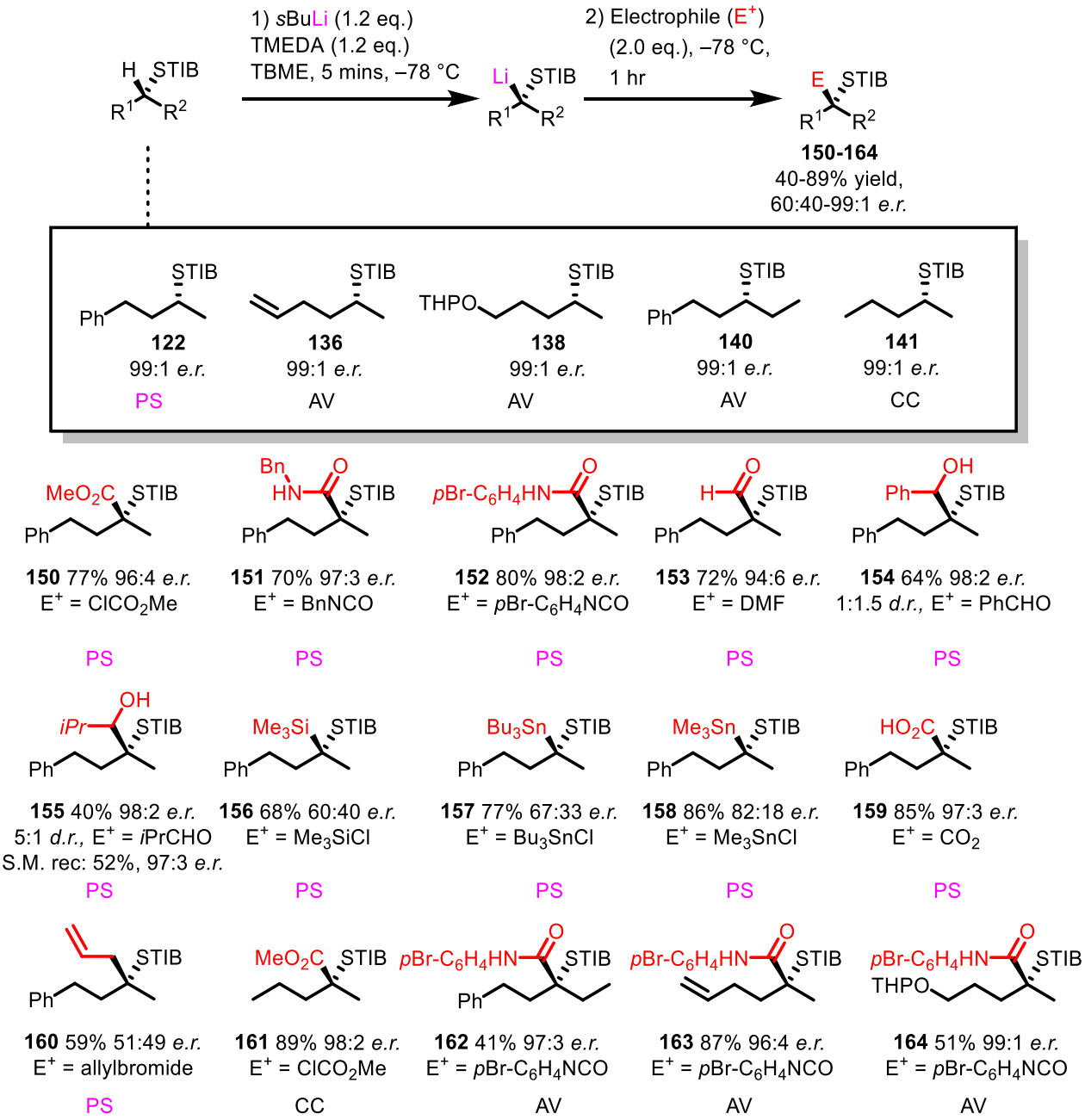
Scheme 53: Solvent-effects on **Li-122** configurational stability.

Whilst screening additional ethereal solvents, such as CPME and TBME (Entry 5-13), it was found that CPME (Entry 5) as solvent enabled better configurational stability after 60 mins lithiation time (92:8 *e.r.* with 100% D incorporation), which was further improved by reducing reaction time to 15 mins (Entry 6). Using TBME produced promising results: after 60 mins (Entry 7) 93:7 *e.r.* and 15 mins (Entry 8) 96:4 *e.r.* were obtained. At this stage a 5-minute lithiation period was attempted to see if this could produce better results (Entry 9). In our favour, we found that D-incorporation product could be obtained in 97:3 *e.r.* and 100% yield.

In an attempt to optimise these conditions, we altered the diamine ligand used in the reaction to (−)-sparteine (Entry 10), to see if this chiral ligand had a mis-match effect on the lithiation. Though high *e.r.* was observed, the D-incorporation was poor. Using other diamine ligands also produced poor results: in TMCDA only 58% D-incorporation was observed, though in high *e.r.* Similarly, PMDTA (Entry 11) did not remedy the situation and resulted in the lowest D-incorporation reported in this table (Entry 12, 6%). Furthermore, using 1,2-dimethoxyethane (DME) (Entry 13) resulted in poor D incorporation (14%) demonstrating that diamine ligands were a better choice for this reaction. In addition, toluene was also tested (Entry 14/15) and though both reactions produced comparable enantiomeric ratios after 15 mins or 60 mins, the D-incorporation for both products were low. Finally, Entry 16/17 showed the use of mixed solvent systems on the lithiation profile of this reaction, with both reactions resulting in quantitative D-incorporation after 60 mins and 15 mins, respectively, but lower *e.r.* than the conditions reported in Entry 9.

Whilst these results clearly demonstrate that **Li-122** configurational stability can be enhanced by reducing lithiation periods and using bulky ethereal solvents. We decided to use Entry 9 as our optimised conditions for the lithiation of thiobenzoates in this work. The next stage of this study requires testing these reaction conditions against various electrophiles to develop a substrate scope.

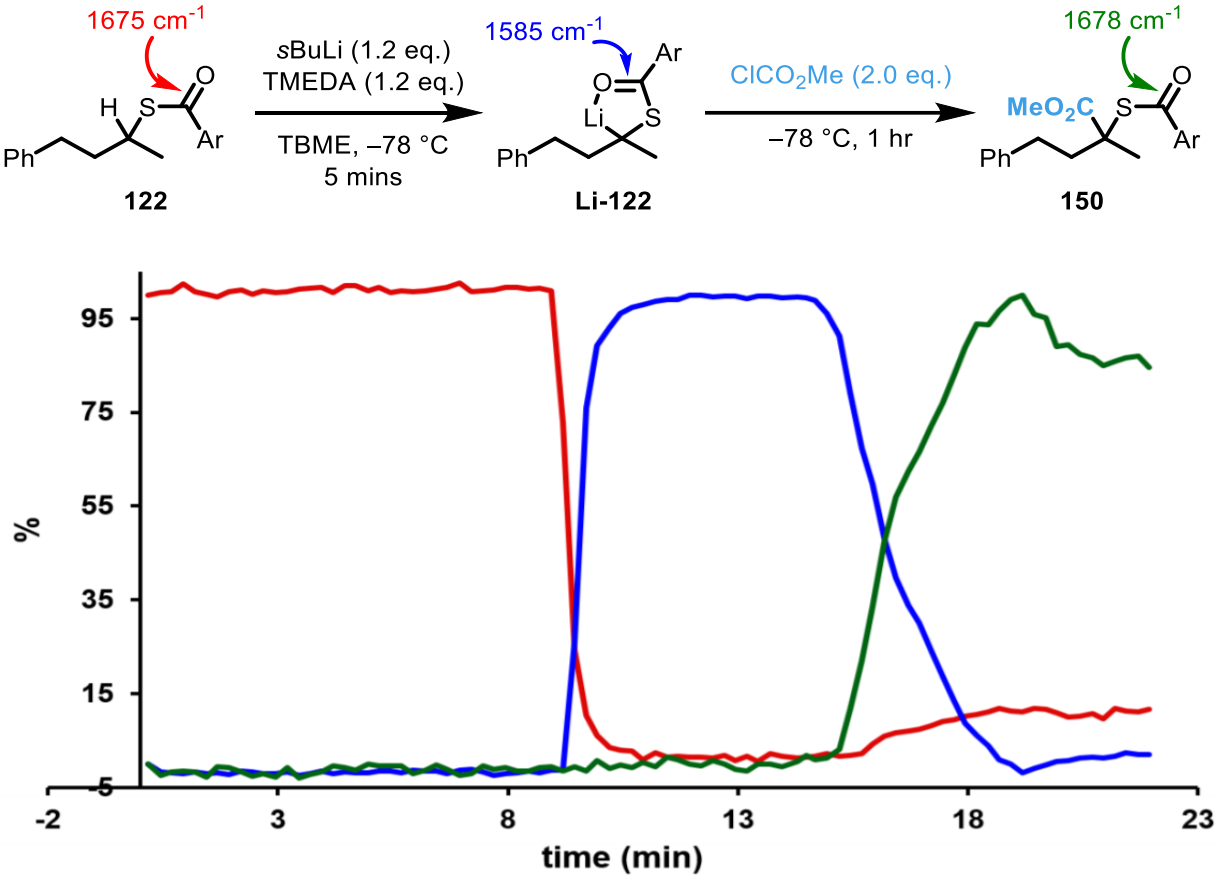
1.4.4. Substrate Scope



Scheme 54: Substrate scope developed for the lithiation-electrophile trapping of thiobenzoates.

Using the most suitable conditions identified for the lithiation of thiobenzoate **122**, and trapping with MeOD, we assessed the scope of electrophiles that could be utilised in this protocol. As shown in Scheme 54, the trapping of the non-stabilized, tertiary thiobenzoate organolithium species derived from thiobenzoates **122**, **136**, **138**, **140** and **141**, gave products in good to high yields and high enantioselectivities in all cases except for allylbromide **160**, trimethylsilyl chloride **156** and Sn-based electrophiles **157** and **158**.

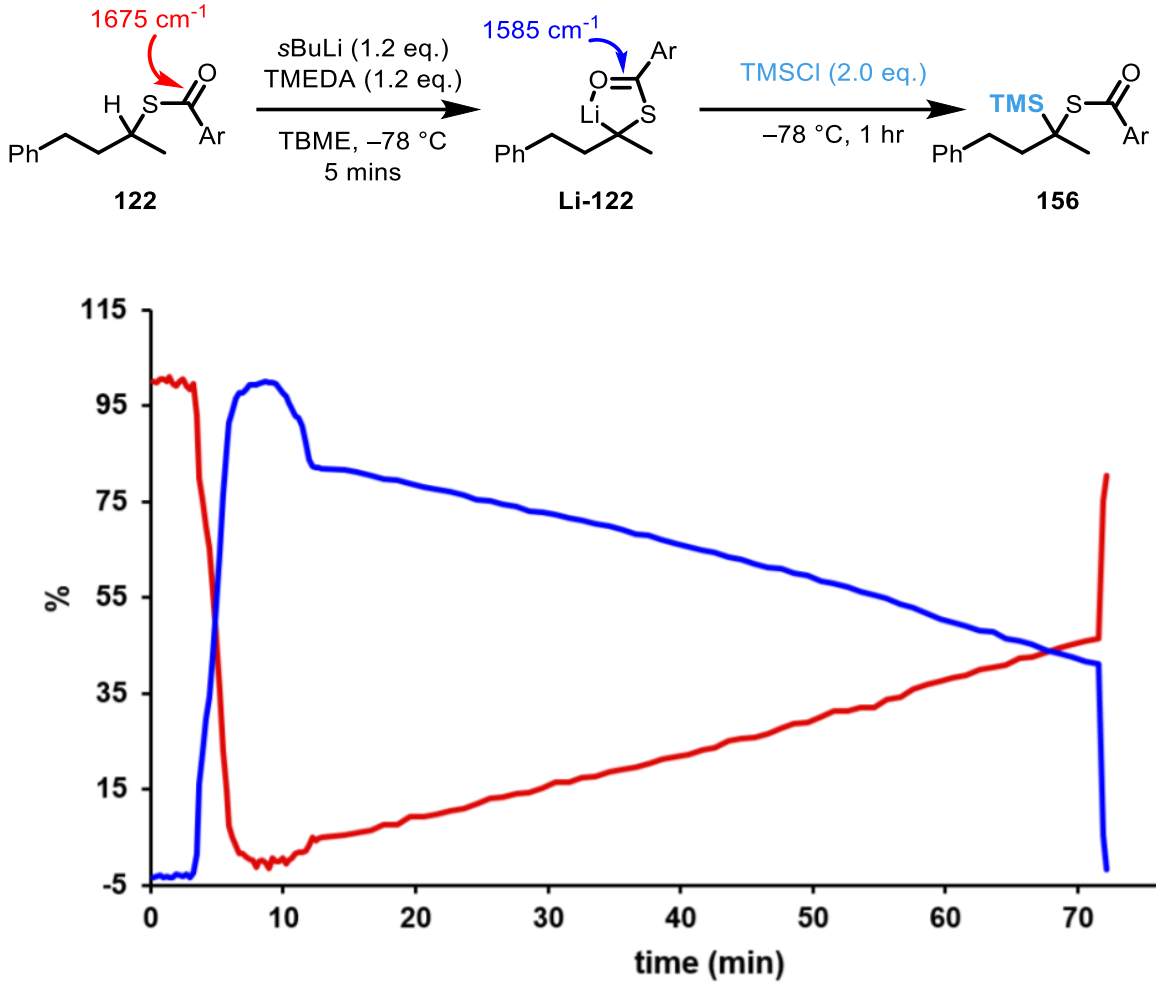
As shown in Scheme 54, trapping **Li-122** with methyl chloroformate gave the methyl ester **150** in high yield and *e.r.* To understand the reaction profile for the methyl chloroformate **150** reaction, an *in-situ* IR spectroscopy was conducted to study the behaviour and fate of the **Li-122** (Scheme 55). Here it is shown that the lithiation of thiobenzoate **122** was rapid, upon addition of *s*BuLi (~ 8 mins), with consumption of thiobenzoate **122** species (red line) to produce **Li-122** (blue line). After 5 minutes the methyl chloroformate was added to the reaction, resulting in consumption of all **Li-122** to produce thiobenzoate product **150**. The reaction profile observed in the IR study suggested that fast electrophile trapping is important to conserve high enantiospecificity.



Scheme 55: *In-situ* IR spectroscopy of the $ClCO_2Me$ trapping of thiobenzoate **122**.

Similarly, secondary amides (**151** and **152**) were also obtained from the corresponding isocyanates, with both electron rich (benzyl-) and electron deficient (*p*Br-C_6H_4-) substituents tolerated in the reaction in comparable yields and *e.r.*

In addition, DMF could be used with **Li-122** to furnish the aldehyde **153**. Similarly, benzaldehyde and isobutyraldehyde were also shown to react with **Li-122** to furnish desired secondary alcohols **154** and **155**, respectively. The diastereomer ratio for both **154** and **155**, were low, due to poor selectivity in the reaction. The moderate yields obtained for isobutyraldehyde **155**, were due to competing α-deprotonation of the aldehyde starting material, which prevented the electrophile from reacting with the **Li-122**.



Scheme 56: *In-situ* IR spectroscopy of the TMSCl trapping of thiobenzoate **122**.

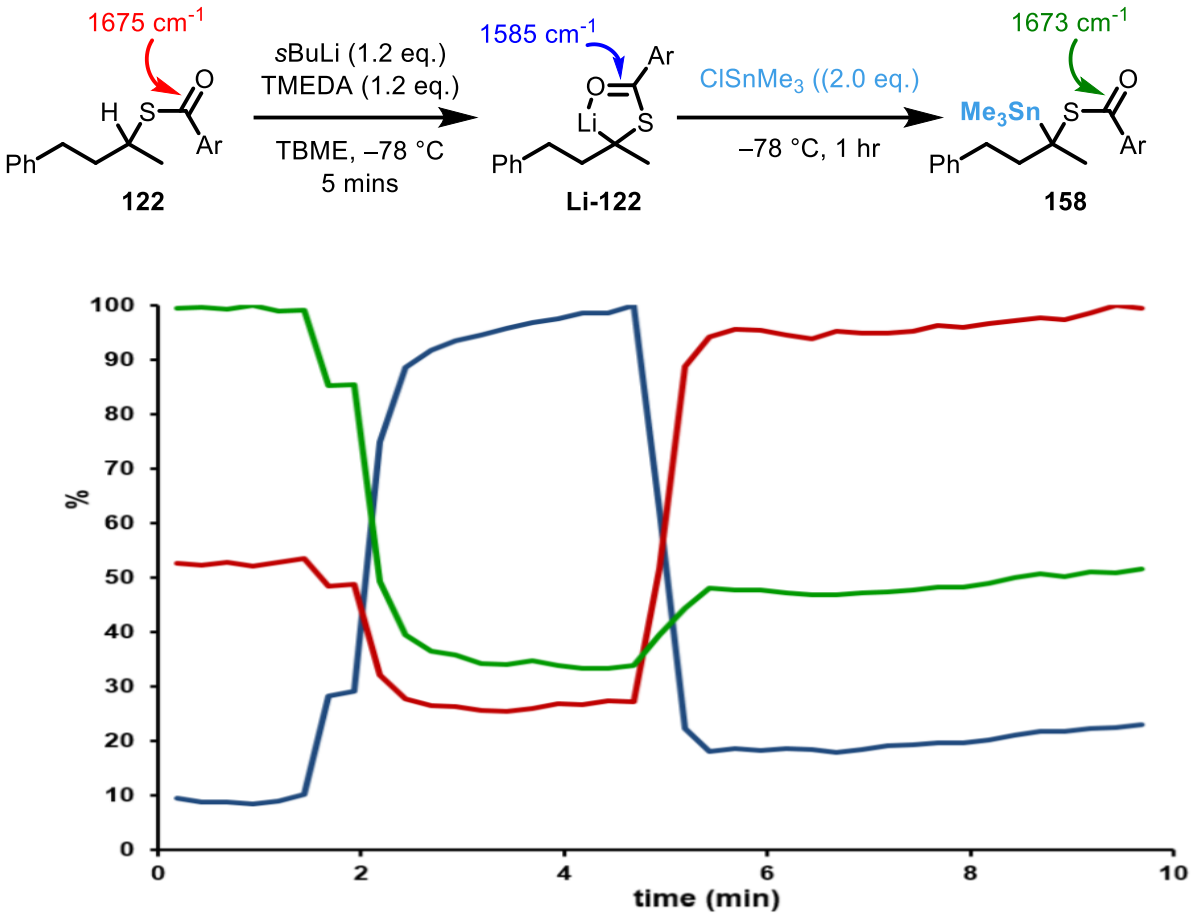
The reaction of TMSCl, produced the silylated product **156** in low *e.r.* (60:40). This was attributed to the slow reactivity of the electrophile with **Li-122**. It was observed that upon addition of the electrophile, allowing the lithiated species to racemise before being quenched at a higher temperature. The use of the more reactive TMSOTf gave only marginally improved 69:31 *e.r.* at the cost of yield (36%).

To understand the poor enantiomeric ratio obtained from this reaction an *in-situ* IR spectroscopy was conducted to study the behaviour and fate of the **Li-122** (Scheme 56). Here it is shown that the lithiation of thiobenzoate **122** is rapid, with consumption of thiobenzoate **122** (red line) to produce **Li-122** (blue line), with full lithiation observed as expected from the previous study. After 5 mins of lithiation the TMSCl electrophile was added and the reaction monitored. The gradual decline in the concentration of **Li-122** over time, suggested that the electrophile was not sufficiently reactive with **Li-122** and after 60 mins the reaction was still not complete. Subsequent addition methanol immediately quenched any unreacted **Li-122** (~ 70 mins).

When using trimethyltin chloride to access product **158**, the organolithium trapping proceeded with retentive addition (S_E2 ret), whereas for tributyltin chloride to access product **157**, inversion was observed (S_E2 inv). The absolute configurations of both **157** and **158** were determined after tin–lithium exchange and protonation of the resultant organolithium species. The resultant product **122** was analysed using HPLC and the traces compared with that of the authentic thiobenzoate **122** sample.

An *in-situ* IR spectroscopy study in the behaviour of trimethyltin chloride, as shown in Scheme 57, showed that the reaction showed a similar IR reaction profile to the profile observed for methyl chloroformate, with rapid lithiation (~1 min) and trapping (~5 mins) of the **Li-122**. This suggested that the tin electrophile was a good partner to the **Li-122**, so there was no observable reason to justify the inversion/retention phenomenon observed in $ClSnMe_3$ and $ClSnBu_3$, other than a steric argument for the latter.

The use of CO_2 to quench the **Li-122**, was also well tolerated giving desired carboxylic acid **159** in good yield and high *e.r.* However, the use of allyl bromide gave product **160** in moderate yield, but poor enantioselectivity (near racemic). This issue can be attributed to the electrophile, which can form stabilised allyl radicals, which reacts preferentially *via* a radical pathway with the **Li-122**, thus leading to racemisation.



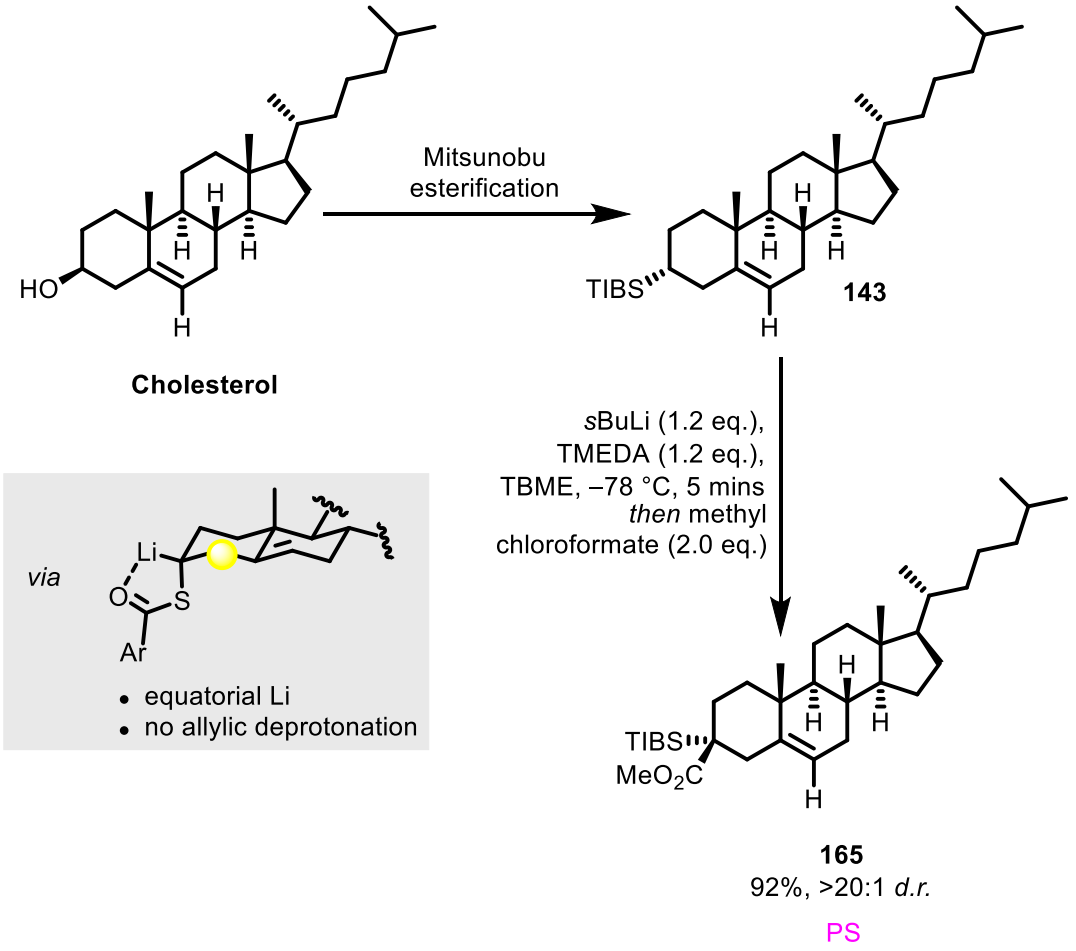
Scheme 57: *In-situ* IR spectroscopy of the $ClSnMe_3$ trapping of thiobenzoate **122**.

Finally using thiobenzoate analogues **136**, **138**, **140** and **141**, Dr. Citti and Dr. Varela showed that various functional group modifications to the model thiobenzoate **122** dialkyl chain, did not substantially affect reactivity of the thiobenzoate organolithium. Dr. Citti showed that simple dialkyl benzoate **141** could be successfully trapped to furnish methyl ester product **161** in high yield and *e.r.*, Similarly, increasing steric congestion by introducing an ethyl branch in thiobenzoate **140** did not hamper reactivity, with product **162** obtained in moderate yield and higher *e.r.* when quenched with para-bromophenyl isocyanate as the electrophile of choice. Furthermore, the allylic thiobenzoate **136** gave product **163** in high yield and *e.r.* Finally, THPO-protected thiobenzoate **138**, also reacted with para-bromophenyl isocyanate in moderate yield and consistently high *e.r.* to give **164**. Overall, this shows that the lithiation-electrophile trapping of the thiobenzoate containing molecules is not influences by the presence of a coordinating substituent on the alkyl chain.

1.4.5. Application to Various Natural Product Derivatives

1.4.5.1. Cholesterol Thiobenzoate Derivative

This work was conducted by Pradip Songara. We further extended the methodology to the STIB-cholesterol derivative **143**, prepared *via* Mitsunobu esterification of cholesterol, which, after exposure to the optimized reaction conditions gave product **165** ($ClCO_2Me$ quench) in excellent yield (92%) and as a single diastereoisomers, as shown in Scheme 58. This example is mechanistically important because: (i) the Li atom adopts an equatorial position which, according to Beak[74] and Reich[106], is unfavorable (the bulky TIBS group prefers to go equatorial) and should readily epimerise to axial and (ii) the α-lithiation of homoallylic systems is frequently plagued by competing elimination of the directing group (TIBS in this case). The success of this example shows the remarkably high kinetic acidity of α-S proton and the configurational stabilization provided by the reaction conditions.



Scheme 58: Lithiation-electrophile trapping of cholesterol derived thiobenzoate **143**.

1.4.5.2. Confirming the Stereochemistry of Cholesterol Thiobenzoate Derivative

Initial attempts to harvest crystals for X-ray crystallography proved difficult for products obtained from thiobenzoate **122**. As most products obtained after electrophile quench were oils. For the materials which were solids crystallisation proved difficult as these materials dissolved in all organic solvents except water. For this purpose, we attempted both evaporation and diffusion crystallisation techniques, but neither gave crystalline product. As a result, we wanted to see whether the cholesterol derivative (not crystalline after electrophile trapping) could be used to understand the configuration of the electrophile trapped products. Though this example is privileged as the structure is conformationally rigid and not as flexible as the linear substrates.

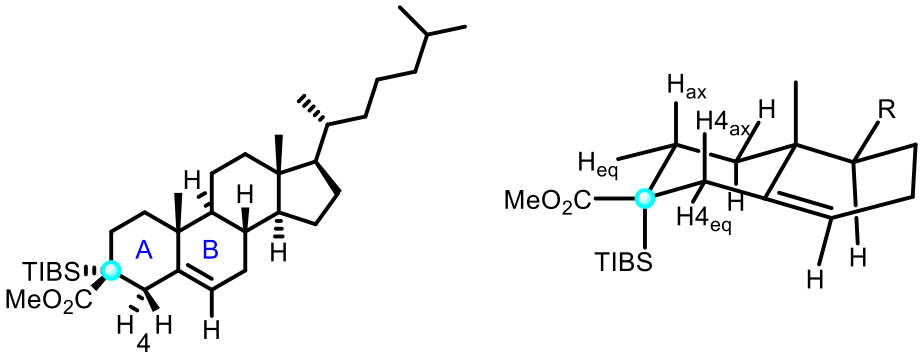


Figure 4: EXSIDE NMR technique to elucidate the stereochemistry of **165**.

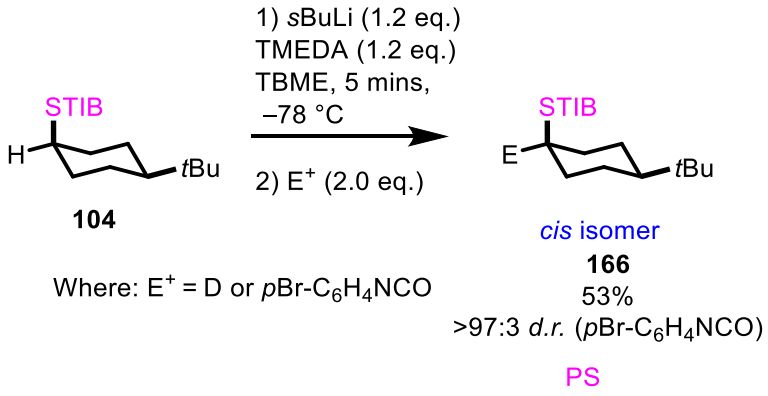
As a result, NMR analysis was used to confirm the absolute stereochemistry of the newly created quaternary stereocenter adjacent to the STIB moiety. Normally, conventional ^{1}H – ^{1}H coupling constants ($^{3}J_{HH}$ in this case) can be used to assign stereochemical relationship between adjacent protons that are three bonds apart, using the Karplus equation (curve). Since this approach is not possible for quaternary centers, long range ^{1}H – ^{13}C coupling constants ($^{n}J_{CH}$, where n = 2,3) have been used instead as these also bear a Karplus-type relationship to dihedral angle between a ^{1}H and any ^{13}C three bonds away ($^{3}J_{CH}$ for instance) or between the ^{1}H and a heteroatom also three bonds away ($^{2}J_{CH}$ for instance). Since the stereocenter of interest in our molecule have no protons attached, the latter method was used.

The stereochemistry of the stereocentre of interest was assigned using $^{n}J_{CH}$ values from the diastereotopic protons (H_{4a} and H_{4b}, Figure 4). These $^{n}J_{CH}$ values were obtained with the EXSIDE experiment (and its variants), a method which provides long range heteronuclear

coupling constants even to non-protonated centres. Of particular interest was the $^{2}J_{CH}$ values as the $^{3}J_{CH}$ values of these protons to the carbon of the carboxylic acid moiety were similar. The diastereotopic allylic protons (H_{4a} and H_{4b}) in question were assigned with ^{1}D NOESY studies to determine proton signals which were axial and equatorial. This was possible only after the protons and carbons of rings A and B, STIB and the ester signals were assigned using ^{1}H, ^{13}C NMRs in combination with HMBC, H2BC and HSQC, PYSCHE and HSQC experiments. For the purpose of this study, only the signals of ring A and B would be considered thus making analysis of this molecule straight forward. This allowed us to confirm that the electrophile trapping event does take place with retention in the case of cholesterol.

1.4.5.3. 4-(*tert*-Butyl)cyclohexyl Thiobenzoate Derivative

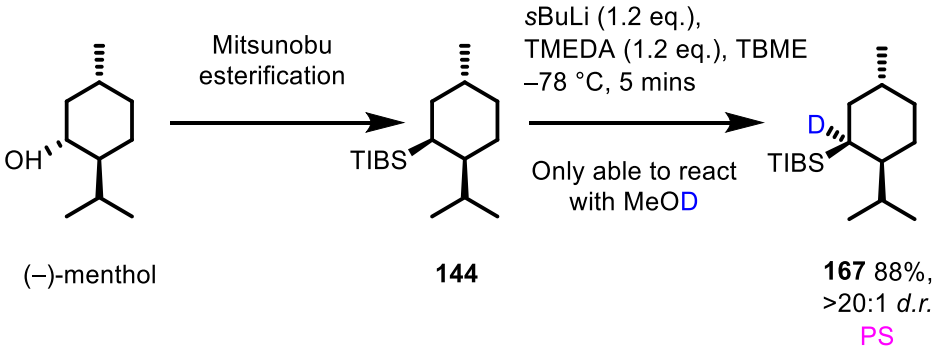
Though the example with cholesterol is important, there is a degree of structural rigidity that increases the stability of the α-S organolithium to epimerisation. To probe this we utilised *S*-((*cis*)-4-(*tert*-butyl)cyclohexyl) 2,4,6-triisopropylbenzothioate **104**, which has been previously shown by Beak to undergo thermodynamic equilibration to the more stable *trans*-organolithium when lithiated. As a result, Beak found that the only product isolated in the lithiation and electrophile trapping of the *cis*-isomer is the *trans*- product. Using our optimised conditions, we obtained product **166** in good yields (53% with *p*bromophenyl isocyanate as the electrophile) as the *cis*-diastereoisomers (>97:3 *d.r.*) as shown in Scheme 59. Therefore, this exemplified that our conditions provided a synthetic viable route to access the previously thought not possible isomer of this substrate as reported by Beak and co-workers[74].



Scheme 59: Re-evaluating Beak's work on thiobenzoate **104**.

To confirm the stability of our *cis*-organolithium result we conducted a lithiation-deuteration study in which we quenched the lithiated thiobenzoate at different time intervals to assess the degree of interconversion from *cis*- organolithium to *trans*- organolithium. For this experiment we found that after 1 hr the ratio of the lithiated thiobenzoate was 70:30 *cis*:*trans* and surprisingly after 7 hrs the ratio was 40:60 *cis*:*trans*. This work overcomes the synthetic challenges reported by Beak, which showed that after 2 hrs in THF (-78 °C) generated solely the *trans*-isomer product when the organolithium is quenched with MeI.

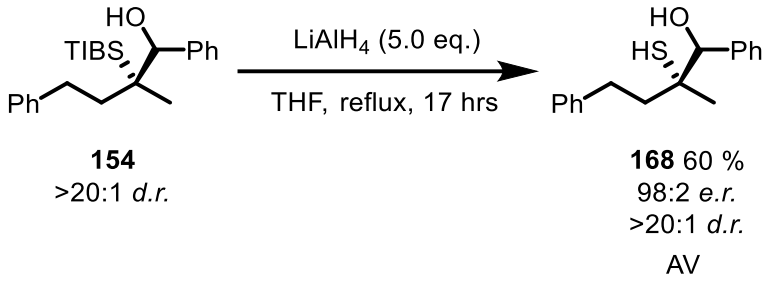
1.4.5.4. (−)-Menthol Thiobenzoate Derivative



Scheme 60: Failed (−)-menthol thiobenzoate **144**.

Based on the above findings on cyclic substrates, the menthol thiobenzoate derivative **144** derived by Mitsunobu esterification of (−)-menthol, was subjected to our lithiation conditions, for which the deuterated product **167** was isolated in high yield and diastereomeric ratio. Unfortunately, this did not transpire when any larger electrophiles were utilised, such as, *p*BrC_6H_4NCO. This was attributed to the steric congestion at the carbanion site which renders the substrate unable to react with anything larger than a deuterium atom (Scheme 60).

1.4.6. Deprotection of Thiobenzoate for the Synthesis of Tertiary Thiol



154
>20:1 *d.r.*

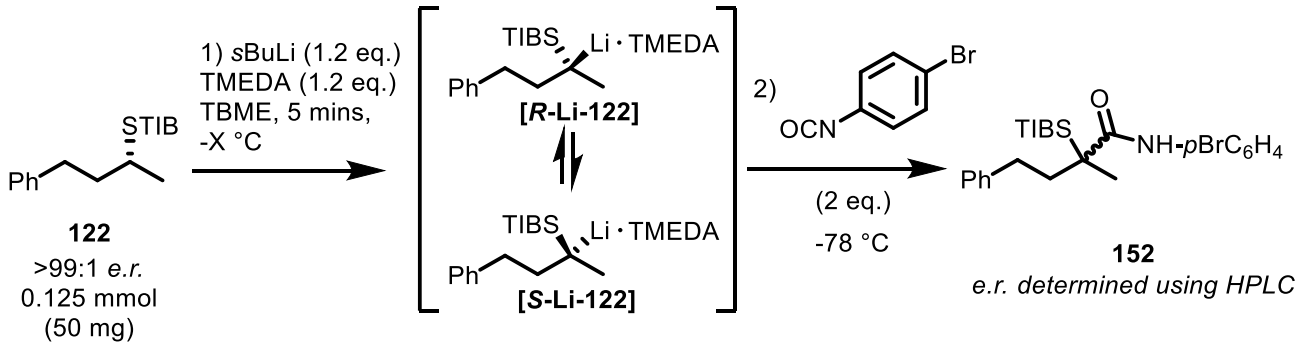
168 60 %
98:2 *e.r.*
>20:1 *d.r.*
AV

Scheme 61: Reduction of thiobenzoate **154** to the corresponding tertiary thiol.

Dr. Varela successfully showed that the reduction of thiobenzoate **154** could be achieved using lithium aluminium hydride under refluxing conditions, as shown in Scheme 61. The desired enantioenriched tertiary thiol **168** was isolated in 60% yield and 98:2 *e.r.*

1.4.7. Evaluating the Barrier to Racemisation and Eyring Plot Studies

To place the chemistry on firmer foundations, we decided to determine the thermodynamic parameters, $\Delta H^{\neq}$ and $\Delta S^{\neq}$ of racemisation. Initial studies by Hoffmann and co-workers identified $\Delta G^{\neq}_{rac(-78\,°C)}$= +15 kcal mol^{-1} and $\Delta G^{\neq}_{rac(-90\,°C)}$= +13 kcal mol^{-1} of racemisation for *S*-Ph and *S*-duryl at –78 ºC (as the lower limit that ensures the configurational stability of thioorganolithiums).[108–110] We have performed detailed kinetic studies on thiobenzoate **122**.



Scheme 62: Barrier to rotation for thiobenzoate **122**.

As shown in Scheme 62, thiobenzoate **122** is lithiated, followed by equilibration at –78, –70, –65 and –60 ºC. This is followed by cooling to –78 ºC and quenching with *p*BrC$_6$H$_4$NCO to give thiobenzoate **152** with varying levels of enantioenrichment (*e.r. determined by HPLC*).

In chemical kinetics, the Eyring equation is used to describe changes in the rate of a chemical reaction against temperature. Assuming electrophile trapping is rapid and irreversible, the enantiomeric ratio of **152** (determined by chiral HPLC) should reflect the enantiomeric ratio of the organolithium species ***R/S*-Li-122** at the point of trapping. The kinetic data for the study was treated under reversible first-order conditions by using the following equation, which was derived using the Arrhenius equation and Gibbs equation:[107]

$$\frac{1}{2} ln\left(\mathrm{T} - 2\left(\left(\frac{[S]}{100}\right)\mathrm{T}\right)\right) = -kt + c$$

Where T = total conc. of **122** (0.125 mmol), [*S*] = conc. *S*-enantiomer [***S*-Li-122**], k = constant, t = time (secs).

Since thiobenzoate **122** has an enantiomeric ratio of >99:1, this composition can be treated as a single enantiomer (i.e. 100% *R*-enantiomer : 0% *S*-enantiomer). As a result, the total

concentration of **122**, (T), is equal to the % of *R*-enantiomer. Therefore, as T = [*R*] = 100, the above equation can be simplified to give:

$$\frac{1}{2}ln\left(100 - 2\left(\left(\frac{[S]}{100}\right)100\right)\right) = \ -kt \ + \ c$$

$$\therefore \frac{1}{2}ln(100 - 2([S]) \ = \ -kt \ + \ c$$

Since the enanotiomeric excess is a difference between the percentage of major enantiomer and minor enantiomer, which in our example is $[R_{major}] - [S_{minor}]$. Mathematically, this difference is the same as 100 – 2([*S*]). For example, if a pair of enantiomers has 96:4 *e.r.* or 92 % *e.e*, then 100 – 2([4]) = 92. On that basis, it is possible to say that 100 - 2([*S*]) = *e.e.* of **152**. This further simplies the equation to give the final form:

$$\frac{1}{2}ln(e.e.) \ = \ -kt \ + \ c$$

Based on the values calculated for individual temperature sets, Table 5, was generated to show the increase in rate of racemisation with temperature (which was plotted in Chart 1). Based on these values a half-life ($t_{½}$) for these organolithium species was calculated, which gave a more comprehensive value for the affect temperature plays on the rate of racemisation (Table 5).

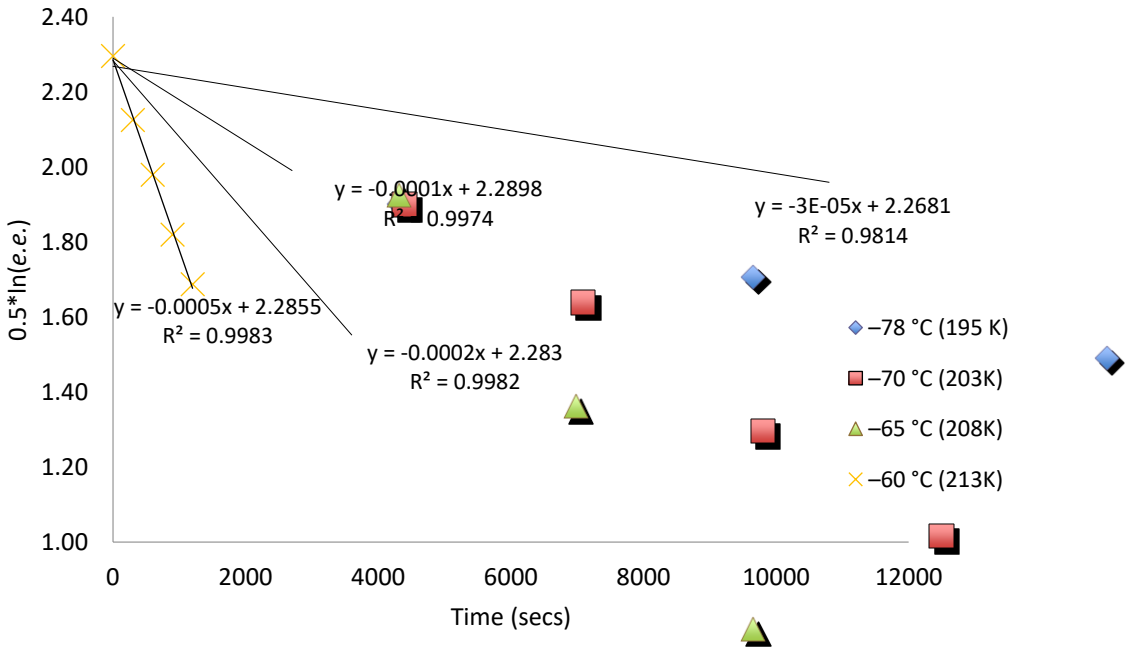


Chart 1: Log plot for the racemisation of **Li-122** with 1.2 eq. of TMEDA in TBME.

Table 5: Thiobenzoate **152** *e.e.* values determined by HPLC measurement (shown graphically in Chart 1) and calculation of half-life and reaction parameters at different temperatures (K).

Temperature °C (K)	Time (secs)	*e.e.*	0.5ln(e.e.)
– 78 (195)	0	96.46	2.285
	1800	85.52	2.2185
	3600	73.04	2.1455
	7200	59.94	2.0467
	10800	51.94	1.9754
–70 (203)	0	96.73	2.2860
	900	81.24	2.1987
	1800	64.61	2.0842
	2700	56.66	1.9914
–65 (208)	0	97.79	2.2914
	900	67.01	2.1024
	1800	44.89	1.9021
	2700	31.53	1.7255
	3600	22.93	1.5663
–60 (213)	0	98.60	2.2956
	300	70.07	2.1247
	600	52.31	1.9786
	900	38.00	1.8188
	1200	29.21	1.6872

	Temperature (K)			
	195 (-78 °C)	**203 (-70 °C)**	**208 (-65 °C)**	**213 (-60 °C)**
k ($secs^{-1}$)	–2.86149E-05	–0.000110931	–0.000203037	–0.000507544
ln (k/T)	–15.73458235	–14.41980848	–13.83966253	–12.94721853
1/T ($secs^{-1}$)	0.005128205	0.004926108	0.004807692	0.004694836
$t_{1/2}$ (secs)	24223.3	6248.5	3413.9	1365.7
$t_{1/2}$ (mins)	403.7	104.1	56.9	22.8

The observed erosion of enantiomeric ratio in these experiments gave rise to an Eyring plot (Chart 2) from which the activation parameters were extracted (for $\Delta H^{\neq}$ and $\Delta S^{\neq}$ of +13 kcal mol^{-1} and +14 kcal mol^{-1} respectively), using the Eyring equation, which follows a y = mx + c linear relationship:

$$\ln\left(\frac{k}{\mathrm{T}}\right) = \frac{-\Delta H^{\ddagger}}{\mathrm{R}}\left(\frac{1}{\mathrm{T}}\right) + \ln\left(\frac{k\mathrm{k}_B}{h}\right) + \frac{\Delta S^{\ddagger}}{\mathrm{R}}$$

Here y = ln(k/T), m = (–ΔH/R), x = (1/T) and c = ln(kk$_B$/h)+ΔS/R; in which k$_B$ = Boltzmann constant, h = Planck's constant and k = reaction rate (k-$_{78°C}$ = 2.9x10^{-5} s^{-1}, as shown in Table 5).

By using the Gibbs equation, the values for the $\Delta H^{\neq}$ and $\Delta S^{\neq}$ were used to calculate the $\Delta G^{\neq}_{\mathrm{rac}}$ at –78 ºC = ~10 kcal mol^{-1}, which is in line with Hoffman's results[108–110]. In addition to providing thermodynamic parameters for racemisation (Table 6), these studies also showed that racemisation of **Li-122** at −78 °C occurred over an extended period of time, as expected.

Chart 2: Eyring plot for the racemisation of **Li-122** with 1.2 eq. of TMEDA in TBME.

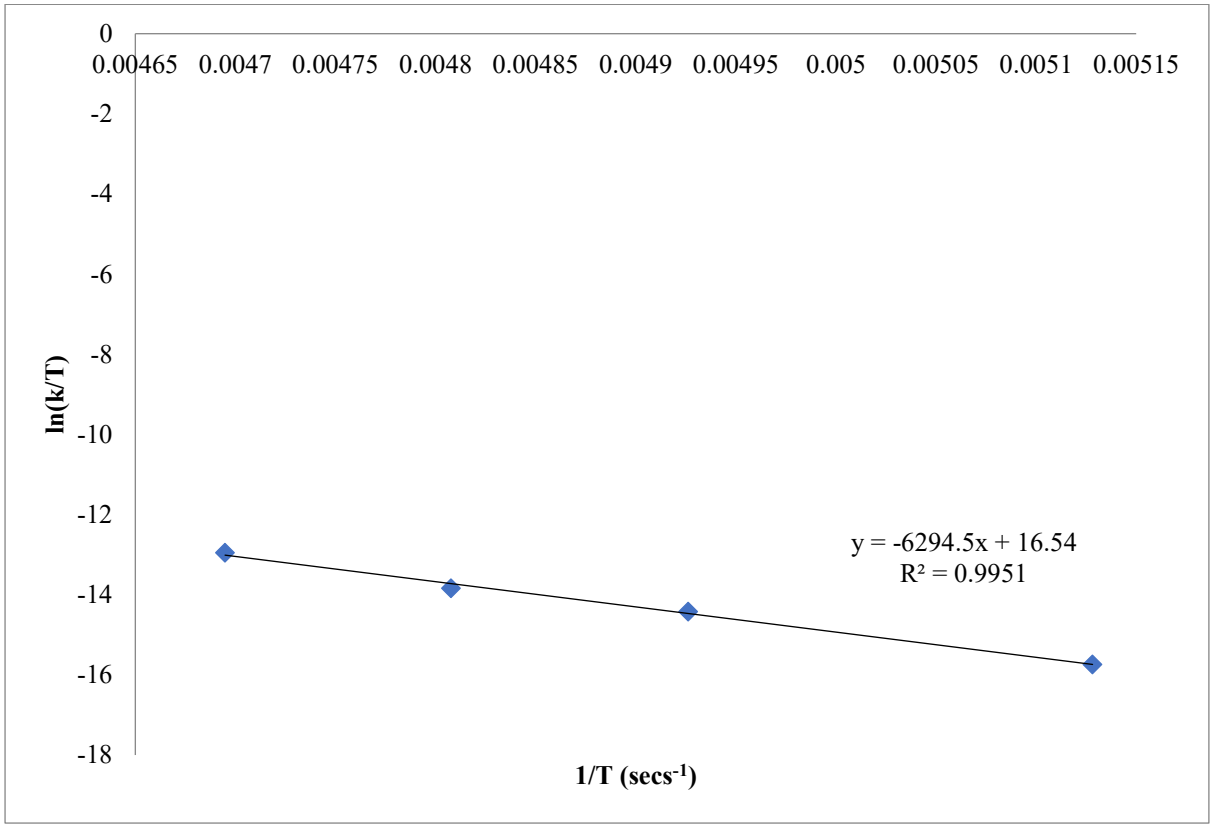
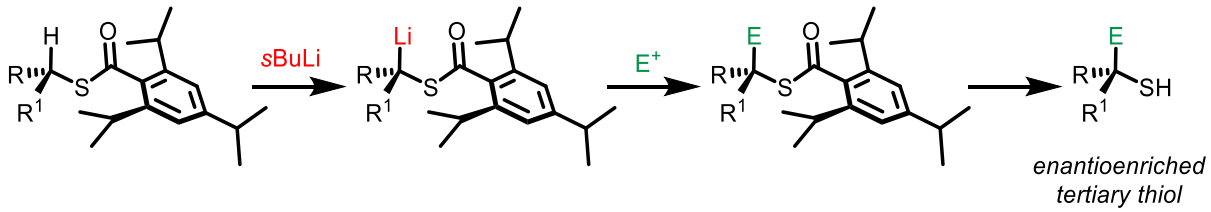


Table 6: Activation parameters for enantiomerisation for thiobenzoate **122**.

$\Delta H^{\ddagger}$ **(kcal/mol)**	12.51 ± 0.62	
$\Delta S^{\ddagger}$ **(cal/mol•K)**	14.30 ± 3.05	
$\Delta G^{\ddagger}$ **(kcal/mol)**	195 (–78 °C)	9.71 ± 0.86
	203 (–70 °C)	9.60 ± 0.88
	208 (–65 °C)	9.50 ± 0.89
	213 (–60 °C)	9.45 ± 0.90

1.5. Conclusion



Scheme 63: Lithiation-electrophile trapping of thiobenzoates for the synthesis of enantioenriched tertiary thiols.

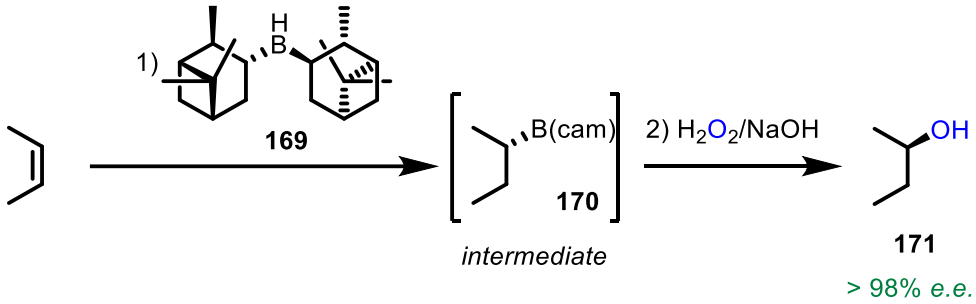
In conclusion, we have found α-S lithiated secondary dialkyl thiobenzoates, previously believed to be configurationally unstable, can both be generated and trapped with electrophiles with high enantiospecificity. The combination of non-coordinating solvents together with short reaction times and the use of reactive electrophiles to ensure immediate trapping of the organolithium species are crucial in achieving high enantioenrichment. The subsequent trapping of the tertiary organolithium intermediates with electrophiles proceeded with excellent enantioselectivity, enabling the synthesis of highly enantioenriched tertiary thiol derivatives. Subsequently, the tertiary thiol can be accessed through the reduction of the thiobenzoate group using $LiAlH_4$ (Scheme 63). Furthermore, this methodology has been applied to cyclic natural products, such as cholesterol and (–)-menthol. Similarly, it has been used on the cyclohexyl substrate reported by Beak and co-workers to showcase the performance advance, by showing that the previously inaccessible *cis*-isomer can be synthesised using the conditions reported herein. Finally, we have reported a kinetic study into the configurational stability of the **Li-122**, to establish an Eyring Plot and calculate parameters for the barrier to racemisation.

Overall, these conditions provide a new class of organolithium reagents for asymmetric synthesis of tertiary thiols, which are challenging to synthesise with existing methodology.

2. The Lithiation-Borylation of Cyclobutyl Benzoates for the Synthesis of 1,1 Di-Substituted Cyclobutanes

2.1. Introduction

Previous advances in carbon-carbon bond formation have waranted the Nobel Prize in Chemistry, such as in 2010, when the prize was awarded for the development of transition metal catalysed sp^2-sp^2 carbon-carbon coupling reactions.[112] Even with such breakthroughs, a persistent challenge encountered in synthetic organic chemistry concerns the ability to control stereochemistry of C–C bond formation.[111] To this extent, lithiation-borylation methodology provides a versatile option for coupling two building blocks to generate enantioenriched products under stereocontrol.[113–116]

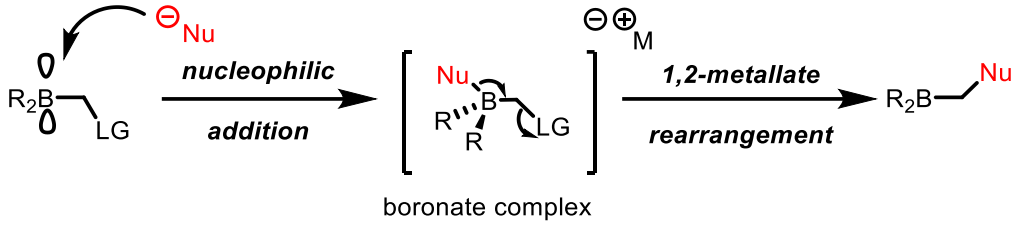


Scheme 64: Brown enantioselective hydroboration of *z*-alkenes.

Pioneering work by H. C. Brown showcased organoboron reagents as candidates for highly stereoselective processes and as synthetic alternatives to analogous enzymatic reactions.[117–119] For example, the enantioselective hydroboration of an unhindered cis-alkene, but-2-ene, using a naturally occurring (+)-α-pinene derivative to give diisopinocampheylborane **169** (Scheme 64). The subsequent boronic ester intermediate **170** was oxidised to give enantioenriched alcohol **171** in high *e.e.*[118,120–122] More recently the versatility of organoboron reagents in asymmetric synthesis has led to significant development of synthetic organic chemistry utilising this functional group.

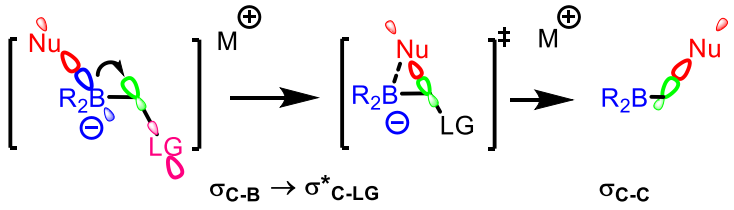
The vacant *p*-orbital on the boron atom of a boronic ester allows for addition of a nucleophile which results in the formation of a boronate complex (scheme 65). This species can undergo a 1,2-metallate rearrangement (also referred to as 1,2-migration), in which a group migrates from

the boron atom to an adjacent carbon atom, simultaneously expelling a leaving group. This produces a homologue of the starting boronic ester.[123–126]



Scheme 65: 1,2-metallate rearrangement of boron-ate complexes.

The migration requires the σ_{CB} bond to align anti-periplanar to the $\sigma^*_{C\text{-}LG}$. As a consequence, this stereoelectronic requirement results in stereoinversion of the carbon centre.[127] The 1,2-migration requires the leaving group and boron atom to have a geminal relationship, as shown in Scheme 66. The stereospecific nature of the concerted mechanism enables this chemistry to produce stereocentres with high stereofidelity.[127]



Scheme 66: The orbital alignment required to facilitate 1,2-migration.

The migratory carbon substituent required in this process can be introduced through a metal carbenoid[128,129] bearing a leaving group. A carbenoid is a carbene-like compound that displays both nucleophilic and electrophilic character.[130,131] Carbenoids can be prepared in a chiral and non-racemic manner by careful choice of leaving group (LG), making these class of compounds useful for the stereoselective homologation of organoboron compounds, by either reagent or substrate control (Figure 5).[123]

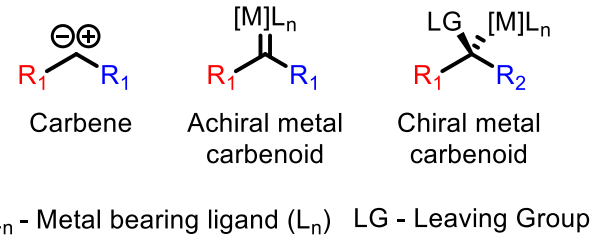
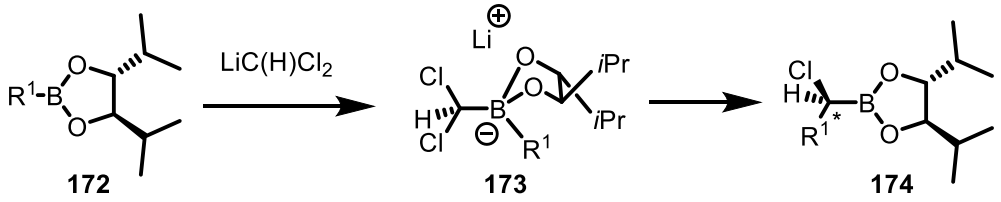


Figure 5: Comparison of carbenoids to carbenes.

2.1.1. Substrate Controlled Homologation of Boronic Esters

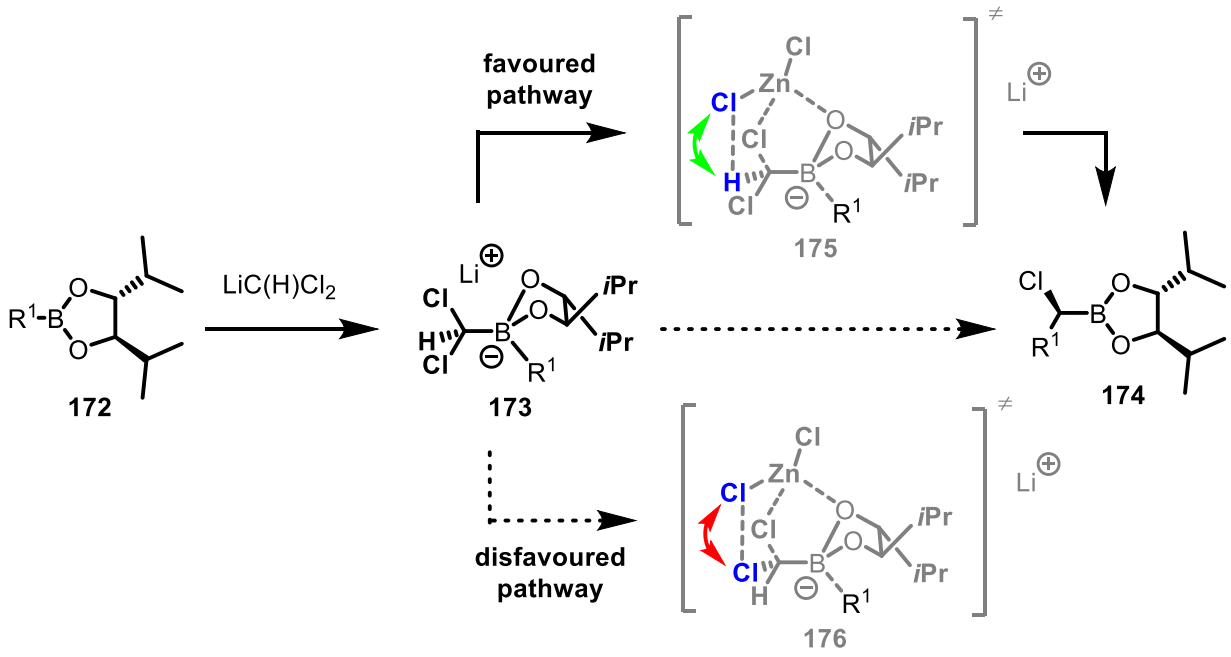
The substrate controlled stereoselective homologation requires the boronic ester to bear a chiral diol ligand **172**. This imparts a diastereoselective 1,2-migration, thus controlling the stereochemical outcome of the homologated product. As shown in Scheme 67, dichloromethyllithium is a useful reagent for homologation. This achiral carbenoid possesses two chloride leaving groups, allowing the product to partake in further homologations. However, the intermediate boronate complex **173** has two ways in which it can migrate (there are two identical leaving groups) and without direction product **174** would be formed as a 1:1 mixture of diastereoisomers. Use of a chiral and non-racemic diol on boron directs the migration affording diastereomerically enriched product **174**. A limitation of this methodology is the requirement for changing the chiral diol if the opposite boron ester isomer is desired. This reduces the practicality of this method for introducing multiple stereocentres through sequential homologation.



Scheme 67: Substrate-controlled boronic ester homologation for stereoselective homologation.

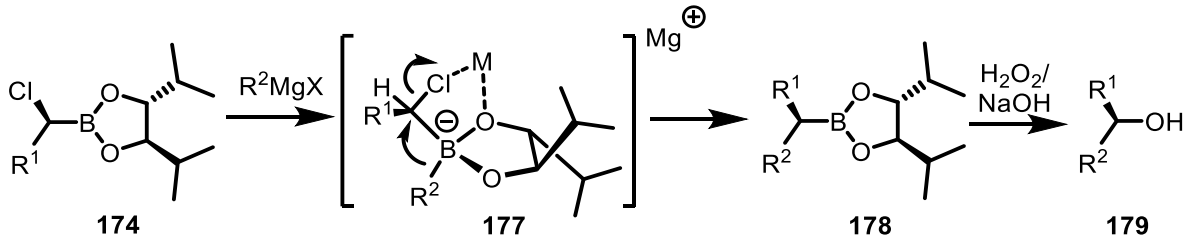
The use of chiral boronic esters for substrate-controlled homologation of boronic esters was first developed by Matteson and co-workers in the 1980's.[132] Here they showed that boronic esters **172** bearing a C_2-symmetrical chiral diol ligand reacted with dichloromethyllithium to furnish boronate complex **173** (Scheme 68). The boronate complex **173** underwent 1,2-migration to furnish both diastereoisomers of homologated boronic ester **175** and **176**. Notably,

this protocol required the addition of a Lewis acid, $ZnCl_2$. The authors suggested that this helped to sequester free chloride ions and prevent erosion of diastereoselectivity.[133134] Subsequent, *ab initio* calculations reported by Midland and co-workers were used to explain the stereoselectivities observed in this reaction, which gives **174**.[135] It was found that the lowest energy transition state (giving **175**), required the $ZnCl_2$ to complex to the least sterically hindered boronate oxygen atom, with the free chloride sitting in an *anti*-configuration to the zinc atom.[135] However, further studies by Aggarwal and co-workers suggested that the preferential hydrogen bonding of the chelated $ZnCl_2$ with the hydrogen atom on dichloromethyllithium, rather than the chlorine atom, reduced the steric clash and promoted diastereoselective 1,2-migration to give **174**.[136]



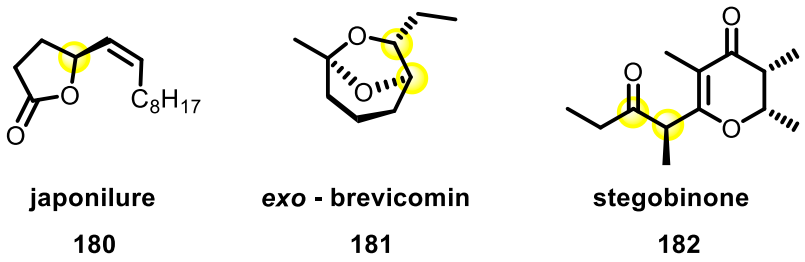
Scheme 68: Role of $ZnCl_2$ in controlling diastereoselectivity of Matteson-type homologation.

Successive treatment of α-chloroboronic ester **174** with carbon nucleophiles furnished boronate complex **177** (Scheme 69). This underwent stereospecific 1,2-migration to access secondary boronic ester **178** and enantioenriched secondary alcohol **179** post oxidation. In addition, a range of heteroatom nucleophiles were also tolerated in this methodology, including, azide, thiol and di(trimethylsilyl)amine.[123]



Scheme 69: Homologation and oxidation of *α*-chloro boronic esters.

This iterative homologation methodology allowed for the incorporation of adjacent stereocentres (highlighted yellow), as later shown by Matteson and co-workers, in the total synthesis of natural products (Figure 6), such as, insect pheromone japonilure[137] **180,** *exo*-brevicomin[138] **181** and stegobinone[133,139] **182**.



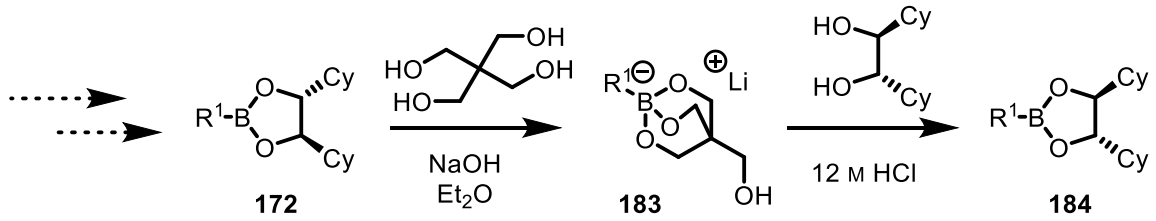
japonilure **180**

***exo* - brevicomin** **181**

stegobinone **182**

Figure 6: Examples of total syntheses achieved using Matteson homologations.

The total syntheses reported also highlight the limitation of this methodology, such that if the opposite boronic ester stereoisomer were required then the chiral diol on the boronic ester would need to be exchanged for its enantiomer. This need for transesterification increases the reaction step count. Bearing this mind, Matteson developed methods to cleave boronic ester diol groups, through transesterification with diethanolamine[140], TAPS (3-{[tris(hydroxymethyl)methyl]amino}propanesulfonic acid)[139] or pentaerythritol[139]. However, these interconversions require two steps, with an associated decrease in reaction yield. For example, the transesterification of boronic ester **172** with pentaerythritol, generated boronic ester **183**, which can be cleaved and esterified with the enantiomer diol to give **184**.



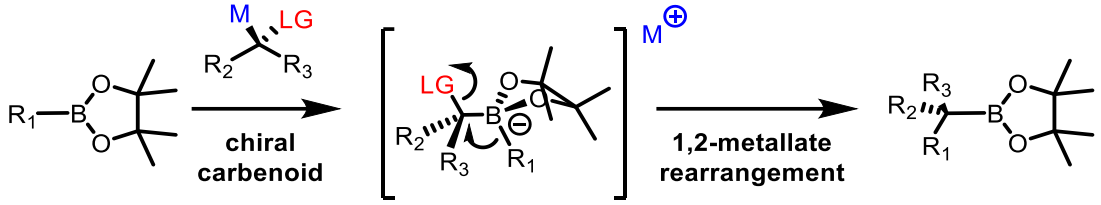
Scheme 70: Exchanging boronic ester diol group (pentaerythritol).

Though the Matteson protocol is excellent for the synthesis of secondary boronic esters, it displays poor diastereoselectivity when attempting to synthesise tertiary boronic esters. The unpredictable reactivity encountered renders it difficult to establish stereochemical outcomes when using various tertiary boronic ester derivatives.[141]

2.1.2. Reagent Controlled Homologation of Boronic Esters

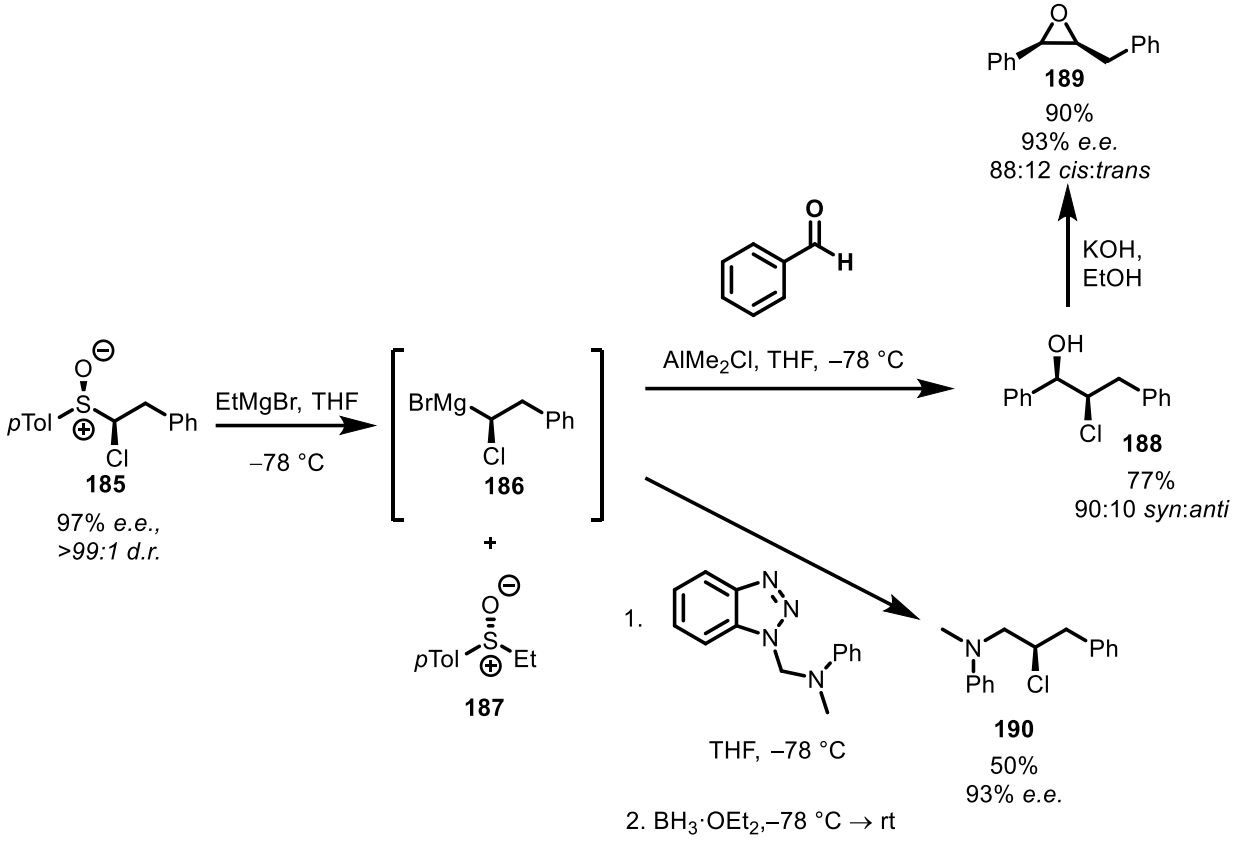
Reagent control of stereochemistry is a complementary strategy to the substrate-controlled, stereoselective homologation of boronic esters. This method requires synthesis of stereochemically defined and configurationally stable chiral carbenoid bearing a suitable leaving group for the migration step. The reaction of such a chiral carbenoid with a boronic ester furnishes a boronate complex with predefined stereochemistry, such that the subsequent stereospecific 1,2-migration transfers the stereochemical information set by the carbenoid to the homologated product. If both enantiomers of the carbenoid can be synthesised, both enantiomers of homologated product can be accessed, without alteration to the ligand on the boronic ester. For this reason, the reagent-controlled approach to stereoselective boronic ester homologation is considered the more versatile synthetic option, when compared to substrate-controlled homologation.[124]

Given the limitations of Matteson's homologation using substrate control of stereochemistry outlined above, a more synthetically efficient route would use reagent-controlled homologation (Scheme 71). This can be achieved by using nucleophilic chiral carbenoid reagents, which are chemically and configurationally stable under reaction conditions, to impart stereochemical information.



Scheme 71: A reagent-controlled approach to boronic ester homologation.

2.1.2.1. Boronic ester homologation of α-Chloro Carbenoids

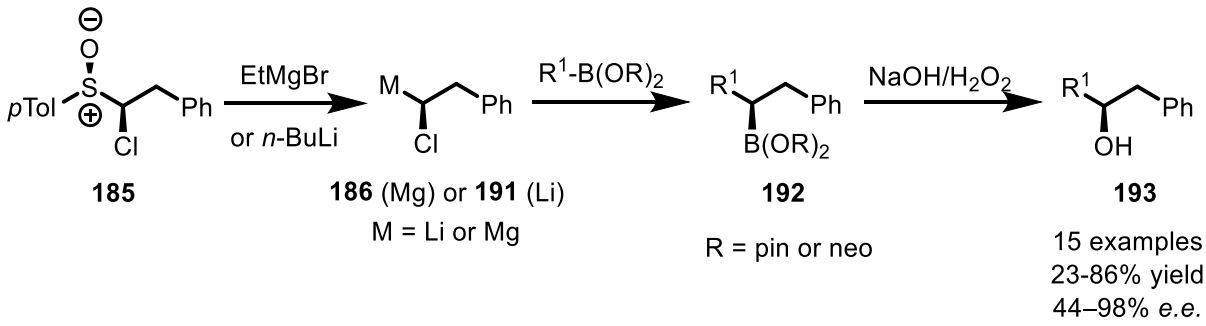


Scheme 72: Sulfoxide ligand exchange for electrophile trapping.

Hoffman and co-workers utilised *α*-chlorosulfoxides **185** (Scheme 72) as precursors to configurationally stable *α*-chloro chiral magnesium carbenoids **186**.[142,143] The stereospecific sulfoxide-magnesium exchange of optically pure sulfoxide **185** with EtMgBr generates chiral organomagnesium reagent **186** and by-product **187**. This reagent **186** was then trapped by benzaldehyde to give chlorohydrin **188**, which was converted to an epoxide **189** to determine the *e.e.* (93%). The high level of stereocontrol in this reaction were achieved due to the *α*-chloro Grignard **186** being configurationally stable below −60 °C.[142,143] A repeat of this experiment,

trapping with α-aminomethylbenzotriazole, gave **190** in high *e.r.* with retention of stereochemistry. The α-chloro organolithium species are less configurationally stable than their magnesium counterparts, with full racemisation at after 15 mins at −50 °C.[144]

Subsequently, Blakemore and co-workers reported the use of α-chloro carbenoids **186/191** as reagents for the stereoselective homologation of boronic esters.[145] The boronic ester products **192** obtained from these reactions were oxidised *in situ* to give secondary alcohols **193** in moderate yield and enantioselectivity (Scheme 72).



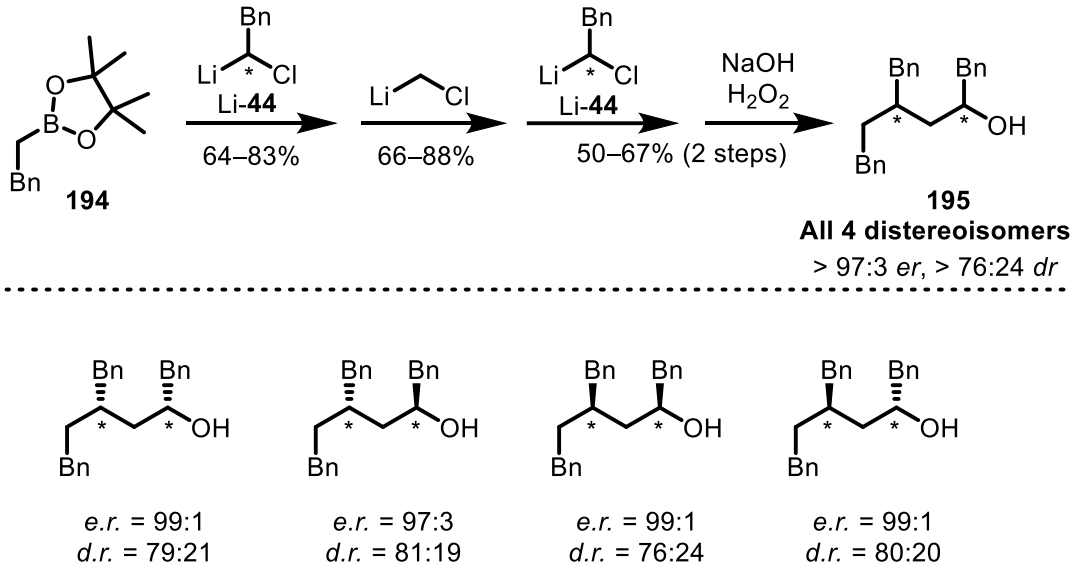
Scheme 73: The asymmetric homologation of α-chloro sulfoxides with boronic esters.

The poor selectivity was attributed to epimerisation of the enantiopure α-chloro Grignard following sulfoxide ligand exchange. At this stage, the authors explored α-chloro alkyllithium reagents, generated through sulfoxide-lithium exchange. However, these reagents were difficult to synthetically exploit due to configurational lability issues encountered at −78 °C.

Blakemore and co-workers overcame these issues through *in situ* generation of the chiral carbenoids which were successfully reacted with a range pinacol or neopentylglycol boronic esters (Bneo) to give secondary boronic esters. These were oxidised *in situ* to afford the secondary alcohols in significantly higher *e.r.*[146] The improvement in *e.r.* was attributed to higher reactivity of the configurationally labile α-chloro alkyllithium reagents, which led to faster trapping of the boronic ester than when using α-chloro Grignard reagents.

Blakemore's reagent-controlled methodology overcomes the ligand exchanges issues apparent in Matteson's methodology, however, the authors struggled to use secondary sulfoxides in this

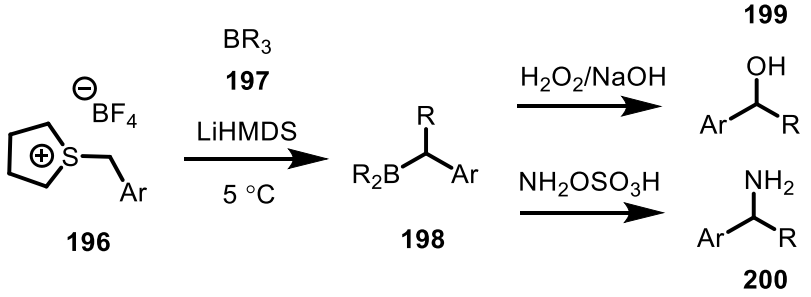
protocol, hence this methodology is generally limited to primary alkyl sulfoxides. Blakemore-type homologations were used to synthesise all 4 stereoisomers of **195**, which were isolated as single enantiomers, through using either enantiomer of the sulfoxide precursor in an iterative manner with boronic ester **194**, in moderate diastereoselectivity (Scheme 74).[146,147]



Scheme 74: *α*-chloro organolithium reagents in the homologation of boronic esters.

2.1.2.2. Borane Homologation using Sulfur Ylides

The homologation of boranes using semi-stabilised sulfur ylides were first reported by Aggarwal and co-workers (Scheme 75). The authors had previously reported using sulfonium ylides **196** for the synthesis of enantioenriched epoxides, cyclopropanes and aziridines.[148]

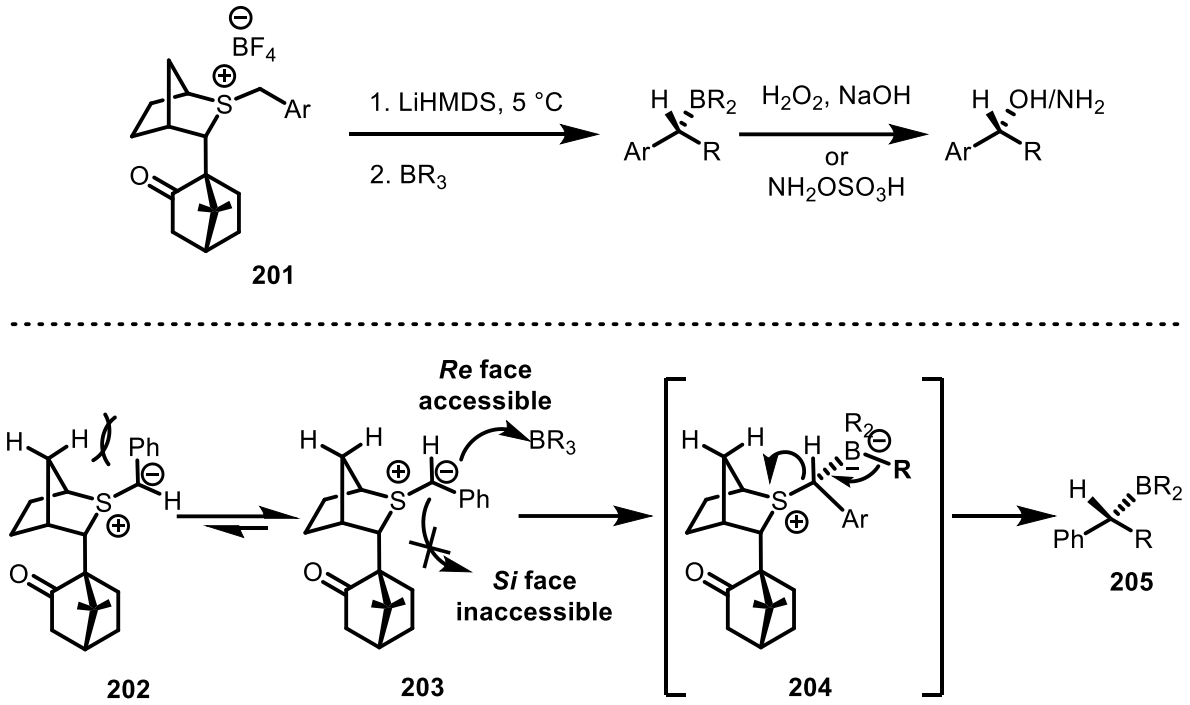


Scheme 75: Borane homologation with sulfur ylides **196**.

Here, aryl sulfonium salts **196** have been used to generate semi-stabilised sulfur ylides *in situ*, using a hindered base (LiHMDS). These highly reactive species act as carbenoids and undergo similar homologations with trialkyl or triaryl boranes **197**, in which the sulfide group is displaced. The homologated boranes **198** were isolated as oxidised alcohols **199** or amine **200**, for ease of handling, in good yield.

This methodology was translated to the stereoselective variant by using chiral sulfonium salts **201**, which underwent homologation with a range of organoboranes at a given temperature (5 °C or -78 °C to improve product *e.r.*) to provide the corresponding secondary alcohols and amines in good yield and high enantioselectivity (Scheme 76). This methodology allowed for the synthesis of either enantiomer of organoborane homologated product, as both enantiomers of sulfonium salt **201** could be readily prepared.

The high stereoselectivities achieved in this methodology are attributed to the conformational bias present in the sulfur ylide, which forces the aromatic group away from the bridging methylene (scheme 76, **201**). This renders the process selective, as reaction with the organoborane can only proceed on the less hindered face **203** (*Si* face) of the sulfur ylide, thus generating the boron ate complex **204** in very high diastereoselectivity.[116,149] The subsequent stereospecific 1,2-migration of the boron ate complex means that the homologated product **205** is obtained in high enantiomeric excess.



Scheme 76: Origin of stereoselectivity in homologation of boranes with sulfur ylides.

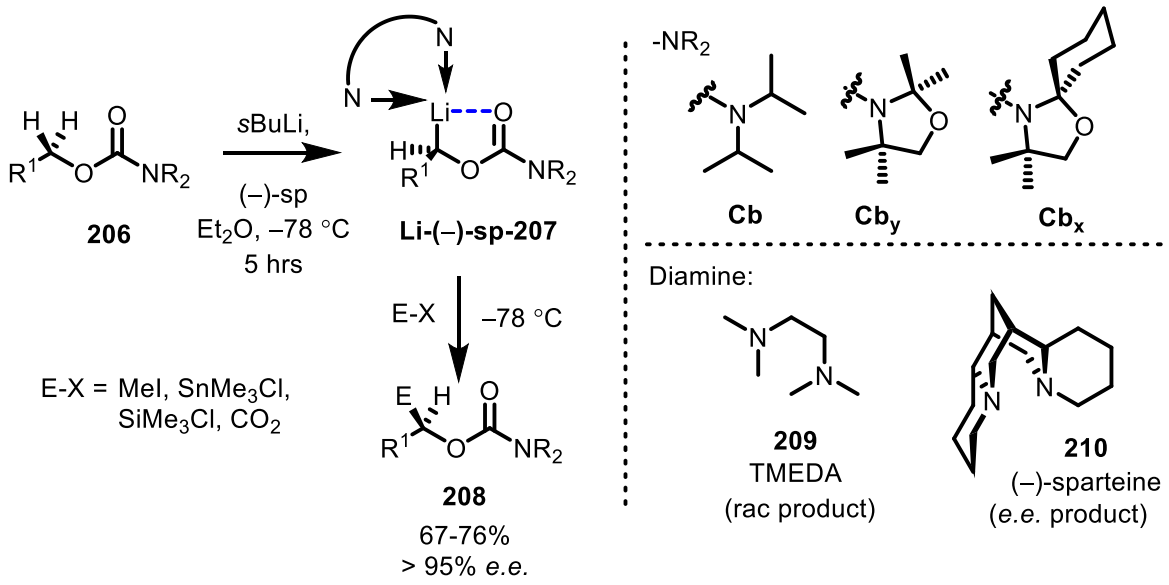
In this methodology, the 1,2-migration of non-symmetrical organoboranes is dependent upon the migratory aptitude of that substituent, thus reducing the functional groups that can be used in this iterative homologation.[127] Furthermore, an aryl substituent had to be present on the semi-stabilised ylide as non-stabilised alkyl or silyl-substituted ylides gave poor enantioselectivities. To overcome the selectivity over which group migrates, boronic esters were utilised in place of boranes, however boronic esters are unreactive to sulfur ylides, due to difficulties associated with the 1,2-migration of the boronate complexes, and therefore not applicable to this methodology.

2.2.1.3. Hoppe's Primary Lithiated Carbamates

Hoppe and co-workers reported the enantioselective deprotonation of primary *O*-alkyl carbamates **206** (Scheme 77), using a stoichiometric chiral and non-racemic diamine [(−)-sparteine) **210** and *s*BuLi to generate lithiated carbamates Li-(−)-sp-**207**. These could be trapped with a range of electrophiles (E-X) to give products **208** in high yields and high *e.r.* (typically with retention of stereochemistry).[150]

If TMEDA **209** is used in place of (−)-sparteine **210**, then the racemic product is achieved through this protocol. Hoppe and co-workers used three types of carbamate groups (Scheme 77): diisopropyl carbamate (Cb) and oxazolidine carbamates (Cb_x and Cb_y). The diisopropyl carbamate can be reduced to the corresponding alcohol in the presence of $LiAlH_4$ and oxazolidine carbamates can be removed by acid/base hydrolysis, to give the corresponding secondary alcohol.

The carbamate electron-withdrawing group enables *α*-deprotonation by initially forming a pre-lithiation complexation, followed by deprotonation.[151,152] The rate of (irreversible) deprotonation of pro-*S* is fifty fold greater than pro-*R*, giving rise to Li-(−)-sp-**207** with high selectivity.[153] This is an example of kinetic control. Li-(−)-sp-**207** shows high chemical and configurational stability in diethyl ether at −78 °C. The presence of bulky, hindered substituents on the carbamate nitrogen prevents the organolithium undergoing nucleophilic addition to the amide.[151]

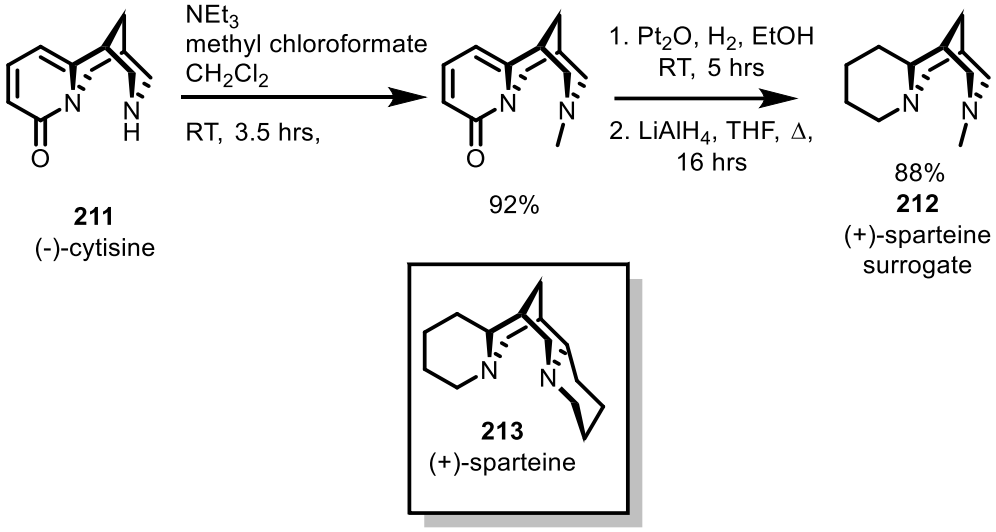


Scheme 77: Lithiation of primary alkyl carbamates and trapping with electrophiles.

The deprotonation of **206** is dependent on solvent, whereby stereoselective lithiation of primary *O*-alkyl carbamates under same conditions in Et_2O, occurs with a higher degree of selectivity than when using THF as solvent.[154] This is due to competing ligation of THF with the lithium

cation over (−)-sparteine, and as a result, 6.0 equivalents of (−)-sparteine with respect to the organolithium base are required for reactions that use THF as solvent.

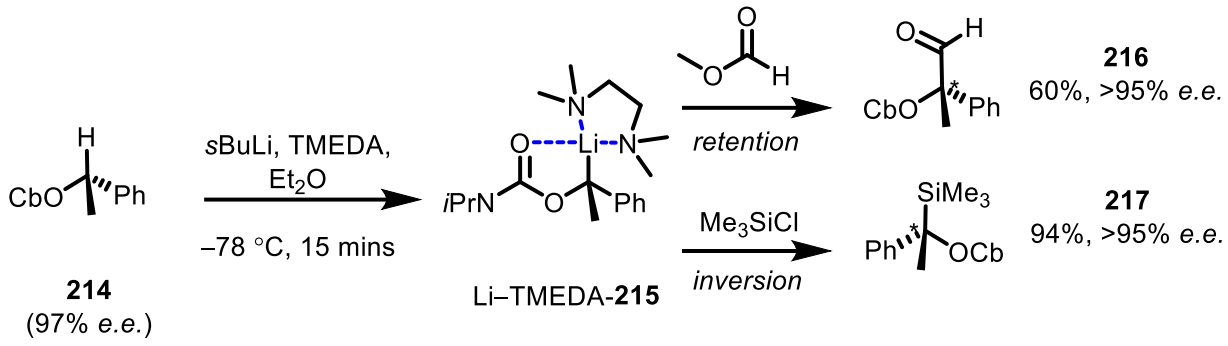
At present, both enantiomers of sparteine are commercially available, however (−)-sparteine **210** is typically more expensive, but (+)-sparteine **213** can also be synthesised.[155] However, (+)-sparteine **213** was more difficult to obtain than (−)-sparteine at the time of Hoppe's work. Hoppe used only (−)-sparteine **210**, as this was a cheaper, readily available natural product, isolated from Lupin seeds.[151] The O'Brien group developed (+)-sparteine surrogate **212**, which could be obtained from (−)-cytisine **211** in 3 steps (Scheme 78). This surrogate induces the opposite enantioselectivity to (−)-sparteine **210** with products usually obtained in high stereoselectivity.[156,157]



Scheme 78: O'Brien's (+)-sparteine surrogate **212** synthesis.

2.1.2.4. Lithiation-Electrophile Trapping of Primary Benzylic Carbamates

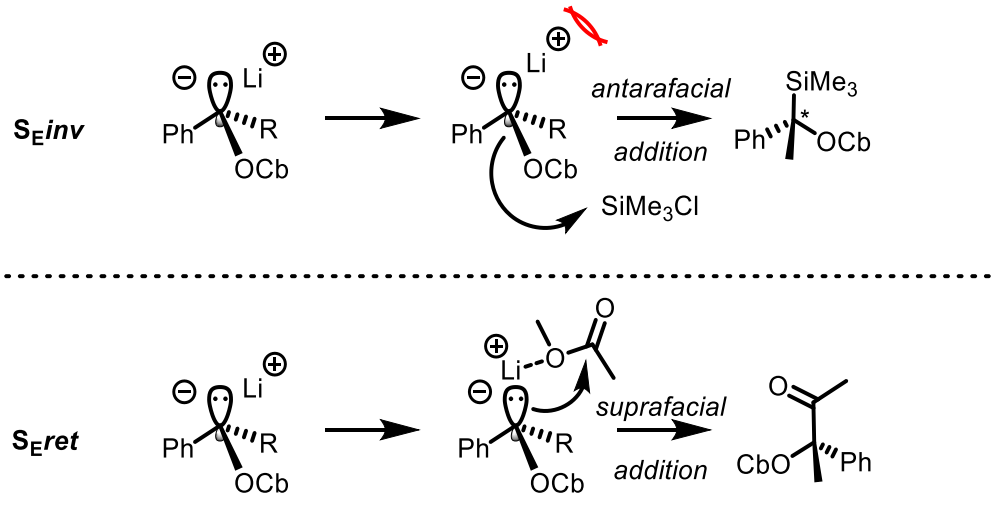
Hoppe and co-workers also explored the lithiation of *O*-benzyl carbamates **214**, which could be generated by using *s*BuLi/TMEDA (Scheme 79), in which the presence of an aromatic ring stabilises the carbanion, by promoting solvent-separated ion pair formation.[150] The choice of solvent also influences the stereoselectivity of secondary benzylic carbamates. For the scope of this reaction, it was found that Et_2O results in a tighter ion pair between the lithium cation and carbanion, giving configurational stability to the lithiated secondary benzylic carbamate.



Scheme 79: Lithiation-electrophile trapping of secondary benzyl carbamates.

The stereochemical outcome of the trapping of Li-TMEDA-**215** is electrophile dependant, such that electrophiles that co-ordinate to the lithium cation react with retention of stereochemistry **216**, whereas electrophiles without coordinating groups reacting with inversion (alkyl halides, stannanes, silyl electrophiles **217**).[158]

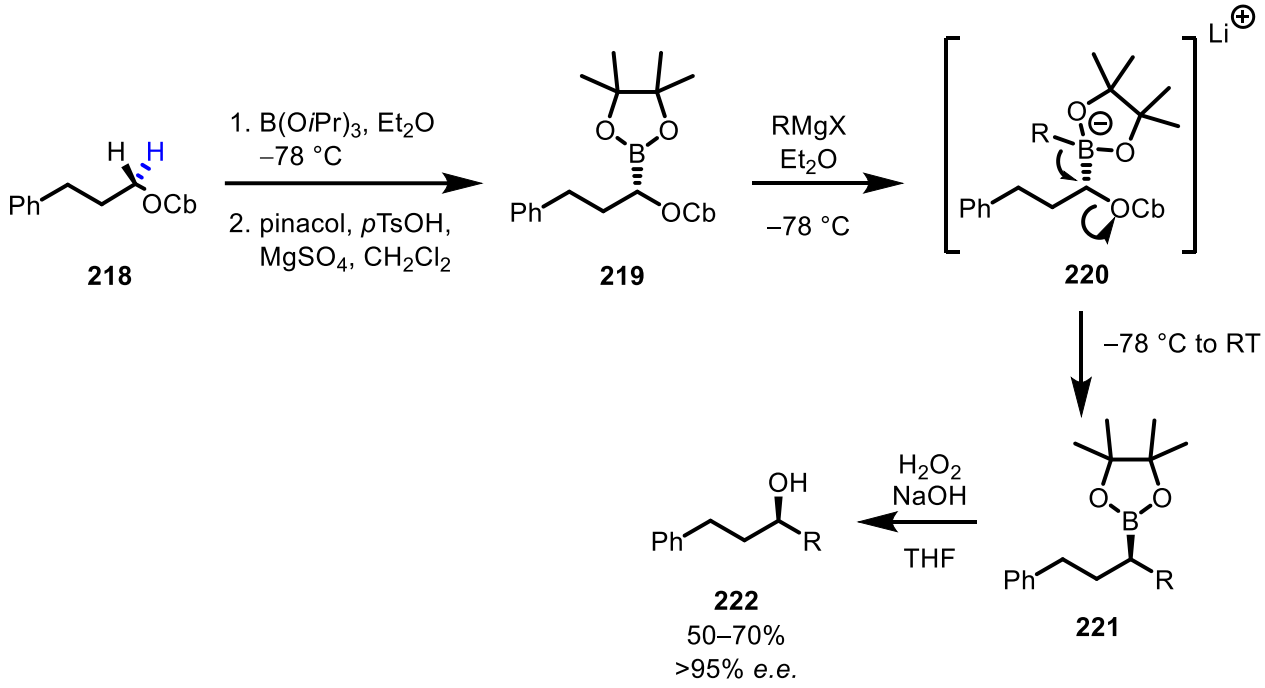
Lithiated secondary benzylic carbamates undergo partial planarization of the carbanion by delocalisation into the adjacent benzene π-system, which increases the electron density on the carbanion back face and so encourages antarafacial approach (Scheme 80), therefore non-coordinating electrophiles (*e.g.* ethyl bromide) react with inversion to avoid the steric interaction with the Li•TMEDA diethyl ether complex. On the other hand, electrophiles which possess coordinating groups (e.g. methyl acetate) react with retention of configuration as pre-coordination to the lithium complex, delivers the electrophile suprafacially.



Scheme 80: Secondary benzylic carbamate electrophile trapping (retention *vs* inversion).

2.1.2.5. Lithiation-Borylation of α-Boryl Carbamates

Homologation of α-boryl carbamates by Hoppe provided an alternate two-step procedure to the existing Matteson homologation methodology.[159,160] The lithiation of *N*,*N*-diisopropylcarbamate **218** with sBuLi/(−)-sparteine, electrophilic trapping of the carbenoid with B(O*i*Pr)$_3$ and transesterification with pinacol, gave α-boryl carbamate **219** (Scheme 81).

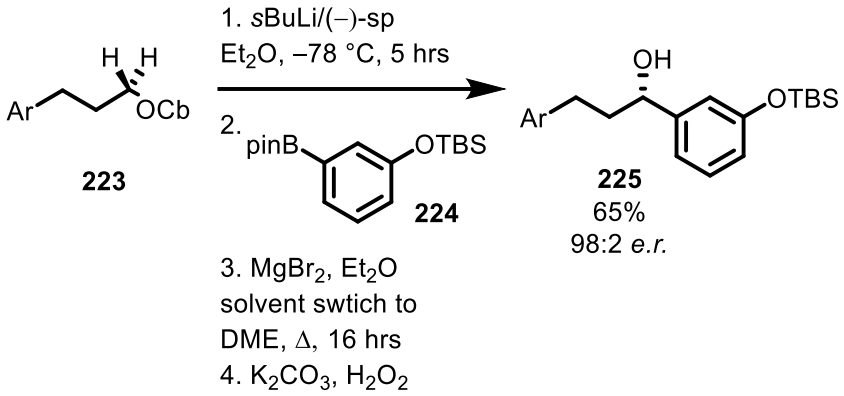


Scheme 81: Two-pot lithiation-borylation reaction of primary *O*-alkyl carbamates.

α-Boryl carbamate **219** could then undergo addition from a suitable Grignard reagent at low temperatures. This affords boronate complex **220**, which, upon heating, undergoes a 1,2-migration to give secondary boronic ester **221**. Subsequent stereoretentive oxidation of the boronic ester gave the corresponding secondary alcohol **222** in high yield and *e.e.* The use of excess Grignard was essential for 1,2-migration to occur, as the Mg salts act as Lewis acids and coordinate to the carbamate leaving group to aid 1,2-migration.

In 2006, Kocienski and co-workers reported a one-pot variant of this reaction, which tolerated homologation of the boronic ester with a lithiated carbamate (Scheme 82).[161] Here aryl boronic ester **224** was added to lithiated carbamate **Li-223** to form a boronate complex and the

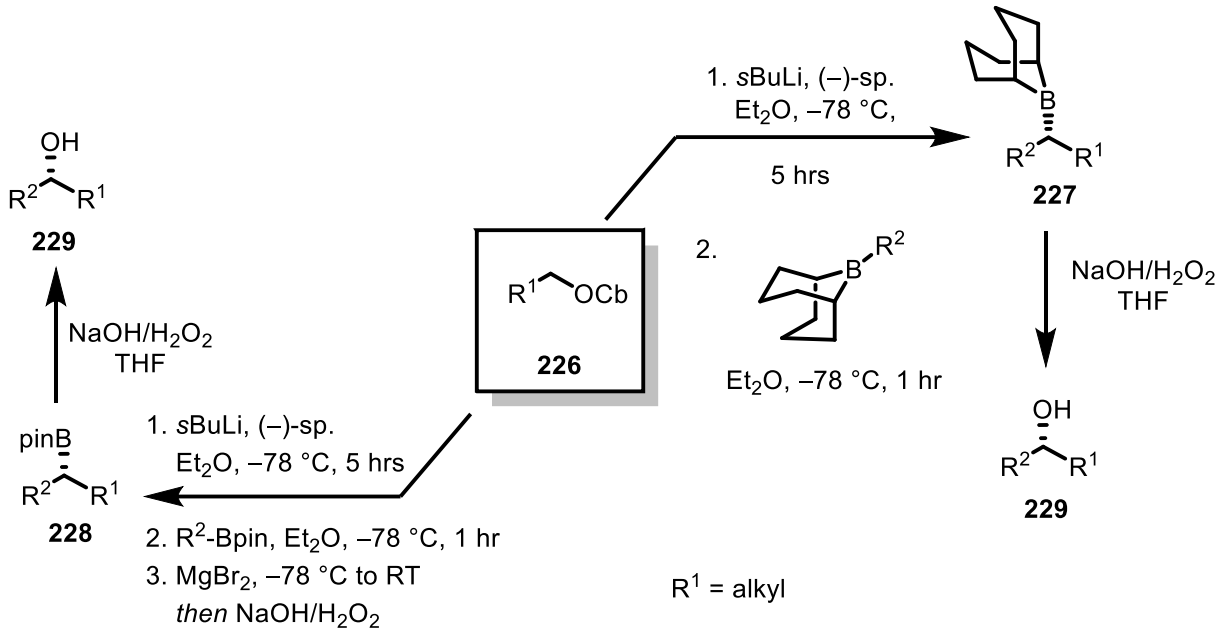
subsequent homologation product isolated upon migration. However, due to slow and inefficient 1,2-migration of the boronate complex, the diethyl ether used for the reaction was exchanged for higher boiling DME and a Lewis acid ($MgBr_2$) was added to the reaction mixture, after which the mixture was heated under reflux. These modified conditions gave the secondary alcohol **225**, after oxidation of the boronic ester, in good yield and excellent *e.r.*



Scheme 82: One pot lithiation-borylation of primary carbamate **223**.

2.1.2.6. One-Pot Homologation of Boranes and Boronic Esters

Kocienski's one pot procedure was further developed by Aggarwal and co-workers, showing that Hoppe-type *O*-alkyl carbamates Li•(−)-sp-**226** could be reacted with both boranes and boronic esters, in good yields and high *e.r.* with retention of stereochemistry (Scheme 83).[162]

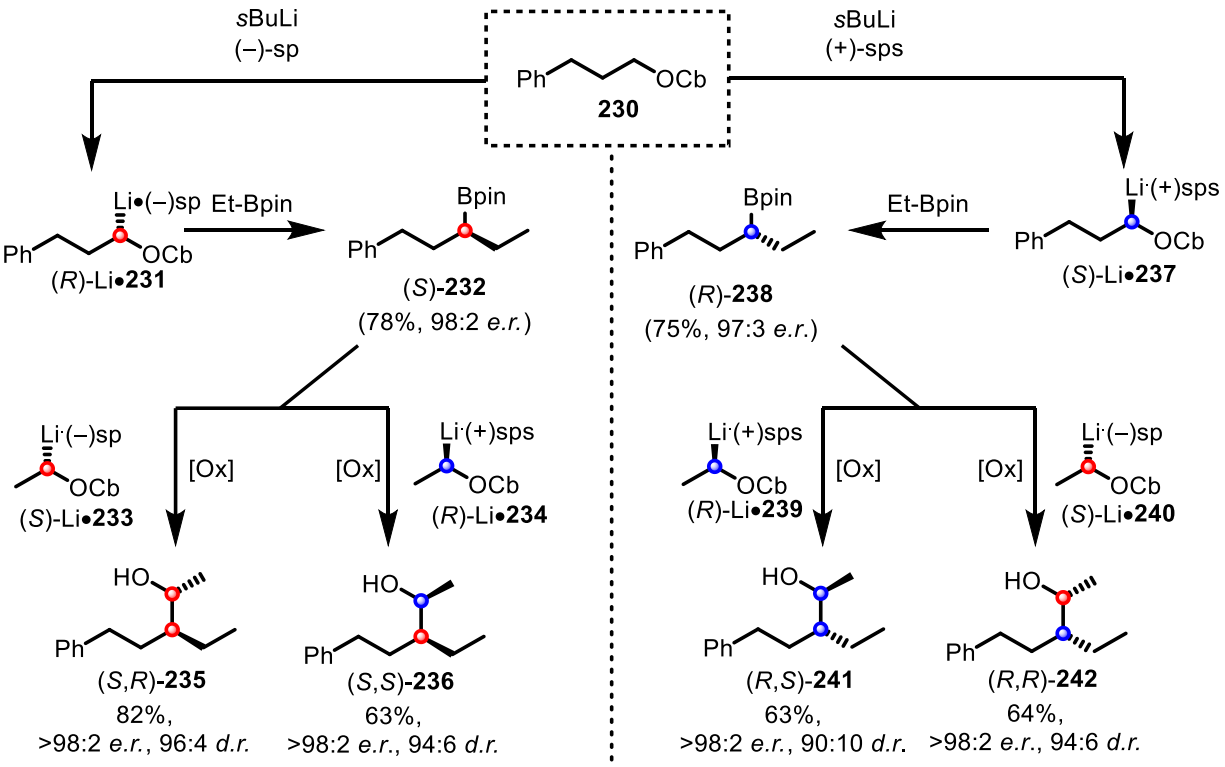


Scheme 83: Aggarwal synthesis of enantioenriched secondary alcohol **229**.

The homologated organoboron products **227** and **228** were isolated as the corresponding secondary alcohols **228** in high *e.r.* after oxidation. The 1,2-migration of boronic ester 'ate' complexes were slower than that of analogous borane 'ate' complexes and required the addition of $MgBr_2/Et_2O$ and heating under reflux for 12 hrs, whereas boranes underwent migration upon warming to RT.

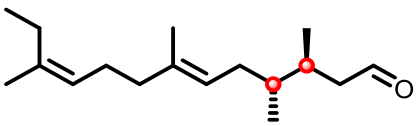
Aggarwal and co-workers showed that primary *O*-alkyl carbamates could be used in an iterative fashion to generate adjacent stereocentres (Scheme 84) by using (−)-sparteine (sp) or O'Brien's (+)-sparteine surrogate (sps).[162] Lithiation of carbamate **230** with *s*BuLi in the presence of (−)-sp gave lithiated intermediate (*R*)-Li•**231**, which was trapped with EtBpin to give boronic ester (*S*)-**232** in good yield and 98:2 *er*. Next, (*S*)-**232**, was reacted with either lithiated carbamate (*S*)- Li•**233** or (*R*)-Li•**234**, to access, after boronic ester oxidation (NaOH, H_2O_2), alcohols (*S,R*)-**235** (82% yield, 96:4 *d.r.*, >98:2 *e.r.*) and (*S,S*)-**236** 82% yield, 96:4 *d.r.*, >98:2 *e.r.*). Repeating the same process with lithiation of carbamate **230** using *s*BuLi in the presence of

(+)-sps gave lithiated intermediate (*S*)-Li•**237**, which was trapped with EtBpin to give boronic ester (*R*)-**238** in good yield and 97:3 *e.r.* Finally, (*R*)-**238**, was reacted with either lithiated carbamate (*R*)-Li•**239** or (*S*)- Li•**240**, to access, after *in situ* oxidation, alcohols (*R,S*)-**241** (63% yield, 90:10 *d.r.*, >98:2 *e.r.*) and (*R,R*)-**242** 64% yield, 94:6 *d.r.*, >98:2 *e.r.*).



Scheme 84: Aggarwal synthesis of enantioenriched secondary alcohols.

The stereochemical outcome of the reaction (high *e.r.* and *d.r.*), suggested that the second homologation is independent of the stereochemistry of the boronic ester employed, making this a powerful tool for the instalment of consecutive stereocentres as desired. This methodology was further exemplified in the total synthesis of Pharaoh's ant pheromone (+)-faranal **243** **(**Figure 7**)**, introducing the two highlighted stereocentres.[163]

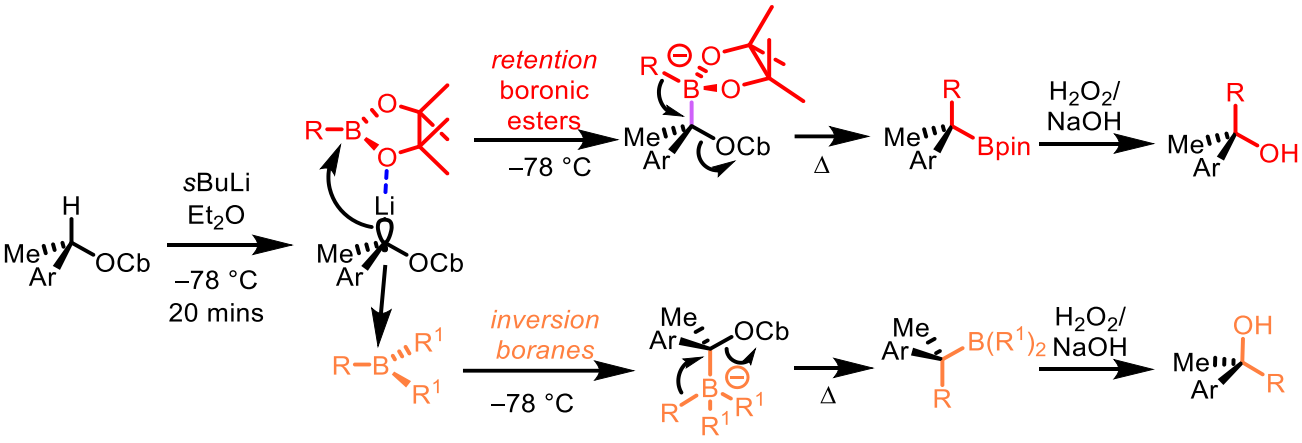


243

Figure 7: (+)-faranal **243**.

2.1.2.7. Lithiation-Borylation of Secondary Benzylic Carbamates

Subsequently, Aggarwal and co-workers incorporated secondary benzylic carbamates into lithiation-borylation methodology to access enantioenriched tertiary alcohols, post oxidation (Scheme 85).[164] Though literature for the asymmetric synthesis of secondary alcohols[165,166] is abundant with examples, the synthesis of tertiary alcohols (quaternary stereocentres) is comparatively underdeveloped, typically relying upon nucleophilic addition to ketones with asymmetric induction using chiral ligands.[28,167,168]

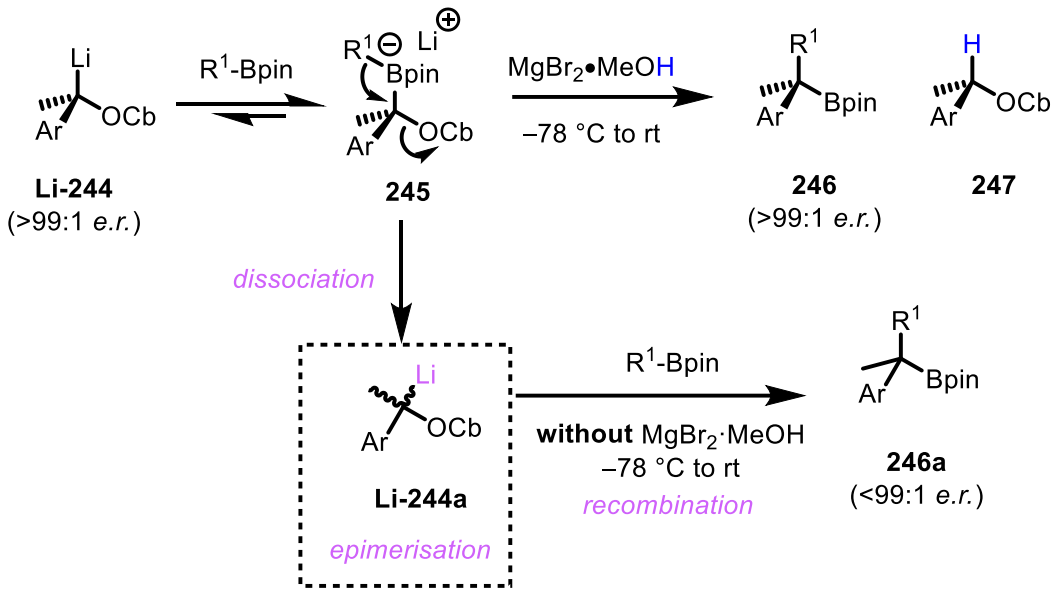


Scheme 85: Lithiation–borylation of secondary benzylic carbamates for the synthesis of tertiary alcohols.

Adapting Hoppe's electrophile dependent retention or inversion of stereochemistry of secondary benzylic carbamates, the use of boranes (inversion, antarafacial addition) and boronic esters (retention, suprafacial addition) allowed the group to access either enantiomer of product from the same carbamate. The reaction can tolerate a broad substrate scope, reacting with alkyl, vinyl, allyl and electron-rich/ deficient aryl/heteroaromatic boronic esters.[164]

However, when sterically hindered, electron-deficient secondary carbamates such as *p*chlorophenyl (98:2 *e.r.*) were used in the homologation of boronic esters, product *e.r.* (4:96 *e.r.*) was lower than expected. This erosion of *e.r.* was studied using a method developed in the Aggarwal group termed the two-electrophile test,[169] to account for the fate of competing reaction pathways that could affect the product *e.r.* Here it was seen that increasing equivalents of boronic ester in the reaction with lithiated carbamate **Li-244** gave product **246** in high *e.r.* This suggested that boronate complex formation was reversible at −78 °C, with the lithiated carbamate **Li-244** and boronate complex **245** existing in equilibrium. As the reaction mixture

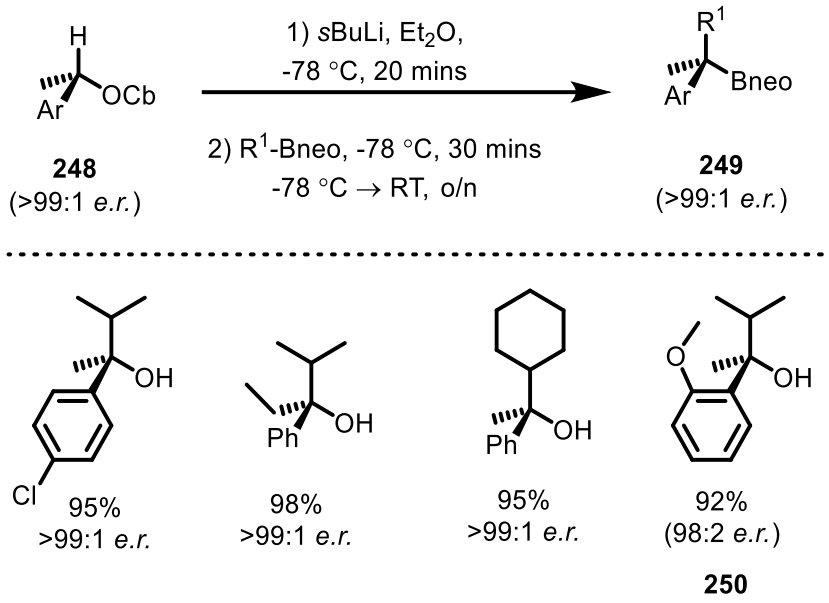
is warmed to higher temperatures to promote 1,2-migration of the boronate complex, the unreacted lithiated carbamate **Li-244a** epimerises before recombining with the boronic ester. This results in a product **246a** with lower *e.r.* (Scheme 86).[170]



Scheme 86: Epimerisation of boronate complex through dissociative pathway.

Early attempts worked by adding an additional, more reactive electrophile (allyl bromide) to the reaction mixture after boronate complex formation. This would out compete the boronic ester to react with any dissociated lithiated carbamate **Li-244**, thus prevent it from recombining with the ester after epimerisation. Though the addition of allyl bromide helped to improve stereoselectivity, the yield of product was lower, as expected. Instead, the addition of Lewis acid $MgBr_2$ in MeOH, known to promote 1,2-migration, restored stereoselectivity and gave product in high yields. The presence of MeOH also quenches any unreacted or dissociated lithiated carbamate **247** and generates product **246** in high enantiomeric excess.

A different strategy to overcome this stereoselectivity issue observed with electron-deficient carbamates **248** was to use neopentyl glycol boronic esters, which can give the analogous boronic esters (Bneo) **249** in similar high yields and stereoselectivities (Scheme 87). A disadvantage of this is that neopentyl boronic esters are less stable than the pinacol counterparts and as such are usually unstable to silica gel chromatography and under air. In addition, there was erosion of product *e.r.* when hindered substrates **250** were utilised, due to reversible ate complex.



Scheme 87: Neopentyl glycol boronic esters in homologation of tertiary carbamates.

2.1.2.8. Lithiation−Borylation with Benzoate Esters

Lithiation-borylation of carbamates provides access to either enantiomer of homologated boronic ester by using either a borane or boronic ester substrate. However, the 1,2-metallate rearrangement of boronate complexes derived from pinacol boronic esters and lithiated carbamates can be slow and inefficient, particularly when using methyl or phenyl boronic esters, and therefore require Lewis acids ($MgBr_2$) to promote this reaction pathway.[171] However, the addition of Lewis acid does not provide a general solution to all substrates. As a result, strategies using alternative leaving groups have been explored.

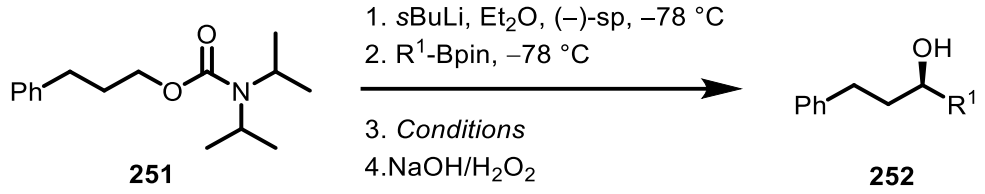
Beak and co-workers initially showed that primary 2,4,6-triisopropyl benzoates could be deprotonated with TMEDA/*s*BuLi to access the configurationally stable lithiated benzoate.[172–175] Subsequently, in 2010, Aggarwal reported the first stereoselective lithiation of primary 2,4,6-triisopropyl benzoates **253**, using (−)-sparteine/*s*BuLi. These lithiated benzoates were successfully used in the homologation of boronic esters to access secondary alcohols **252** in higher yields and similar (ca. 95:5 for a benzoate and 97:3 for the corresponding carbamate) *e.r.* to the analogous carbamates **251** (Table 7). The superior leaving group potential of the benzoate group circumvents a need for Lewis acid ($MgBr_2 \cdot Et_2O$) in this protocol. In addition,

shorter reflux times were required for the benzoate 1,2-migration (2 hrs) in comparison to carbamate 1,2-migration (16 hrs).

This methodology works well for primary and secondary benzylic benzoates and carbamates. However, non-activated, secondary dialkyl benzoates/carbamates are difficult to use in this methodology, with previous work from Beak[175] and Hoppe[150], reporting difficulty in abstraction of the α-oxy proton.

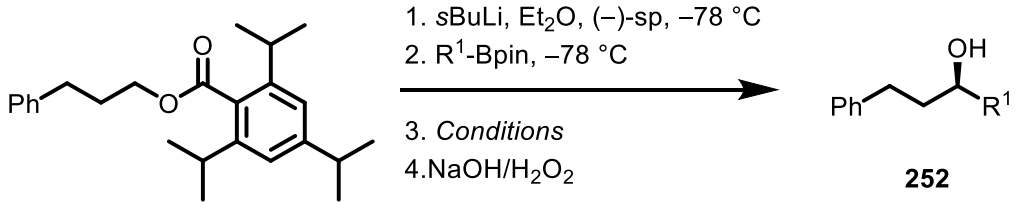
It should be noted that although Matteson homologations can also produce enantioenriched tertiary alcohols, these reactions suffer from poor and difficult to predict selectivity.[141]

Table 7: Carbamates in the lithiation-borylation of boronic esters. Conditions: A: $MgBr_2 \cdot Et_2O$ (2.0 eq.), 16 hrs reflux; B: 16 hrs reflux; C: 2 hrs reflux.



251 **252**

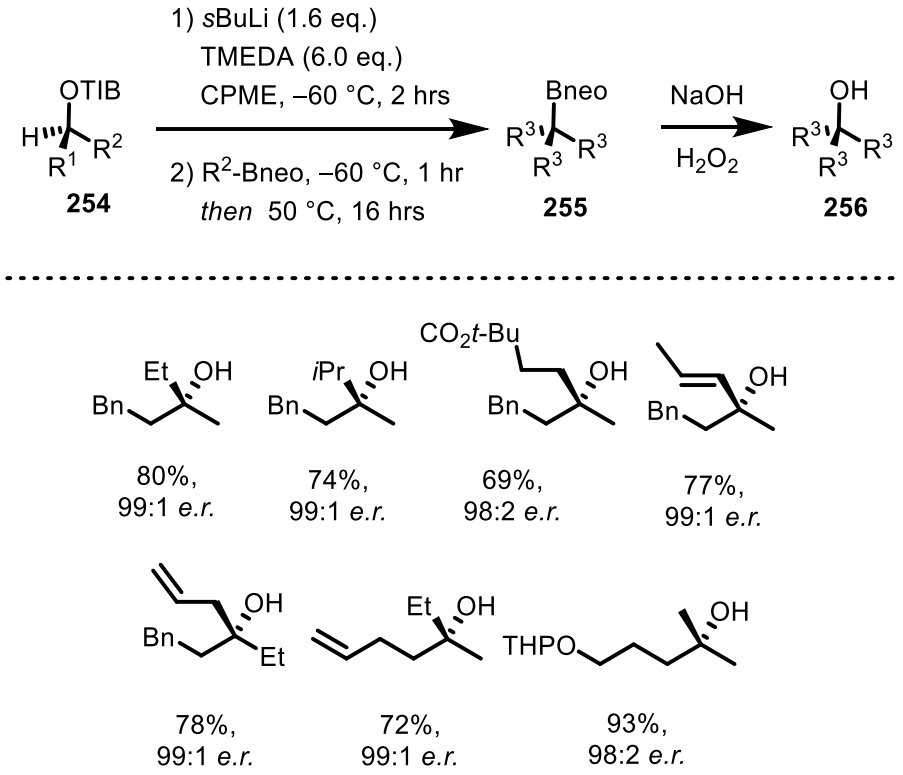
	R^1-Bpin	Yield (%)	*e.r.*	Conditions
1	Me	50	95:5	A
2	*c*Pr	71	98:2	B
3	$(CH_2)_2COO^tBu$	35	93:7	A
4	$(CH_2)_2CN$	0	N.A.	A
5	Ph	88	99:1	A



253 **252**

	R^1-Bpin	Yield (%)	*e.r.*	Conditions
1	Me	76	96:4	C
2	*c*Pr	86	96:4	C
3	$(CH_2)_2COO^tBu$	63	96:4	B
4	$(CH_2)_2CN$	46	97:3	B
5	Ph	79	96:4	C

In 2012, Aggarwal and co-workers reported the synthesis of enantioenriched tertiary boronic esters using lithiation/borylation of enantioenriched secondary alkyl benzoates (Scheme 88).[169] This feat was achieved by performing the lithiation of enantioenriched benzoate **254** with *s*-BuLi (1.6 eq.) and an excess of TMEDA (6.0 eq.) in CPME as the solvent at −60 ˚C. The enantioenriched lithiated benzoate was reacted with a broad range of neopentyl glycol boronic esters in good yield and complete enantiospecificity to produce tertiary boronic esters **255**. These can be oxidised to the corresponding enantioenriched tertiary alcohols **256**. The analogous dialkyl carbamates were trialled in a lithiation-deuteration under optimised conditions however; they demonstrated low recovery (49%) of material with low deuterium incorporation (10%).



Scheme 88: Lithiation–borylation of dialkyl benzoates.

The Aggarwal protocols for lithiation-borylation have been successfully applied to 'assembly line' synthesis, in which up to 10 iterative homologations are used to introduce 10 adjacent methyl stereocentres,[176] with control over the absolute and relative stereochemistry of the compounds produced through this synthetic route. In addition, natural products such as (+)-

kalkitoxin[177] and (+)- hydroxyphthioceranic acid[177] (Figure 8), were synthesised through this synthetic approach.

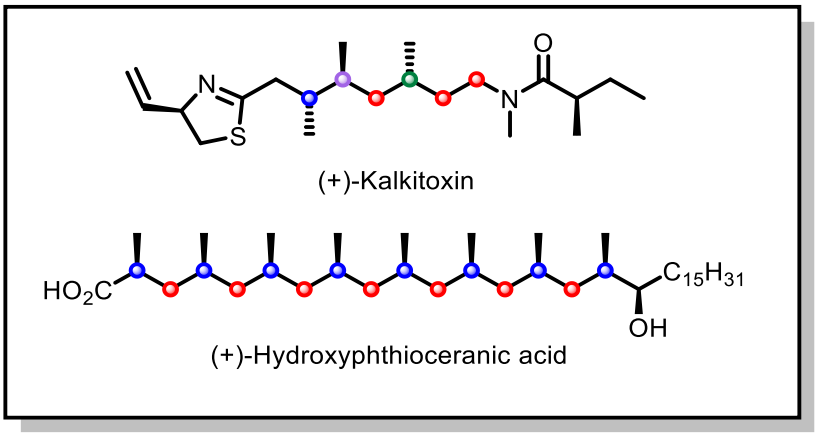


Figure 8: (+)-Kalkitoxin and (+)-Hydroxyphthioceranic acid with coloured highlights indicating the carbon centres introduced through lithiation–borylation reactions.

2.1.3. Boronic Ester Functional Group Interconversion

In the homologation methodology discussed so far, the boronic esters have been used to create carbon-carbon bonds through means of a boronate complex undergoing 1,2-migration.[178,179]

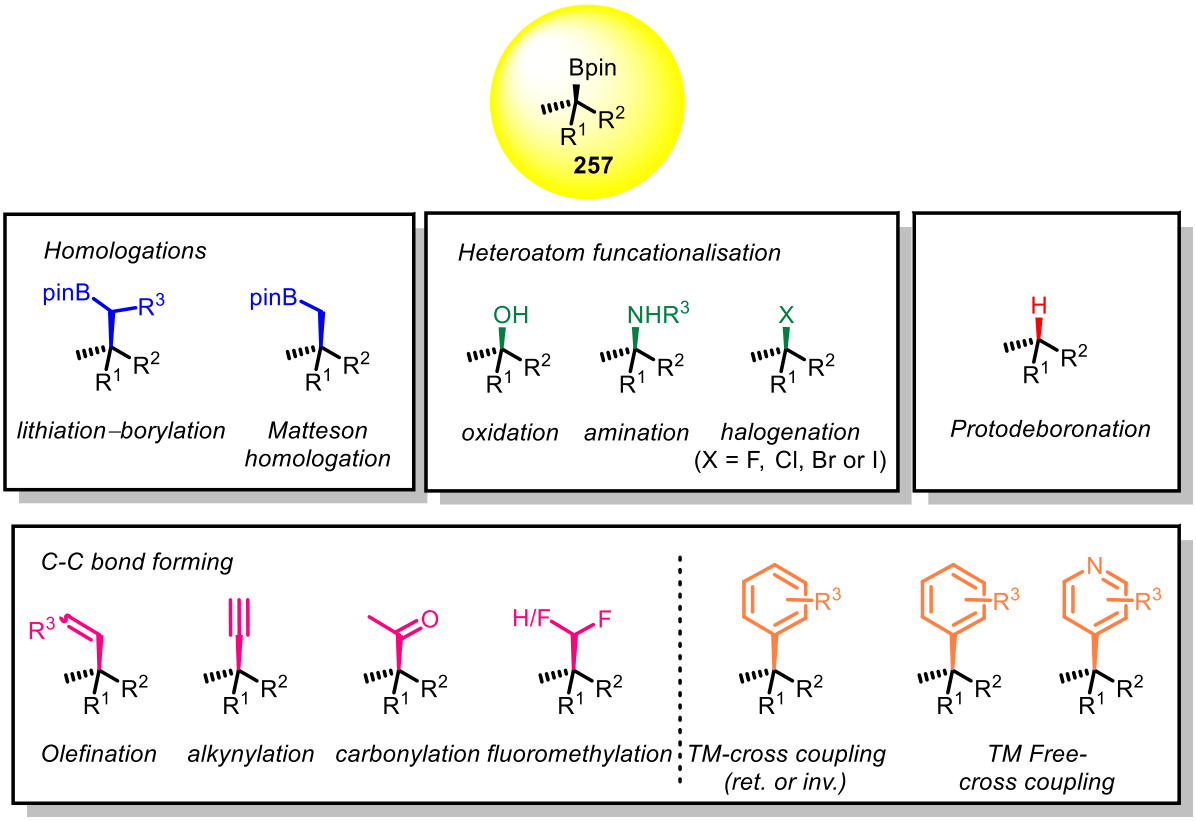


Figure 9: Examples of boronic ester transformations **257**.

Typically, the boronic ester moiety is retained as a functional handle to undergo subsequent homologations. However, the boron atom can be interconverted to various other functional groups, further expanding the use and application of this chemistry.[178] Beyond the scope of this report, the boronic ester transformations are highlighted in Figure 9, and are grouped by modification. Boronic ester **257** could undergo further lithiation-borylation type reactions, either through Aggarwal or Matteson type reactions[133]. Similarly, the boronic ester can be exchanged for a heteroatom, giving access to alcohols, secondary amines, or halides (F[180], Cl[171], Br[171] or I[171]). Furthermore, the boronic ester can be exchanged for a hydrogen atom through protodeboronation.[181,182] There are also additional carbon-carbon bond forming processes available. The boronic ester can be converted to an alkene via Zweifel olefination,[183184] terminal alkyne,[185] ketone[169] or fluoromethyl/ gem-difluoromethyl[186] group. Finally, the boronic ester can be cross coupled, *via* conventional transition metal-based

protocols and transition metal-free routes.[187] Most boronic ester/borane transformations are stereospecific and therefore retain the stereocentre installed through lithiation–borylation (or any other boron installation) methodologies.

The 1,2-metallate rearrangement observed in boron-ate complexes can be used to explain many of the transformations in organoboron chemistry.

2.1.4. *In-situ* Spectroscopy in Lithiation-Borylation

Traditionally, infrared spectroscopy (IR) provides an analytical method to assess chemical molecules, by exposing the chemical to IR radiation, which is absorbed by the chemical.[188] This absorption information is then presented as an IR spectrum, which shows the absorption "fingerprint", bespoke to each molecule, in a range that spans from 4000-400 cm^{-1}. By a chemical entity absorbing IR radiation, the bonding and even structure can be elucidated.

The bond vibration frequency (ν) at temperature T, is proportional to the square root of the bond strength and inversely proportional to the root mass of the atom (equation below). Therefore, higher order of bonding, (*i.e.*) single → double → triple, will increase bonding strength and therefore result in a higher wavenumber. Finally, higher reduced masses will produce a lower wavenumber.

$$\nu = k\sqrt{\left(\frac{F}{\mu}\right)}$$

Where:

ν = wavenumber/ vibration frequency (cm^{-1});

k = (rate constant);

F = bond strength;

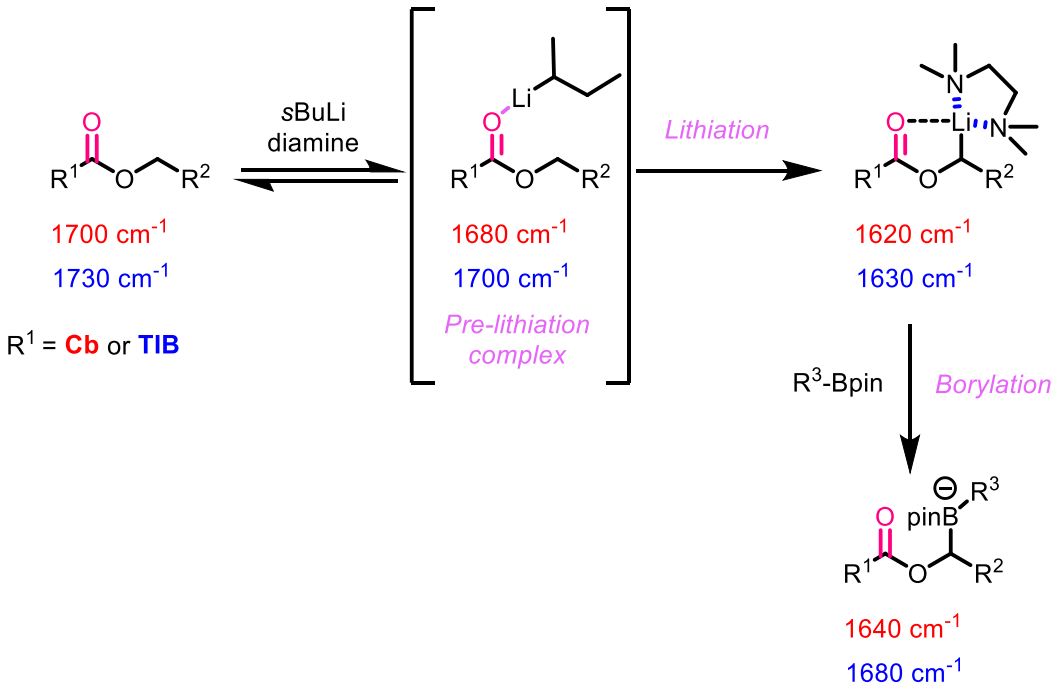
μ = reduced mass.

IR spectroscopy is only possible if the molecule produces a change in dipole moment upon IR absorption. Typically bonds such as carbonyl (C=O), which possess a strong dipole (electronegativity difference between O and C atoms) produce very strong IR signals.

In situ IR spectroscopy allows real-time monitoring of a reaction mixture using IR spectroscopy, through the means of a probe placed in the reaction mixture.[189] An IR spectrum can be produced periodically throughout the course of the reaction, thus providing a depiction of any changes that may occur to the molecule.

As lithiation–borylation makes use of carbamate and benzoate directing groups, the bond order of the carbonyl in these groups can be followed throughout the reaction using in situ IR

spectroscopy. As the carbonyl is involved in the lithiation by coordination to lithium, the bond order reflects the reaction coordinate. The carbonyl group of the carbamate appears at ~1700 cm[1] and the benzoate at ~1730 cm^{-1} (Scheme 89). After addition of the organolithium, the lithiation of the carbamate (~1620 cm^{-1}) and benzoate (~1630 cm^{-1}) are observed. In slower lithiations, a pre-coordination complex (~1680 cm^{-1} for carbamate and ~1700 cm^{-1} for benzoate), in which the lithium and carbonyl form a complex before deprotonation has occurred, can also be seen.[190] Next, boronic ester addition, forms a boronate complex (~1640 cm^{-1} for carbamate and ~1680 cm^{-1} benzoate) (Scheme 89). All reported wavenumber values were obtained from by Mykura *et. al*.[191] The by-product of the benzoate 1,2 migration is lithium benzoate, LiOTIB, which appears at ~1580 cm^{-1}. These changes in the above wavenumbers can be followed through the course of the reaction through a live trace. In situ IR spectroscopy is well suited for lithiation–borylation as the intermediates are only stable at cryogenic temperatures and are not air stable. As boronate complexes are typically air stable (and due to a large difference in chemical shift between boronic esters and boronate complexes) this step is easily followed by ^{11}B NMR.



Scheme 89: Monitoring lithiation-borylation *via in-situ spectroscopy*, carbamate *vs* benzoate.

2.1.5. 1,1-Disubstituted Cyclobutanes

Cyclobutane derivatives are highly strained, small-ring systems found in biologically active natural products and pharmaceutical treatments.[192–196] Many of the natural products are found to possess antibacterial, anti-cancer and antimicrobial properties.

Given these attributes, cyclobutane motifs have attracted interest from the pharmaceutical industry, to deviate from "flatland" (flatland is the region of chemical space occupied by sp^2 rich pharmaceuticals) and explore sp^3/3D molecules to help produce more efficacious treatments.[4,5] Cyclobutane derivatives address many of these issues, providing a sp^3 scaffold that is rigid, with spatially defined arrangement of substituents[197–199], which can be classed as privileged structural bioisostere to aromatic rings in structure-based drug design.[200–204]

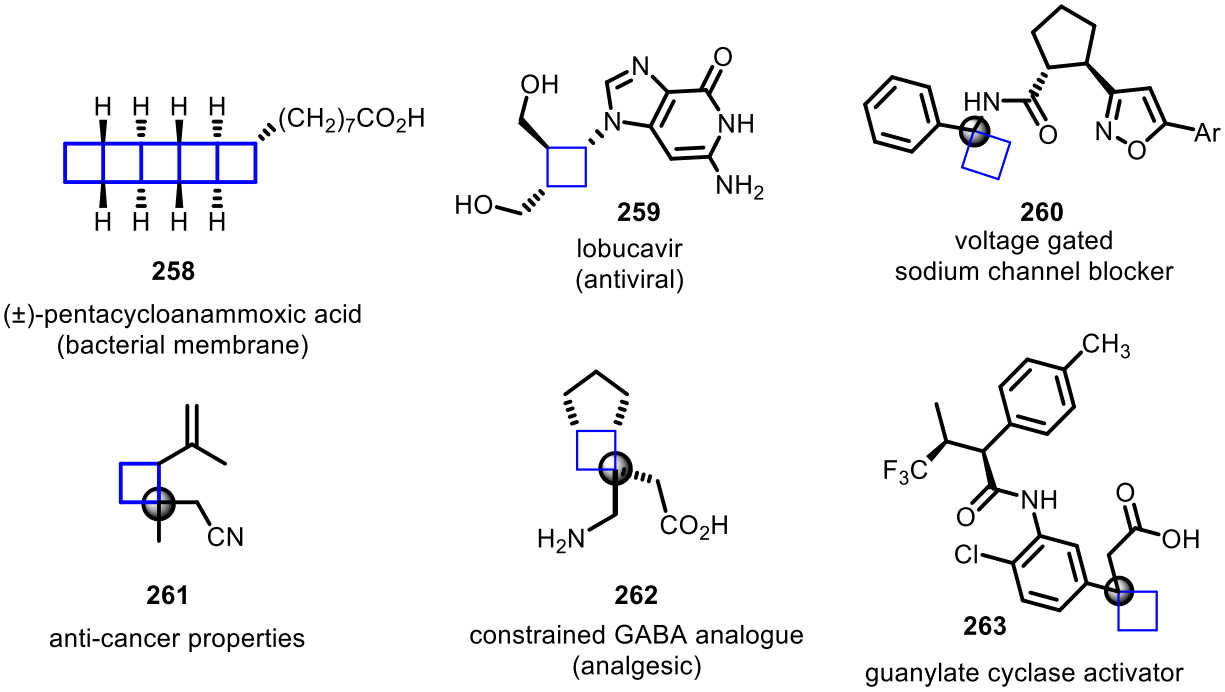


Figure 10: Cyclobutane containing natural products and bioactive molecules.

As shown in Figure 10, a range of natural and synthetic cyclobutane motifs have been isolated or synthesised. 1,1-Disubstituted cyclobutanes are also commonly seen in natural sources (quaternary centre) (black circle). (±)-Pentacycloanammoxic acid **258**, a fatty acid found in bacterial cell membranes, was isolated from *Candidatus Brocadia anammoxidans*. This

molecule contains an unusual [5]-ladderane motif.[205] Similarly, **261**, was isolated from the leaves and fruits of Egyptian *Schinus* mole and *S. terebinthifolius*, found to be an effective inhibitor of breast and brain cancer cell lines.[206] Other synthetic molecules containing the cyclobutane motif include the anti-viral agent, lobucavir **259**, produced by Bristol-Myers Squibb. **260** is a voltage gated sodium blocker, useful for treating cardiac arrhythmia.[207] Finally, GABA analogue[208] **262**, for Parkinson's and epilepsy and guanylate cyclase activator **263** provide additional examples of cyclobutane-containing derivatives in biologically active molecules.

2.1.5.1. Cyclobutane Properties

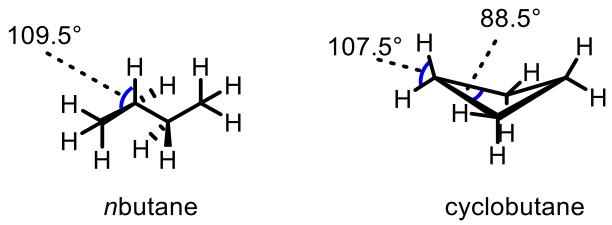


Figure 11: Cyclobutane bond angles.

Unlike acyclic *n*butane, which adopts a sp^3 tetrahedral geometry and C-C bond angles of 109.5°, cyclobutane has a smaller internal C-C bond angle (88.5°), this ~29° deviation in bond angle leads to Baeyer ring strain, making the cyclobutyl core less stable than higher order cycloalkanes (Figure 11).[209–211] As a result of the ring strain a part of the molecule is rotated out of the plane by 26°, resulting in the "butterfly" conformation. The ring strain makes cyclobutane motifs ideal for ring-opening reactions. A key feature of cyclic compounds is that deprotonation becomes progressively easier with decreasing ring size due to the increasing s-character of the C-H bond.[212,213] This feature is exploited in the subsequent section.

2.1.5.2. Synthesis of 1,1-Disubstituted Cyclobutanes Through Functionalisation

As cyclobutanes are of interest in both natural product synthesis and medicinal chemistry,[214] there have been numerous methods developed for their preparation.[215–218] Most (non-functionalising[219]) methods are focussed on the construction of cyclobutane cores. These include [2+2] cycloadditions,[220–230] α-alkylation of cyclobutanones,[231] ring-expansion of cyclopropanes[232] and cyclisations (such as, boryl carbanions[233]), and 1,4-radical addition-polar cyclisation[234] (Figure 12).

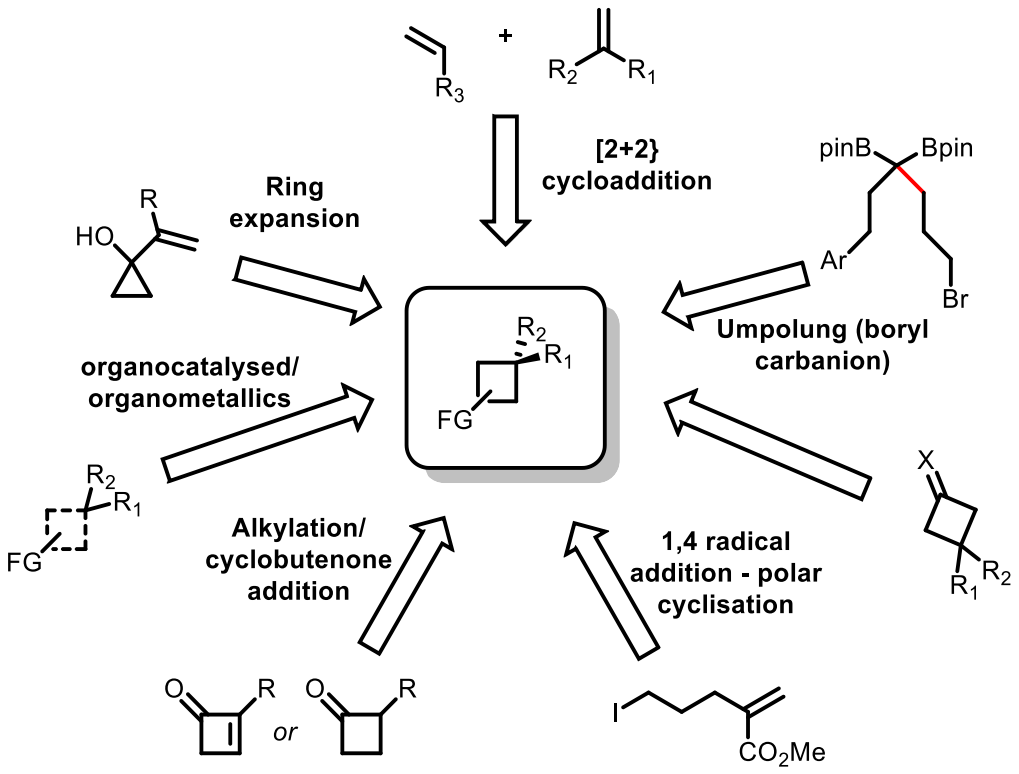
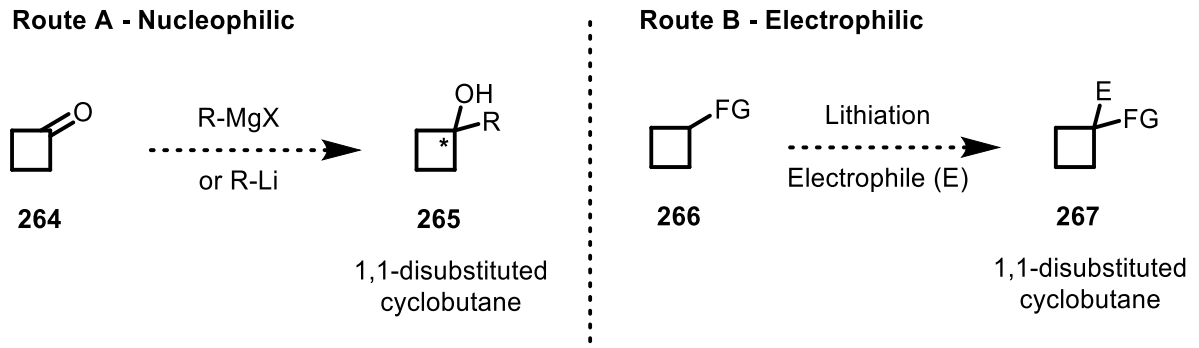


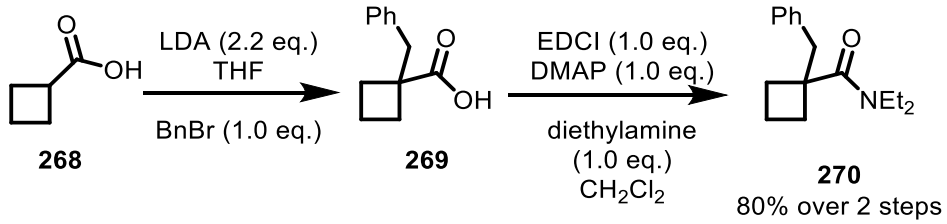
Figure 12: Synthetic routes to access cyclobutanes.

It could be envisaged a simple route to furnish 1,1-disubstituted cyclobutanes would be the reaction of Grignard reagents or organolithiums (nucleophilic addition) with cyclobutanone **264**, to give the corresponding racemic tertiary alcohol **264** (Scheme 90, Route A). The scope of R groups introduced in this manner would be limited, due to compatibility issues with nucleophilic organometallic reagents.



Scheme 90: Simple 1,1-disubstituted cyclobutanes.

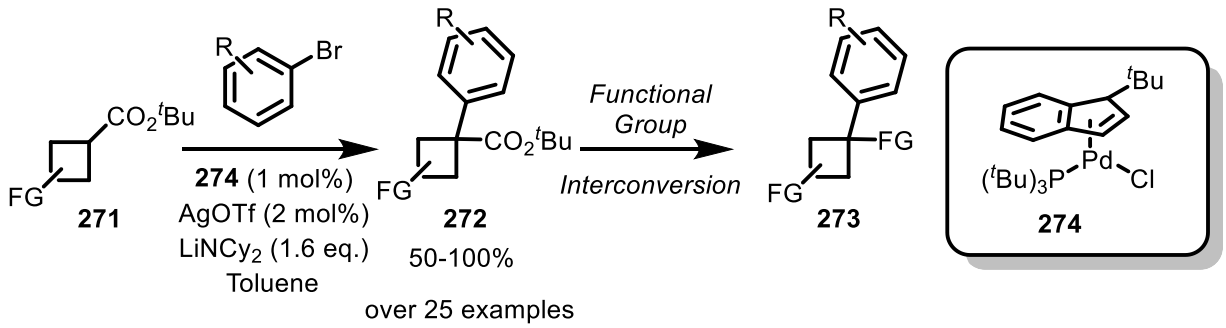
Alternatively, in a reversal of reactivity (Route B), a functional handle **266** could activate lithiation-electrophile trapping of cyclobutyl derivatives to give a functionalised disubstituted products **267**. A recent publication from Xu and co-workers,[235] reported the synthesis of cyclobutanecarboxamide **270**, using an adapted procedure for the preparation of cyclopropanecarboxamide homologues (Scheme **91**).[236]



Scheme 91: Lithiation of cyclobutanecarboxylic acid **268**.

Here, cyclobutanecarboxylic acid **268**, was deprotonated with LDA and then alkylated with benzyl bromide. The subsequent conversion of the carboxylic acid **269** to the corresponding amide, gave cyclobutanecarboxamide **270** in 80 % yield over two steps.

Most recently, Hartwig and co-workers[237] reported a palladium-catalysed α-arylation of simple cyclobutyl esters **271** (Scheme 92), expanding upon existing Negishi cross-coupling of cyclobutyl nitriles.[238–240] This methodology provides a general route to the α-arylation of small rings.

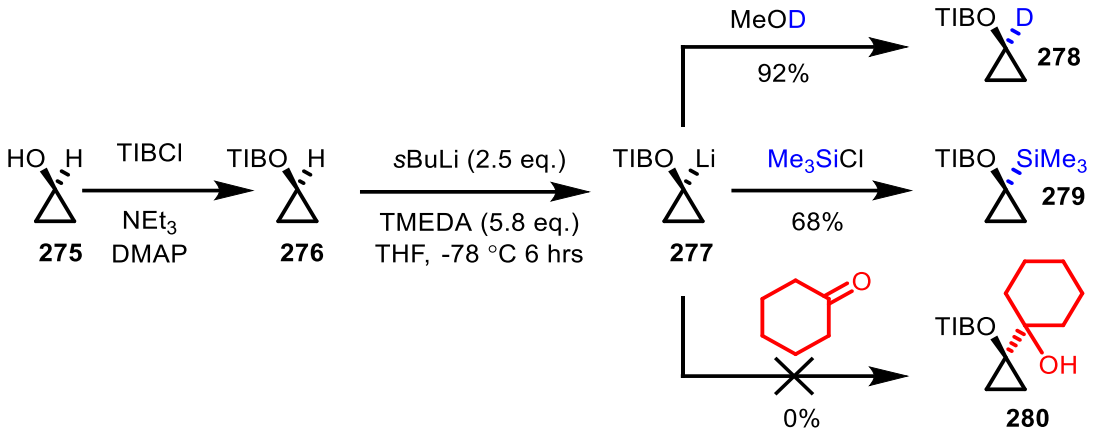


Scheme 92: Palladium-catalysed α-arylation of cyclobutyl esters.

The reaction scope is broad, with > 25 examples, consisting of electron rich and deficient aryl groups including heterocyclic substituents, with reported yields of **272** ranging 50-100%. These compounds underwent a functional group interconversion to give a library of compounds **273**.

2.1.5.3. Studies into the Lithiation of Cycloalkanes

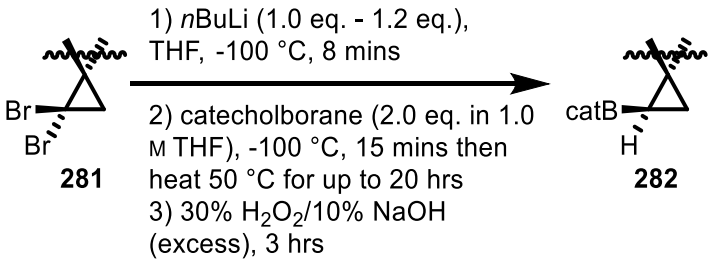
In 1985, Gadwood and co-workers reported the successful lithiation of cyclopropyl 2,4,6-triisopropylbenzoate **276**, derived from cyclopropanol **275**, using *s*BuLi (2.5 eq.), TMEDA (5.8 eq.) at –78 °C for 6 hrs in THF (Scheme 93).[241] Prior to this study, only various dipole-stabilised (*α*-alkoxyalkyl)lithiums had been generated *via* deprotonation of alkyl ethers. As expected, the presence of ring strain on cyclopropane renders the *α*-proton more acidic than in the acyclic secondary dialkyl benzoate due to the increased s-character of the C–H bond. The lithiation-deuteration of **277** afforded deuterated product **278** in 92% (90% D-incorporation by NMR, D_2O quench). In addition, trapping with trimethylsilyl chloride afforded **279** in 68% yield. However, reaction with cyclohexanone failed to afford **280**, even when the reaction was warmed to RT. The authors suggested steric hindrance was an issue when using cyclohexanone as an electrophile, similarly, quenching of organolithium **277** by *α*-proton transfer from the ketone was also suggested.[174]



Scheme 93: Lithiation of cyclopropyl 2,4,6-triisopropylbenzoate **276**.

2.1.5.4. Lithiation-Borylation of Cycloalkanes

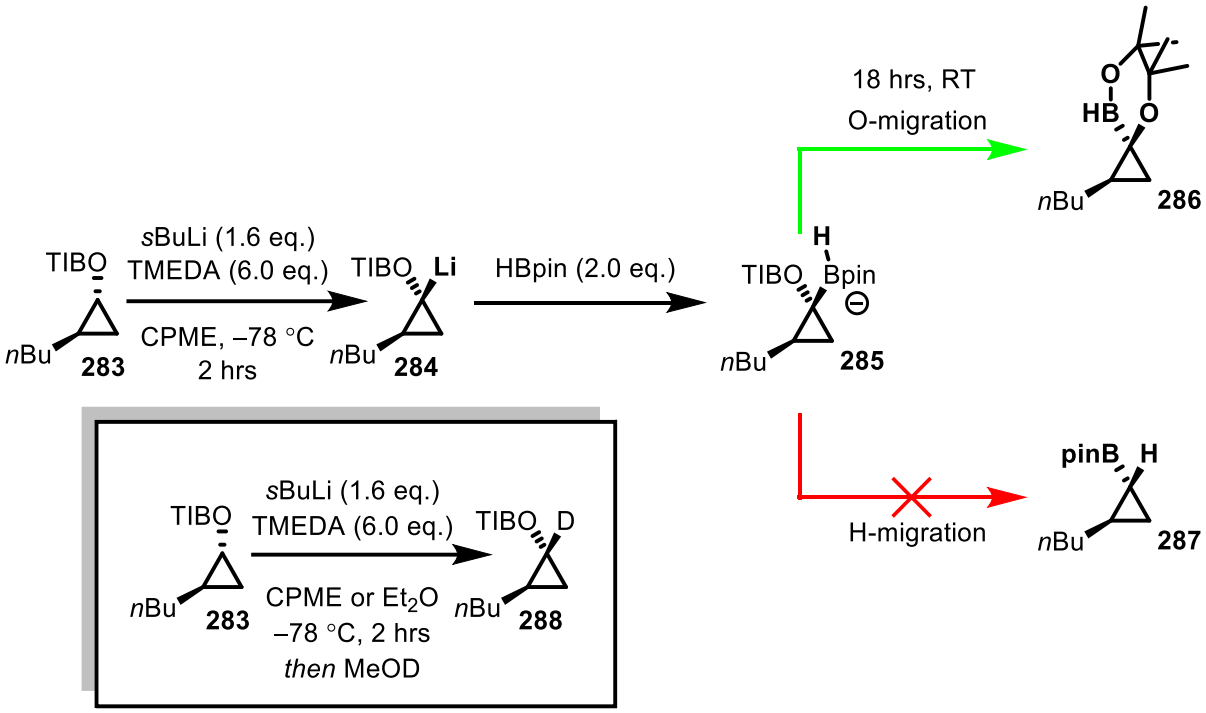
Previous literature reports from Danheiser,[242] showed that lithiation-borylation of substituted *α*-dibromo-cyclopropane **281** in the presence of catechol borane to give cyclopropyl boronic ester **282** after 1,2-migration of the hydride substituent (Scheme 94). This reaction benefits from having a good bromide leaving group.



Scheme 94: Lithiation-borylation of α-dibromo-cyclopropane **281**.

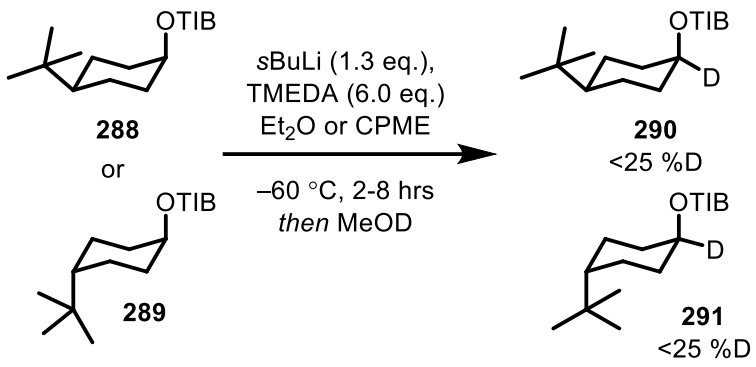
Related studies on lithiation-borylation of cyclopropyl 2,4,6-triisopropylbenzoate **283** were conducted by Daniel Blair[243] (Scheme 95). Although benzoate **283** deprotonation was facile, (as observed in the initial lithiation-deuteration study in which D-incorporated **288** was

obtained) subsequent reaction of lithiated benzoate **284** with pinacol borane failed to give the desired product **287**. It was suggested that the strained cyclopropyl ring, prevented the boronate complex **285** from forming the required anti-periplanar configuration required for 1,2-migration. Instead the boronic ester oxygen was found to migrate, giving only O-migration[116] product **286** (which was identified by ^{11}B NMR) after 18 hrs at RT.



Scheme 95: Lithiation-borylation of cyclopropyl 2,4,6-triisopropylbenzoate **283**.

Daniel Blair also studied the lithiation–deuteration of cyclohexyl benzoates **288** and **289**. Given the larger ring size, this cyclic derivative would suffer from lower acidity than cyclopropyl benzoates. Indeed, this reaction proved challenging. Even after 8 hrs of lithiation, less than 25% D-incorporation was observed in products *cis*-**290** and *trans*-**291** (Scheme 96). These results are in accordance with the lithiation of secondary benzoates, which displayed poor lithiation in the absence of an acidifying groups, such as vinyl or phenyl.[169]



Scheme 96: Lithiation of cyclohexyl 2,4,6-triisopropylbenzoate **288/289**.

A formal lithiation for cyclobutane 2,4,6-triisopropyl benzoate has not been reported to date nor has this motif been studied in lithiation-borylation methodology. The above results, indicate that the success of cycloalkyl benzoates in lithiation-borylation, is a fine balance between ring size and ring strain (Figure 13). As the ring size increases, the benzoate is more difficult to deprotonate. However as the ring size decreases, ring strain prevents the boronate complex from occupying the required *anti*-periplanar configuration to undergo 1,2-migration and furnish product.

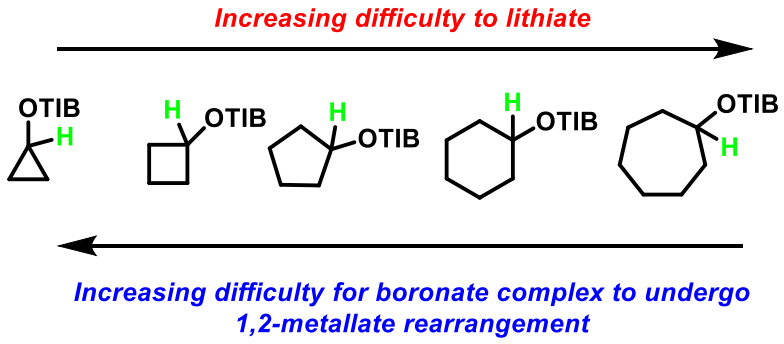


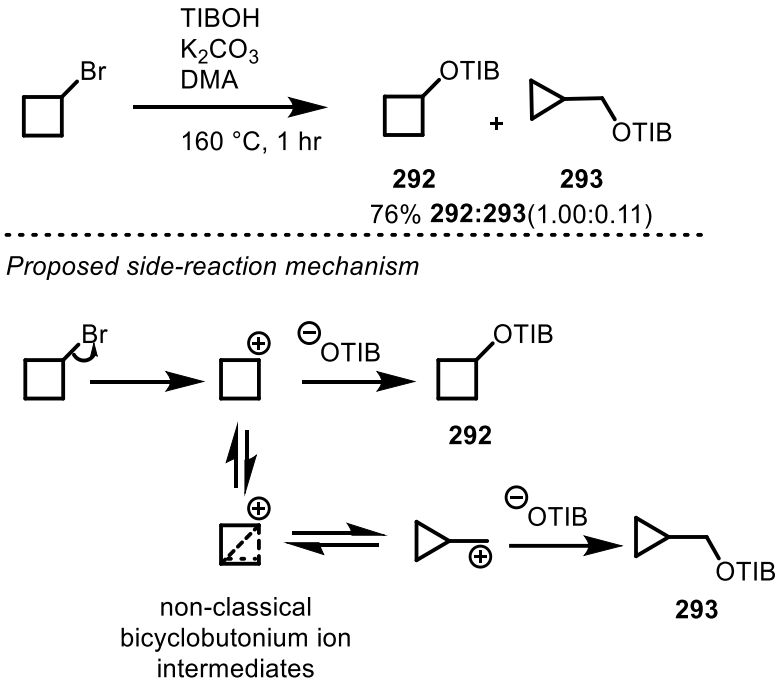
Figure 13: Comparison of hydrocarbon.

The limited methods for the preparation of cyclobutanes with versatile functional groups prompted us to explore the area of lithiation-borylation of this class of compounds.[244]

2.2. Previous Work

The work completed in the previous work section of this thesis was carried out by Eugenia Luc and Rory Mykura.[245] The work disclosed here includes the synthesis of cyclobutyl benzoate, which has been used as test substrate for boronic ester homologations in the substrate scope. There is also inclusion of *in-situ* IR spectroscopy traces to summarise this aspect of the work. All tables and diagrams discussed in the previous work have been adapted/ reproduced from Eugenia Luc's Masters thesis.[245]

2.2.1. Synthesis of Cyclobutyl Benzoate *via* Cyclobutylbromide



Scheme 97: Proposed route to the synthesis of cyclobutyl 2,4,6-triisopropylbenzoate **292**.

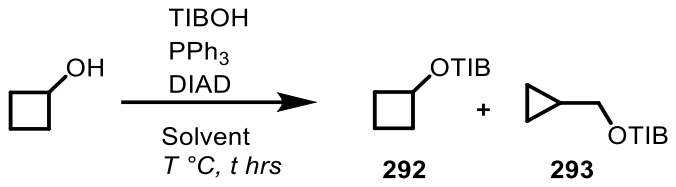
Initial attempts to synthesise benzoate **292** utilised S_N2 displacement of cyclobutylbromide by the hindered benzoate nucleophile, which is generated by base *in-situ* deprotonation of 2,4,6-triisopropylbenzoic acid (TIBOH) as shown in Scheme 97. Whilst this gave the desired product, a competing side-reaction, giving the ring contraction cyclopropyl methyl benzoate **293** was also observed.

The formation of benzoate **293** side-reaction is possible due to equilibrating non-classical cationic intermediates, as reported by Robert and co-workers in their isotopic labelling experiments.[246] The rearrangement is thought to arise due to formation of an equilibrating non-classical bicyclobutonium ion intermediate, as shown in scheme 97.[247,248] The subsequent trapping of the more stable cationic species with the benzoate nucleophile gives the ring contracted side product. This competing side pathway takes place via S_N1 mechanism.

Due to the difficulties in purification and separating the side product from the desired product, attempts were made to eliminate the side product formation, however, these were also unsuccessful. Therefore, the cyclobutyl benzoate substrate, containing a small percentage of side-product **293** (~10%) was used without further purification and the side-product did not interfere with the lithiation-borylation reaction.

Attempts by Eugenia Luc to access the cyclobutyl benzoate through the reaction between the acyl chloride and cyclobutanol, did not yield desired product. Therefore, Eugenia Luc explore the Mitsunobu reaction as a potential route. Initial attempts to synthesise desired benzoate **292** were performed in DMA at 120 ˚C, resulting in a 1.00:0.38 ratio of **292**:**293** (Table 8, entry 1). Repeating the same reaction at RT improved ratios in favour of desired benzoate **292** 1.00:0.26, (entry 2). This would suggest heating the reaction mixture favours S_N1 over S_N2, hence the larger ratio of side product **293** in entry 1. Using apolar toluene, entry 3, improved the ratio to 1.00:0.18 of **292**:**293**. Further study of solvent effect on ratio, showed that THF was optimum giving the least side product (entry 4, 1.00:0.07).

Table 8: Optimisation of Mitsunobu esterification for the synthesis of cyclobutyl benzoate **292**.



Entry	Solvent	*T*/ °C	*t* / hrs	292:293[a)]	Yield[b)] %	292:293[a)]
1	DMA	120	5	1.00:0.38	-	-
2	DMA	RT	16	1.00:0.26	39	1.00:0.27
3	PhMe	50	16	1.00:0.21	43	1.00:0.18
4	THF	RT	16	-	68	1.00:0.07

[a)] Crude ratio of benzoates **292:293** *via* ^{1}H NMR. [b)] Yield of isolated benzoate **292**.

2.2.2. Optimising Lithiation-Borylation Conditions

To accelerate the development of conditions for the lithiation-borylation reaction, *in-situ* IR spectroscopy was utilised to study the formation and depletion of intermediates throughout the reaction. *In-situ* IR spectroscopy is a powerful tool that can help determine optimal reagent stoichiometries, reaction times and stability of intermediates.

When initially screening conditions, Eugenia Luc used 2-phenylethyl-1-boronic acid pinacol ester **294**, an air-stable primary boronic acid as the substrate for lithiation–borylation due to its ease of synthesis from the corresponding boronic acid.

2.2.3. *In-situ* IR Spectroscopy of the Lithiation–Borylation of Cyclobutyl Benzoate

The lithiation-borylation of cyclobutyl 2,4,6-triisopropylbenzoate **292**, was investigated by Eugenia Luc using *in-situ* IR spectroscopy and reported in a graph as a function of absorbance (a.u.) against time (mins) (Figure 14).

Benzoate **292** was converted to lithiated species **295**, after addition of *s*BuLi, with maximum lithiation at ~21 mins. The addition of *s*BuLi results in dilution of the reaction mixture, as shown in Figure 14, which accounts for the concentration of benzoate **292** falling to less than zero absorbance. Similarly, the dilution effects also contribute to the initial sharp decrease in the benzoate **292** concentration.

The lithiation of cyclobutyl benzoate **292**¸ showed that the lithiated species **295** is chemically unstable under the reaction conditions over time through generation of lithium 2,4,6-triisopropylbenzoate species (green line). Upon addition of boronic ester **294** at ~ 51mins, the lithiated species **295** was rapidly consumed to give boronate complex **296**.

The lithiation-borylation of cyclobutyl benzoate **292** was a promising result and provided a starting point for the optimisation of reaction conditions to synthesise the desired product. The fast rate of lithiation (~9 minutes) is due to the increased s-character of the C-H bond of the 4 membered ring in comparison to acyclic secondary TIB esters which require >2hrs to achieve 30% deprotonation at -60 ˚C and a large equivalent of TMEDA.[169] The lithiated benzoate species **295** is chemically unstable with about 15% decomposition being observed over 50 minutes. Using this information, Eugenia optimised the 1,2 borylation step and reagent equivalents to establish optimised conditions for the lithiation-borylation of cyclobutyl benzoate **292**.

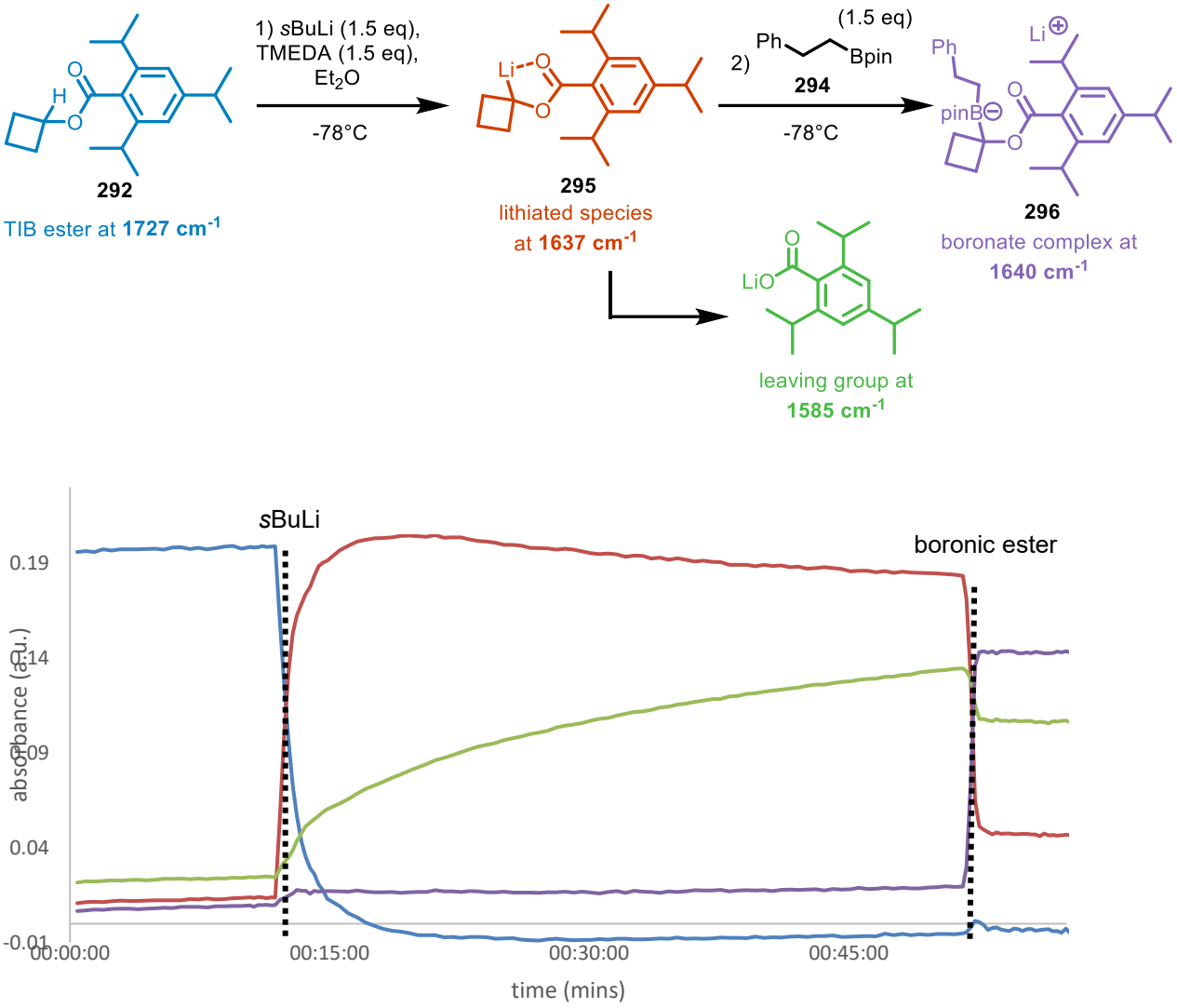
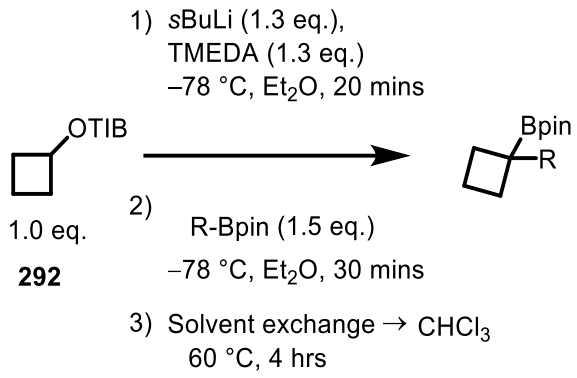


Figure 14: Lithiation-borylation of benzoate **292** monitored by *in-situ* IR spectroscopy.

2.2.4. Optimised Lithiation–Borylation Conditions for Cyclobutyl Benzoate



Scheme 98: Optimised lithiation–borylation conditions.

By using a combination of techniques, such as *in-situ* IR spectroscopy, complete lithiation had been achieved after 9 minutes, with the species stable for an additional 25 minutes. After boronic ester addition, a solvent exchange to $CHCl_3$ was carried out and the reaction heated to 60 °C to promote 1,2-migration, with reactions complete after 4 hours of heating (Scheme 98). Finally, workup was performed by simply filtering the crude reaction through a short silica plug, to ensure maximum recovery of the desired product.

2.3. Project Aims

Having established optimised conditions for the lithiation-borylation of cyclobutyl 2,4,6-triisopropyl benzoate **292**, using *in-situ* IR spectroscopy, it is imperative to develop a substrate scope for this methodology for the synthesis of 1,1-disubstituted cyclobutanes.

A range of primary, secondary, tertiary and sp^2-hybridised (aryl and alkenyl) boronic esters was to be tested in this methodology. In addition, enantioenriched boronic esters and natural product boronic ester derivatives (cholesterol and lithocholic acid) can also be tested in this methodology to show broader application. Furthermore, boronic ester functional group interconversions of a homologated product from this methodology can used to emphasise the potential of the products obtained from this protocol.

Finally, i*n-situ* IR spectroscopic methods will be used to establish lithiation–borylation conditions for other small-ring systems, such as, substituted cyclobutyl rings, oxetane and azetidine benzoates, to explore the scope of these derivatives.

2.4. Results and Discussion

2.4.1. Collaboration Disclaimer

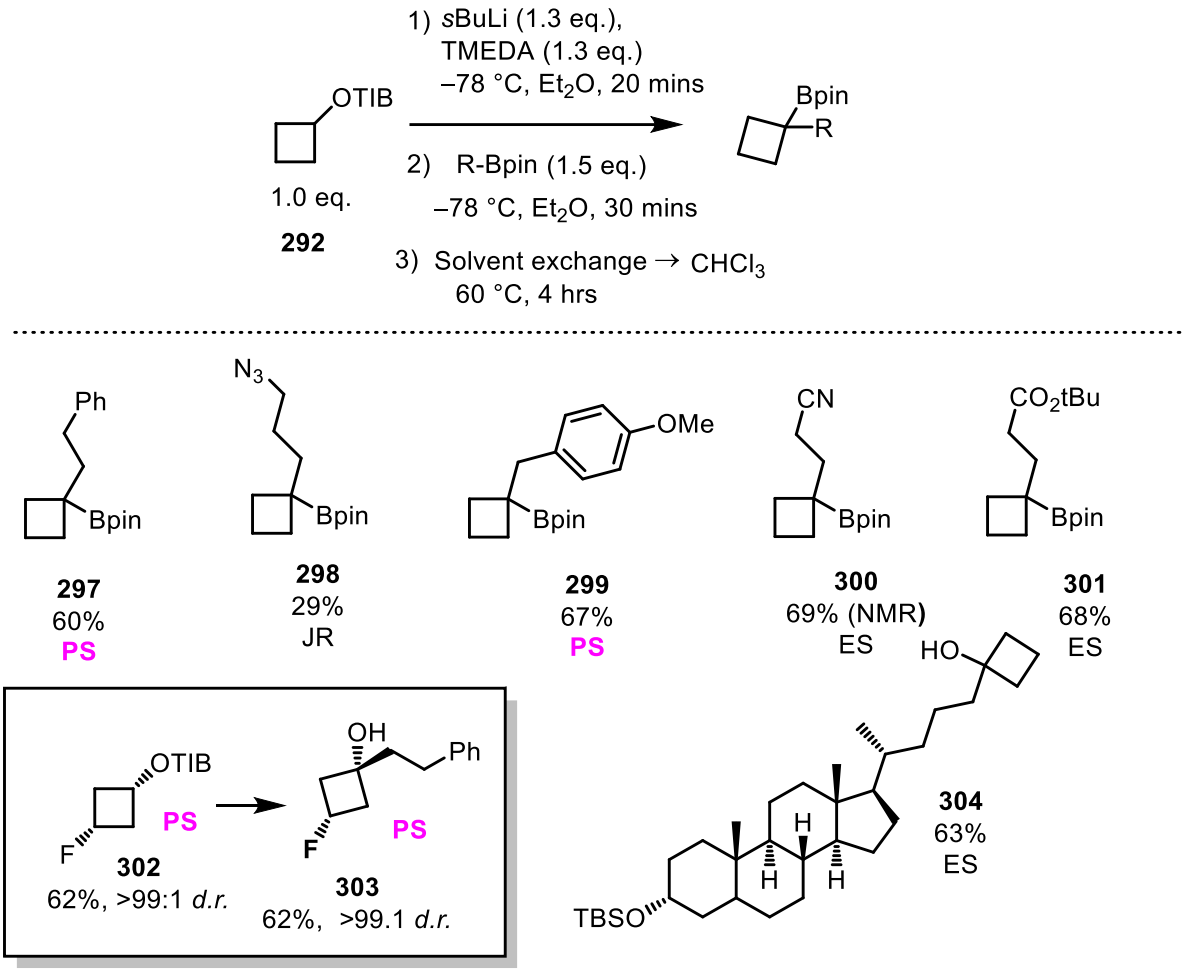
Parts of this project/chapter contain work that has been completed in collaboration with Rory Mykura (RM), Eugenia Luc (EL), Jack Rogers (JR) and Ellie Stammers (ES), which formed the basis for a publication[249]. In the substrate scope, work contribution from myself have been highlighted with my initials (PS). The remaining substrates were produced by the above collaborators and it has been included to provide a complete story for this chapter. However, the Experimental Chapter includes information only of the products that PS synthesised.

2.4.2. Substrate Scope of Lithiation-Borylation

Having optimised lithiation-borylation conditions using 2-phenylethyl-1-boronic acid pinacol ester **294**, the generality of the reaction was explored by performing a substrate scope using a range of boronic esters. Primary, secondary, tertiary, sp^2 and enantioenriched boronic esters were tested and moderate to good yields were achieved.

2.4.2.1 Primary Boronic Esters

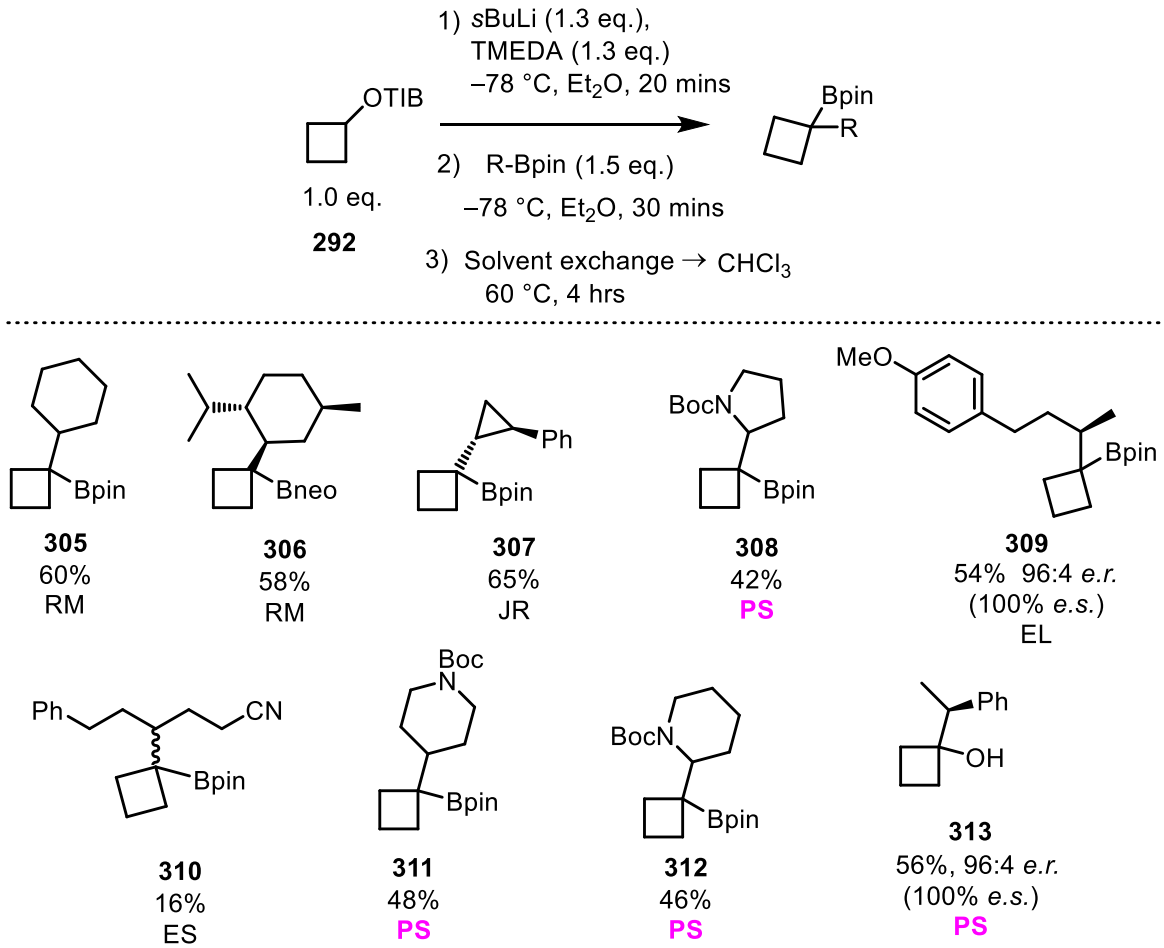
As shown in Scheme 99, the standard substrate, phenylethyl-1-boronic acid pinacol ester **294**, gave **297** in 60% yield. The use of linear primary boronic ester substrates bearing *tert*-butyl ester **301** and nitrile **300** functional groups were tolerated in this reaction. The yield for nitrile **300** is given as a ^{1}H NMR yield (using dibromomethane as an internal standard), due to the difficulty in separating a co-eluting side product.



Scheme 99: Range of primary boronic esters synthesised.

The azide functional group for substrate **298,** was the only poorly tolerated substrate, possibly due to addition of the organolithium to the azide. The presence of a para-methoxy benzyl group was well tolerated **299** (69%). The subjection of *trans*-3-fluoro-cyclobutylbenzoate **302** to the optimized conditions gave **303** in 62% yield and high *d.r.* (starting from a single diastereoisomers of the TIB ester), demonstrating that the presence of a fluorine atom on the cyclobutyl ring does not affect the reaction pathway. The scope of the reaction was also successfully expanded to biologically relevant compounds such as lithocholic acid derivative **304** (63%), which was synthesized in-house from TBS protected lithocholic acid by decarboxylative borylation to give the corresponding primary boronic ester.[250]

2.4.2.2. Secondary Boronic Esters



Scheme 100: Range of secondary boronic esters synthesised.

Expanding boronic ester scope to include secondary boronic esters gave poor to good yields (Scheme 100, 16-65%). Cyclohexyl boronic ester gave compound **305** in 60% yield. However, increasing the steric bulk on the cyclohexyl ring moiety, when using a menthol derived boronic acid pinacol ester (Bpin), failed to give the desired product. This is a consequence of the vicinal isopropyl group on the cyclohexyl ring, which hinders the borylation, as no boronate complex was observed (^{11}B NMR). Using the less sterically hindered neopentyl boronic ester analogue (Bneo) gave **306** in 58% yield.

The use of a phenyl cyclopropyl boronic ester gave compound **307**. However, using nitrile containing secondary dialkyl boronic ester gave the desired product (compound **310**) in poor yield (16%), which can only be attributed to the steric bulk hindering the borylation step, as

opposed to any incompatibility with the nitrile group, as the reaction worked well when using primary propanenitrile boronic acid pinacol ester **(300,** 69%). As the less sterically hindered Bneo group has been shown in previous attempts to facilitate reactions that were poor yielding or non-occurring when using Bpin analogues, perhaps the yield of this reaction could be improved by using the Bneo group.

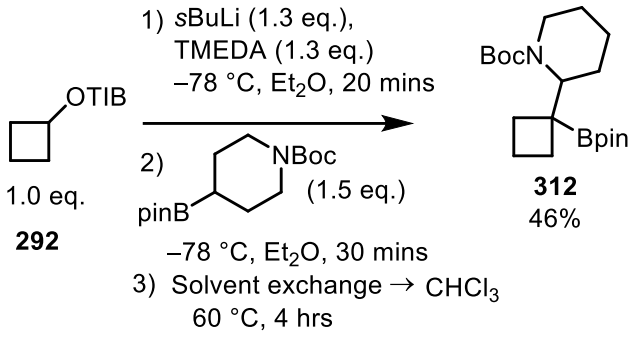
A similar steric congestion was observed in the synthesis of enantioenriched boronic ester **309**, which gave the desired product in 54% yield, albeit lower than less challenging secondary boronic esters. In comparison to compound **310**, it is evident the replacement of a one bulky alkyl group with a simple methyl group afforded reduced steric congestion, which reflects on the better yield. These observations demonstrate the sensitivity of the hindered secondary lithiated species to the steric environment of the pertinent boronic ester, whether during borylation or 1,2-migration.

The presence of heterocyclic ring systems was well tolerated in the lithiation borylation of the cyclobutyl benzoate, especially given the presence of an adjacent bulky Boc protecting group on the ring nitrogen for two examples. The 2-substituted NBoc pyrrolidine (compound **308**) was obtained in 42% yield, similarly the 4-substitued NBoc piperidine derivative (compound **311**) was also obtained in good yield (48%).

However, when 1-Boc-piperidine-3-boronic acid pinacol ester was utilised (to synthesis compound **312**), desired product was obtained in 31% yield (Table 9**,** entry 1). It was noted in entry 1 that the 1,2-migration step had not reached completion (boronate still present by ^{11}B NMR); this was reflected in the starting boronic ester recovered (36%). A subsequent reaction (entry 2) was left for a longer duration (48 hrs) at standard conditions, with ^{11}B NMR taken every ~16 hrs (3 NMR's taken over 48 hrs) which indicated that no further 1,2-migration occurred after 32 hrs. Using this reaction time, a better yield was obtained (42%), with a lower starting boronic ester recovery (25%). The improved yield is a consequence of heating the reaction for a longer period, which indicates that the 1,2-migration is slow and requires a prolonged reaction time under standard conditions. Consequently, the solvent was exchanged for a higher boiling solvent, such as toluene (entry 3) during the 1,2-migration step instead of chloroform. This reaction mixture was heated to 110 ˚C. This gave a 4% increase in yield (46%) after 48 hours. In a final attempt to improve yield, magnesium bromide diethyl etherate (entry

4); a Lewis-acid known to promote 1,2-migration was utilized. However, after 16 hours, the reaction gave a 46% isolated yield. Depending on the chemist's requirements, either entry 3, which uses toluene at reflux, or entry 4, requiring preparation and addition of fresh $MgBr_2$.Et_2O, can be used to prepare this boronic ester in moderate yield.

Table 9: Reaction conditions tested in the lithiation-borylation of compound **312**.



Reaction Entry	Conditions	Time (hrs)	Isolated Yield (%)	Starting Boronic ester recovery (%)
1	Standard[a)]	16	31	36
2	Standard[a)]	48	42	25
3	Et_2O →Toluene	48	46	22
4	$MgBr_2$.Et_2O	16	46	25

Conditions: [a)] standard: TMEDA/*s*BuLi (1.3 eq.) in Et_2O at -78 ˚C, 20 mins. Then R-Bpin (1.5 eq.) at -78 ˚C for 30 mins. Warm, solvent exchange to $CHCl_3$ and reflux (4 hrs).

1-Phenylethyl boronic acid pinacol ester product (pre-oxidation **313)**, presented problems with isolation and purification under standard conditions during lithiation-borylation. After promising NMR yields, the product and starting boronic ester could not be separated. To overcome purification issues, the crude reaction mixture was oxidized with H_2O_2/NaOH, to convert the boronic ester to alcohol **313,** which was isolated in 18% yield. This yield did not correspond to the ^{1}H NMR yield, therefore the reaction was repeated and studied with *in-situ*

IR spectroscopy (Figure 15). It was found that the reaction had undergone complete lithiation and subsequent borylation but failed to undergo 1,2-migration. Further studies helped to elucidate and improve reaction conditions for compound **313** (Table 10).

Table 10: Reaction conditions tested in the lithiation-borylation of compound **313**.

Reaction Entry	Conditions	Time (hrs)	Isolated Yield (%)
1	Standard[a)]	16	18
2	$Et_2O \rightarrow$Toluene	20	58 (*rac*)/56 (*e.e*)
3	$MgBr_2.Et_2O$	16	0

Conditions: [a)] standard: TMEDA/*s*BuLi (1.3 eq.) in Et_2O at -78 ˚C, 20 mins. Then R-Bpin (1.5 eq.) at -78 ˚C for 30 mins. Warm, solvent exchange to $CHCl_3$ and reflux (4 hrs).

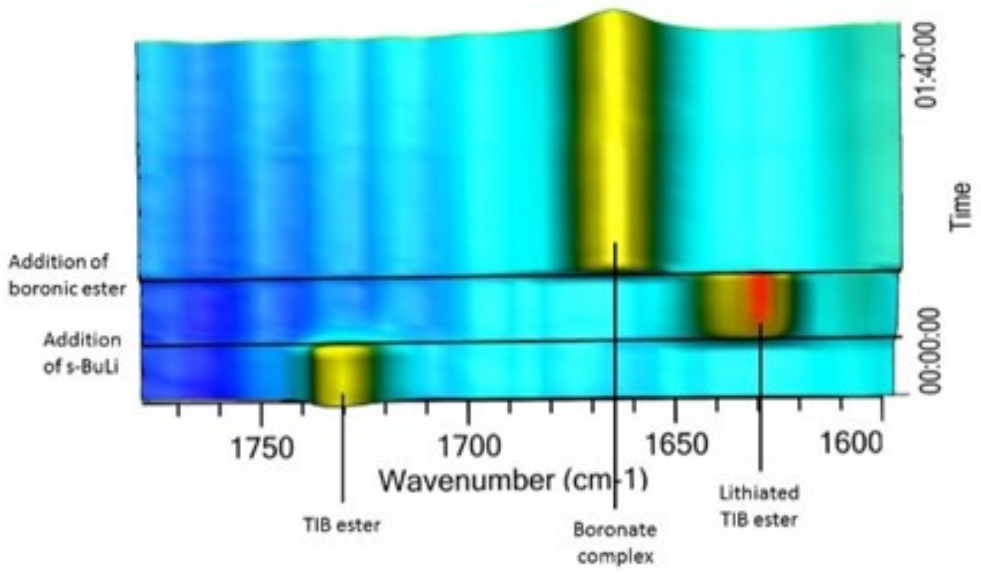
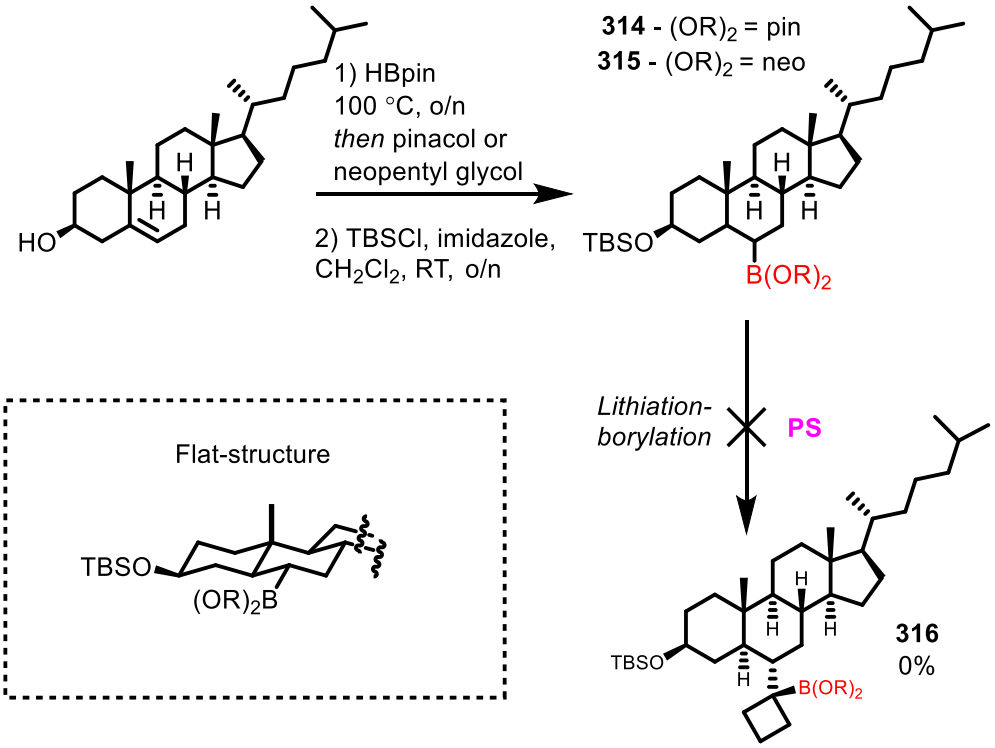


Figure 15: *In-situ* IR spectroscopy study into the lithiation-borylation of compound **313.**

Entry 1 (Table 10), shows the reaction under standard conditions. Interestingly, solvent exchange to toluene (instead of chloroform, entry 2) provided a better yield after 20 hours (58 % (*rac*)/56 % (*e.e.*). Finally, Lewis-acid $MgBr_2 \cdot Et_2O$ (entry 3) was also tested. Unfortunately, after peroxide oxidation, no product was obtained but 1-phenylethan-1-ol (21%) was isolated, from oxidation of the starting boronic ester. The synthesis of compound **313** also confirmed the enantiospecificity of the 1,2-migration process, compound **313** was analysed by supercritical fluid chromatography (SFC) to show 96:4 *e.r.* (starting boronic ester >95:5 *e.r.*). This result indicates that the reaction occurs with high (essentially complete) stereospecificity (100% *e.s.*).

Finally, the methodology was tested on a derivative of cholesterol pending an alcohol moiety that was TBS protected, where the secondary boronic ester was installed through hydroboration (**314**) as shown in Scheme 101.



Scheme 101: Failed attempts to synthesis cholesterol derived products.

As shown in Table 11, all attempts to synthesise compound cholesterol derivatives **316**, were unsuccessful, with only starting boronic ester recovery **(314/315)**. Similar to the menthyl

product **306**, the substituted cyclohexane motif presents too much steric hinderance to allow addition to the boronic ester from the lithiated cyclobutyl TIB ester. However, the lack of result even swapping to the Bneo demonstrates the sheer size of the cholesterol moiety most likely shields the boronic ester from reacting with the lithiated species.

Table 11: Reaction conditions tested in the lithiation-borylation of compound **315**.

Reaction Entry	$B(OR)_2$	Conditions	Time (hrs)	Isolated Yield (%)	Starting Boronic ester re-isolated (%)
1	Bpin **314**	Standard[a)]	16	0	72
2	Bpin **314**	Et_2O →Toluene	48	0	65
3	Bpin **314**	$MgBr_2$•Et_2O	16	0	68
4	Bneo **315**	Standard[a)]	16	0	49

Conditions: [a)] standard: TMEDA/*s*BuLi (1.3 eq.) in Et_2O at -78 ˚C, 20 mins. Then R-Bpin (1.5 eq.) at -78 ˚C for 30 mins. Warm, solvent exchange to $CHCl_3$ and reflux (4 hrs).

Entry 1, using standard conditions, only gave starting materials back, even though boronate complex was visible by ^{11}B NMR (5 ppm). Comparatively, a larger signal for unreacted boronic ester was also present on the ^{11}B NMR. It was thought at this point that two problems were causing this reaction to fail. Firstly, the sterically encumbered boronic ester may not be completely reacting with the lithiated species (as seen by the ^{11}B NMR). Secondly, the boronate complex is sterically congested around the boron atom, restricting access to the required anti-periplanar conformation for 1,2-migration, such that migration is not feasible. This could lead to decomposition or reversal of the boronate complex to regenerate starting boronic ester **314**. It was proposed that exchanging solvent to a higher boiling point solvent (entry 2) would force the small portion of boronate complex to undergo 1,2-migration, however solvent exchange did not help. Similarly, using Lewis-acid (entry 3) also failed to give desired product, and only starting materials were recovered. Finally, analogous boronic ester **315**, with a less sterically bulky neopentyl glycol ligand (in comparison to pinacol) on boron was investigated (entry 4). This would potentially aid boronate complex formation given the reduced steric hinderance around the boron atom and reduce the steric bias during 1,2-migration. However, this attempt

also failed to produce any desired product. At this stage, the cholesterol derivative was abandoned, and attention directed to other types of boronic esters.

2.4.2.3. Tertiary Boronic Esters

This work on tertiary boronic esters was completed by Jack Rogers & Rory Mykura. The use of tertiary boronic ester demonstrated the limitations of lithiation-borylation on small rings. Here, *t*butyl boronic acid pinacol ester was used to synthesize compound **317** (Figure 16), however, the first attempt proved unsuccessful with starting cyclobutyl benzoate **292** recovered (90%). The lack of borylation could be attributed to the bulky *t*Bu group rendering the borylation step reversible and so lithiated TIB-ester complex is reobtained. Upon work-up this would return starting cyclobutyl benzoate **292**.

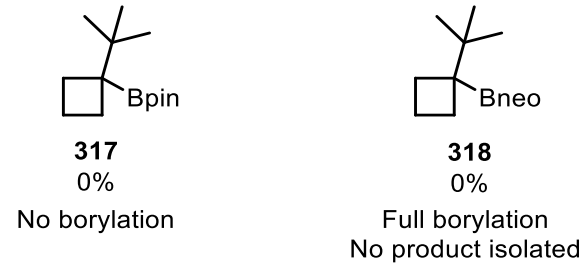


Figure 16: Tertiary boronic esters tested using optimised conditions.

To test this hypothesis, the reaction was repeated and monitored using i*n-situ* IR spectroscopy (Figure 17). The lithiated species did not react with *t*butyl pinacol boronic acid pinacol ester when this was added to the reaction mixture at -78 °C. This can be attributed to the steric bulk of the *t*Bu group, which hinders the boronic ester from reaction to form boronate complex. An attempt to warm the reaction mixture to RT also did not encourage boronate complex formation.

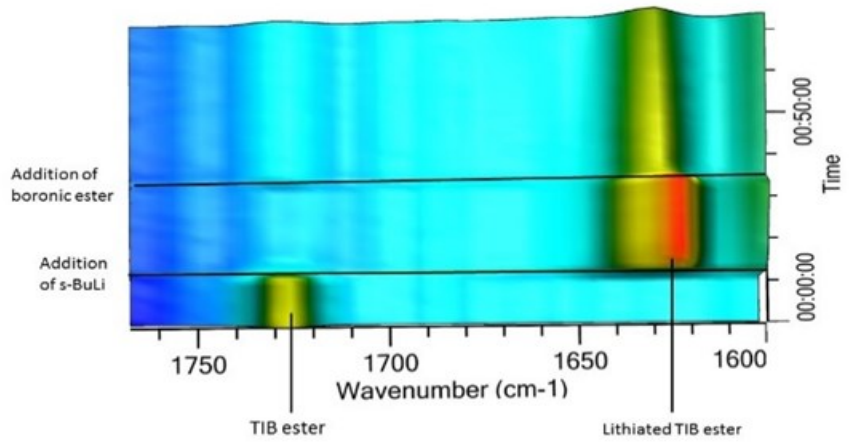
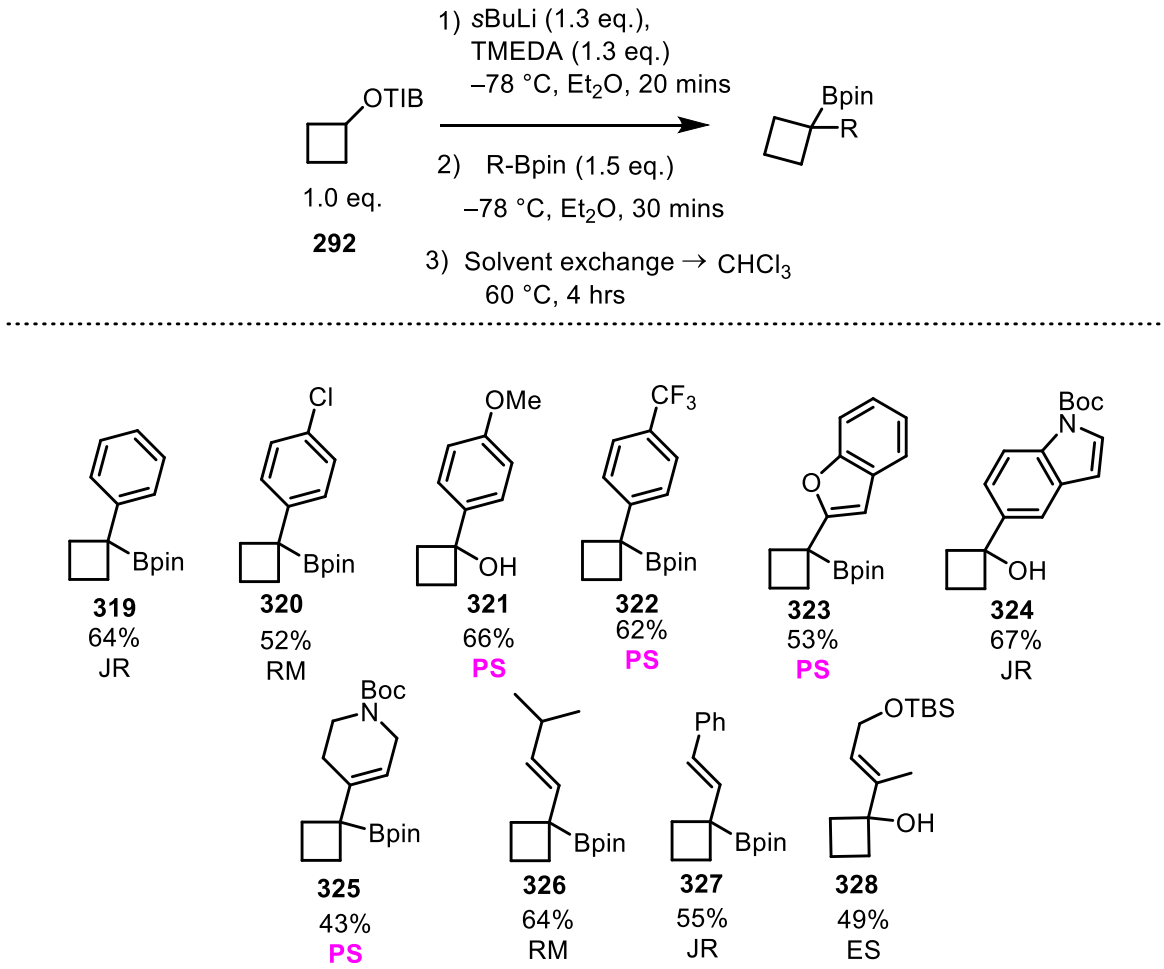


Figure 17: *In-situ* IR spectroscopy study into the synthesis of compound **317**.

In a final attempt, the pinacol group was exchanged for Bneo to increase the reactivity of the boronic ester, which should facilitate the borylation step to take place giving product **318**. However, though boronate complex was observed by ^{11}B NMR, no borylation product was obtained from the reaction. This would suggest again the bulky *t*butyl group on the boronic ester was too large to generate a boronate complex that can undergo 1,2-migration, most likely due to competing reversibility, leading to recovered cyclobutyl benzoate **292** (90%).

With no success using tertiary substrates, attention was focused on sp^2 boronic esters.

2.4.2.4. sp^2 Boronic Esters

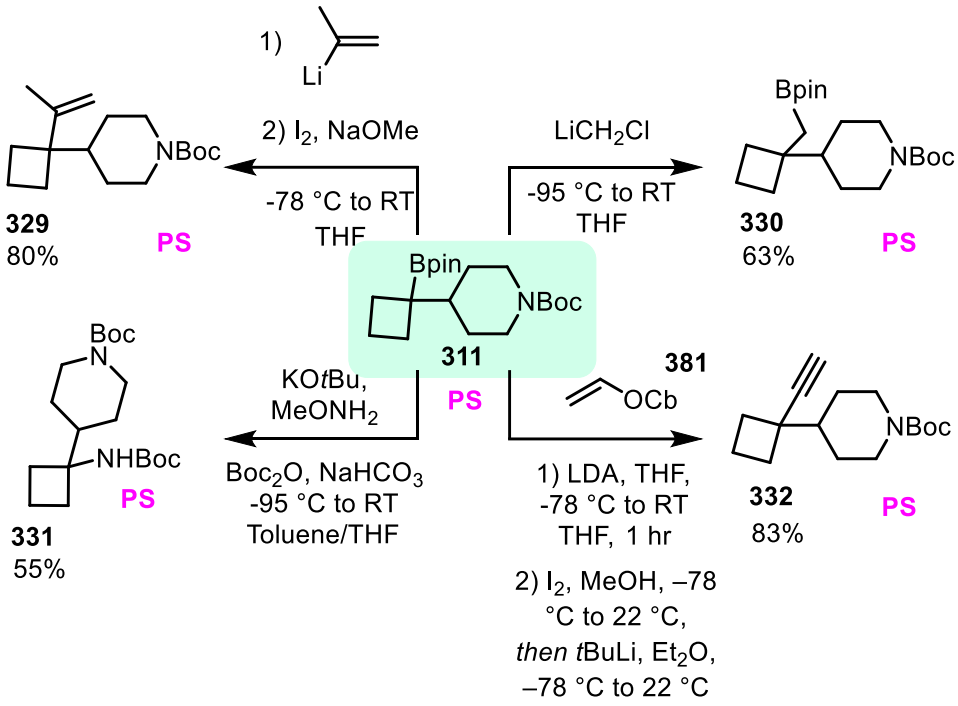


Scheme 102: sp^2 boronic esters tested using optimised conditions.

A range of alkenyl, aryl, heteroaromatic boronic esters were tested with good yields obtained (43-67%) as shown in Scheme 102. Reaction of phenyl Bpin gave the product **319** in good yields (64%). Subsequent, addition of electron withdrawing groups on the aryl ring (Cl, **320** and CF_3, **322**) did not hinder reaction. Similarly, the electron donating group such as *p*-methoxy group was also tolerated (**321**). However, the *p*-methoxy boronic ester product, had to be oxidised to the corresponding alcohol **321**, due to issues with separating the boronic ester starting material from the desired product during purification by column chromatography. In addition, compound **323** was synthesised from 2-benzofuran Bpin (**375**) in 53% yield and compound **324** from NBoc protected indole pinacol boronic ester in 67% yield. The use of NBoc protected tetrahydropyridine boronic esters (**376**) was also shown to furnish **325** in 43%.

A range of alkenyl boronic esters were used successfully, where mono-substituted alkenes with alkyl (compound **326**) and styrenyl groups (compound **327**) tolerated. Furthermore, substitution at the α-position of the olefin was also tolerated **328**. However, like previous boronic esters synthesised, the crude reaction for boronic ester derivative of compound **328** was difficult to purify, due to co-elution of the starting boronic ester. A mixture of H_2O_2/ NaOH was used to oxidise the boronic ester to the analogous alcohol. However, compound **328** was found to be incompatible with these conditions and so milder oxidation conditions using $NaBO_3.4H_2O$ were used. The poor isolated yield is a result of oxidation, rather than poor borylation reaction yield, as the ^{1}H NMR prior to oxidation (88%) was better than the isolated yield (49%).

2.4.3. Boronic Ester Functionalisation Group Interconversions

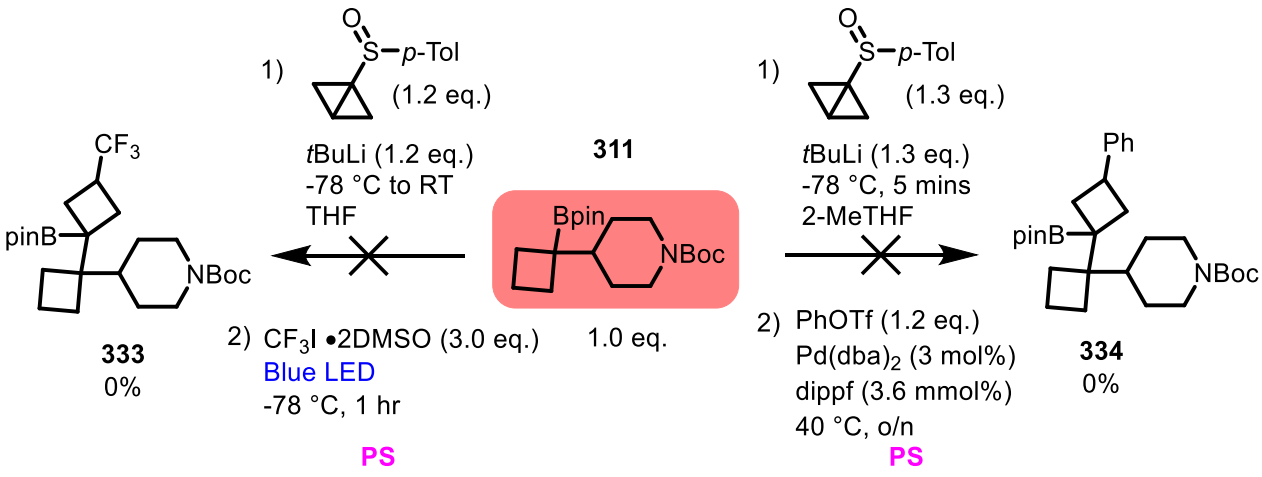


Scheme 103: Functional group interconversions of **311**.

To illustrate the synthetic utility of the reaction products, tertiary boronic ester **311** was subjected to several boronic ester functional group interconversions, which proceeded with excellent yields (Scheme 103). Oxidation of boronic ester products to their respective alcohols has previously been described (for example compound **303** or **313**). However, additional reactions such as Zweifel olefination[183], to convert the boronic ester to an alkene (compound

329, 80%), along with an alkynylation with vinyl carbamate (**381**), to give compound **332** (83%) in excellent yield were also demonstrated.[251] In addition, Matteson homologation[252] provided the methylene homologated primary boronic ester, compound **330**, in good yield and amination[253] and Boc protection, compound **331**, installed a protected tertiary amine in moderate yield (55%).

Some functional group interconversion reactions failed to give desired products as shown in Scheme **104**. The first functional group interconversion was attempted by radical addition to strained σ-bonds, as reported by Aggarwal and co-workers for other molecules, to produce compound **333**.[254] Here bicyclo[1.1.0]butyl (BCB) sulfoxide undergoes sulfoxide-lithium exchange, followed by addition of boronic ester starting material **311**, to give a boronate complex. Visible light irradiation (blue LED) in the presence of CF_3I•2DMSO, generates an electron deficient $^{\bullet}CF_3$ radical, which can add the strained central σ-bond of the BCB boronate complex. Subsequent one-electron oxidation of this radical to a carbocation triggers 1,2-metalate migration to give 1,3-cylobutyl cyclobutane boronic ester (**333**). The literature published by our group on this methodology, has an example of a 1,1-cyclobuty-substituted 1,3 cyclobutane[254].



Scheme 104: Failed functional group interconversions.

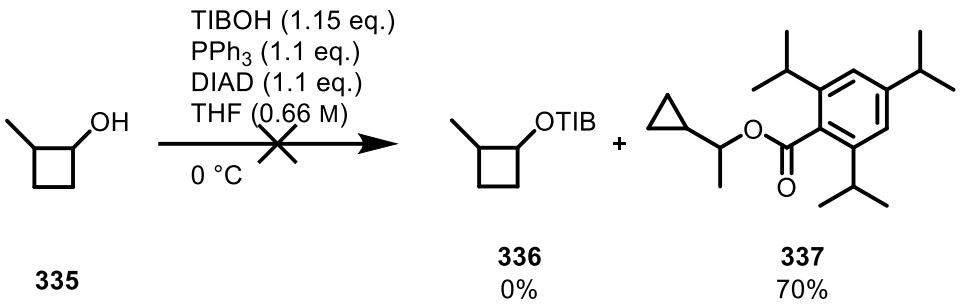
However, noticeably, the reported yield (41%) for this reaction is lower than that of other substrates reported (typical yields reported 60-90%). The literature example possesses a methyl group, whereas the failed reaction features a larger piperidine group, this suggests that the reaction is sensitive to sterically encumbered groups.

After not obtaining compound **333**, an alternate route, to access 1,3 cyclobutyl cyclobutane boronic esters, was attempted using C–C σ-bond carbopalladation, using a protocol published by Aggarwal and co-workers[255], which would have given compound **334**. Here, an aryl palladium(II) complex undergoes addition to the strained BCB boronate complex derived from boronic ester **311** to access cyclobutyl derivatives. However, this reaction also failed to give desired compound **334**. Again, the steric congestion expected at the boron atom centre, could explain why this reaction failed to give any desired product. At this stage, further attempts to synthesise a 1,3-cyclobutyl cyclobutane was abandoned.

2.4.4. Expanding Methodology to Complex Cyclobutyl-Containing Motifs

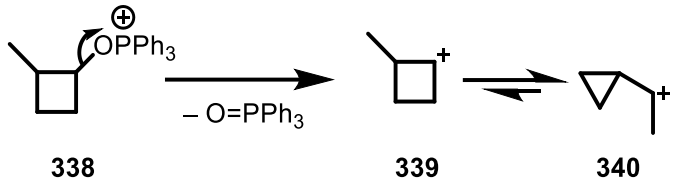
2.4.4.1. 2-Methylcyclobutyl 2,4,6-triisopropylbenzoate

(±)-2-Methylcyclobutyl-1-ol (**335**) was subjected to Mitsunobu esterification, to produce compound **336**, as shown in Scheme 105. Though the reaction profile, by TLC was clean, purification of the reaction mixture indicated that the reaction had not yielded desired product **336**. Instead, the cyclopropane ester **337** was obtained in excellent yield (70%). This side-reaction was also an issue when conducting the Mitsunobu reaction on cyclobutanol, where cyclopropylmethyl 2,4,6-triisopropylbenzoate **293** (7%), was inseparable from cyclobutyl 2,4,6-triisopropylbenzoate **292**.



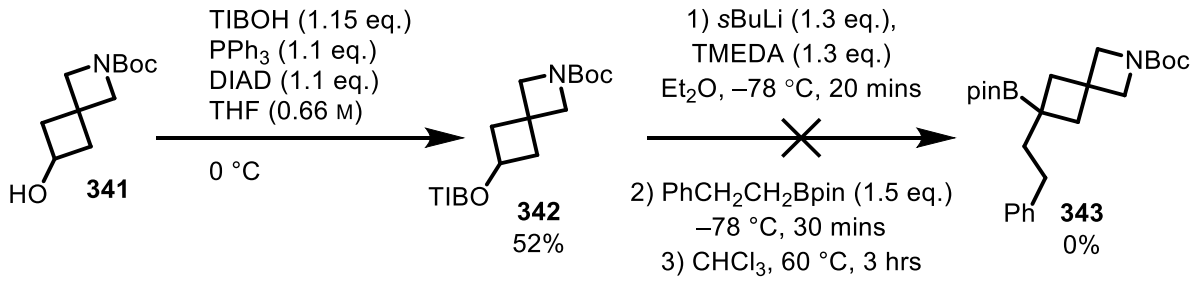
Scheme 105: Synthesis of 2-methylcyclobutyl 2,4,6-triisopropylbenzoate **336**.

However, the Mitsunobu reaction of 2-methylcyclobutanol gave no desired product as described above. This can be attributed to the formation of a non-classical cyclobutonium ion intermediate **339** from **338** (Scheme 106) which for 2-methylcyclobutanol, is now stabilised by the adjacent methyl group. This leads to the formation of a more stable secondary cyclopropylcarbocation **340** (as opposed to the primary carbocation for cyclobutanol, § 2.2.1.). As no desired benzoate product could be obtained through the Mitsunobu reaction, the reaction was abandoned.



Scheme 106: Side reaction in the Mitsunobu reaction of 2-methylcyclobutanol.

2.4.4.2. Lithiation-Borylation of *tert*-Butyl 6-((2,4,6-triisopropylbenzoyl)oxy)-2-azaspiro[3.3]heptane-2-carboxylate



Scheme 107: Synthesis and lithiation-borylation of *tert*-butyl 6-hydroxy-2-azaspiro[3.3]heptane-2-carboxylate **342**.

The second cyclobutyl core to be tested, contained a 2-azaspiro[3.3]heptane motif. The desired benzoate (compound **342**) was synthesised *via* Mitsunobu esterification of **341**, as shown in Scheme 107. Subsequent lithiation-borylation, under standard conditions, using 2-phenylethyl boronic acid pinacol ester **294**, as shown in Scheme 107, failed to give the desired product **343**.

Instead, starting benzoate **342** (80%) and 2-phenylethyl boronic acid pinacol ester **294** (66%) were recovered. The large recovery of starting benzoate **342** suggested lithiation was not taking place, so to better understand the reaction profile *in-situ* IR spectroscopy was used.

2.4.4.3. *In-Situ* IR Spectroscopy Studies into the Lithiation-Borylation of *tert*-Butyl 6-((2,4,6-triisopropylbenzoyl)oxy)-2-azaspiro[3.3]heptane-2-carboxylate

During the *in-situ* spectroscopy study, a probe is inserted into the reaction vessel, such that the tip of the probe contacts the surface of the reaction solvent. It is crucial that the reaction mixture is homogenous, otherwise the IR study will not be accurate. When attempting to dissolve benzoate **342**, in Et_2O at -78 ˚C the benzoate was found to precipitate onto the surface of the probe, ruining the experiment. To overcome this, THF (0.22 mL) was added in addition to the reaction solvent (Et_2O). Subsequent lithiation of compound **342** was attempted using *s*BuLi (1.3 eq.), TMEDA (1.3 eq.) in Et_2O/THF (0.22 mL) (0.2 M) at -60 °C (cryostat).

The *in-situ* IR spectroscopy study, as shown in Figure **18**, showed that the reaction profile for this substrate was complex. The first addition of *s*BuLi to the reaction caused a drop in the IR signal for both $ROTIB_{C=O}$ = 1730 cm^{-1} and $NBoc_{C=O}$ = 1708 cm^{-1}, due to dilution effects in the solvent as well as fluctuation in the reaction mixture temperature.

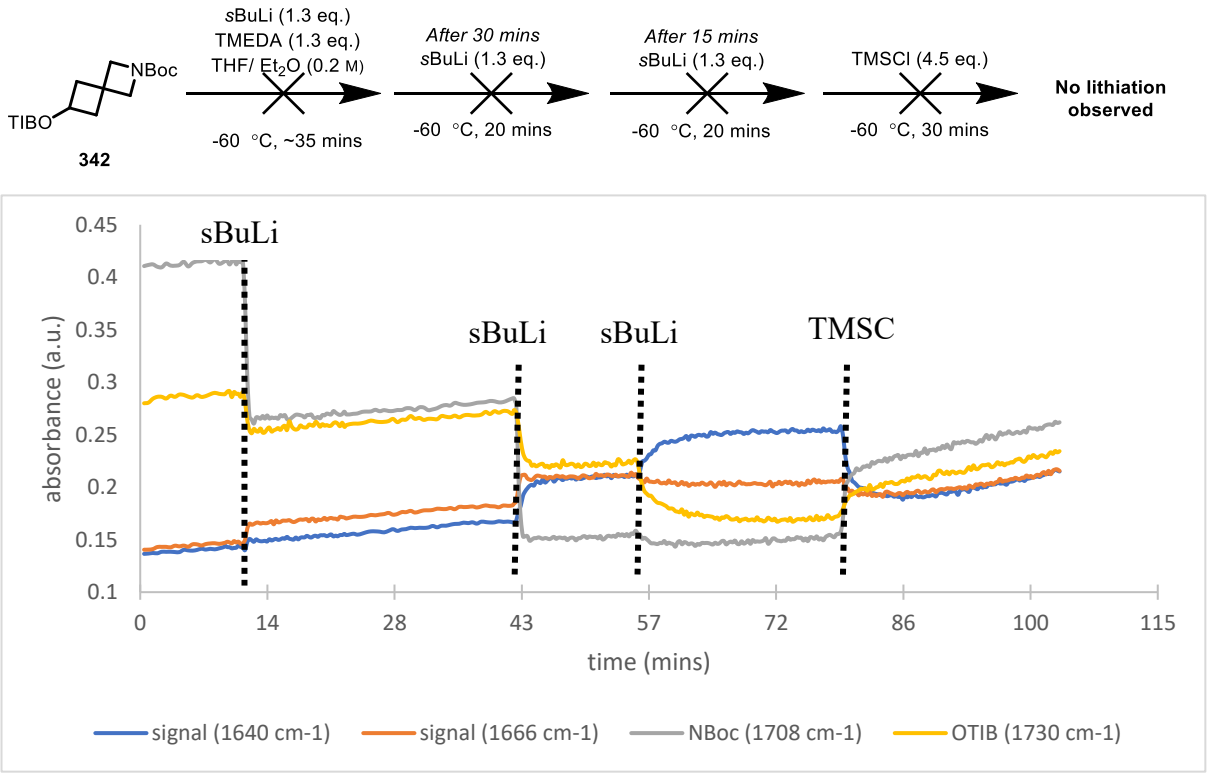
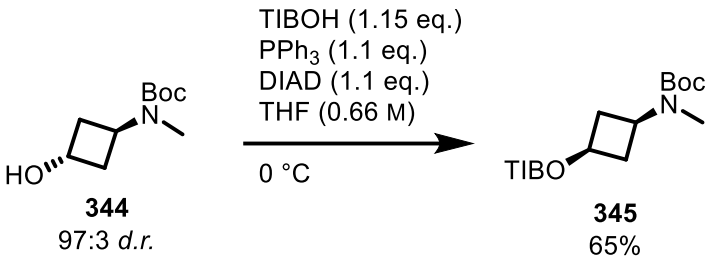


Figure 18: Lithiation-borylation *in-situ* IR spectroscopy study of *tert*-butyl 6-((2,4,6-triisopropylbenzoyl)oxy)-2-azaspiro[3.3]heptane-2-carboxylate **342**. Reagents: *s*BuLi (1.3 eq.) x3, TMEDA (1.3 eq.) Et_2O/THF (0.2 M) at -60 °C (cryostat).

Though a new signal (1666 cm^{-1}) appeared, this was not characteristic of organolithium formation (normally seen in the range of 1600-1650 cm^{-1}), which suggested lithiation had not occurred. The signal seen at 1666cm^{-1}, could be because of a co-ordination complex forming between the *s*BuLi and NBoc group, that could be preventing lithiation. So, after 30 minutes at -60 ˚C, another 1.3 equivalents of *s*BuLi were added, to promote lithiation. Again, there was a drop in signal, due to solvent dilution effects, however, there was no sign of lithiation having taken place. A final, additional equivalents of *s*BuLi was added after 15 minutes, there was no observable lithiation by *in-situ* IR spectroscopy. The reaction mixture was left to stir at -60 ˚C for ~ 30 minutes, after which TMSCl (4.5 eq.) was added to trap any lithiated species to enable column chromatography isolation.

However, TLC confirmed that the major constituents in the reaction mixture were still the two starting materials (benzoate and boronic ester), and no trimethylsilyl-containing products were obtained. A total of 3.9 equivalents of *s*BuLi was added, however no lithiation occurred, as suggested above. Thus, this molecule is inert to lithiation, potentially due to coordination of the base to the NBoc group. Therefore, further studies were not carried out.

2.4.4.4. Synthesis of *tert*-Butyl 6-((2,4,6-triisopropylbenzoyl)oxy)-2-azaspiro[3.3]heptane-2-carboxylate



Scheme 108: Mitsunobu esterification of *tert*-butyl ((1R,3R)-3-hydroxycyclobutyl)(methyl)carbamate **344**.

Commercially available *trans-tert*-butyl (3-hydroxycyclobutyl)(methyl)carbamate **344** (97:3 *d.r. trans:cis*), from which the desired benzoate **345** was synthesised *via* Mitsunobu esterification, as shown in Scheme 108, in 65% yield and isolated >99:1 *d.r.* Next, the core's lithiation-borylation prospect was directly tested using *in-situ* IR spectroscopy.

2.4.4.5. *In-situ* IR Spectroscopy Studies into the Lithiation-Borylation of (1s,3s)-3-((*tert*-butoxycarbonyl)(methyl)amino)cyclobutyl 2,4,6-triisopropylbenzoate

Due to complexity of the lithiation-borylation methodology, it was decided that a simple lithiation-electrophile trap would be conducted initially, which would be monitored *via in-situ* IR spectroscopy. The electrophiles used in the reaction were TMSCl (3.0 eq., large excess), followed by MeOD (3.0 eq., large excess). Due to the steric congestion around the cyclobutyl ring in compound **345**, TMSCl might fail to react with the lithiated species. However, adding MeOD, would ensure the lithiated species are quenched, with D-incorporation. The crude reaction mixture can be evaluated by ^{1}H NMR. Similarly, the tri-methyl groups on the TMS group, are distinctly up-field due to the presence of the silicon heteroatom.

The appending N-methyl carbamate would also provide insight into OTIB *vs* N(Me)Boc C*H* lithiations, since azetidine NBoc substrates were found to be resistant to *α*-lithiation with *s*BuLi/TMEDA.[256] Reaction conditions were adapted from the attempted lithiation-borylation of azaspiro **342** reaction (-60 ˚C), due to similar solubility issues of **345** at -78 °C, therefore the solvent used was a mixture of Et_2O/THF (0.2 M). As shown in Figure 19, addition of *s*BuLi (1.3 eq.) to the cooled benzoate **345** ($ROTIB_{C=O}$ = 1731 cm^{-1} and $NBoc_{C=O}$ = 1700 cm^{-1}) at t =

~24 min, showed the signal attributed to NBoc group drop to the baseline, whilst the signal attributed to the OTIB group did not change in intensity. In addition, a signal at 1731 cm^{-1} had now appeared and continued to increase. This combination would suggest lithiation adjacent to nitrogen. After 10 mins (t= ~36 mins) another 1.3 equivalents of *s*BuLi was added to the reaction, to see if this would affect the lithiation profile, however, only dilution effects were observed. Over the following 20 minutes, no change in the intensity of any signals was observed, suggesting the lithiated species generated were chemically stable. TMSCl (3.0 eq.) was added to the reaction mixture to quench the reaction (t = ~56 mins). The addition saw immediate decrease in the population of lithiated species (1731 cm^{-1}), similarly the $NBoc_{C=O}$ = 1700 cm^{-1}, which had disappeared had now returned. After 5 min, MeOD (3.0 eq.) was added to the reaction mixture to quench any unreacted lithiated species. A total of 2.6 eq. *s*BuLi was added to the reaction mixture followed by 3.0 eq. TMSCl and MeOD, however no ring-lithiated derived products (**345a/b**) were obtained from this reaction. The crude reaction mixture was filtered using a short silica plug and submitted for NMR. However, ^{1}H NMR, showed no TMS incorporated on the cyclobutyl ring C*H* adjacent to the N(Me)Boc group. However, the N-methyl singlet (CH_3N) (3H, 2.86 ppm) had now become a singlet (2H, 2.66 ppm). Similarly, there was an upfield methyl signal that would suggest TMS incorporated (9H, 0.00 ppm). Subsequent TLC analysis showed two spots (eluted 10% EtOAc/pentane), the lower of which was the starting benzoate **345**. Isolation of the top spot (50% yield), followed by NMR spectroscopy and mass spectroscopy analysis, confirmed compound **348**, where lithiation has taken place on the N-*methyl* group followed by electrophile trapping (TMS) as shown in Scheme 109.

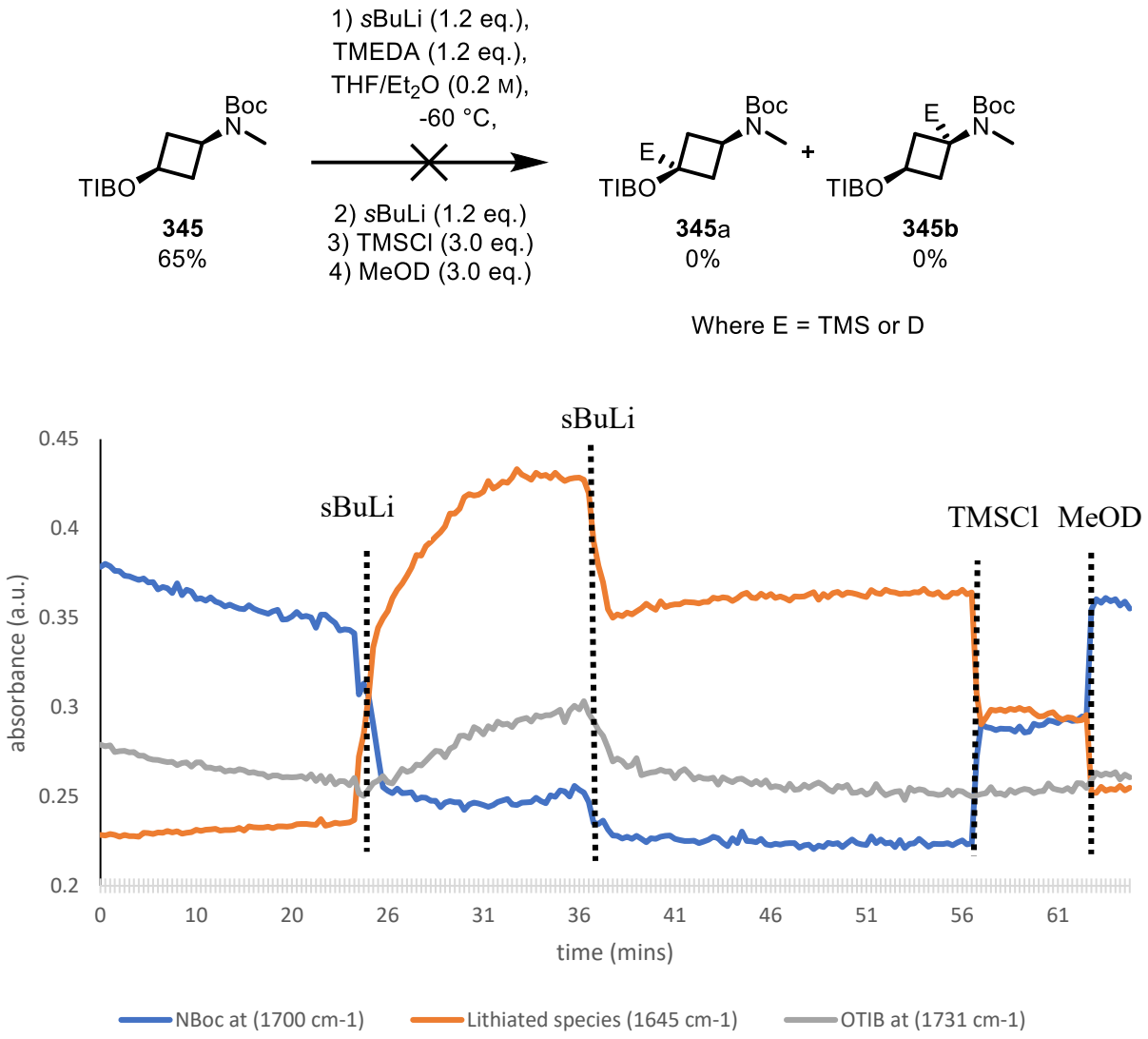
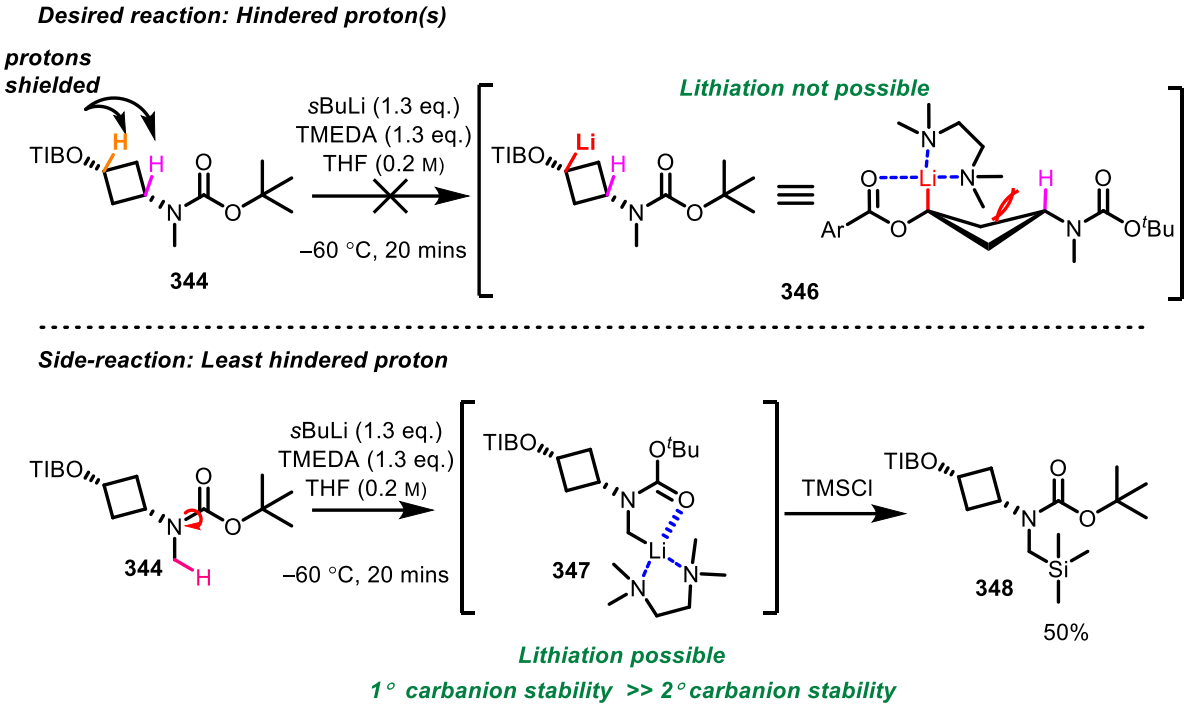


Figure 19: Lithiation-borylation *in-situ* IR spectrsoscopy study of (1s,3s)-3-((*tert*-butoxycarbonyl)(methyl)amino)cyclobutyl 2,4,6-triisopropylbenzoate **345**. Reagents: *s*BuLi (1.3 eq.) x2, TMEDA (1.3 eq.) in THF/Et_2O (0.3 M) at -60 °C (cryostat).

The presence of bulky substituents on the cyclobutane ring (NBoc and OTIB), increases steric bulky around the ring (**346)** and hinders ring deprotonation of **344**. The side reaction is promoted by the presence of the NBoc carbamate group, which can form a 5-bond co-ordination complex with the lithiated species (**347**), as shown in scheme 109. Furthermore, the stability of primary carbanion over the secondary carbanion, may provide an electronic argument for the selective deprotonation of the methyl group to give product **348**. No other products were isolated from this reaction. As a result, this reaction shows the difficulty in deprotonating secondary TIB esters.



Scheme 109: Proposed cause of side reaction in lithiation-electrophile trapping study of (1s,3s)-3-((*tert*-butoxycarbonyl)(methyl)amino)cyclobutyl 2,4,6-triisopropylbenzoate **344**.

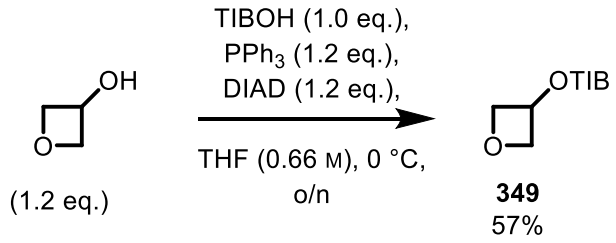
2.4.5. Expanding Methodology to Heterocyclic Analogues

To expand upon the methodology established for cyclobutyl benzoates, our attention turned to heterocycle analogues of cyclobutane, such as oxetanes and azetidines. As demonstrated in the cyclobutyl benzoate chemistry, this area of small ring lithiation is under-studied. Therefore, this work would provide insight into a) the lithiation properties and stabilities of 3-substituted oxetane and azetidine substrates and b) develop conditions for the novel lithiation-borylation chemistry of these heterocycles, to explore new chemical space.

2.4.5.1. Synthesis of Oxetan-3-Benzoate

There have been some literature reports into the lithiation-electrophile trapping of 2-substituted oxetanes, where electron withdrawing groups in the 2-position, such as aryl[257,258], sulfonyl[259],

provide suitable activation and stability of the lithiated intermediate to facilitate the reaction. However, the lithiation of 3-subsituted oxetane has not been reported.

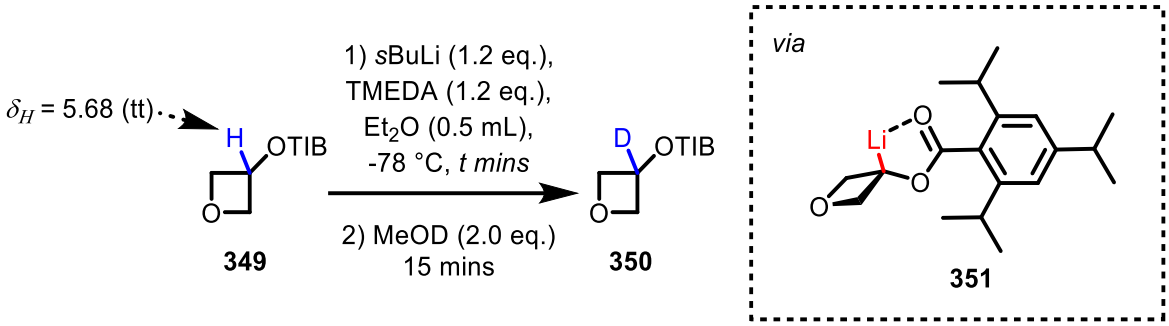


Scheme 110: Mitsunobu esterification of oxetan-3-ol.

Oxetan-3-ol was subjected to Mitsunobu esterification, using standard conditions applied to cyclobutanol (Scheme 110). The reaction produced desired benzoate **349** in 57% yield after column chromatography. No side products were observed in the reaction, thus demonstrating the oxetane's preference to not undergo the rearrangement process (as seen in cyclobutyl benzoate derivatives).

2.4.5.2. Lithiation-deuteration study of Oxetan-3-Benzoate

Having successfully synthesised benzoate **349**, the substrate was initially subjected to *in-situ* IR spectroscopy monitored using conditions derived from the lithiation-borylation reactions of cyclobutyl benzoate **292** (§ 2.4.5.4), however this attempt was unsuccessful. Therefore, the whole process was simplified by attempting to first establish lithiation conditions for the substrate. For this purpose, lithiation-deuteration studies were undertaken, where the model substrate was lithiated with *s*BuLi (1.2 eq.)/ TMEDA (1.2 eq.) for 1, 2, 5, 10 and 20 minutes at -78 ˚C, after which MeOD (2.0 eq.) was added to the reaction mixture to quench any potential lithiated species **351** to give product **350** (Scheme 111). Subsequent, ^{1}H NMR (with 1.0 equivalents of 1,3,5-trimethoxybenzene, TMB) would allow for an ^{1}H NMR yield to be calculated. This simple exercise would confirm if lithiation occurred, and if so, where. If the desired lithiation-deuteration occurred, then the oxetane ring C*H* signal which appears at 5.68 ppm (tt) would disappear. The reagent equivalents were chosen to ensure full lithiation of **349**.



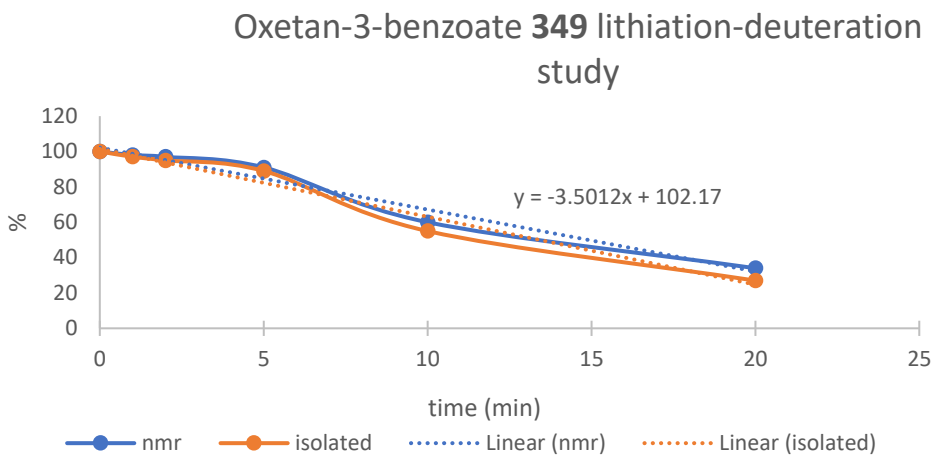
Scheme 111: Lithiation-deuteration study of oxetan-3-benzoate **349**.

As shown in Table 12 lithiation of oxetan-3-benzoate **349** is rapid, with full lithiation observed within 1 min. Unfortunately, the lithiated species generated is not chemically stable and decomposes over time. As shown in Chart 3, the decay of lithiated **351** gives a half-life ($t_{½}$) for this species of ~13 min.

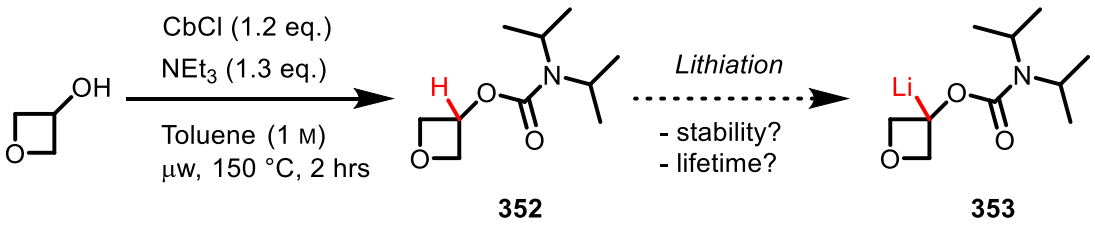
Table 12: Lithiation-deuteration results for benzoate **349**.

Time (t/mins)	% D-incorporation (^{1}H NMR)	% Yield (^{1}H NMR)	% Yield isolated
1	100	98	97
2	100	97	95
5	100	91	89
10	100	60	55
20	100	34	27

Chart 3: Lifetime of lithiated oxetan-3-benzoate **351**.



Though the lithiated species **351** is chemically unstable, the fast and quantitative lithiation could be beneficial if the species is immediately trapped with a boronic ester. There is also the potential to try the carbamate derivative of oxetane **352**, however, compared to the rapid lithiation observed for benzoate **349**, analogous carbamates are typically slower to deprotonate. However, we did not undertake these studies at this time (Scheme 112).

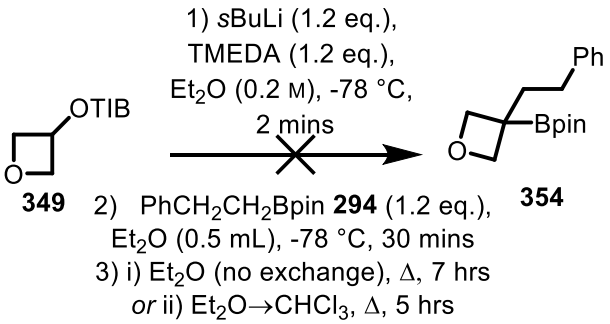


Scheme 112: Lithiation of oxetan-3-carbamate **352**.

2.4.5.3. Lithiation-Borylation of Oxetan-3-Benzoate

Studies into the lithiation-borylation of **349** was also explored, as shown in Scheme 113, in this reaction 1.0 eq. benzoate **349**, 1.2 eq. TMEDA/ *s*BuLi in diethyl ether (1 mL, 0.35 M) were used for the lithiation reaction at -78 ˚C for 2 mins, after which boronic ester phenylethyl boronic acid pinacol ester **294** (1.2 eq.) in diethyl ether (0.5 mL) was added to the reaction

mixture and left to stir at -78 ˚C for 30 min. The first reaction mixture i) was left to reflux in diethyl ether, whereas ii) was exchanged for chloroform and then refluxed. Both reactions were refluxed for 7 and 5 hours respectively with monitoring *via* ^{11}B NMR to assess boronate complex consumption.



Scheme 113: Initial attempt at lithiation borylation of **349**.

Subsequent, ^{1}H NMR of both crude reaction mixtures (TMB internal standard), showed a messy reaction profile, with no signals matching that of desired product **354**. Purification of both reaction mixtures confirmed that no product had been generated, however starting boronic ester **294** was recovered from both mixtures, 63% and 55%, respectively for i) and ii).

Though benzoate **349** has been shown to undergo lithiation and trapping with MeOD, the reaction outcome from the above study does not show successful lithiation-borylation. ^{11}B NMR had shown a signal corresponding to a boronate complex at 5 ppm, which was consumed over time (^{11}B NMR taken every 2 hr) giving rise to a boronic ester signal at 34 ppm. This demonstrated that boronate complex has been consumed. The two obvious pathways for the consumption of boronate complex are 1,2-migration (desired) and reversal of the boronate complex back to the lithiated species and starting boronic ester. To confirm that the lithiated benzoate **349**, was reacting with boronic ester, *in-situ* IR spectroscopy studies were undertaken.

2.4.5.4. *In-situ* IR Spectroscopy Studies into the Borylation of Oxetan-3-Benzoate

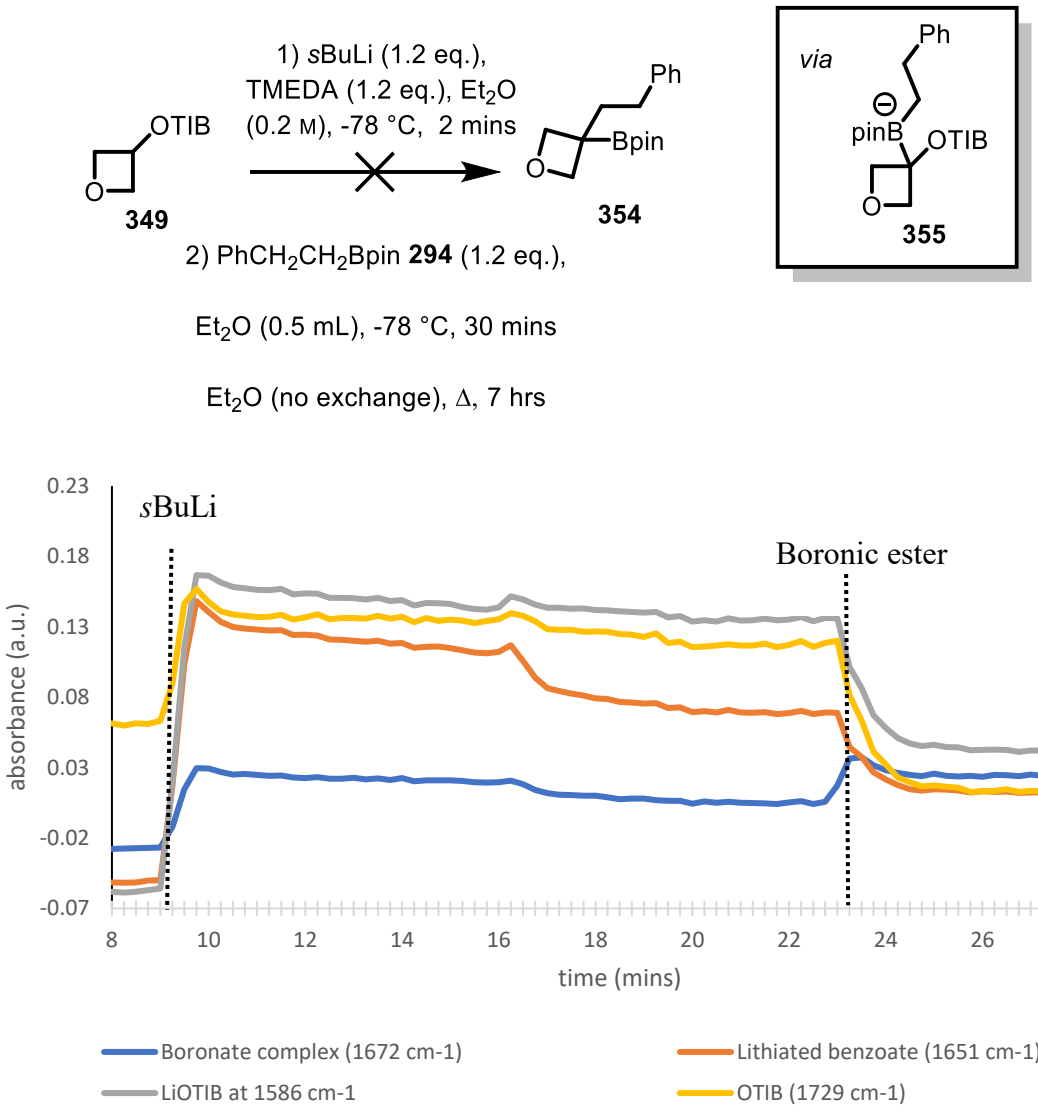


Figure 20: Lithiation-borylation of oxetan-3-benzoate **349** using *in-situ* IR spectroscopy.

For the lithiation-borylation of benzoate **349**, *in-situ* IR spectrsoscopy was conducted at the same conditions as the optimised conditions for the cyclobutyl benzoate **292** substrate, no solvent exchange was made (Figure 20). The lithiation of **349** is rapid (yellow line, $OTIB_{CO}$= 1729 cm^{-1}) with full consumption of starting benzoate **349** within 1 min, giving rise to lithiated species **351** (orange line, $LiTIB_{CO}$= 1651 cm^{-1}), which was left to stir at -78 ˚C for 15 mins. This time was chosen due to the previously established $t_{½}$= ~13 mins. The *in-situ* IR spectroscopy study confirmed the chemical instability of lithiated species derived from **349**, which begins to decompose immediately after lithiation. The addition of boronic ester **294**

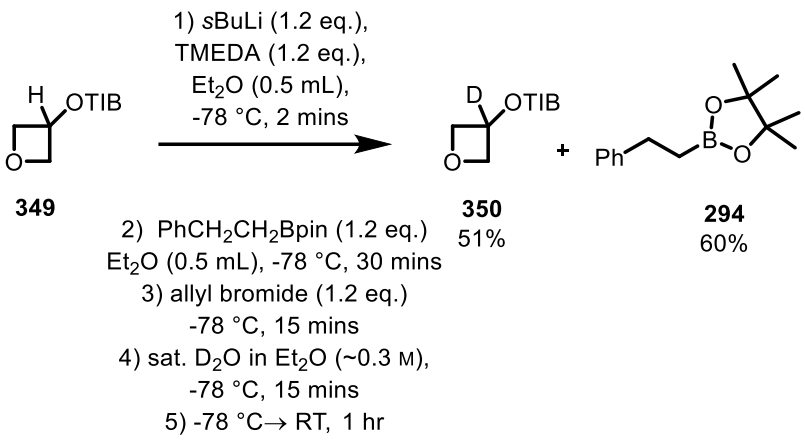
gives rise to boronate complex **355** (blue line, B-ate$^{-}_{CO}$= 1672 cm^{-1}) and lithiated species **351** are consumed as the signal declines. The reaction sample was refluxed and left to stir for 7 hrs, with no solvent exchange. The 1,2 migration was monitored with ^{11}B NMR, as shown in Table 13.

Table 13: ^{11}B NMR **355:294** ratio from lithiation-borylation of **349**.

Entry	Time (hrs) after reflux started	Boronate (355): Boronic ester (294) ratio
1	3	50:50
2	6	6:94
3	7	0:100

However, ^{1}H NMR (with TMB as internal standard) of the crude reaction mixture sample showed a similar trace to that obtained from the initial test reaction, TLC also verified that starting boronic ester **294** (49% isolated yield) and starting benzoate **349** (15% isolated yield), were the only materials present in the crude. At this point it was clear that though unstable, the lithiated intermediate was reacting with the boronic ester and forming a boronate complex **355**. However, the fate of the boronate complex was uncertain. It could be possible that the boronate complex, unable to undergo 1,2-migration may revert to starting boronic ester **294** and lithiated benzoate **351**. The lithiated benzoate would decompose in time, leaving the boronic ester, as the only recovered product from the reaction. To address the fate of the 1,2-migration step a two-electrophile test was conducted, as shown in Scheme 114.

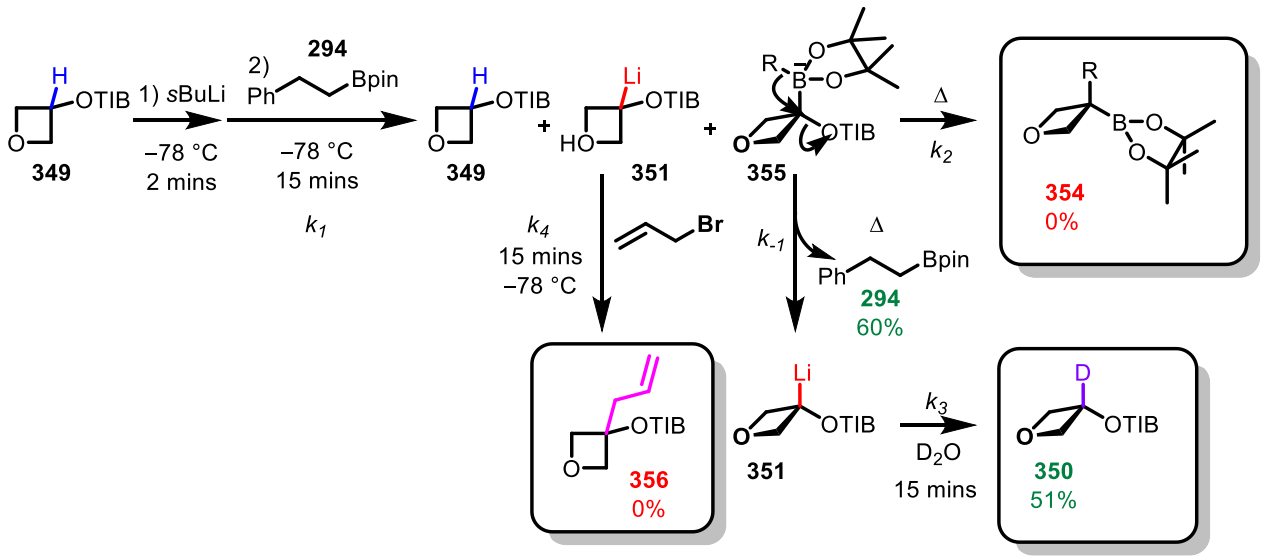
2.4.5.5. Two-Electrophile Test on Oxetan-3-Benzoate



Scheme 114: Two-electrophile test for oxetanyl benzoate **349**.

The two-electrophile test is a one pot multi-component reaction (Scheme 115).[170] Benzoate **349,** TMEDA and diethyl ether were added to the flask, which is cooled to -78 ˚C. After the addition of *s*BuLi, the reaction is stirred for 2 min at -78 ˚C. After which the boronic ester **294** was added to the reaction mixture followed by a further 15 mins of stirring at -78 ˚C. The literature example leaves the reaction mixture to stir for 30 mins, however given the short lifetime of the lithiated species the borylation time had to be shortened. Next, allyl bromide (first electrophile) was added to the reaction mixture and stirred for 15 mins at -78 ˚C. The purpose of this electrophile is to trap unreacted lithiated benzoate **351** to give allylation product **356**. Finally, D_2O (the second electrophile) was added to the reaction mixture, with a further 15 mins of stirring at -78 ˚C. The D_2O will lead to the formation of D-incorporated benzoate **350**, should the boronate complex **355** be reversible and revert to lithiated benzoate **351**. This renders the two-electrophile test a powerful tool for identifying issues with the reactivity of **351** (k_1 and k_4)**,** the boronate step (k_2) and reversibility of borylation (k_{-1} and k_3).

From this experiment, it is conclusive that the lithiated species **351** reacts with boronic ester **294** to form boronate complex **355**. As no allylated product **356** was obtained from this experiment, it also confirms that within 15 minutes of reaction time all the lithiated benzoate **351** has been consumed. However, failure to obtain the desired boronic ester **354** (k_2), suggests that there is an issue with the 1,2-migration step. Post-reaction recovery gave only D-incorporated benzoate **350** (51%) (k_3) and starting boronic ester **294** (60%), therefore verifying that the boronate complex formation is reversible (k_{-1}).

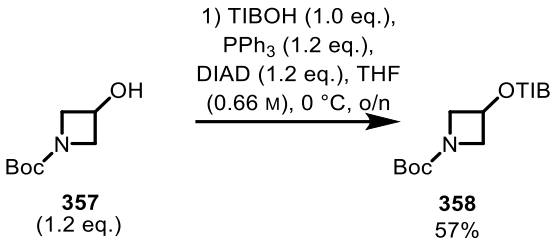


Scheme 115: Two-electrophile test reaction pathways for benzoate **349**.

Interestingly, changing from cyclobutane to oxetane renders boronate complex formation reversible. This could be due to inductive effects of the oxygen in the ring which makes the lithiated oxetane more stable. No further studies were conducted on the lithiation-borylation of oxetane benzoate **349**.

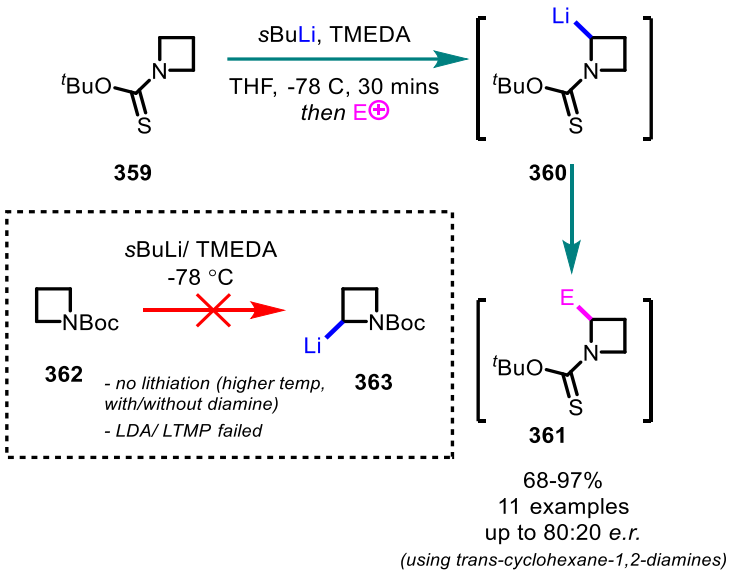
2.4.5.6. Synthesis of Azetidine Benzoate

There have been literature reports into the lithiation-electrophile trapping of the 2-position of *N*-thiopivaloyl/ *tert*butoxythiocarbonyl-azetidines (Scheme 116), where a range of electrophiles were tolerated.[260,261] The ring-lithiation of the 2-positions of azetidines does not occur when a Boc group is used.[260] Neither the study into the lithiation of 3-subsituted azetidine benzoates **358** nor the electrophile trapping of these species have previously been reported.



Scheme 116: Synthesis of azetidine benzoate **358** *via* Mitsunobu esterification.

Azetidine benzoate **358** was synthesised *via* Mitsunobu esterification in 57% yield from the corresponding alcohol **357**, in which the TIBOH was the limiting reagent. As shown by Hodgson *et. al.*[260], the lithiation of N-Boc azetidine 2-position **362** was unsuccessful (Scheme 117) and therefore lithiated species **363** was not observed. Instead, it was found that ring-lithiation **360** was only possible when using thiopivaloyl protecting group (Botc) **359**, which gave various 2-substituted products upon reacting with suitable electrophiles **361**. Thus the lithiation of **358** should be favoured, without competition, at the 3-position.



Scheme 117: Hodgson precedent for lithiation-electrophile trapping of NBoc-azetidines.

2.4.5.7. *In-situ* IR Spectroscopy Study of Azetidine Benzoate

Having successfully, synthesised compound **358**, focus turned to evaluation of lithiation-borylation parameters for **358**, by *in-situ* IR spectroscopy study of the benzoate. For this reaction (Figure 21), 1.0 eq. azetidine benzoate **358**, 1.2 eq. TMEDA/ *s*BuLi in diethyl ether (1 mL, 0.35 M) were used for lithiation at -78 ˚C for 12 mins (length of time determined by monitoring changes to IR spectra over time), after which boronic ester **294** (1.2 eq.) in diethyl ether (0.5 mL) was added to the reaction mixture and left to stir at -78 ˚C for 15 mins. The reaction mixture was left to reflux in Et_2O for 7 hours and then the reaction mixture analysed by ^{11}B NMR and subsequent isolation of reaction species. However, the reaction failed to give desired product **364**. Instead, the starting boronic ester was recovered (60%).

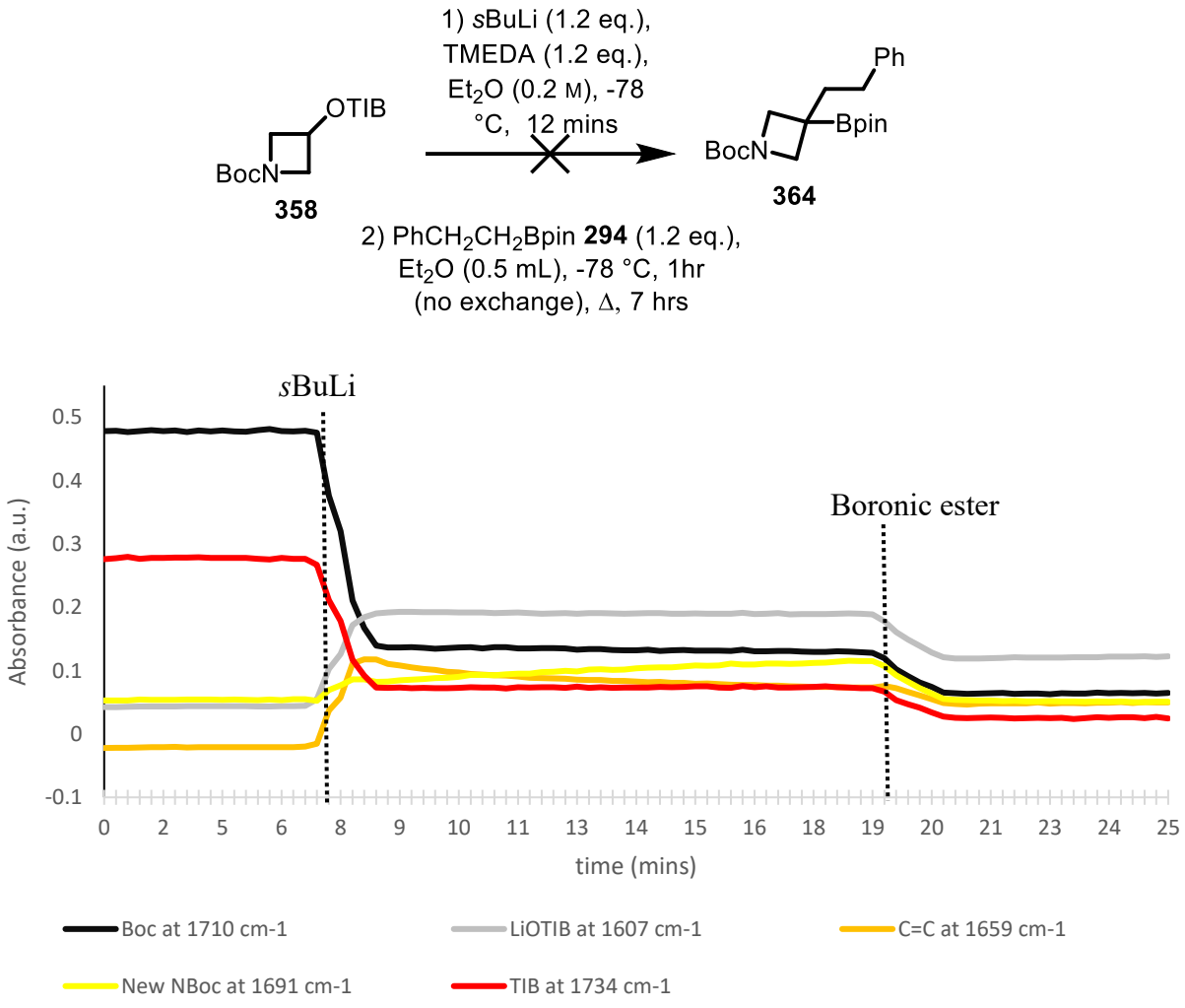
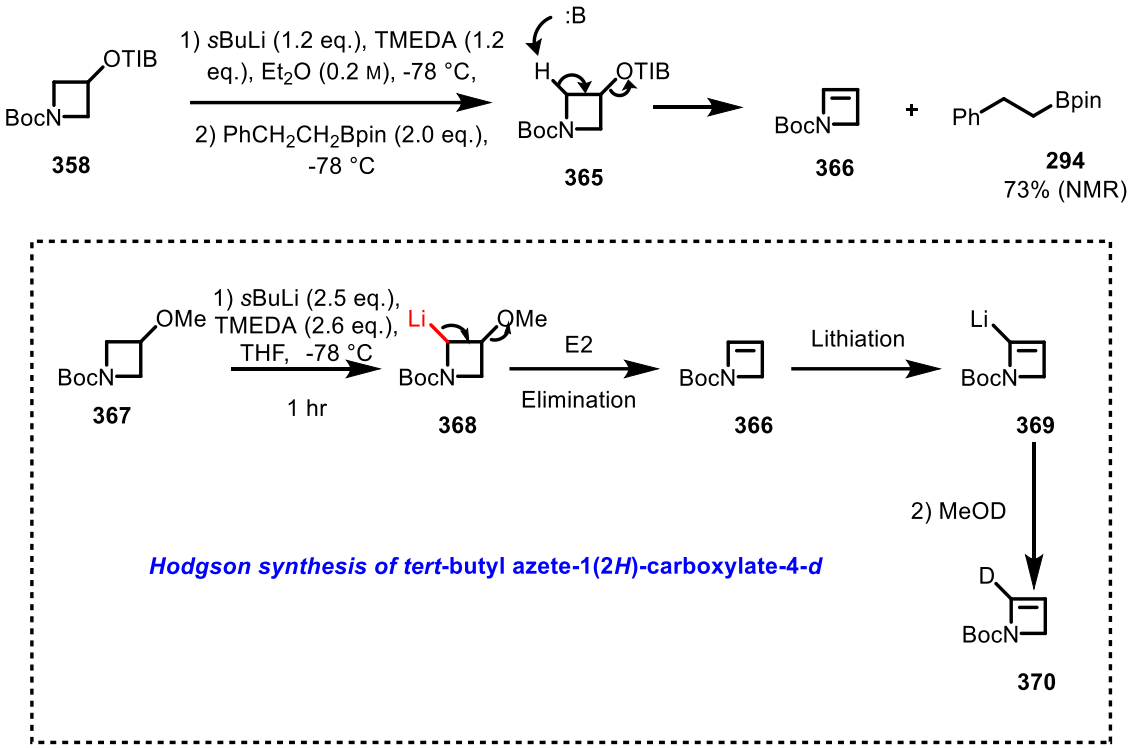


Figure 21: *In-situ* IR spectroscopy trace for lithiation-borylation of azetidine benzoate **358**.

As shown by the **red** ($ROTIB_{C=O}$ = 1734 cm^{-1}) and **black** ($NBoc_{C=O}$ = 1710 cm^{-1}) traces, addition of *s*BuLi to the reaction mixture at 7.37 mins results in a decrease in intensity for both IR signals, though this could be a result of solvent dilution effects, as observed previously in other *in-situ* IR spectroscopy studies. The presence of lithiated benzoate **(light grey trace)** ($LiOTIB_{C=O}$ = 1607 cm^{-1}) however, suggests that **358** is undergoing a side-reaction, in which the OTIB group is being eliminated from azetidine benzoate **365** to give azetidene **366** (Scheme 118). This type of reaction has been observed by Hodgson *et. al.,* where they report the elimination of the methoxy group in *tert*-Butyl 3-methoxyazetidine-1-carboxylate **367**, *via* a lithiation-elimination pathway **368** to **366**.[256] Then **366** can undergo an additional lithiation in the presence of excess *s*BuLi to give **369**, which can be trapped through deuteration (MeOD) to give **370**. In a similar manner, it is proposed that a formal lithiation of **358** occurs followed by elimination of the OTIB group.

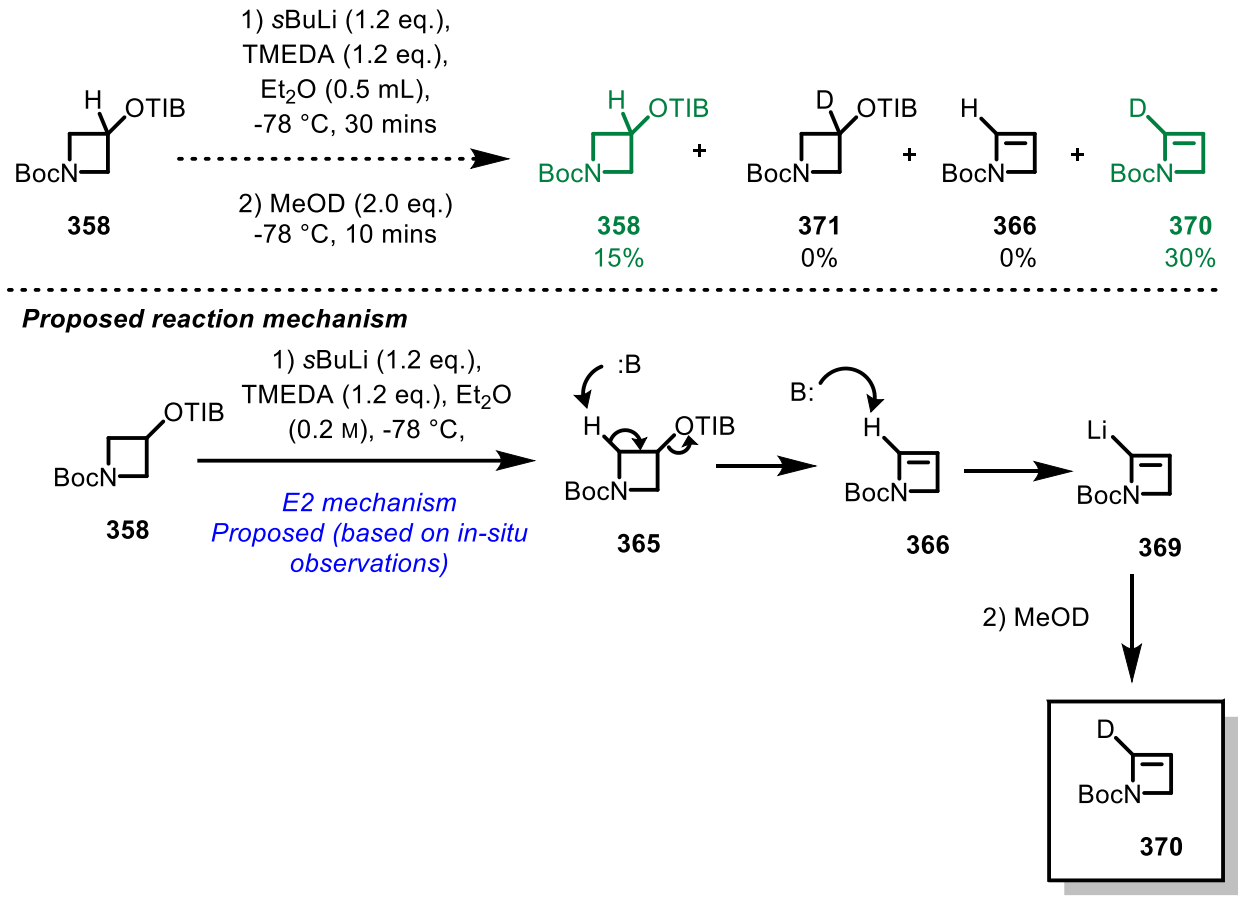
It is also important to note that no pre-lithiation complex between the NBoc group and *s*BuLi/ TMEDA was observed (~1675 cm^{-1}) in the reaction before the elimination reaction occurred. There was also no evidence of ring lithiation at *α*-C*H*-OTIB (~1640 cm^{-1}). The reaction was left to stir at -78 ˚C for 15 mins, however the profile of the reaction IR did not change over this period. Subsequently, boronic ester **294** was added to the reaction mixture and left to stir at -78 ˚C for 30 mins. The addition of boronic ester showed a further drop in signal intensity, however, the uniformity of the change suggests this could be a result of dilution effects. This was confirmed to be the case when no desired products or side-products with boronic ester incorporation were obtained after crude ^{1}H NMR of the reaction mixture. Instead, only the starting boronic ester **294** was observed in 73% NMR yield (TMB internal standard). There were also NMR signals present in the crude composition that suggested side-product **366** had also been formed.



Scheme 118: Proposed lithiation-deuteration mechanism of azetidine benzoate **358**.

2.4.5.8. Lithiation-Deuteration Study of Azetidine Benzoate

Having failed to obtain desired azetidine boronic ester **364**, further studies were taken to understand the lithiation profile of this substrate. Although it was suspected that lithiation was not taking place, lithiation-deuteration study was conducted (Scheme 119), to elucidate any side-product pathways occurring. Furthermore, the addition of MeOD would act to trap any lithiated **369**, which is formed due to the unsaturated and more strained 2-azetidene, undergoing lithiation as shown in Scheme 118. The crude reaction mixture was filtered through a small plug of silica (to remove salts), concentrated, and submitted for ^{1}H NMR analysis with internal standard (TMB). The results from the NMR would help to determine the ratio of **358:371:366:370** and ^{1}H NMR yield for D-incorporated product to starting benzoate **358**.

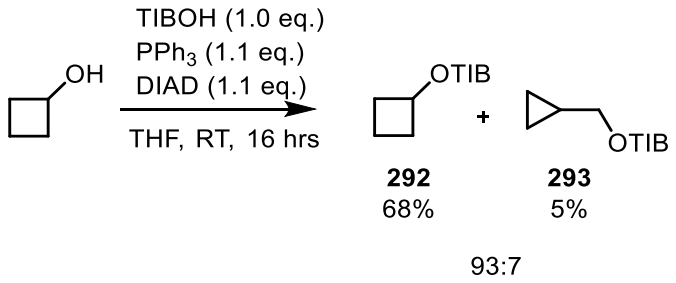


Scheme 119: Proposed lithiation-deuteration study of azetidine benzoate **358**.

The deuteration study confirmed the proposed reaction pathway, whereby no ring lithiation-deuterations products were obtained (**371**). Similarly, **366** was also not present from crude NMR comparisons with literature, suggesting that **366** is short lived in the presence of *s*BuLi. The only products obtained from the reaction are **370** (30%) and starting benzoate **358** (15%). As this side-pathway is the only reaction taking place in this reaction, this would suggest that azetidine benzoate **358** is not a suitable substrate for lithiation-borylation. For this reason, further studies into the lithiation-borylation reaction of azetidine benzoate **358** were not undertaken.

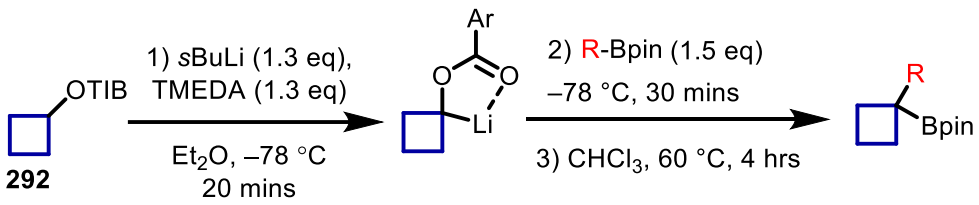
2.5. Conclusion

A range of suitable cyclobutyl-containing substrates were synthesised to explore the lithiation-borylation pathway. The Mitsunobu esterification of cyclobutanol to synthesise **292** was difficult due to partial rearrangement of cyclobutanol, giving an inseparable, cyclopropylmethyl 2,4,6-triisopropylbenzoate **293**. However, to our advantage, cyclopropylmethyl 2,4,6-triisopropylbenzoate **293**, did not affect the lithiation-borylation reaction outcome. Subsequently, we have shown cyclobutyl 2,4,6-triisopropylbenzoate **292**, undergoes rapid lithiation and reaction with boronic esters.



Scheme 120: Optimised Mitsunobu esterification of cyclobutyl 2,4,6-triisopropylbenzoate **292**.

The lithiation–borylation methodology for cyclobutane benzoates has been established (Scheme 121) and the methodology has been successfully tested against a range of boronic ester substrates, as shown in Figure 22. The scope explored demonstrates that this methodology is applicable to a range of substrates, provides an additional tool to the well-established lithiation-borylation methodologies and allows access to 1,1-disubstituted cyclobutyl boronic esters.



Scheme 121: Methodology for lithiation borylation of cyclobenzoate **292**.

Furthermore, boronic ester **311** was successfully reacted in functional group interconversions, such as, Matteson homologation, amination, Zweifel olefination and alkynylation (Figure 22).

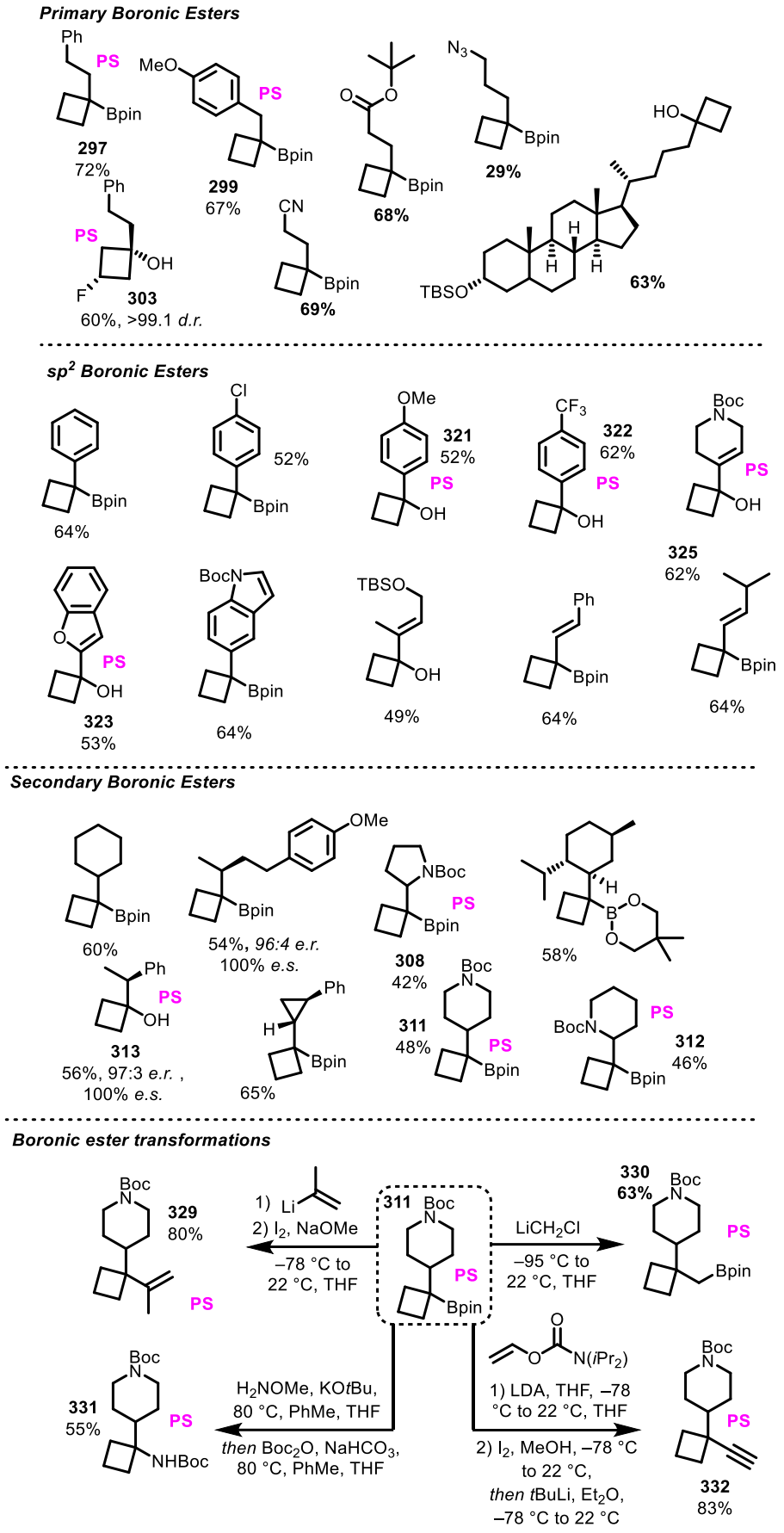


Figure 22: Scope of boronic esters successfully tested.

A range of modified cyclobutyl motifs have been test against the established methodology, though the reaction outcomes have been unsuccessful with no lithiation-borylation observed. Subsequent, *in-situ* IR spectroscopy studies allowed an in depth understanding of the difficulty in performing the methodology with these benzoates (Figure 23). Here it was shown that benzoate **335** could not be synthesised by Mitsunobu due to competing ring rearrangement which gave only the cyclopropyl benzoate **337**. Similarly, **342** failed to undergo lithiation under tested conditions and **344** underwent lithiation and electrophile trapping (TMSCl), at the N*Me* group instead of the ring C*H*.

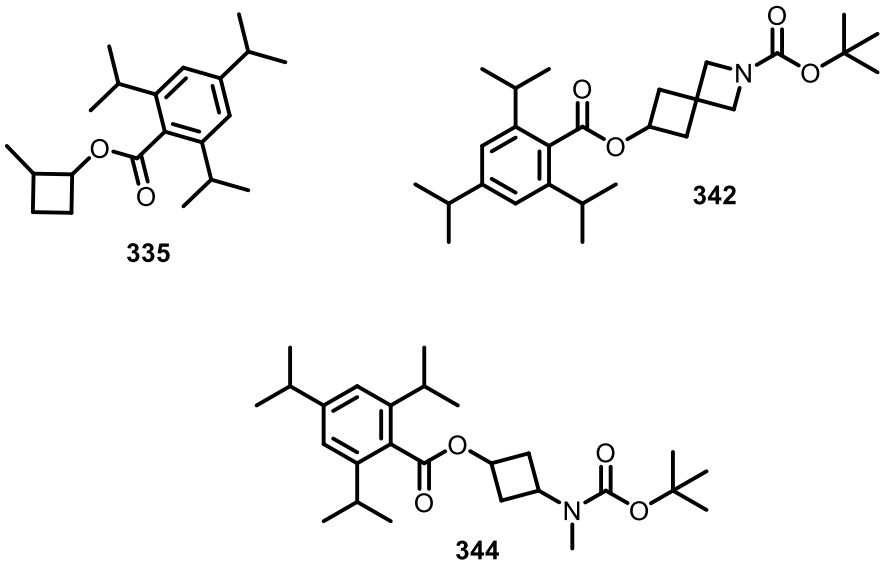


Figure 23: Failed benzoate motifs.

Finally, oxetane benzoate **349** and azetidine benzoate **358** were also synthesised *via* Mitsunobu esterification (Figure 24).

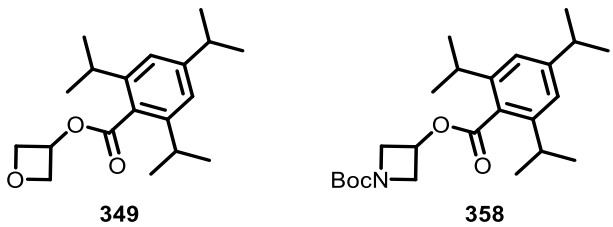


Figure 24: Study into the lithiation-borylation of oxetane benzoate **349** and azetidine benzoate **358**.

However, these small-ring molecules proved challenging in lithiation-borylation methodology. The oxetane benzoate **349**, though lithiated rapidly within minutes, the lithiated species proved

chemically unstable and degraded over time. The subsequent trapping of the species was also achieved using test boronic ester **294**, however a two-electrophile test confirmed the boronate complex to be reversible. Similarly, the studies into the lithiation-borylation of azetidine benzoate **358**, were also difficult, due to a competing side reaction, whereby substrate **358**, was undergoing E2 elimination, with loss of OTIB, to generate the unsaturated azetidene **366**. Then azetidene **366**, can undergo lithiation in the presence of *s*BuLi to give azetidene **369** intermediate, which have been shown to undergo electrophile trapping to give **370** in previous literature reports.[256] However, the side-reaction means that **358** is not suitable for this methodology. For these reason, the above two substrates were not studied further.

3. Experimental

Parts of the experiemental have been adapted from the following articles:

Pulis, A. P.; Varela, A.; Citti, C.; Songara, P.; Leonori, D.; Aggarwal, V. K., *Angew. Chem. Int. Ed.* **2017**, *56*, 10835.

&

Mykura, R. C.; Songara, P.; Luc, E.; Rogers, J.; Stammers, E.; Aggarwal, V. K., *Angew. Chem. Int. Ed.* **2021**, Article ASAP. DOI: 10.1002/ange.202101374 (accessed 05-03-2021)

3.1. General Information

Anhydrous solvents were either dried using an Anhydrous Engineering alumina column drying system (THF, toluene, CH_2Cl_2) or obtained as Acroseal bottles and used directly. All other employed solvents were reagent grade solvents and were used directly. Petroleum ether refers to the fraction collected between 40 – 60 °C. Reactions requiring anhydrous conditions (where specified) were conducted under a N_2 / Argon atmosphere using standard Schlenk techniques unless otherwise stated. All reagents were purchased from commercial sources and used as received, unless otherwise stated. Flash column chromatography was carried out using Aldrich silica gel (40-63 μm) or on a Biotage isolera one machine (following λall) using the column and gradient specified (CV = column volumes). Reactions were monitored by thin-layer chromatography (TLC) when practical, using Merck Kieselgel 60 F254 fluorescent treated silica which was visualized under UV light (254 nm) or by staining with an aqueous basic potassium permanganate or p-anisaldehyde solution or ninhydrin as stated. **^{1}H NMR** spectra were recorded using either Jeol ECS/ECZ 400 MHz, Bruker 101 MHz, Bruker Cryo 500 MHz, or Varian VNMR (400 MHz or 500 MHz) spectrometers. Chemical shifts (δ) are given in parts per million (ppm) and coupling constants (J) are given in Hertz (Hz) and reported to the nearest 0.1 Hz. **^{13}C NMR** spectra were recorded using either Jeol ECS/ECZ 400 MHz Varian VNMR 400 (101 MHz or 126 MHz), Bruker 101 MHz or Bruker Cryo 500 (126 Hz) spectrometers. NMR assignments for all compounds reported were determined using a combination of ^{1}H NMR, ^{13}C NMR, Heteronuclear Single Quantum Coherence (HSQC), Heteronuclear Multiple Bond Correlation (HMBC), DEPT-135 and NOE (where applicable). High resolution mass spectra (**HRMS**) were recorded on a Bruker Daltonics Apex IV by Electrospray Ionisation (ESI). **IR** spectra were recorded on a Perkin Elmer Spectrum One FT-IR as a thin film. Only

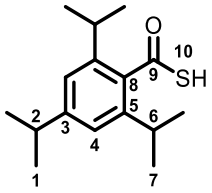
selected absorption maxima (ν_{max}) are reported in wavenumbers (cm^{-1}). Melting points were recorded in degrees Celsius (°C) using a Stuart SMP30 melting point apparatus. **Optical rotations** (**$[\alpha]^D$ T**) were measured on a Bellingham & Stanley Ltd. ADP 220 polarimeter. ADP220 polarimeter and is quoted in (° mL)(g dm)$^{-1}$. **Chiral HPLC** was performed on a HP Agilent 1100 with an isocratic gradient and a specified column eluting iPrOH/hexane at a given temperature, monitoring by DAD (Diode Array Detector).

3.2. Chapter 1

3.2.1. Synthesis of Starting Materials

2,4,6-Triisopropylbenzothioic *S*-acid (123)

Route 1: TIBCl – Acyl chloride thiolation



NOTE: Exclusion of oxygen from the reaction mixture and crude product at all staged is crucial to avoid significant formation of the corresponding disulfide of **124**.

A suspension of NaS_2 (3.29 g, 42.2 mmol) and 2,4,6-triisopropylbenzoyl chloride (5.62 g, 21.1 mmol) in THF (45 mL) was heated at reflux overnight (~16 hrs) under a N_2 atmosphere. The reaction was allowed to reach ambient temperature and the reaction vessel was connected to a gas trap containing 6 M $NaOH_{(aq.)}$. A long needle attached to a N_2 line was inserted through a septa of the reaction vessel. The reaction vessel was placed under a positive pressure of N_2 (through the long needle) to create a steady stream of bubbles through the NaOH trap. The needle attached to the N_2 line was positioned below the level of the solvent to create a steady stream of N_2 bubbles though the reaction mixture. The reaction was quenched with the slow addition of 2 M HCl in Et_2O (55 mL) (see Figure 25**,** below). The reaction was stirred for 1 hr while N_2 was bubbled through the reaction mixture. The solvent was then removed *in vacuo*. Pentane and Et_2O (1:1 v.v, 50 mL) was added to the yellow solid and the suspension was

transferred *via* cannula onto a silica pad under N_2 and the filtrate collected into a pre-weighed Schlenk flask (see Figure 25, below). The reaction flask was washed with a mixture of pentane and Et_2O (1:1 v.v, 2 × 50 mL), transferring the washings onto the silica filter cake and collecting the filtrate into the same Schlenk flask as before. The solvent was removed *in vacuo* to give *thiobenzoic acid* **123** (5.01 g, 89%) as a pale green solid that contained approximately 5 mol% of the corresponding disulfide **124**. Thioic acid **123** was stored under N_2 to prevent disulfide formation.

Thioacid (123)

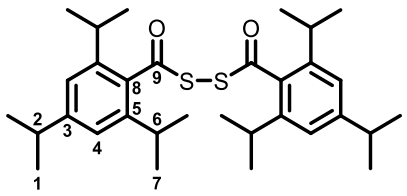
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.02 (2H, s, H4), 3.16 (2H, hept., J = 7.0 Hz, H6), 2.90 (1H, hept., J = 7.0 Hz, H2), 1.27 (12H, d, J = 7.0 Hz, H7), 1.26 (6H, d, J = 7.0 Hz, H1) ppm;

^{13}C NMR (101 MHz, $CDCl_3$): δ = 196.8 (C9), 150.7 (C3), 143.5 (C5), 137.1 (C8), 121.2 (C4), 34.4 (C2), 30.8 (C6), 24.3 (C7), 23.9 (C1) ppm;

IR (ν_{max}/ cm^{-1}, neat): 2961, 2929, 2869, 1682, 1669, 1604, 1458, 947, 825;

HRMS (ESI) calc. for $[C_{16}H_{24}OS + H]^+$ 265.1626. Found 265.1622.

Disulfide (124)



^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.08 (4H, s, H4), 3.21 (4H, hept., J = 7.0 Hz, H6), 2.94 (2H, hept., J = 7.0 Hz, H2), 1.27-1.37 (36H, m, H1/H7) ppm;

^{13}C NMR (101 MHz, $CDCl_3$): δ = 192.4 (C9), 151.5 (C3), 145.6 (C5), 133.1 (C8), 121.3 (C4), 34.5 (C2), 30.7 (C6), 24.4 (C7), 23.9 (C1) ppm;

IR (ν_{max}/ cm^{-1}, neat): 2962, 2929, 2870, 1717, 1603, 1462, 865;

HRMS (ESI) calc. for $[C_{32}H_{46}O_2S_2 + Na]^+$ 549.2816. Found 549.2831.

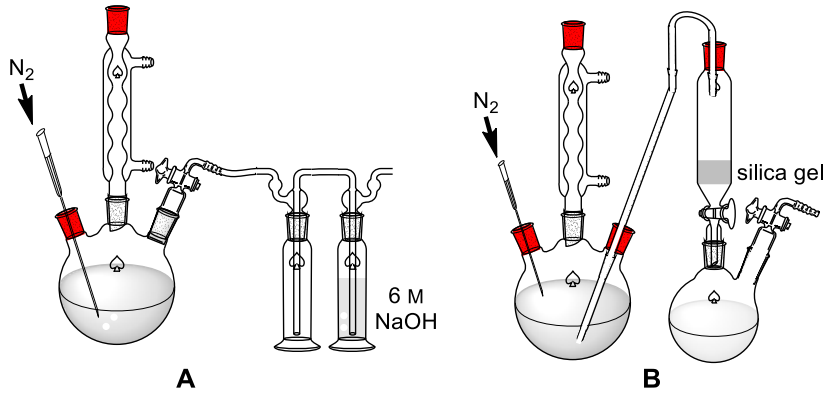


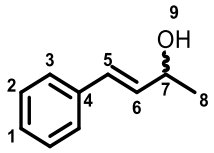
Figure 25: Apparatus and set up for workup during the synthesis of thio acid 122. A: during HCl quench. B: for filtration through silica gel.

Route 2 – Lawesson's reagent route

Using a modified procedure reported by Danishefsky *et al.*[1], a large flame-dried microwave vial (fitted with a suba seal) and a flame-dried round-bottom flask were both purged with N_2 gas. Then, the round-bottom flask was charged with 2,4,6-triisopropylbenzoic acid (TIBOH) (1.00 g, 4.00 mmol, 1.00 eq.), Lawesson's reagent (1.63 g, 2.20 mmol, 0.55 eq.) and CH_2Cl_2 (10 mL) followed by stirring at RT for 1 min to dissolve the suspension. The solution was then transferred to the microwave vial by syringe. Next, the suba seal, whilst under positive N_2 pressure was rapidly replaced with a microwave vial cap and crimped immediately. The sample was irradiated with a microwave irradiator for 15 mins at 80 ˚C. The resultant solution was cooled to RT and then the solution was transferred *via* cannula onto a silica pad under N_2 and the filtrate collected into a pre-weighed Schenk flask (see Figure 25). The reaction flask was washed with a mixture of pentane and Et_2O (1:1 v.v, 2 × 15 mL), transferring the washings onto the silica filter cake and collecting in the same Schlenk flask. The solvent was removed in vacuo to give thiobenzoic acid **123** (880 mg, 83%) as a pale green solid.

Spectral data is in accordance with that from the TIBCl method.

(*rac,E*)-4-Phenylbut-3-en-2-ol (132)



Following a modified procedure from Titu and Chadha[262], to a stirred solution of (*E*)-4-phenylbut-3-en-2-one (20.0 g, 0.137 mol) in MeOH (50 mL) at 0 °C (salt/ice bath) under a N_2 atmosphere was added $NaBH_4$ (5.67 g, 0.150 mol) portionwise at such a rate that the internal temperature did not rise above 10 °C. After stirring for 45 mins, crushed ice (10 g) was added followed by the slow addition of saturated $NH_4Cl_{(aq.)}$ (25 mL) and the mixture stirred at ambient temperature. Once effervescence had ceased, the mixture was extracted with Et_2O (4 × 70 mL), the combined organic phases were washed with brine, dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude material was purified by flash column chromatography (25% EtOAc/petrol) to give alcohol **132** (18.6 g, 92%) as a colourless oil.

R_f = 0.20 (15% EtOAc/petrol);

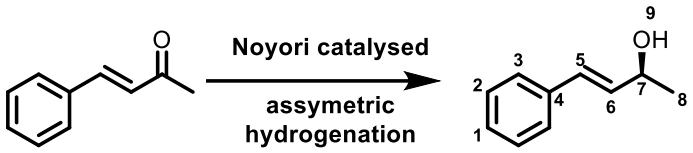
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.41-7.37 (2H, m, H2), 7.35-7.30 (2H, m, H3), 7.25 (1H, m, H1), 6.59 (1H, d, *J* = 15.9 Hz, H5), 6.28 (1H, dd, *J* = 15.9, 6.3 Hz, H6), 4.50 (1H, dq, *J* = 6.3, 6.3 Hz, H7), 1.76 (1H, br. s, H9), 1.39 (3H, d, *J* = 6.3 Hz, H8) ppm;

^{13}C NMR (101 MHz, $CDCl_3$): δ = 136.6 (C4), 133.5 (C5), 129.3 (C2), 128.5 (C3), 127.6 (C1), 126.4 (C6), 68.9 (C7), 23.4 (C8) ppm.

Spectral data is in accordance with the literature.[263]

Route 1: Noyori Catalyst (98:2 *e.r.*)

(*S,E*)-4-phenylbut-3-en-2-ol (132)



Following a procedure from Noyori *et al.*,[264] to a solution of (*S,E*)-4-phenylbut-3-en-2-ol (11.0 g, 68.4 mmol) and potassium carbonate (18 mg, 0.10 mmol%) in *i*PrOH (20 mL) at ambient temperature was added $RuCl_2$[(*R*)-DM-BINAP][(*R*)-DAIPEN] (16 mg, 0.10 mol%). The reaction flask was transferred to an autoclave, purged with N_2, and then pressurised with hydrogen gas (50 bars). The reaction mixture was left to stir at ambient temperature for 48 hrs. Subsequent GCMS analysis of the reaction mixture showed quantitative conversion of starting material to product. The reaction mixture was filtered through Celite ® and the filter cake washed with CH_2Cl_2 after which the solvent was removed *in vacuo*. Next, the material was purified by flash column chromatography (CH_2Cl_2). The solvent was removed *in vacuo* to give a pale-yellow oil (11.1 g, 98%, 98:2 *e.r.*).

R_f = 0.30 (CH_2Cl_2);

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.41-7.36 (2H, m, H2), 7.35-7.28 (2H, m, H3), 7.27-7.20 (1H, m, H1), 6.56 (1H, d, *J* = 16.0 Hz, H5), 6.26 (1H, dd, *J* = 16.0, 6.3 Hz, H6), 4.50 (1H, dq, *J* = 6.3, 6.2 Hz, H7), 1.75 (1H, br. s, H9), 1.38 (3H, d, *J* = 6.2 Hz, H8) ppm;

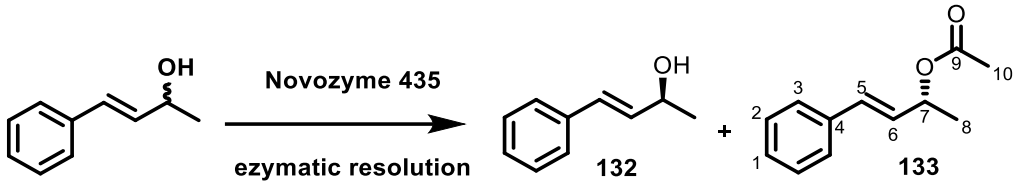
^{13}C NMR (101 MHz, $CDCl_3$): δ = 136.8 (C4), 133.7 (C5), 129.5 (C2), 128.7 (C3), 127.8 (C1), 126.6 (C6), 69.1 (C7), 23.5 (C8) ppm;

IR (ν_{max}/ cm^{-1}, neat): 3329, 2971, 2869, 1449, 1056, 965.

Spectral data is in accordance with the literature.[2]

Route 2: Novozyme enzymatic resolution (>99:1 *e.r.*)

(*S,E*)-4-Phenylbut-3-en-2-ol (132) and (*R,E*)-4-phenylbut-3-en-2-yl acetate (133)



To a stirred mixture of allylic alcohol (19.8 g, 6.75 mmol), and freshly activated crushed 4Å molecular sieves (50% wt. of alcohol, 9.90 g) in pentane (60 mL) at ambient temperature, was sequentially added vinyl acetate (3.11 mL, 33.7 mmol) and Novozyme 435 (lipase acrylic resin from *Candida antarctica*, 1.52 g), filtering the reaction at 49% conversion after 7 hrs, followed by flash column chromatography (25% EtOAc/petrol) gave enantiopure (*S,E*)-**132** (449 mg, 45%, >99:1 *e.r.*) as a colourless liquid and (*R,E*)-**133** (642 mg, 50%, 95:5 *e.r.*)* as a pale yellow liquid.

Alcohol (132)

Chiral HPLC (IB, 4% *i*PrOH/hexane) T_R = 27.60 mins.

$[\alpha]_D^{22}$ –33.4 (*c* 1.02, $CHCl_3$), Lit. +33.2 for (*R*) (c 1.02 $CHCl_3$, >99:1).[262]

Spectral data were in accordance with the literature reported racemic alcohol.

Acetate (133)

$\mathbf{R}_f$ = 0.71 (25% EtOAc/petrol);

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.41-7.37 (2H, m, H2), 7.35-7.30 (2H, m, H3), 7.25 (1H, m, H1), 6.61 (1H, dd, *J* = 15.9, 1.2 Hz, H5), 6.20 (1H, dd, *J* = 15.9, 6.6 Hz, H6), 5.54 (1H, dqd, *J* = 6.6, 6.4, 1.2 Hz, H7), 2.09 (3H, s, H10), 1.42 (3H, d, *J* = 6.4 Hz, H8) ppm;

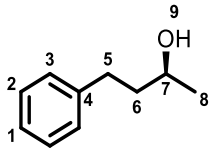
^{13}C NMR (101 MHz, $CDCl_3$): δ = 170.3 (C9), 136.3 (C4), 131.5 (C5), 128.8 (C3), 128.5 (C3), 127.9 (C1), 126.5 (C6), 71.0 (C7), 21.4 (C10), 20.4 (C8) ppm;

IR (ν_{max}/ cm^{-1}, neat): 2981, 1732 (C=$O_{acetate}$), 1370, 1233, 1040.

Spectral data was in accordance with the literature.[266]

(*S*)-4-Phenylbutan-2-ol (121)

Route 1 – Hydrogenation of vinylbenzene



To a solution of (*S,E*)-4-phenylbut-3-en-2-ol (10.0 g, 82.9 mmol, >99:1 *e.r.*) in MeOH (70 mL) under a N_2 atmosphere, was added 10% Pd on carbon (10% wt., 813 mg). The N_2 atmosphere was flushed out with a hydrogen balloon and the mixture was stirred at ambient temperature and pressure for 16 hrs. The reaction mixture was filtered through a pad of Celite ® and the filter cake washed with Et_2O (50 mL). After removal of the solvent under reduced pressure, the residue was purified by flash column chromatography (30% Et_2O/pentane) to give (*S*)-4-phenylbutan-2-ol **121** (11.1 g, 92%, 99:1 *e.r.*) as a colourless liquid.

Route 2 – Epoxide ring opening

Benzylmagnesium chloride (1 M in Et_2O, 28 mL, 28 mmol, 2.0, eq.) was added dropwise to a solution of (*S*)-2-methyloxirane (813 mg, 14 mmol, 1.0 eq.) and CuI (2.6 g, 14 mmol, 1.0 eq.) in THF (14 mL) at −78 °C. The reaction was quenched after 2 hrs through addition of sat. NH_4Cl (50 mL) and the aqueous phase extracted with Et_2O (3 × 50 mL). The organics were combined, dried ($MgSO_4$) and concentrated under reduced pressure to give an oil. Subsequently, purification by column chromatography (30% Et_2O/pentane) gave (*S*)-4-phenylbutan-2-ol **121** as an amorphous white solid (1.87 g, 89%, >99:1 *e.r.*).

R_f = 0.30 (20% EtOAc/PE);

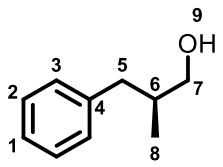
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.29 (2H, m, H2), 7.23-7.19 (3H, m, H1/H3), 3.84 (1H, br. sext., *J* = 6.2 Hz, H7), 2.82-2.64 (2H, m, H5), 1.86-1.72 (2H, m, H6), 1.36 (1H, s, H9), 1.24 (3H, d, *J* = 6.2 Hz, H8) ppm;

^{13}C NMR (101 MHz, $CDCl_3$): δ = 142.0 (C4), 128.4 (C2), 128.3 (C3), 125.8 (C1), 67.5 (C7), 40.8 (C5), 32.1 (C6), 23.6 (C8) ppm;

$[\alpha]_D^{25}$ +14.8 (c 1.0, $CHCl_3$).

Spectral data were in accordance with the literature.[2]

(*S*)-2-Methyl-3-phenylpropan-1-ol (134)



(*S*)-2-Methyl-3-phenylpropan-1-ol **134** was isolated from the epoxide ring opening reaction as a colourless oil (126mg, 6%).

R_f = 0.18 (25% EtOAc/PE);

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.28 (2H, m, H2), 7.21-7.17 (3H, m, H1/H3), 3.54 (1H, dd, *J* = 10.5, 6.0 Hz, H7a), 3.47 (1H, dd, *J* = 10.5, 7.5 Hz, H7b), 2.75 (1H, dd, *J* = 13.5, 6.0 Hz, H5a), 2.42 (1H, dd, *J* = 13.5, 8.0 Hz, H5b), 1.95 (1H, m, H6), 1.36 (1H, br. s, H9), 0.91 (3H, d, *J* = 6.5 Hz, H8) ppm;

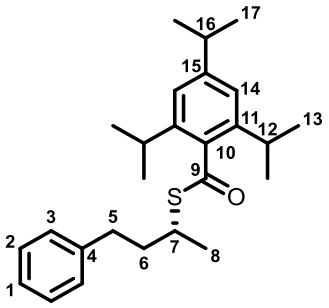
^{13}C NMR (101 MHz, $CDCl_3$): δ = 140.6 (C4), 129.2 (C2), 128.3 (C3), 125.8 (C1), 67.5 (C7), 39.8 (C5), 37.7 (C6), 16.8 (C8) ppm.

Spectral data were in accordance with the literature.[267]

3.2.1.1 General Procedure for the Synthesis of S-Thiobenzoates from Secondary Alcohols (GP1)

DIAD (325 µL, 1.65 mmol, 1.10 eq.) was added dropwise over 5 mins to a stirred solution of PPh_3 (472 mg, 1.80 mmol, 1.20 eq.) in THF (8 mL) at 0 °C (ice) under a N_2 atmosphere. After stirring for 20 mins at 0 °C a solution of alcohol (1.80 mmol, 1.20 eq.) and 2,4,6-triisopropylbenzothioic *S*-acid (476 mg, 1.50 mmol; *ca.* 10 mol% of 2,4,6-triisopropylbenzoic dithioperoxyanhydride, 1.00 eq.) in THF (3 mL) was added and the mixture stirred at 0 °C for 2-5 hrs. The volatiles were removed *in vacuo* and the residue was triturated with pentane (20 mL). The white suspension was filtered and the filter cake washed with pentane (3 × 20 mL). The solvent was removed *in vacuo* and the residue purified by flash column chromatography (10-30% toluene/pentane) to give pure *S*-thiobenzoates.

(*R*)-*S*-(4-Phenylbutan-2-yl) 2,4,6-triisopropylbenzothioate (122)



Following **GP1** using (*S*)-4-phenylbutan-2-ol (3.11 g, 20.7 mmol, >99:1 *e.r.*) gave (*R*)-*S*-thiobenzoate **122** (4.67 g, 63%, >99:1 *e.r.*) as a viscous colourless oil and *O*-thiobenzoate **122a** (1.34 g, 18%) as a yellow oil.

***S*-thiobenzoate 122:**

$\mathbf{R}_f$ = 0.28 (30% toluene/pentane);

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35-7.29 (2H, m, H2), 7.25-7.20 (3H, m, H1/H3), 7.03 (2H, s, H14), 3.85 (1H, app. br. sext., J = 7.0 Hz, H7), 3.13-2.72 (5H, m, H5/H12/H16), 2.00 (2H, m, H6), 1.48 (3H, d, J = 7.0 Hz, H8), 1.27 (18H, br. d, J = 7.0 Hz, H13/H17) ppm;

^{13}C NMR (101 MHz, $CDCl_3$): δ = 198.1 (C9), 150.3 (C15), 144.4 (C11), 141.6 (C4), 135.8 (C10), 128.5 (C2), 128.4 (C3), 126.0 (C1), 121.0 (C14), 40.1 (C7), 38.1 (C5), 34.4 (C16), 33.4 (C6), 30.6 (C12), 24.5 (br. s, C13), 23.9 (C17), 21.5 (C8) ppm;

IR (ν_{max}/ cm^{-1}, neat): 2960, 2927, 2868, 1675 (C=O_{TIB}), 1657, 1456, 1206, 895, 698;

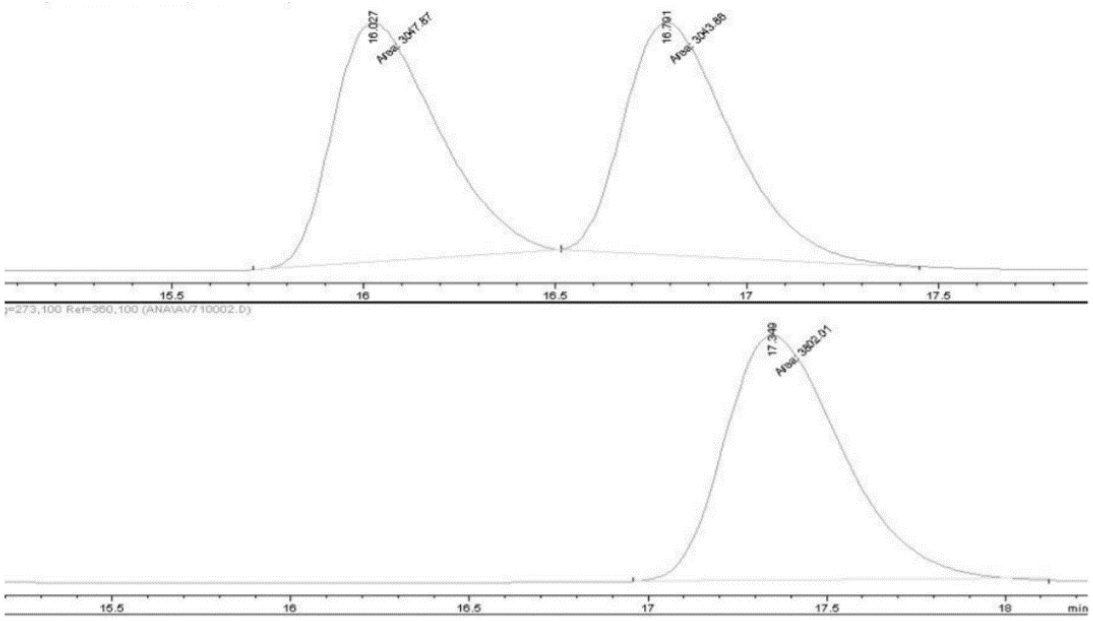
Elemental analysis: calc. for $C_{26}H_{36}OS$: C, 78.73; H, 9.15. Found: C, 78.25; H, 9.00;

HRMS (CI) calc. for $[C_{26}H_{36}OS + H]^+$ 397.2565. Found 397.2569;

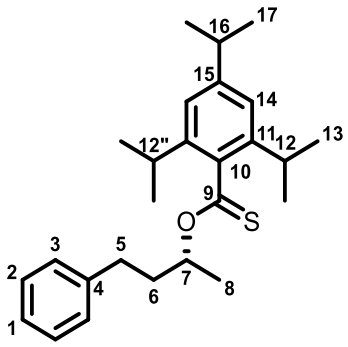
LRMS (CI): 397.3, 231.2 (basepeak);

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ −22.0 (*c* 3.0, $CHCl_3$);

Chiral HPLC (IB, 0.1% *i*PrOH/hexane, 0.35 mL/min, 0 °C) T_R = 16.0 mins (minor), 16.8 mins (major).



***O*-thiobenzoate (122a)**



R_f = 0.65 (30% toluene/pentane);

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35-7.29 (2H, m, H2), 7.25-7.20 (3H, m, H1/H3), 7.02 (1H, s H14), 7.01 (1H, s, H14), 5.90 (1H, app. br. sext., *J* = 6.2 Hz, H7), 3.13 (1H, hept., *J* = 7.0 Hz, H12 or H12"), 3.01 (1H, hept., *J* = 7.0 Hz, H12 or H12"), 2.90 (1H, hept., *J* = 7.0 Hz, H16), 2.85-2.67 (2H, m, H5), 2.26-2.16 (1H, m, H6), 2.06-1.96 (1H, m, H6), 1.49 (3H, d, *J* = 6.2 Hz, H8), 1.23-1.30 (18H, m, H13/H17) ppm;

^{13}C NMR (101 MHz, $CDCl_3$): δ = 218.9 (C9), 149.0 (C15), 143.4 (C11), 143.3 (C11), 141.3 (C4), 138.8 (C10), 128.5 (C2), 128.3 (C3), 126.0 (C1), 121.03 (C14), 120.98 (C14), 78.6 (C9), 37.3 (C6), 34.3 (C16), 31.7 (C5), 30.8 (C12 or C12"), 30.4 (C12 or C12"), 24.5 (C13), 24.4 (C13), 24.3 (C13), 24.0 (C13), 23.8 (C17), 18.8 (C8) ppm;

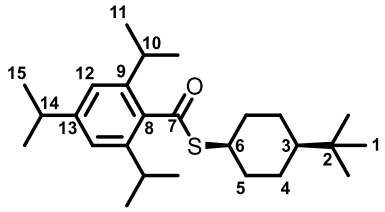
IR (ν_{max}/ cm^{-1}, neat): 2959, 2927, 2868, 1605, 1457, 1223, 696;

HRMS (CI) calc. for $[C_{26}H_{36}OS + H]^+$ 397.2565. Found 397.2551;

LRMS (CI): 397.3, 265.2 (basepeak), 231.2;

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ +9.8 (*c* 3.06, $CHCl_3$).

***S*-((*cis*)-4-(*tert*-Butyl)cyclohexyl) 2,4,6-triisopropylbenzothioate (104)**



Following **GP1** using *trans*-4-*tert*-butylcyclohexanol (344 mg, 2.20 mmol, >20:1 *trans*:*cis*, obtained after flash column chromatography of commercially available *cis*/*trans* mixture) gave *cis*-thiobenzoate **104** (523 mg, 64%, >20:1 *cis:trans*) as an amorphous solid.

$\mathbf{R}_f$ = 0.31 (20% toluene/pentane);

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.01 (2H, s, H12), 4.22 (1H, br. m, H6), 3.01 (2H, hept., *J* = 7.0 Hz, H10), 2.90 (1H, hept., *J* = 7.0 Hz, H14), 2.04 (2H, br. d, *J* = 13.9 Hz, H5a), 1.83 (2H, tt, *J* = 13.9, 3.6 Hz, H5b), 1.71 (2H, br. d, *J* = 12.7 Hz, H4a), 1.26 (18H, br. d, *J* = 7.0 Hz, H11/H15), 1.29-1.17 (2H, m, H4b), 1.05 (1H, tt, *J* = 12.0, 3.0 Hz, H3), 0.85 (9H, s, H1) ppm. *Many of the small vicinal couplings on the 6-membered ring were not resolved and gave broad lines*;

^{13}C NMR (101 MHz, $CDCl_3$): δ = 197.9 (C7), 150.2 (C13), 144.4 (C9), 136.1 (C8), 121.0 (C12), 47.8 (C6), 42.3 (C3), 34.4 (C14), 32.5 (C2), 31.9 (C5), 30.6 (C10), 27.3 (C1), 24.4 (br. s, C11), 23.9 (C15), 23.3 (C4) ppm;

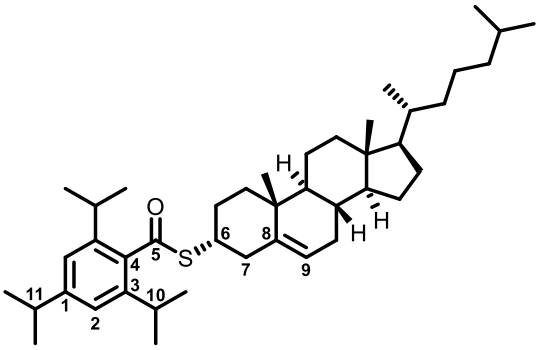
M.P: 89-91°C (EtOAc);

IR (ν_{max}/ cm^{-1}, neat): 2957, 2863, 1674 ($C{=}O_{TIB}$), 1362, 899;

HRMS (ESI) calc. for $[C_{26}H_{42}OS{+}Na]^+$ 425.2849. Found 425.2869;

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{22}}$ +11 (c 1.0, $CHCl_3$).

***S*-((3*R*,8*S*,9*S*,10*R*,13*R*,14*S*,17*R*)-10,13-Dimethyl-17-((*R*)-6-methylheptan-2-yl)-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthren-3-yl) 2,4,6-triisopropylbenzothioate (143)**



Following **GP1** using cholesterol (1.00 g, 2.59 mmol) gave thiobenzoate **143** (540 mg, 32%) as a white foam.

$\mathbf{R}_f$ = 0.45 (20% toluene/pentane);

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.97 (2H, s, H2), 5.35-5.26 (1H, m, H9), 4.21 (1H, pent., J = 3.0 Hz, H6), 2.99 (2H, m), 2.85 (2H, m), 2.25 (1H, m), 2.09 (2H, m), 1.99 (2H, m), 1.83 (2H, m), 1.72 (1H, m), 1.53 (4H, m), 1.34 (4H, m), 1.24 (20H, m), 1.11 (4H, m), 1.03 (3H, s), 0.99 (3H, m), 0.92 (3H, d, J = 6.7 Hz), 0.87 (6H, dd, J = 6.7, 1.6 Hz), 0.67 (3H, s) ppm;

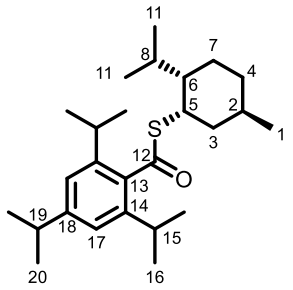
^{13}C NMR (101 MHz, $CDCl_3$): δ = 198.2 (C5), 150.2 (C1), 144.4 (C3), 139.0 (C8), 136.1 (C4), 122.8 (C9), 121.0 (C2), 56.7 (CH), 56.1 (CH), 50.2 (CH), 43.9 (C6), 42.2 (4º C), 39.7 (CH_2), 39.5 (CH_2), 37.6 (CH_2), 37.2 (CH_2), 36.2 (CH_2), 35.8 (CH_2), 35.7 (4º C), 34.4 (CH), 31.9 (CH_2), 31.7 (CH), 30.6 (2 x CH), 28.2 (CH_2), 28.0 (CH), 27.3 (CH_2), 24.4 (4 x CH_3), 24.0 (2 x CH_3), 23.8 (CH_3), 22.8 (CH_3), 22.6 (CH_3), 20.7 (CH_2), 19.3 (CH_3), 18.7 (CH_3), 11.9 (CH_3) ppm;

IR (ν_{max}/ cm^{-1}, neat): 2958, 1676 ($C{=}O_{TIB}$), 1460, 1206, 896;

HRMS (ESI) calc. for $[C_{43}H_{68}OS + Na]^+$ 655.4883. Found 655.4853;

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{22}}$ +20 (c 1.0, $CHCl_3$).

***S*-((1*S*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl) 2,4,6-triisopropylbenzothioate (144)**



Following **GP1** using (–)-menthol (338 mg, 2.16 mmol) gave thiobenzoate **144** (108 mg, 15%, >20:1 *cis:trans*) as an amorphous solid.

$\mathbf{R}_f$ = 0.45 (20% toluene/pentane);

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.00 (2H, s, H17), 4.34 (1H, br. s, H5), 3.01 (2H, hept., J = 7.0 Hz, H15), 2.89 (1H, hept., J = 7.0 Hz, H19), 2.03 (1H, br. d, J = 13.8 Hz, H3), 1.86 (1H, m, H7), 1.78-1.64 (2H, m, H4/H8), 1.55-1.37 (2H, m, H2/H3), 1.25 (18H, br. d, J = 7.0 Hz, H16/H20), 1.22 (1H, m, H6), 1.00-0.87 (2H, m, H4/H7), 0.97 (3H, br. d, J = 6.6 Hz, H11a), 0.92 (3H, br. d, J = 6.6 Hz, H11b), 0.91(3H, br. d, J = 6.2 Hz, H1) ppm. *Many of the small vicinal couplings on the 6-membered ring were not resolved and gave broad lines*;

^{13}C NMR (101 MHz, $CDCl_3$): δ = 197.8 (C12), 150.4 (C18), 144.5 (C14), 136.5 (C13), 121.1 (C17), 47.7 (C6), 46.0 (C5), 42.1 (C3), 35.2 (C4), 34.6 (C19), 31.0 (C2), 30.8 (C15), 28.4 (C8), 28.0 (C7), 24.5 (br. s, C16), 24.1 (C20), 22.3 (C1), 21.2 (C11), 20.7 (C11) ppm;

HRMS (ESI) calc. for $[C_{26}H_{42}OS + Na]^+$, 425.2953. Found, 425.2945;

IR (ν_{max}/cm^{-1}, neat): 2956, 2860, 1675 (C=O_{TIB}), 1366, 898;

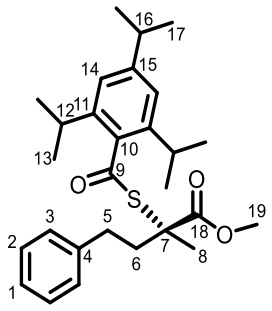
$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{22}}$ – 8 (c 1.0, $CHCl_3$).

3.2.2. Lithiation and Electrophilic Trapping of Dialkyl S-Thiobenzoates

3.2.2.1. General Procedure for Lithiation/Electrophilic Trapping of Dialkyl S-Thiobenzoates (GP2)

*s*BuLi (1.3 M in hexane, 1.20 eq., 230 µL, 0.30 mmol) was added dropwise over 2 mins to a vigorously stirred solution (without splashing) of *S*-thiobenzoate **122** (1.00 eq., 0.250 mmol) and TMEDA (1.20 eq., 0.30 mmol, 35 µL) in anhydrous TBME (1.5 mL) at –78 °C under a N_2 atmosphere. After the specified time, a solution of the electrophile (2.00 eq., 0.50 mmol) in TBME (0.25 mL) was added dropwise over 2 mins. The reaction mixture was stirred at –78 °C for 1 hr and then the cooling bath was removed. The reaction was allowed to reach RT and was quenched with H_2O (2 mL) or sat. $NH_4Cl_{(aq)}$ (2 mL). The phases were separated and the aqueous phase was extracted with Et_2O (4 × 15 mL). The combined organic phases were washed with brine and dried over $MgSO_4$. The solvent was removed *in vacuo* and the crude material purified by flash chromatography to give pure *S*-benzothioate.

(*R*)-2-methyl-4-phenyl-2-((2,4,6-triisopropylbenzoyl)thio)butanoate (150)



Following a **GP2** using (*R*)-*S*-benzothioate **122** (41 mg, 0.12 mmol, >99:1 *e.r.*) and methyl chloroformate (57 µL, 0.74 mmol) and purification by flash chromatography (5% Et_2O/pentane) gave thiobenzoate **150** (42 mg, 88%, 96:4 *e.r.*) as a colourless oil.

$\mathbf{R_f}$ = 0.42 (5% Et_2O/pentane);

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.29 (2H, m, H2), 7.22-7.15 (3H, m, H1/H3), 7.00 (2H, s, H14), 3.79 (3H, s, H19), 3.11 (2H, hept., J = 7.0 Hz, H12), 2.89 (1H, hept., J = 7.0 Hz, H16), 2.75 (1H, ddd, J = 13.5, 10.2, 7.1 Hz, H5a), 2.67 (1H, ddd, J = 13.5, 10.2, 6.9 Hz, H5b), 2.25 (2H, m, H6), 1.81 (3H, s, H8), 1.25 (18H, br. d, J = 7.0 Hz, H13/H17) ppm;

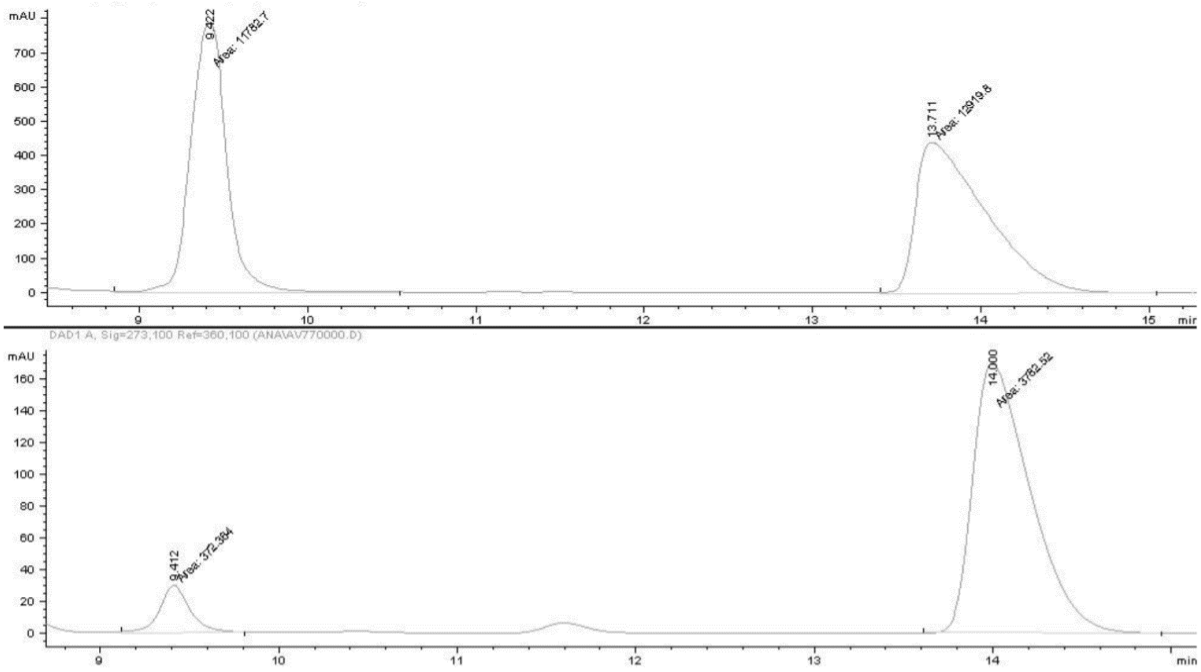
^{13}C NMR (101 MHz, $CDCl_3$): δ = 197.1 (C9), 173.5 (C18), 150.8 (C15), 144.9 (C11), 141.0 (C4), 134.5 (C10), 128.5 (C2), 128.3 (C3), 126.1 (C1), 121.0 (C14), 55.9 (C19), 52.7 (C7), 39.9 (C6), 34.4 (C16), 31.2 (C5), 30.3 (C12), 24.4 (br. s, C13) 23.9 (C17), 23.5 (C8) ppm;

IR (ν_{max}/cm^{-1}, neat): 1739 (C=O$_{ester}$), 1678 (C=O$_{TIB}$), 1459;

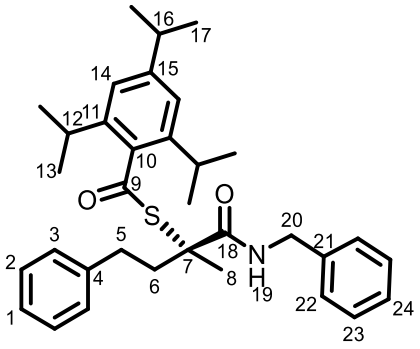
HRMS (ESI) calc. for $[C_{28}H_{38}O_3S + Na]^+$ 477.2434. Found 477.2441;

$[\alpha]_D^{22}$ + 11 (c 1.0, $CHCl_3$);

Chiral HPLC (IA, 2% *i*PrOH/hexane, 0.5 mL/min) T_R = 9.42 mins (minor), 13.7 mins (major).



(*R*)-*S*-(1-(benzylamino)-2-methyl-1-oxo-4-phenylbutan-2-yl) 2,4,6-triisopropylbenzothioate (151)



Following a **GP2** using (*R*)-*S*-benzothioate **122** (99 mg, 0.25 mmol, >99:1 *e.r.*) and benzyl isocyanate (62 μL, 0.50 mmol) and purification by flash chromatography (5% Et_2O/pentane) gave thiobenzoate **151** (67 mg, 70 %, 96:4 *e.r.*) as a white solid.

R_f = 0.42 (5% Et_2O/pentane);

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.41-7.35 (5H, m, H22/H23/H24), 7.31 – 7.26 (3H, m, H1/H3), 7.22 – 7.14 (2H, m, H2), 6.97 (2H, s, H14), 4.53 (1H, d, *J* = 1.7 Hz, H20a), 4.51 (1H, d, *J* = 1.7 Hz, H20b), 2.89 (3H, hept., *J* = 7.0 Hz, H12/H16), 2.78 (1H, m, H5a), 2.68 (1H, m, H5b), 2.37 – 2.28 (2H, m, H6), 1.83 (3H, s, H8), 1.24 (6H, d, *J* = 7.0 Hz, H17), 1.17 (12H, d, *J* = 7.0 Hz, H13) ppm;

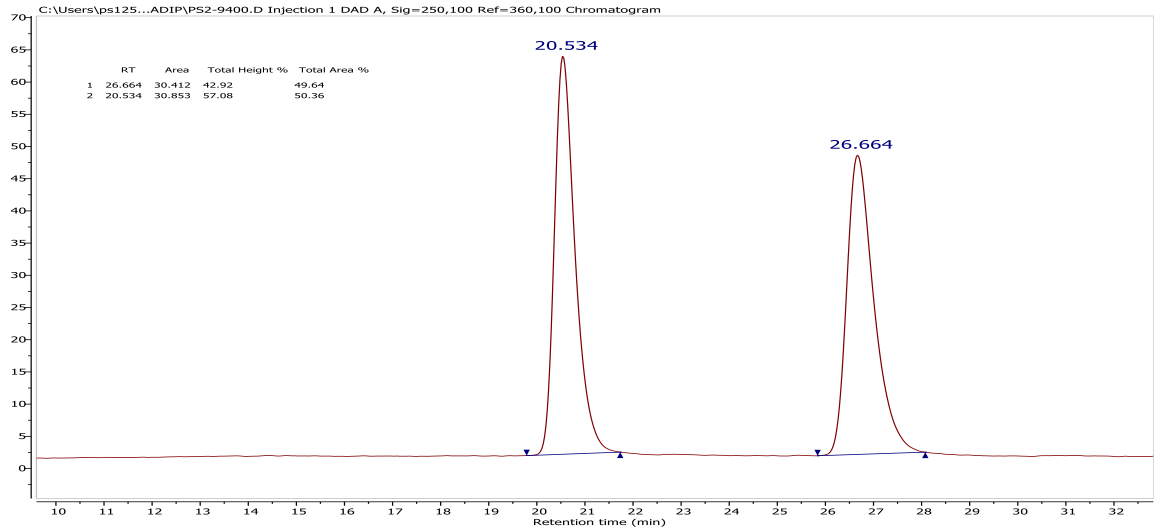
^{13}C NMR (101 MHz, $CDCl_3$): δ = 198.2 (C9), 172.3 (C18), 151.1 (C15), 144.6 (C11), 141.0 (C4), 138.1 (C21), 134.4 (C10), 128.8 (C23), 128.5 (C2), 128.4 (C3), 127.9 (C22), 127.5 (C24), 126.1 (C1), 121.1 (C14), 57.7 (C7), 44.4 (C20), 40.3 (C6), 34.4 (C12), 31.1 (C5), 30.7 (C16), 24.2 (br. s, C13), 23.9 (C17), 22.7 (C8) ppm;

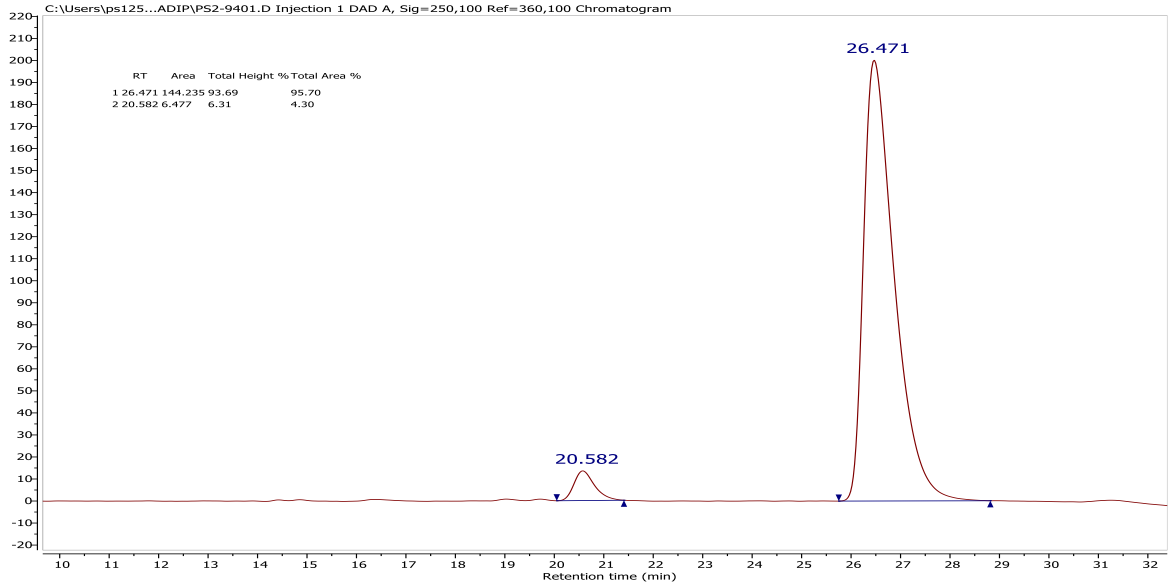
IR (ν_{max}/cm^{-1}, neat): 3346 (NH), 1674 (C=O_{TIB}), 1650 (C=O_{CONH});

HRMS (ESI) calc. for $[C_{34}H_{43}NO_2S + Na]^+$ 552.2901. Found 552.2907;

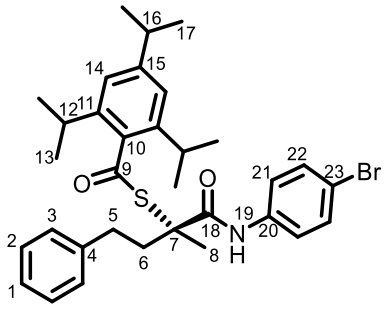
$[\alpha]_D^{22}$ + 6 (c 1.0, $CHCl_3$);

Chiral HPLC (IB, 2% *i*PrOH/hexane, 0.5 mL/min, RT) T_R = 20.6 mins (minor), 26.5 mins (major).


C:\Users\ps125...ADIP\PS2-9400.D Injection 1 DAD A, Sig=250,100 Ref=360,100 Chromatogram
RT Area Total Height % Total Area %
1 26.664 30.412 42.92 49.64
2 20.534 30.853 57.08 50.36
20.534
26.664
Retention time (min)


C:\Users\ps125...ADIP\PS2-9401.D Injection 1 DAD A, Sig=250,100 Ref=360,100 Chromatogram
RT Area Total Height % Total Area %
1 26.471 144.235 93.69 95.70
2 20.582 6.477 6.31 4.30
26.471
20.582
Retention time (min)

(*R*)-*S*-(1-((4-bromophenyl)amino)-2-methyl-1-oxo-4-phenylbutan-2-yl)2,4,6 triisopropylbenzothioate (152)



Following **GP2** using (*R*)-*S*-benzothioate **122** (50 mg, 0.13 mmol, >99:1 *e.r.*) and 4-bromophenyl isocyanate (99 mg, 0.50 mmol) and purification by flash chromatography (2% Et_2O/pentane) gave thiobenzoate **152** (60 mg, 80%, 98:2 *e.r.*) as a white solid.

$\mathbf{R_f}$ = 0.40 (2% Et_2O/pentane);

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.18 (1H, s, H19), 7.51-7.43 (4H, m, H21/H22), 7.33 – 7.27 (2H, m, H2), 7.24 – 7.18 (3H, m, H1/H3), 7.00 (2H, s, H14), 2.89 (3H, hept., J = 7.0 Hz. H12/H16), 2.78 (1H, m, H5a), 2.68 (1H, m, H5b), 2.37 – 2.28 (2H, m, H6), 1.83 (3H, s, H8), 1.24 (6H, d, J = 7.0 Hz, H17), 1.17 (12H, d, J = 7.0 Hz, H13) ppm;

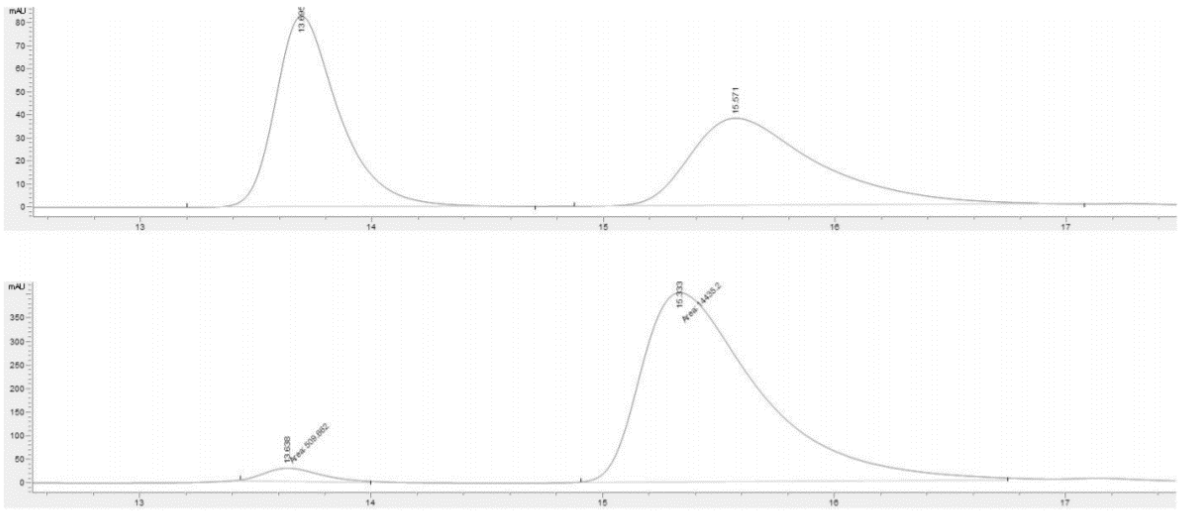
^{13}C NMR (101 MHz, $CDCl_3$): δ = 198.2 (C9), 172.3 (C18), 151.1 (C15), 144.6 (C11), 141.0 (C4), 138.1 (C20), 134.4 (C10), 132.2 (C22), 128.5 (C2), 128.4 (C3), 126.1 (C1), 121.4 (C21), 121.1 (C14), 116.9 (C23), 57.7 (C7), 40.3 (C6), 34.4 (C16), 31.1 (C5), 30.7 (C12), 24.7 (br. s, C13), 23.9 (C17), 22.4 (C8) ppm;

IR (ν_{max}/cm^{-1}, neat): 3346 (NH), 1674 (C=O_{TIB}), 1650 (C=O_{CONH});

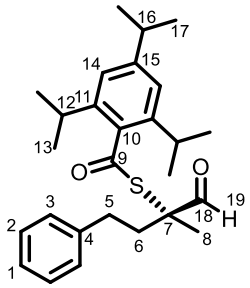
HRMS (EI) calc. for $[C_{33}H_{40}NO_2BrS]^+$ 593.1963. Found 593.1971;

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{22}}$ + 5 (c 1.0, $CHCl_3$);

Chiral HPLC (IB, 2% *i*PrOH/hexane, 0.5 mL/min, RT) T_R = 13.7 mins (minor), 15.6 mins (major).



(*R*)-*S*-(2-methyl-1-oxo-4-phenylbutan-2-yl) 2,4,6-triisopropylbenzothioate (153)



Following a **GP2** using (*R*)-*S*-benzothioate **122** (99 mg, 0.25 mmol, >99:1 *e.r.*) and *N,N*-dimethyl formamide (39 µl, 0.50 mmol) and purification by flash chromatography (5% Et_2O/pentane) gave thiobenzoate **153** (76 mg, 72%, 94:6 *e.r.*) as an oil.

R_f = 0.27 (5% Et_2O/pentane);

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.69 (1H, s, H19), 7.33-7.27 (2H, m, H2), 7.24-7.15 (3H, m, H1/H3), 7.01 (2H, s, H14), 3.05 (2H, hept., *J* = 7.0 Hz, H12), 2.89 (1H, hept., *J* = 7.0 Hz, H16), 2.77 (1H, app. td, *J* = 12.5, 5.3 Hz, H5a), 2.69 (1H, app. td, *J* = 12.5, 5.3 Hz, H5b), 2.25 (1H, ddd, *J* = 14.3, 12.5, 5.3 Hz, H6a), 2.14 (1H, ddd, *J* = 14.3, 12.5, 5.3 Hz, H6b), 1.64 (3H, s, H8), 1.25 (18H, br. d., *J* = 7.0 Hz, H13/H17) ppm;

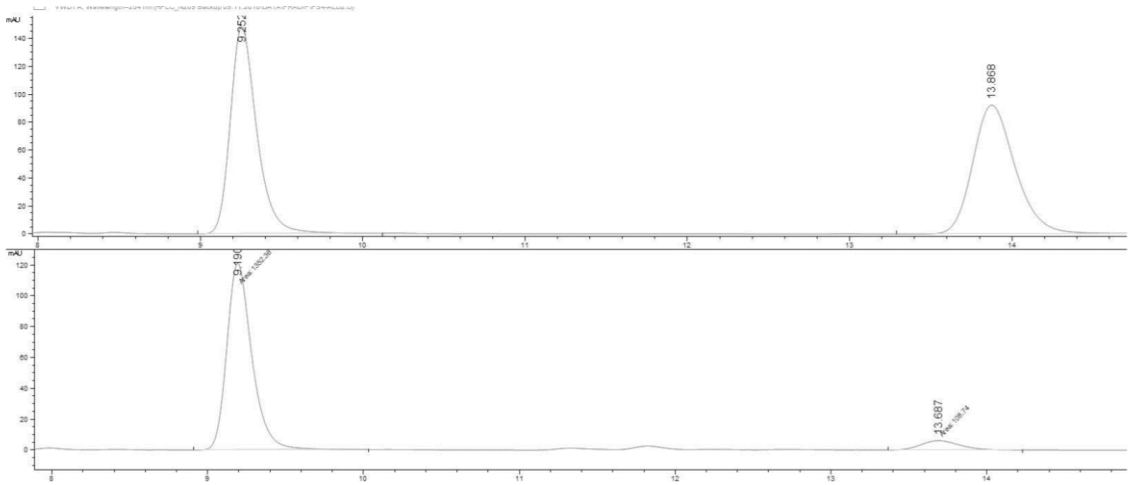
^{13}C NMR (101 MHz, $CDCl_3$): δ = 198.4 (C18), 197.1 (C9), 151.2 (C15), 144.8 (C11) 141.0 (C4), 128.7 (C2), 128.4 (C3), 126.5 (C1), 121.3 (C14), 60.7 (C7), 36.7 (C6), 34.6 (C16), 30.9 (C12), 30.6 (C5), 24.6 (br. s, C13), 24.0 (C17), 19.6 (C8) ppm;

IR (ν_{max}/cm^{-1}, neat): 1727 (C=O$_{ALD}$), 1675 (C=O$_{TIB}$), 1654, 1456;

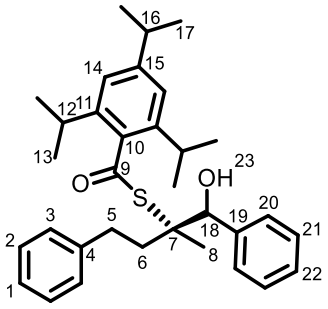
HRMS (EI) calc. for $[C_{27}H_{36}O_2S + Na]^+$ 447.2328. Found 447.2327;

$[\alpha]_D^{22}$ + 11.3 (c 1.0, $CHCl_3$);

Chiral HPLC (IC, 4% *i*PrOH/hexane, 0.5 mL/min, RT) T_R = 9.25 mins (major), 13.86 mins (minor).



***S*-((1*R*,2*R*)-1-hydroxy-2-methyl-1,4-diphenylbutan-2-yl) 2,4,6-triisopropylbenzothioate (154)**



Following a **GP2** using (*R*)-*S*-benzothioate **122** (99 mg, 0.25 mmol, >99:1 *e.r.*) and benzaldehyde (50 µL, 0.50 mmol) and purification by flash chromatography (10% EtOAc/petroleum ether) gave thiobenzoate **154** (80 mg, 64 %, 1:1.5 *d.r.*) as an oil. Further purification by preparative HPLC (5% EtOAc/hexane) gave diastereomer A (22 mg, 23%, 98:2 *e.r.*) as an oil and diastereomer B (17 mg, 18%, 98:2 *e.r.*) as an amorphous solid.

Diastereomer A:

R_f = 0.34 (10% EtOAc/petroleum ether);

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.43 (2H, m, H2), 7.36 – 7.25 (5H, m, H20/H21/H22), 7.22 – 7.15 (3H, m, H1/H3), 7.01 (2H, s, H14), 5.30 (1H, br. d, J = 4.0 Hz, H23), 3.87 (1H, br. d, J = 4.0 Hz, H18), 3.16 (2H, hept., J = 7.0 Hz, H12), 3.00-2.85 (2H, m, H5a/H16), 2.81-2.65 (2H, m, H5b/H6a), 1.97 (1H, app. td, J = 11.4, 3.3 Hz, H6b), 1.36 (3H, s, H8), 1.28 (6H, d, J = 7.0 Hz, H17), 1.25 (12H, d, J = 7.0 Hz, H13) ppm;

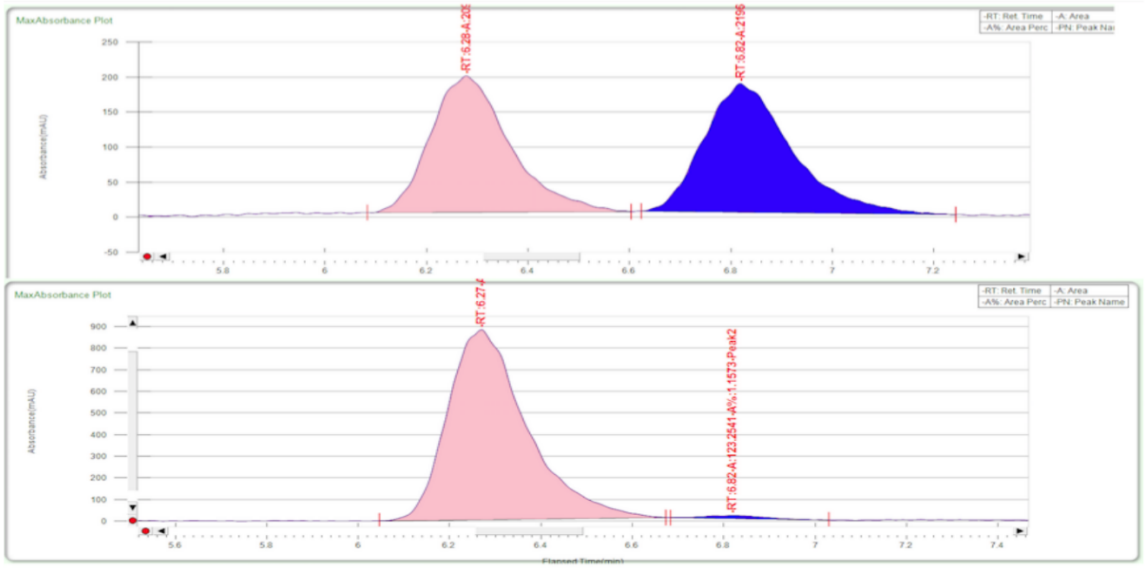
^{13}C NMR (101 MHz, $CDCl_3$): δ = 200.8 (C9), 150.9 (C15), 144.7 (C11), 141.8 (C4), 139.9 (C19), 135.2 (C10), 128.6 (C21), 128.5 (C2), 128.2 (C3), 128.0 (C20), 127.9 (C22), 126.1 (C1), 121.3 (C14), 78.8 (C18), 64.0 (C7), 38.5 (C6), 34.5 (C16), 31.5 (C5), 31.0 (C12), 24.8 (br. s, C13), 24.0 (C17), 19.8 (C8) ppm;

IR (ν_{max}/cm^{-1}, neat): 3400 (OH), 1679 (C=O_{TIB}), 1649, 1454;

HRMS (ESI) calc. for $[C_{33}H_{42}O_2S + Na]^+$ 525.2798. Found 525.2792;

$[\alpha]_D^{22}$ + 3 (c 0.5, $CHCl_3$);

Chiral SFC (IB, 4% MeOH, 4 mL/min, 125 bar, RT) T_R = 6.28 mins (major), 6.82 mins (minor).



Diastereomer B:

R_f = 0.34 (10% EtOAc/petroleum ether);

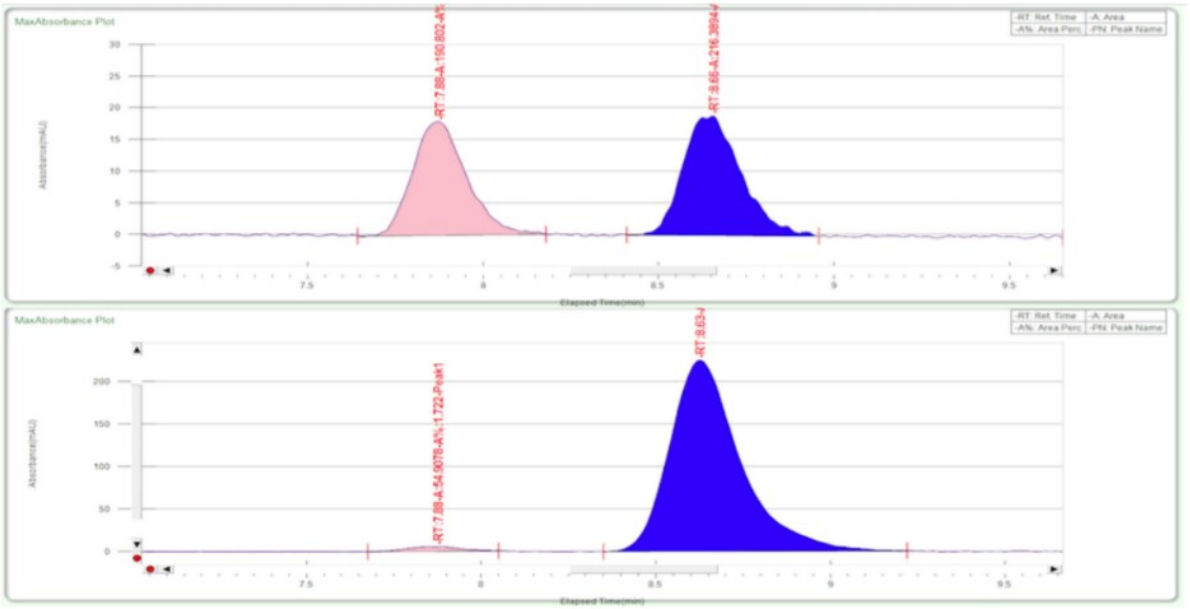
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.44 (2H, m, H2), 7.36 – 7.28 (5H, m, H20/H21/H22), 7.22 – 7.12 (3H, m, H1/H3), 7.02 (2H, s, H14), 5.29 (1H, br. d, *J* = 3.7 Hz, H23), 4.04 (1H, br. d, *J* = 3.7 Hz, H18), 3.15 (2H, hept., *J* = 7.0 Hz, H12), 2.90 (1H, hept., *J* = 7.0 Hz, H16), 2.83 (1H, app. td, *J* = 12.8, 4.4 Hz, H5), 2.70 (1H, td, *J* = 12.8, 5.2 Hz, H5), 2.30 (1H, app. td, *J* = 12.8, 4.4 Hz, H6), 1.95 (1H, app. td, *J* = 13.0, 5.2 Hz, H6), 1.66 (3H, s, H8), 1.30 (6H, d, *J* = 7.0 Hz, H17), 1.26 (12H, d, *J* = 7.0 Hz, H13) ppm;

^{13}C NMR (101 MHz, $CDCl_3$): δ = 201.2 (C9), 150.9 (C15), 144.7 (C11), 141.7 (C4), 140.1 (C19), 135.3 (C10), 128.6 (C21), 128.5 (C2), 128.2 (C3), 128.0 (C20), 127.8 (C22), 126.2 (C1), 121.2 (C14), 80.3 (C18), 63.3 (C7), 36.5 (C6), 34.5 (C16), 31.1 (C5), 31.1 (C12), 24.6 (br. s, C13), 24.0 (C17), 22.3 (C8) ppm;

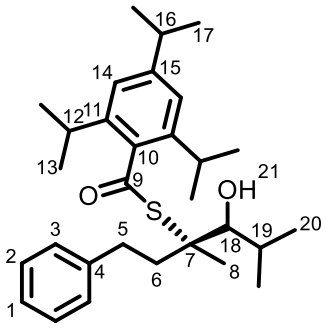
IR (ν_{max}/cm^{-1}, neat): 3388 (OH), 1671 (C=O$_{TIB}$), 1454;

$[\alpha]_D^{22}$ + 2 (*c* 0.5, $CHCl_3$);

Chiral SFC (IB, 4% MeOH, 4 mL/min, 125 bar, RT) T_R = 7.88 mins (minor), 8.66 mins (major).



_S_-((3_R_,4_R_)-4-hydroxy-3,5-dimethyl-1-phenylhexan-3-yl) 2,4,6-triisopropylbenzothioate (155)



Following a **GP2** using (*R*)-*S*-benzothioate **122** (99 mg, 0.25 mmol, >99:1 *e.r.*) and iso-butyraldehyde (46 µL, 0.5 mmol) and purification by flash chromatography (5% Et_2O/pentane) gave thiobenzoate **155** (30 mg, 40%, 98:2 *e.r.,* 5:1 *d.r.*) as an oil.

Major diastereomer:

R_f = 0.21 (5% Et_2O/pentane);

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.31 (2H, m, H2), 7.25-7.18 (3H, m, H1/H3), 6.98 (2H, s, H14), 4.80 (1H, d, *J* = 3.2 Hz, H18), 3.49 (1H, br. s, H21), 3.08 (2H, hept., *J* = 7.0 Hz, H12, 2.93 – 2.74 (3H, m, H16, H5), 2.41 (1H, ddd, *J* = 14.0, 10.8, 6.0 Hz, H6), 2.31 (1H, ddd, *J* =14.0, 10.8, 6.8 Hz, H6), 2.05 (1H, hd, *J* = 6.8, 3.2 Hz, H19), 1.49 (3H, s, H8), 1.25 (18H, d, *J* = 7.0 Hz, H13/H17), 1.10 (3H, d, *J* = 6.8 Hz, H20), 1.05 (3H, d, *J* = 6.8 Hz, H20) ppm;

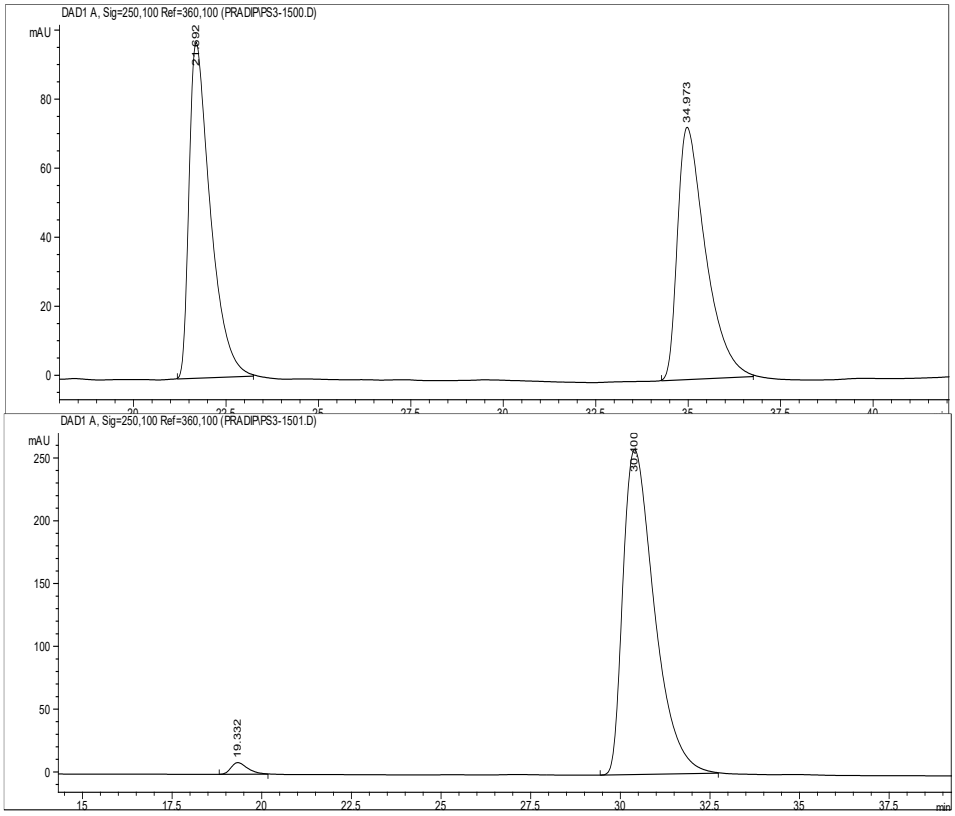
^{13}C NMR (101 MHz, $CDCl_3$): δ = 201.1 (C9), 150.8 (C15), 144.7 (C11), 142.0 (C4), 135.18 (C10), 128.6 (C2), 128.5 (C3), 126.0 (C1), 121.2 (C14), 81.0 (C18), 64.0 (C7), 39.8 (C19), 34.5 (C6), 31.2 (C16), 30.8 (C5), 24.7 (br. s, C13), 24.0 (C17), 23.5 (C20), 21.9 (C20), 17.7 (C8) ppm;

IR (ν_{max}/cm^{-1}, neat): 3350 (OH), 1672 (C=O_{TIB}), 1638, 1459;

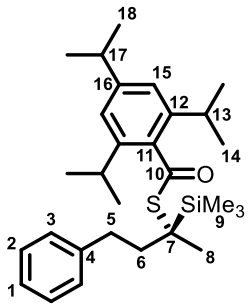
HRMS (ESI) calc. for $[C_{30}H_{44}O_2S + Na]^+$ 491.2941. Found 491.2939.

$[\alpha]_D^{22}$ + 4 (c 0.5, $CHCl_3$);

Chiral HPLC (IB with guard, 0.5% *i*PrOH/hexane, 0.5 mL/min, RT) T_R = 19.3 mins (minor), 30.4 mins (major).



(*R*)-*S*-(4-phenyl-2-(trimethylsilyl)butan-2-yl) 2,4,6-triisopropylbenzothioate (156)



Following **GP2** using (*R*)-*S*-benzothioate **122** (99 mg, 0.25 mmol, >99:1 *e.r.*) and trimethylsilyl chloride (60 μL, 0.50 mmol) and purification by flash chromatography (10% toluene/pentane) gave thiobenzoate **156** (80 mg, 68%, 60:40 *e.r.*) as an oil.

$\mathbf{R}_f$ = 0.36 (10% toluene/pentane);

^{1}H NMR (101 MHz, $CDCl_3$): δ = 7.32 (2H, m, H2), 7.25 – 7.19 (3H, m, H1/H3), 7.00 (2H, s, H15), 3.23 (2H, hept., J = 7.0 Hz, H13), 2.99 – 2.78 (3H, m, H5/H17), 2.33 (2H, m, H6), 1.70

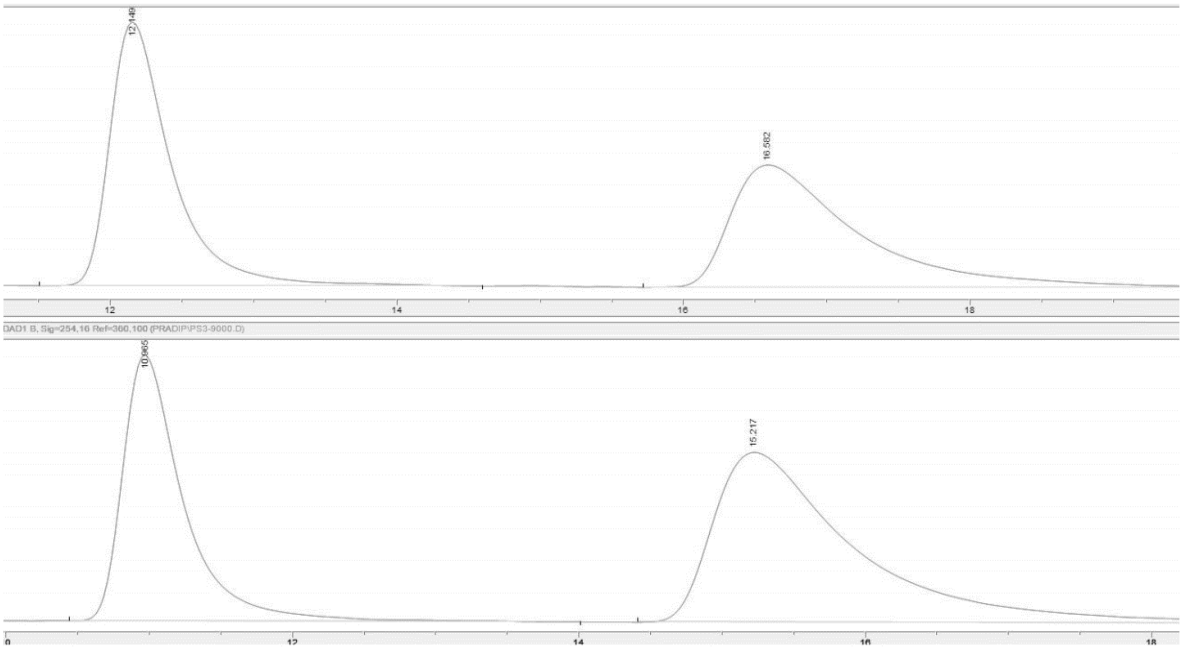
(3H, s, H8), 1.33 (6H, d, J = 7.0 Hz, H18), 1.25 (12H, d, J = 7.0 Hz, H14), 0.16 (9H, s, H9) ppm;

^{13}C NMR (101 MHz, $CDCl_3$): δ = 199.5 (C10), 150.3 (C16), 144.6 (C12), 142.7 (C4), 136.6 (C11), 128.5 (C2), 125.9 (C3) 121.1 (C1), 43.0 (C7), 38.9 (C6), 34.5 (C17), 32.6 (C5), 30.7 (C13), 24.5 (br. s, C14) 24.0 (C18), 21.1 (C8), –2.78 (C9) ppm;

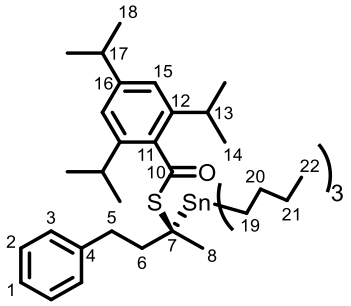
IR (ν_{max}/cm^{-1}, neat): 1672 (C=O_{TIB}), 1653, 1459;

HRMS (ESI) calc. for $[C_{29}H_{44}OSSi + Na]^+$ 491.2762. Found 491.2762;

Chiral HPLC (IA, 0.1% *i*PrOH/hexane, 0.5 mL/min, 0°C) T_R = 12.4 mins (major), 15.2 mins (minor).



(*R*)-*S*-(4-Phenyl-2-(tributylstannyl)butan-2-yl) 2,4,6-triisopropylbenzothioate (157)



Following **GP2** using (*R*)-*S*-benzothioate **122** (30 mg, 0.076 mmol, >99:1 *e.r.*) and tributyltin chloride (62 μL, 0.15 mmol) and purification by flash chromatography (2% toluene/pentane) gave thiobenzoate **157** (40 mg, 77%, 67:33 *e.r.*) as an oil.

$\mathbf{R_f}$ = 0.52 (5% toluene/pentane);

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.30 (2H, m, H2), 7.23 – 7.16 (3H, m, H1/H3), 7.00 (2H, s, H15), 3.14 (2H, hept., *J* = 7.0 Hz, H13), 2.93-2.80 (2H, m, H5/H17), 2.65 (1H, td, *J* = 13.2, 4.5 Hz, H5), 2.41 (1H, td, *J* = 13.7, 4.5 Hz, H6), 2.23 (1H, td, *J* = 13.2, 4.5 Hz, H6), 1.79 (3H, s, H8), 1.56 (6H, m, H20), 1.36 (6H, m, H22) 1.24 (18H, br. d, *J* = 7.0 Hz, H14/H18), 1.06 (6H, m, H19), 0.92 (9H, t, *J* = 7.2 Hz, H22) ppm;

^{13}C NMR (101 MHz, $CDCl_3$): δ = 200.8 (C10), 150.2 (C16), 144.6 (C12), 142.1 (C4), 135.2 (C11), 128.4 (C2), 128.3 (C3), 125.9 (C1), 121.0 (C15), 42.9 (C6), 42.8 (C7), 34.1 (C5), 33.5 (C17), 30.5 (C13), 25.9 (C8), 24.4 (C14), 23.9 (C18), -7.59 (C19) ppm;

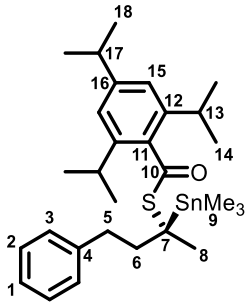
IR (ν_{max}/cm^{-1}, neat): 2957, 1673 ($C{=}O_{TIB}$), 1646, 1459, 901;

HRMS (ESI) calc. for $[C_{38}H_{62}OSSn + Na]^+$ 709.3442. Found 709.3411;

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{22}}$ + 2 (c 0.5, $CHCl_3$);

Chiral HPLC (IA, 0.1% *i*PrOH/hexane, 0.5 mL/min, 0 °C) T_R = 22.40 mins (major), 24.15 mins (minor). Absolute stereochemistry determined after tin-lithium exchange (*n*BuLi, TMEDA, TBME, – 60 °C) and MeOD quench, followed by comparison of the Chiral HPLC with the starting material **122**.

(*S*)-*S*-(4-phenyl-2-(trimethylstannyl)butan-2-yl) 2,4,6-triisopropylbenzothioate (158)



Following **GP2** using (*R*)-*S*-benzothioate **122** (99 mg, 0.25 mmol, >99:1 *e.r.*) and trimethyltin chloride (57 μL, 0.50 mmol) and purification by flash chromatography (2% toluene/pentane) gave thiobenzoate **158** (120 mg, 88%, 82:18 *e.r.*) as a white solid.

$\mathbf{R_f}$ = 0.44 (2% toluene/pentane);

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.29 (2H, m, H2), 7.22 – 7.15 (3H, m, H1/H3), 6.99 (2H, s, H15), 3.08 (2H, hept., J = 7.0 Hz, H13), 2.88 (1H, hept., J = 7.0 Hz, H17), 2.81 (1H, m, H5), 2.66 (1H, m, H5), 2.19 (2H, dd, J = 9.8, 7.6 Hz, H6), 1.65 (3H, s, H8), 1.25 (18H, br. d, J = 7.0 Hz, H14/H18), 0.28 (9H, s, H8) ppm;

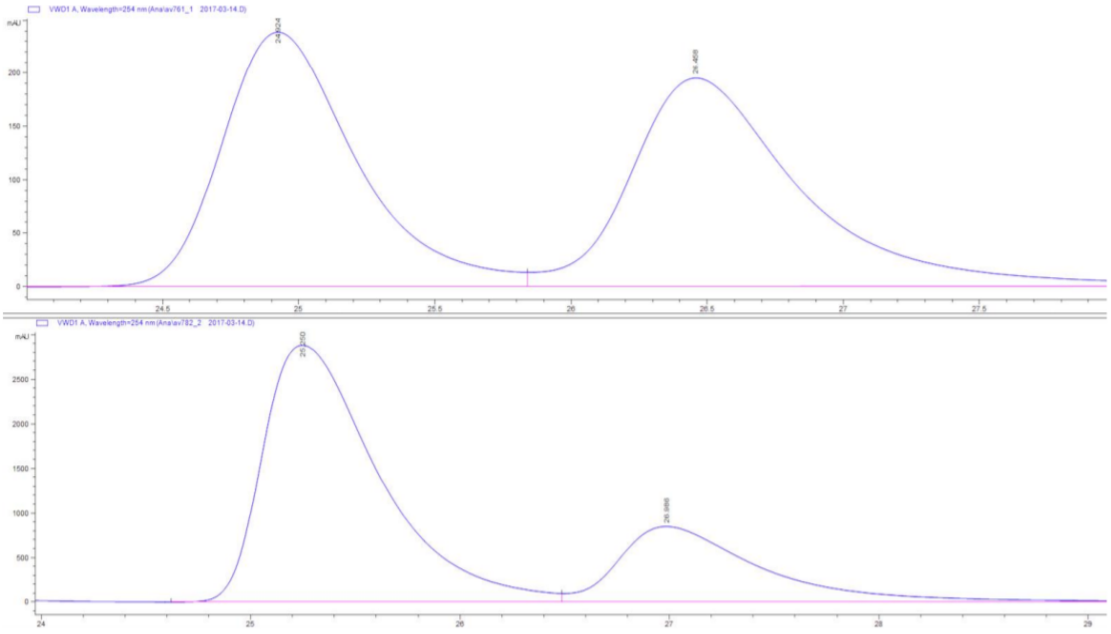
^{13}C NMR (101 MHz, $CDCl_3$): δ = 200.8 (C10), 150.4 (C16), 144.7 (C12), 142.0 (C4), 135.2 (C11), 128.4 (C2), 128.3 (C3), 125.9 (C1), 121.0 (C15), 42.8 (C6), 40.7 (C7), 34.4 (C5), 33.5 (C17), 30.5 (C13), 25.9 (C8), 24.4 (C14), 23.9 (C18), -7.59 (C9) ppm;

IR (ν_{max}/cm^{-1}, neat): 1673 ($C{=}O_{TIB}$), 1654, 1460;

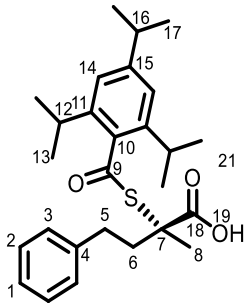
HRMS (ESI) calc. for $[C_{17}H_{24}OSSn + Na]^+$ 583.2031. Found 583.2028;

$[\alpha]_D^{22}$ + 6 (c 1.0, $CHCl_3$);

Chiral HPLC (IB with guard, 0.1% *i*PrOH/hexane, 0.1 mL/min, 0 °C) T_R = 36.9 mins (major), 39.7 mins (minor). Absolute stereochemistry determined after tin-lithium exchange (*n*BuLi, TMEDA, TBME, – 60 °C) and MeOD quench, followed by comparison of the Chiral HPLC with the starting material **122**.



(*R*)-2-methyl-4-phenyl-2-((2,4,6-triisopropylbenzoyl)thio)butanoic acid (159)



Following a **GP2** using (*R*)-*S*-benzothioate **122** (99 mg, 0.25 mmol, >99:1 *e.r.*) and dry ice (*passed over dry* $MgSO_4$) and purification by flash chromatography (5% Et_2O/pentane) gave thiobenzoate **159** (94 mg, 85 %, > 97:3 *e.r.*) as an oil.

$\mathbf{R_f}$ = 0.20 (1% MeOH/CH_2Cl_2);

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.24 (2H, m, H2), 7.20-7.13 (3H, m, H1/H3), 7.01 (2H, s, H14), 3.13 (2H, m, H12), 2.91(1H, hept., J = 7.0 Hz, H16), 2.75 (2H, m, H5), 2.29 (2H, m, H6) 1.84 (3H, s, H8), 1.24 (18H, br. d., J = 7.0 Hz, H13/H17) ppm;

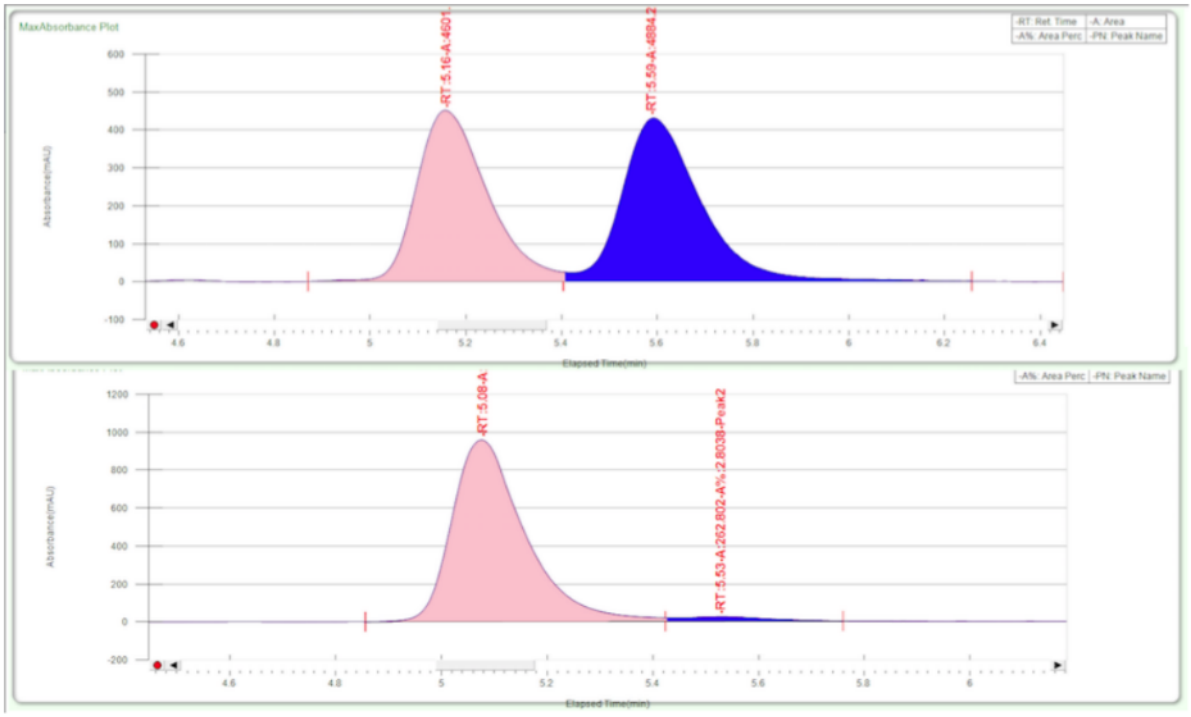
^{13}C NMR (101 MHz, $CDCl_3$): δ = 197.6 (C9), 178.8 (C18), 151.2 (C15), 144.8 (C11), 141.0 (C4), 134.1 (C10), 128.7 (C2), 128.4 (C3), 126.5 (C1), 121.3 (C14), 60.7 (C7), 36.7 (C6), 34.6 (C16), 30.9 (C12), 30.6 (C5), 24.6 (br. s, C13), 24.0 (C17), 19.6 (C8) ppm;

IR (ν_{max}/cm^{-1}, neat): 2971, 1719 (C=O$_{COOH}$), 1675 (C=O$_{TIB}$), 1656, 1461;

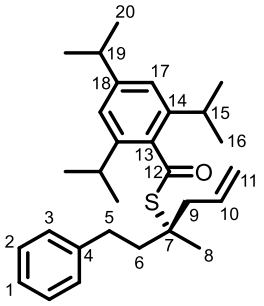
HRMS (ESI) calc. for $[C_{27}H_{36}O_3S + Na]^+$ 463.2277. Found 463.2272;

$[\alpha]_D^{22}$ + 13.5 (c 1.0, $CHCl_3$);

Chiral SFC (Chiracel IA, 4% *i*PrOH/hexane (1:1, v:v), 4mL/min, 125 bar, 40 ºC) T_R = 5.08 mins (major), 5.53 mins (minor).



(*R*)-*S*-(3-methyl-1-phenylhex-5-en-3-yl) 2,4,6-triisopropylbenzothioate (160)



Following **GP2** using (*R*)-*S*-benzothioate **122** (99 mg, 0.25 mmol, >99:1 *e.r.*) and allyl bromide (61 mg, 43 µL, 0.50 mmol) and purification by flash chromatography (5% toluene/pentane) gave thiobenzoate **160** (64 mg, 59%, 51:49 *e.r.*) as an oil.

$\mathbf{R}_f$ = 0.42 (5% toluene/pentane);

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.29 (2H, m, H2), 7.23 – 7.17 (3H, m, H1/H3), 6.99 (2H, s, H17), 5.92 (1H, ddt, *J* = 17.2, 10.1, 7.2 Hz, H10), 5.22 – 5.13 (2H, m, H11), 3.14 (2H, hept., *J* = 7.0 Hz, H15), 2.94 – 2.65 (5H, m, H5/H9/H19), 2.29 (1H, ddd, *J* = 14.1, 12.1, 5.5 Hz, H6), 2.08 (1H, ddd, *J* = 14.1, 12.1, 5.5 Hz, H6), 1.57 (3H, s, H8), 1.34 – 1.23 (18H, d, *J* = 7.0, H16/H20) ppm;

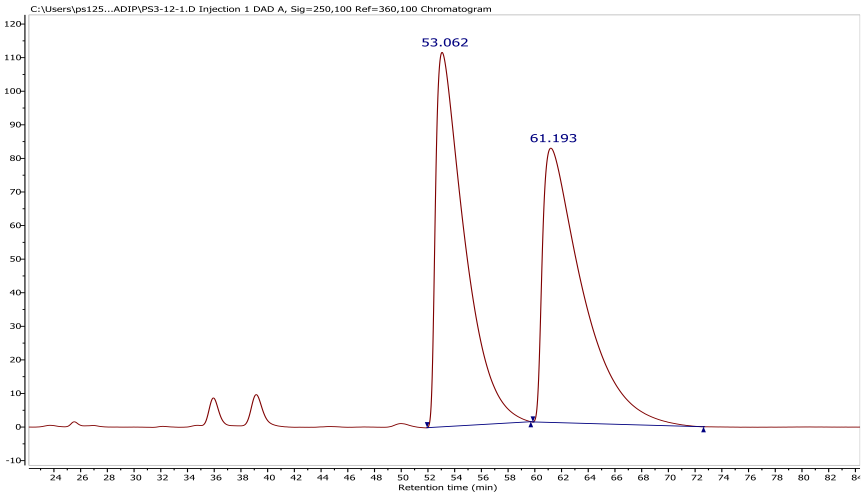
^{13}C NMR (101 MHz, $CDCl_3$): δ = 198.7 (C12), 150.3 (C18), 144.5 (C14), 142.0 (C4), 133.6 (C10), 128.4 (C2), 128.3 (C3), 125.9 (C1), 121.0 (C17), 118.4 (C11), 56.0 (C7), 43.7 (C9), 41.1 (C5), 34.4 (C19), 31.2 (C6), 30.5 (C15), 24.7 (br. s, C16), 23.9 (C20), 19.9 (C8) ppm;

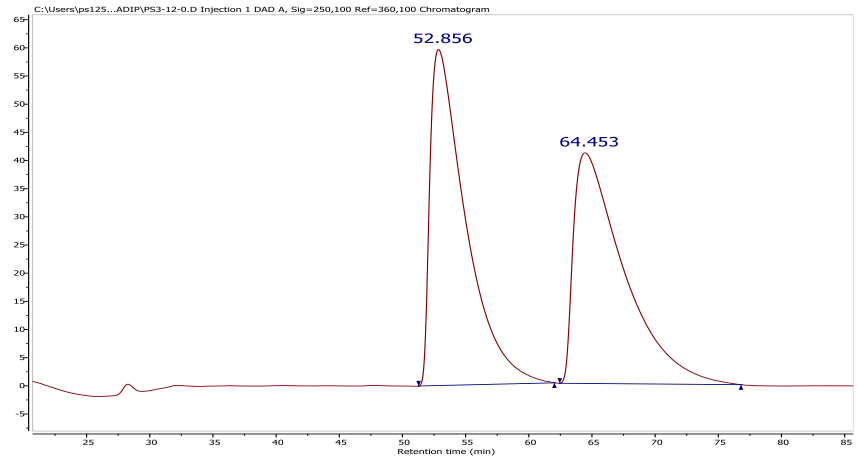
IR (ν_{max}/cm^{-1}, neat): 1675 (C=O$_{TIB}$), 1645, 1460;

HRMS (ESI) calc. for $[C_{23}H_{36}O_3S + Na]^+$ 459.2691. Found 459.2686;

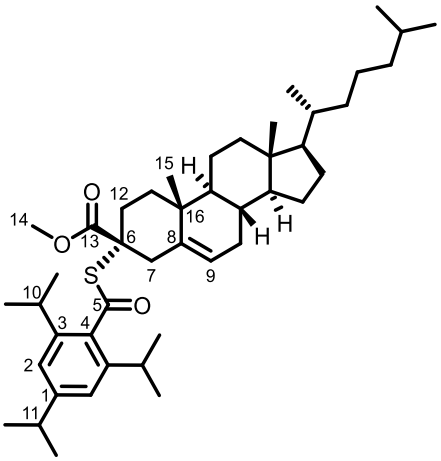
$[\alpha]_D^{22}$ 0 (c 1.0, $CHCl_3$);

Chiral HPLC (IC with guard, 0.1% *i*PrOH/hexane, 0.15 mL/min, RT) T_R = 53.1 mins (minor), 61.2 mins (major).


C:\Users\ps125...ADIP\PS3-12-1.D Injection 1 DAD A, Sig=250,100 Ref=360,100 Chromatogram
53.062
61.193
Retention time (min)


C:\Users\ps125...ADIP\PS3-12-0.D Injection 1 DAD A, Sig=250,100 Ref=360,100 Chromatogram
52.856
64.453
Retention time (min)

Methyl (3*R*,8*S*,9*S*,10*R*,13*R*,14*S*,17*R*)-10,13-dimethyl-17-((*R*)-6-methylheptan-2-yl)-3-((2,4,6-triisopropylbenzoyl)thio)-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthrene-3-carboxylate (165)



Following **GP2** using (*S*)-*S*-benzothioate **143** (200 mg, 0.31 mmol) and methyl chloroformate (48.0 μL, 0.62 mmol) and purification by flash chromatography (4% toluene/pentane) gave (*R*)-*S*-thiobenzoate **165** (173 mg, 81%) as a white foam.

$\mathbf{R_f}$ = 0.35 (5% Et_2O/pentane);

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.97 (2H, s, H2), 5.37 (1H, m, H9), 3.78 (3H, s, H14), 3.06 (2H, m, H10), 3.00 (1H, m, $H7_{ax.}$), 2.87 (1H, hept., J = 6.5 Hz, H11), 2.60 (1H, dd, J = 14.6, 2.1 Hz, Hz, $H7_{eq.}$), 2.22 (1H, m, $H12_{ax.}$), 2.14 (1H, m, $H12_{eq.}$), 2.02 (2H, m), 1.81 (2H, m), 1.57 (2H, m), 1.47 (5H, m), 1.34 (4H, m), 1.24 (20H, m), 1.12 (4H, m), 1.04 (3H, s, H15), 0.99 (2H, m), 0.92 (3H, m), 0.87 (6H, dd, J = 6.5, 1.7 Hz), 0.68 (3H, s) ppm;

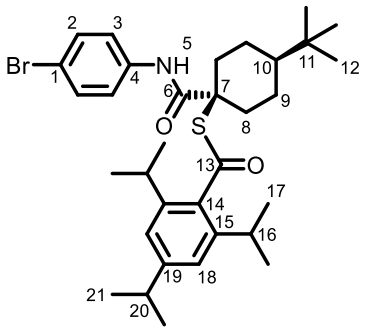
^{13}C NMR (101 MHz, $CDCl_3$): δ = 197.2 (C5), 174.1 (C13), 150.6 (C1), 144.9 (C3), 138.0 (C8), 134.8 (C4), 120.9 (C9), 120.8 (C2), 59.2 (C6), 56.7 (CH), 56.0 (CH), 52.6 (C14), 50.2 (CH), 42.2 (4º C), 39.5 (CH_2), 39.1 (C7), 36.6 (C16), 36.2 (CH_2), 35.6 (CH_2), 34.4 (C11), 32.0 (CH_2), 31.7 (C10), 30.2 (2 x CH_2), 29.7 (CH), 28.1 (CH_2), 28.0 (CH), 25.2 (4 x CH_3), 24.2 (CH_2), 23.9 (2x CH_3), 23.8 (CH_2), 22.8 (CH_3), 22.5 (CH_3), 20.8 (CH_2), 19.4 (C15), 18.7 (CH_3), 11.8 (CH_3) ppm;

HRMS (ESI) calc. for $[C_{45}H_{70}O_3S + Na]^+$ 713.4937. Found, 713.4920;

IR (ν_{max}/cm^{-1}, neat): 2958, 1737 ($C{=}O_{ester}$), 1677 ($C{=}O_{TIB}$), 1460, 1248, 987;

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{22}}$ + 10 (c 1.0, $CHCl_3$).

***S*-((1*S*,4*R*)-1-((4-bromophenyl)carbamoyl)-4-isopropylcyclohexyl) 2,4,6-triisopropylbenzothioate (167)**



Following **GP2** using (*S*)-*S*-benzothioate **144** (99 mg, 0.25 mmol, >20:1 *d.r.*) and 4-bromophenyl isocyanate (99 mg, 0.50 mmol) and purification by flash chromatography (4% toluene/pentane) gave thiobenzoate **167** (78 mg, 53%, >20:1 *d.r.*) as an amorphous solid.

$\mathbf{R_f}$ = 0.50 (4% toluene/pentane);

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.07 (1H, s, H5), 7.50-7.46 (4H, m, H2/H3), 6.99 (2H, s, H18), 2.95 (2H, hept., J = 7.0 Hz, H16), 2.88 (1H, hept., J = 7.0 Hz, H20), 2.55 (2H, m, $H8_{eq.}$), 2.00 (2H, td, J = 13.5, 3.5 Hz, $H8_{ax.}$), 1.81 (2H, m, $H9_{eq.}$), 1.44 (2H, qd, J = 13.5, 3.2 Hz, $H9_{ax.}$), 1.26 (1H, m, H10), 1.24 (18H, d, J = 7.0 Hz, H17/H20), 0.89 (9H, s, H12) ppm. *Some of the small vicinal couplings on the 6-membered ring were not resolved and gave broad lines*;

^{13}C NMR (101 MHz, $CDCl_3$): δ = 200.8 (C13), 171.6 (C6), 151.3 (C19), 144.7 (C15), 137.4 (C4), 134.4 (C14), 131.9 (C2), 121.3 (C18), 121.2 (C3), 116.5 (C1), 60.4 (C7), 47.1 (C10), 34.4 (C16), 32.5 (C11), 32.3 (C8), 30.9 (C20), 27.4 (C12), 24.7 (br. s, C21) 23.8 (C17), 22.9 (C9) ppm;

HRMS (ESI) calc. for $[C_{33}H_{46}BrNO_2S + Na]^+$ 622.3659. Found, 622.3655;

IR (ν_{max}/cm^{-1}, neat): 2956 (Ar), 2865 (Ar), 1681 ($C{=}O_{CONH}$), 1675 ($C{=}O_{TIB}$), 1492, 1266, 899;

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{22}}$ + 8 (c 1.0, $CHCl_3$).

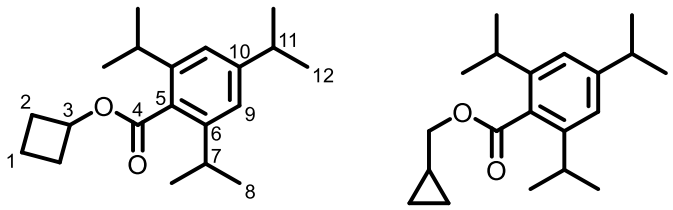
3.3. Chapter 2

3.3.1. Synthesis of Benzoate Derivatives

3.3.1.1. General Procedure for the Synthesis of Benzoates from Secondary Alcohols (GP3)

To a flame-dried flask under nitrogen was added 2,4,6-triisopropylbenzoic acid (1.00 eq.) and PPh_3 (1.10 eq.). The flask was then treated to three vacuum N_2 cycles with stirring. THF (0.66 – 1.00 M) and alcohol (1.10 eq.) were added. The flask was cooled to 0 °C and DIAD (1.10 eq.) was added dropwise over a period of 15 mins. After 10 mins, the reaction was warmed to RT and left to stir at RT for 16 hrs. The crude material was concentrated *in vacuo* and the residue was dissolved in minimal pentane (<25 mL) and stirred vigorously at RT for 10 mins. The resultant white precipitate was filtered and washed with pentane (<100 mL). The filtrate was concentrated *in vacuo* and purified by column chromatography (3-20% Et_2O/PE) to afford the desired ester product.

Cyclobutyl 2,4,6-triisopropylbenzoate (292)



93 : 7

292 **293**

Following **GP3** using 2,4,6-triisopropylbenzoic acid (6.26 g, 25.2 mmol, 1.00 eq.), PPh_3 (7.26 g, 27.7 mmol, 1.10 eq.), cyclobutanol (2.17 mL, 27.7 mmol, 1.10 eq.) and DIAD (5.44 mL, 27.7 mmol, 1.10 eq.) in THF (25 mL, 1 M), followed by column chromatography purification (3-6% Et_2O/PE) afforded a mixture of products (5.26 g, 69%, 93:7 ratio of desired benzoate **292** to inseparable ring contracted benzoate **293**).

$\mathbf{R_f}$ = 0.57 (10% Et_2O/petrol, *p*-anisaldehyde);

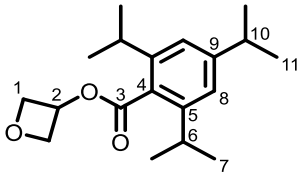
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.00 (2H, s, H9), 5.25 (1H, p, J = 7.5 Hz, H3), 2.94 – 2.82 (3H, m, H7/H11), 2.51 – 2.40 (2H, m, H2), 2.23 – 2.11 (2H, m, H2), 1.91 – 1.80 (1H, m, H1), 1.77 – 1.64 (1H, m, H1), 1.25 (12H, d, J = 6.8 Hz, H8), 1.24 (6H, d, J = 6.8 Hz, H12) ppm;

^{13}C NMR (101 MHz, $CDCl_3$): δ = 170.3 (C4), 150.2 (C10), 144.9 (C6), 130.7 (C5), 121.0 (C9), 69.4 (C3), 34.6 (C11), 31.5 (C7), 30.5 (C2), 24.3 (C8), 24.1 (C12), 14.1 (C1) ppm;

HRMS (ESI) calc. for $[C_{20}H_{30}O_2 + Na]^+$ 325.2143. Found, 325.2140;

IR (ν_{max}/cm^{-1}, neat): 2959, 2869, 1721 (C=O_{TIB}), 1606, 1463, 1248, 1136, 1080, 937, 879, 755, 612.

Oxetan-3-yl 2,4,6-triisopropylbenzoate (349)



Following **GP3** using 2,4,6-triisopropylbenzoic acid (6.09 g, 24.6 mmol, 1.00 eq.), PPh_3 (7.08 g, 27.1 mmol, 1.10 eq.), oxetan-3-ol (2.00 g, 27.1 mmol, 1.10 eq.) and DIAD (5.30 mL, 27.1 mmol, 1.10 eq.) in THF (25 mL, 1 M), followed by column chromatography purification (3-20% Et_2O/PE) afforded desired product **349** as a white solid (4.50 g, 57%).

R_f = 0.22 (5% Et_2O/pentane, *p*-anisaldehyde);

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.06 (2H, s, H8), 5.70 (1H, tt, J = 6.4, 5.3 Hz, H2), 5.02 (2H, dd, J = 7.5, 6.4 Hz, H1), 4.79 (2H, dd, J = 7.5, 5.3 Hz, H1) 2.91 (1H, hept., J = 6.8 Hz, H10), 2.90 (2H, hept., J = 6.8 Hz, H6), 1.26 (12H, d, J = 6.8 Hz, H7), 1.25 (6H, J = 6.8 Hz, H11) ppm;

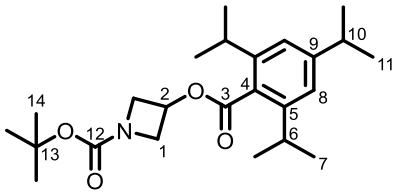
^{13}C NMR (101 MHz, $CDCl_3$): δ = 170.1 (C3), 150.7 (C9), 145.1 (C5), 129.3 (C4), 121.0 (C8), 77.6 (C1), 68.5 (C2), 34.5 (C10), 31.6 (C6), 24.2 (C7), 24.0 (C11) ppm;

HRMS (ESI) calc. for $[C_{19}H_{28}O_3 + Na]^+$ 327.1936. Found, 327.1936;

IR (ν_{max}/cm^{-1}, neat): 2968, 2871, 1720 (C=O_{TIB}), 1610, 1468, 1252, 1238, 1137, 1039, 974, 843, 765;

M.P: 80-81 °C (EtOAc);

***tert*-Butyl 3-((2,4,6-triisopropylbenzoyl)oxy)azetidine-1-carboxylate (358)**



Following **GP3** using 2,4,6-triisopropylbenzoic acid (2.60 g, 10.4 mmol, 1.00 eq.), PPh_3 (3.03 g, 11.5 mmol, 1.10 eq.), tert-butyl 3-hydroxyazetidine-1-carboxylate (2.0 g, 11.5 mmol, 1.10 eq.) and DIAD (2.27 mL, 11.5 mmol, 1.10 eq.) in THF (25 mL, 1 M), followed by column chromatography purification (3-20% Et_2O/PE) afforded desired product **358** as a white solid (2.50 g, 57%).

$\mathbf{R_f}$ = 0.17 (10% Et_2O/pentane, *p*-anisaldehyde);

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.02 (2H, s, H8), 5.38 (1H, tt, *J* = 6.9, 4.2 Hz, H2), 4.34 (2H, ddd, *J* = 10.3, 6.9, 0.7 Hz, H1), 4.00 (2H, ddd, *J* = 10.3, 4.2, 0.7 Hz, H1), 2.89 (1H, hept., *J* = 6.8 Hz, H11), 2.83 (2H, hept., *J* = 6.8 Hz, H6), 1.45 (9H, s, H14), 1.25 (12H, d, *J* = 6.8 Hz, H7), 1.24 (6H, d, *J* = 6.8 Hz, H11) ppm;

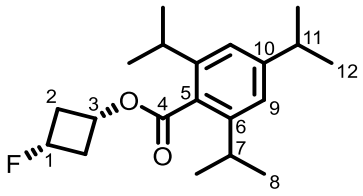
^{13}C NMR (101 MHz, $CDCl_3$): δ = 170.3 (C3), 156.2 (C12), 150.9 (C9), 145.1 (C5), 129.4 (C4), 121.1 (C8), 80.1 (C13), 64.0 (C2), 56.5 (br.s, C1), 34.6 (C10), 31.7 (C6), 28.5 (C14), 24.3 (C7), 24.1 (C11) ppm;

HRMS (ESI) calc. for $[C_{24}H_{37}NO_4 + Na]^+$ 426.2620. Found, 426.2608;

IR (ν_{max}/cm^{-1}, neat): 2964, 2878, 1723 (C=O_{TIB}), 1720 (C=O_{amide}), 1604, 1402, 1285, 1252, 1133, 1108, 1073;

M.P: 80-82 °C (EtOAc);

(1*S*,3*S*)-3-Fluorocyclobutyl 2,4,6-triisopropylbenzoate (302)



Following **GP3** using 2,4,6-triisopropylbenzoic acid (633 mg, 2.55 mmol, 1.15 eq.), PPh_3 (640 mg, 2.44 mmol, 1.10 eq.), (1*s*,3*s*)-3-fluorocyclobutan-1-ol (200 mg, 2.22 mmol, 1.00 eq.) and DIAD (0.48 mL, 2.44 mmol, 1.10 eq.) in THF (3.7 mL, 0.66 M), followed by column chromatography purification (0-10% Et_2O/PE) afforded desired product **302** as a white solid (440 mg, 62%, >99:1 *d.r.*).

$\mathbf{R_f}$ = 0.41 (10% Et_2O/pentane, *p*-anisaldehyde);

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.01 (2H, s, H9), 4.84 (1H dp, J = 55.7$_{JH\text{-}F}$, 6.6 Hz, H1), 4.83 (1H, pd, J = 7.1, 3.8 Hz, H3), 3.02 (2H, ddtd, J = 13.7$_{JH\text{-}F}$, 10.2, 7.1, 6.6, 3.8 Hz, H2) 2.89 (1H, hept., J = 6.9 Hz, H11), 2.84 (2H, hept., J = 6.9 Hz, H7), 2.43 (2H, m, H2), 1.25 (12H, d, J = 6.9 Hz, H8), 1.24 (6H, d, J = 6.9 Hz, H12) ppm;

^{13}C NMR (101 MHz, $CDCl_3$): δ = 170.3 (C4), 150.6 (C10), 145.0 (C6), 130.0 (C5), 121.1 (C9), 80.9 (d, $J_{C\text{-}F}$ = 211.5 Hz, C1), 60.3 (d, $J_{C\text{-}F}$ = 22.8 Hz, C3), 39.2 (d, $J_{C\text{-}F}$ = 21.2 Hz, C2), 34.6 (C11), 31.6 (C7), 24.2 (C8), 24.1 (C12) ppm;

^{19}F NMR (376 MHz, $CDCl_3$): δ = -169.6 (dtt, $J_{H\text{-}F}$ = 55.7, 25.1, 13.7 Hz) ppm;

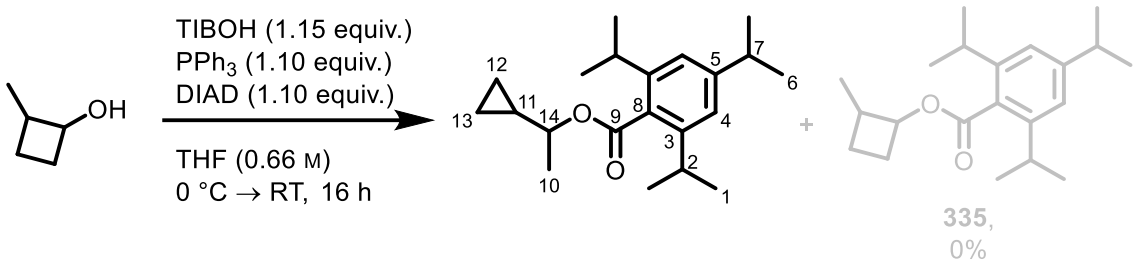
HRMS (ESI) calc. for $[C_{20}H_{29}FO_2 + Na]^+$ 343.2103. Found, 343.2112;

IR (ν_{max}/ cm^{-1}, neat): 3675, 2969, 1725 (C=O_{TIB}), 1462, 1394, 1260, 1060, 879, 748;

M.P: 63-65 °C **(**EtOAc);

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{23}}$ +0.06 (*c* 1.0, $CHCl_3$).

1-Cyclopropylethyl 2,4,6-triisopropylbenzoate (337)



Following **GP3** using 2,4,6-triisopropylbenzoic acid (663 mg, 2.67 mmol, 1.15 eq.), PPh_3 (670 mg, 2.56 mmol, 1.10 eq.), 2-methylcyclobutan-1-ol (200 mg, 2.32 mmol, 1.00 eq.) and DIAD (0.50 mL, 2.56 mmol, 1.10 eq.) in THF (3.52 mL, 0.66 M), followed by column chromatography purification (2-10% Et_2O/PE) to afford the ring contracted side product **337** as a colourless oil (515 mg, 70%).

$\mathbf{R_f}$ = 0.62 (10% Et_2O/pentane, *p*-anisaldehyde);

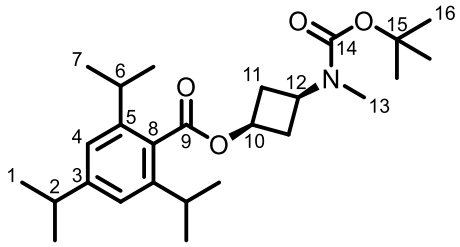
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.00 (2H, s, H4), 4.57 (1H, dq, J = 9.1, 6.3 Hz, H14), 3.07 (1H, hept., J = 6.8 Hz, H7), 2.94 (2H, hept., J = 6.8 Hz, H2), 1.43 (3H, d, J = 6.3 Hz, H10), 1.08 (1H, m, H11), 0.63-0.52 (2H, m, H12/13), 0.48 (1H, m, H12), 0.31 (1H, m, H13) ppm;

^{13}C NMR (101 MHz, $CDCl_3$): δ = 170.5 (C9), 150.1 (C5), 145.5 (C3), 131.2 (C8), 121.2 (C4), 76.7 (C14), 34.6 (C7), 31.6 (C2), 24.4 (C1), 24.0 (C6), 19.9 (C10), 16.6 (C11), 4.2 (C12), 2.9 (C13) ppm;

HRMS (ESI) calc. for $[C_{21}H_{32}O_2 + Na]^+$ 317.2475. Found, 317.2471;

IR (ν_{max}/cm^{-1}, neat): 2960, 2871, 1725 (C=O_{TIB}), 1462, 1250, 1081.

(1S,3S)-3-((*tert*-butoxycarbonyl)(methyl)amino)cyclobutyl 2,4,6-triisopropylbenzoate (344)



Following **GP3** using 2,4,6-triisopropylbenzoic acid (284 mg, 1.14 mmol, 1.15 eq.), PPh_3 (287 mg, 1.09 mmol, 1.10 eq.), *tert*-butyl ((1R,3R)-3-hydroxycyclobutyl)(methyl)carbamate (200 mg, 0.99 mmol, 1.00 eq.) and DIAD (0.22 mL, 1.09 mmol, 1.10 eq.) in THF (1.50 mL, 0.66 M), followed by column chromatography purification (2-10% Et_2O/PE) to afford the desired product **344** colourless oil (429 mg, 65%).

$\mathbf{R_f}$ = 0.40 (10% Et_2O/pentane, *p*-anisaldehyde);

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.02 (2H, s, H4), 5.28 (1H, tt, J = 7.4, 2.4 Hz, H10), 4.76 (1H, br. s, H12), 2.90 (3H, hept., J = 6.8 Hz, H2/H6), 2.85 (3H, s, H13), 2.64 (2H, dddd, J = 14.3, 7.4, 3.7, 2.4 Hz, H11), 2.46 (2H, ddt, J = 14.3, 8.3, 2.4, 2.4 Hz, H11), 1.45 (9H, s, H16), 1.27 (12H, d, J = 6.8 Hz, H7), 1.25 (6H, d, J = 6.8 Hz, H1) ppm;

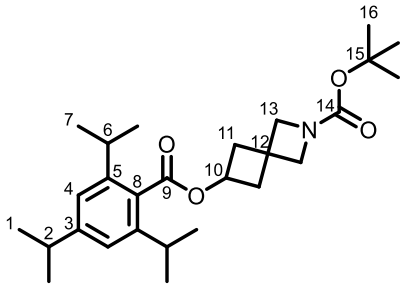
^{13}C NMR (101 MHz, $CDCl_3$): δ = 170.6 (C9), 155.8 (C14), 150.3 (C3), 144.9 (C5), 130.3 (C8), 120.9 (C4), 79.7 (C15), 67.7 (C10), 48.7 (br. s, C12), 35.0 (C11), 34.5 (C2), 31.5 (C6), 29.7 (C13), 28.5 (C16), 24.2 (C7), 24.0 (C1) ppm;

HRMS (ESI) calc. for $[C_{26}H_{41}NO_4 + Na]^+$ 454.2928. Found, 454.2922;

IR (ν_{max}/cm^{-1}, neat): 2962, 1726 (C=O_{ester}), 1697 (C=O_{amide}), 1461, 1364, 1251, 1148, 1077;

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{22}}$ 0 (*c* 1.0, $CHCl_3$), starting material showed no optical rotation.

***tert*-Butyl 6-((2,4,6-triisopropylbenzoyl)oxy)-2-azaspiro[3.3]heptane-2-carboxylate (342)**



Following **GP3** using 2,4,6-triisopropylbenzoic acid (200 mg, 0.81 mmol, 1.15 eq.), PPh_3 (202 mg, 0.77 mmol, 1.10 eq.), tert-butyl 6-hydroxy-2-azaspiro[3.3]heptane-2-carboxylate (150 mg, 0.70 mmol, 1.00 eq.) and DIAD (0.15 mL, 0.77 mmol, 1.10 eq.) in THF (1.10 mL, 0.66 M), followed by column chromatography purification (2-10% Et_2O/PE) to afford the desired product **342** as a colourless oil (162 mg, 52%).

$\mathbf{R_f}$ = 0.16 (10% Et_2O/pentane, *p*-anisaldehyde);

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.00 (2H, s, H4), 5.16 (1H, p, J = 7.0 Hz, H10), 3.97 (2H, s, H13), 3.92 (2H, s, H13), 2.88 (1H, hept., J = 6.6 Hz, H2), 2.83 (2H, hept., J = 6.6 Hz, H6), 2.73 (2H, ddd, J = 10.5, 7.0, 2.8 Hz, H11), 2.32 (2H, ddd, J = 10.5, 7.0, 2.8 Hz, H11), 1.43 (9H, s, H16), 1.24 (12H, d, J = 6.6 Hz, H7), 1.23 (6H, d, J = 6.6 Hz, H1) ppm;

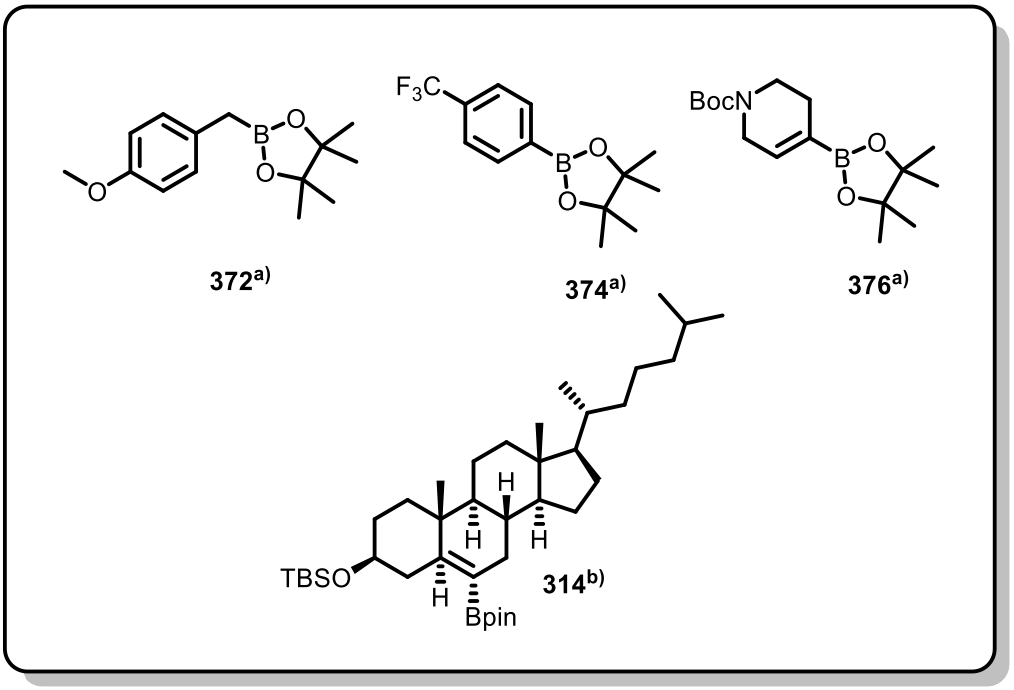
^{13}C NMR (101 MHz, $CDCl_3$): δ = 170.2 (C9), 156.2 (C14), 150.4 (C3), 144.8 (C5), 130.1 (C8), 120.9 (C4), 79.6 (C15), 64.9 (C10), 61.4 (C13), 60.6 (C13), 40.8 (C11), 34.5 (C2), 31.6 (C12), 31.5 (C6), 28.4 (C16), 24.2 (C7), 24.0 (C1) ppm;

HRMS (ESI) calc. for $[C_{27}H_{41}NO_4 + Na]^+$ 466.2928. Found, 466.2923;

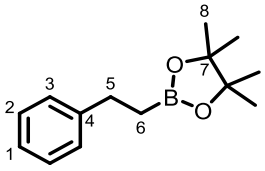
IR (ν_{max}/ cm^{-1}, neat): 3675, 2970, 2901, 1725 ($C{=}O_{ester}$), 1699 ($C{=}O_{amide}$), 1404, 1259, 1101, 1074, 1067, 878, 764.

3.3.2. Preparation of Boronic Ester Starting Materials

The following boronic esters were purchased from suppliers[a)] or synthesised in house by colleagues[b)187]:



4,4,5,5-tetramethyl-2-phenethyl-1,3,2-dioxaborolane (294)



2-phenethylboronic acid (10.0 g, 66.7 mmol) and pinacol (7.9 g, 66.7 mmol) and anhydrous $MgSO_4$ (4.0 eq.) in Et_2O (0.5 M) was stirred at RT for 16 hrs. The reaction mixture was filtered and concentrated *in vacuo*. The crude material was purified by flash column chromatography to give the pure boronic ester **294** as a white crystalline solid (15.4 g, 99%).

R_f = 0.49 (10% EtOAc/PE, *p*-anisaldehyde);

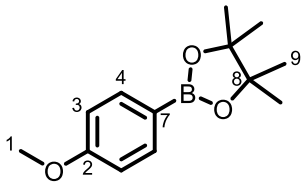
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.20-7.13 (4H, m, H2/H3), 7.07 (1H, m, H1), 2.67 (2H, t, *J* = 8.2 Hz, H5), 1.14 (12H, s, H8), 1.07 (2H, t, *J* = 8.2 Hz, H6) ppm;

^{13}C NMR (101 MHz, $CDCl_3$): δ = 144.4 (C4), 128.2 (C2), 128.0 (C3), 125.5 (C1), 83.1 (C7), 29.9 (C5), 24.8 (C8) ppm. *C6 (next to B) not observed due to quadrupolar relaxation*;

^{11}B NMR ($CDCl_3$, 128 MHz): δ = 34.0 ppm.

Data in accordance with that reported in the literature.[268]

4-Methoxyphenyl-4,4,5,5-tetramethyl-[1,3,2]-dioxaborolane (373)



A mixture of 4-methoxyphenylboronic acid (3.80 g, 25 mmol, 1.00 eq.) and pinacol (2.96 g, 25 mmol, 1.00 eq.) in Et_2O (50 mL) was stirred at ambient temperature for 16 hrs. Then, flame-dried $MgSO_4$ (3.01 g, 25 mmol, 1.00 eq.) was added and the reaction mixture was stirred for an additional 1 hour. The resultant solution was then filtered under argon through a plug of anhydrous $MgSO_4$ (~1 cm), the solids were washed with diethyl ether (2 × 20 mL) and combined filtrates were concentrated *in vacuo* at ambient temperature. The residue was subjected to Kugelrohr distillation (80→120 °C/0.1 mbar) to afford the desired product **373** (5.26 g, 98%) as a colourless oil.

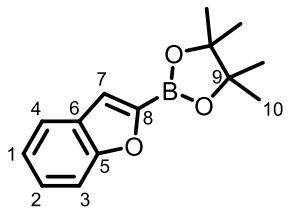
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.79 (2H, *app.* d, J = 8.9 Hz, H3), 6.89 (2H, *app.* d, J = 8.9 Hz, H4), 3.81 (3H, s, H1), 1.36 (12H, s, H9) ppm;

^{13}C NMR (101 MHz, $CDCl_3$): δ = 162.2 (C2), 136.6 (C4), 113.3 (C3), 83.6 (C8), 55.1 (C1), 24.9 (C9) ppm. *C7 (next to boron) not observed due to quadrupolar relaxation*;

^{11}B NMR (128 MHz, $CDCl_3$): δ = 30.0 ppm.

Data in accordance with that reported in the literature.[164]

2-(Benzofuran-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (375)



The corresponding aryl boronic acid (1.00 g, 6.17 mmol, 1.00 eq.) and pinacol (801 mg, 6.79 mmol, 1.10 eq.) were dissolved in anhydrous Et_2O (3.0 mL, 0.50 M) under an Ar atmosphere. The mixture was stirred for 16 hrs at RT and concentrated under reduced pressure. The crude product was purified by column chromatography (3% EtOAc/pentane) to yield the desired product **375** (1.20 g, 80%).

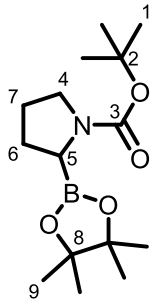
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.63 (1H, m, H3), 7.57 (1H, m, H4), 7.40 (1H, d, J = 1.0 Hz, H2), 7.34 (1H, ddd, J = 8.4, 7.2, 1.0 Hz, H1), 7.23 (1H, m, H7), 1.39 (12H, s, H10) ppm;

^{13}C NMR (101 MHz, $CDCl_3$): δ = 157.6 (C5), 127.6 (C6), 126.1 (C2), 122.9 (C1), 122.0 (C4), 119.7 (C3), 112.1 (C7), 84.8 (C9), 24.9 (C10) ppm. *C8 (next to boron) not observed due to quadrupolar relaxation*;

^{11}B NMR (128 MHz, $CDCl_3$): δ = 28.0 ppm.

Data in accordance with that reported in the literature.[273]

***tert*-Butyl 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrrolidine-1-carboxylate (377)**



N-Boc-pyrrolidine (1.00 g, 5.84 mmol, 1.00 eq.) and TMEDA (1.10 mL, 7.00 mmol, 1.20 eq.) were dissolved in Et_2O (50 mL). The solution was cooled to –78 °C and *s*BuLi (1.3 M in hexanes, 6.00 mL, 7.00 mmol, 1.20 eq.) was added dropwise. The solution was stirred for 3 hrs at –78 °C, then *i*PrOB(pin) (1.63 g, 8.80 mmol, 1.30 eq.) was added dropwise. The solution was stirred for 1 hr at –78 °C, then allowed to warm up to RT slowly. Aqueous 1 M HCl (50 mL) was added and the layers were separated. The organic layers were washed with brine (3 x 20 mL) and the combined aqueous layers were extracted with Et_2O (3 x 50 mL). The organic layers were combined, dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by fast column chromatography on silica gel, eluting with 15% EtOAc/PE, to give **377** as a white solid (987 mg, 57%).

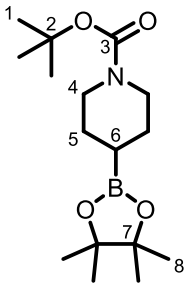
^{1}H NMR (500 MHz, DMSO-d_6, 90°C): δ = 3.23 (1H, m, H5), 3.14 (1H, m, H4), 2.80 (1H, m, H4), 1.87 (2H, m, H7), 1.74 (2H, m, H6), 1.37 (9H, s, H1), 1.19 (12H, m, H9) ppm;

^{13}C NMR (125 MHz, DMSO-d_6, 90°C): = δ 83.5 (C8), 78.5 (C2), 46.4 (C4), 28.7 (C1), 25.4 (C7), 25.2 (C9), 24.8 (C6) ppm. *C3 (C=O) peak not observed, C5 (next to B) not observed due to quadrupolar relaxation;*

^{11}B NMR (96 MHz, $CDCl_3$): δ = 33.1 ppm;

Data in accordance with that reported in the literature.[269]

***tert*-Butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)piperidine-1-carboxylate (378)**



In air, CuI (72 mg, 10 mmol%, 0.10 eq.), PPh_3 (129 mg, 13 mmol%, 0.13 eq.), LiOMe (288 mg, 7.57 mmol, 2.00 eq.) and bis(pinacolato)diboron (1.44 g, 5.68 mmol, 1.50 eq.) were added to a Schlenk tube equipped with a magnetic stir bar. The vessel was evacuated and filled with argon three times. DMF (7.5 mL) and *tert*-butyl 4-bromopiperidine-1-carboxylate (1.00 g, 3.78 mmol, 1.00 eq.) were added in turn under Ar. The reaction mixture was heated at 37 °C for 24 hrs. The reaction mixture was cooled and diluted with EtOAc (10 mL) and the resultant slurry was filtered through a silica pad (~2 cm) and washed with EtOAc (40 mL). The crude solution was concentrated *in vacuo* and purified by silica column chromatography (5-10% EtOAc/pentane), to afford the desired compound **378** (966 mg, 82%) as a clear oil.

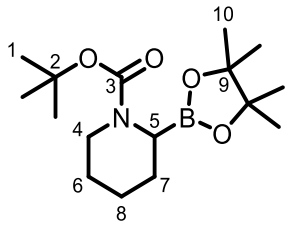
$\mathbf{R_f}$ = 0.50 (10% EtOAc/pentane, anisaldehyde);

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.77 (2H, br. d, J = 12.8 Hz, H4), 2.91 (2H, ddd, J = 12.8, 10.1, 3.2 Hz, H4), 1.62 (2H, dq, J = 13.2, 10.4, 3.8, 3.2 Hz, H5), 1.46 (2H, qd, J = 13.2, 10.4, 10.1, 3.8 Hz, H5), 1.43 (9H, s, H1), 1.22 (12H, s, H8), 1.09 (1H, tt, J = 10.4, 3.8 Hz, H6) ppm. *Many of the small vicinal couplings on the 6-membered ring were not resolved and gave broad lines due to rotamers about the amide ;*

^{13}C NMR (101 MHz, $CDCl_3$): δ = 155.0 (C3), 83.3 (C2), 79.1 (C7), 45.2 (C4), 28.6 (C1), 27.1 (C5), 24.9 (C8), 20.1 (br. s, C6) ppm;

Data in accordance with that reported in the literature.[268]

tert-Butyl 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)piperidine-1-carboxylate (379)



tert-Butyl piperidine-1-carboxylate (2.00 g, 10.8 mmol, 1.00 eq.) and TMEDA (1.95 mL, 13.0 mmol, 1.20 eq.) were dissolved in Et_2O (100 mL). The solution was cooled to –78 °C and *s*BuLi (1.3 M in hexanes, 10.0 mL, 13.0 mmol, 1.20 eq.) was added dropwise. The solution was stirred for 3 hours at –78 °C, then *i*PrOB(pin) (2.61 g, 2.86 mL, 14.0 mmol, 1.30 eq.) was added dropwise. The solution was stirred for 1 hr at –78 °C, then allowed to warm up to RT slowly. Aqueous HCl (1 M, 150 mL) was added and the layers were separated. The organic layer was washed with brine (3 x 50 mL) and the combined aqueous layers were extracted with Et_2O (3 x 100 mL). The organic layers were combined, dried over $MgSO_4$ and concentrated under vacuum. The crude product was purified by fast column chromatography (15% EtOAc/PE), to give the desired compound **379** as an oil (1.49 g, 44%).

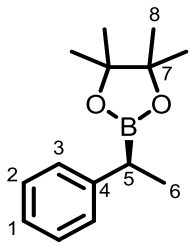
^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.72 (1H, br. d, J = 12.7 Hz, H4), 2.74 (1H, td, J = 12.7, 2.9 Hz, H4), 2.30 (1H, dd, J = 12.6, 3.2 Hz, H5), 1.81 (1H, m, H7), 1.65-1.54 (2H, m, H6/H8), 1.49 (9H, s, H1), 1.44 (1H, m, H6), 1.40-1.29 (2H, m, H7/H8), 1.19 (12H, s, H10) ppm. *Many of the small vicinal couplings on the 6-membered ring were not resolved and gave broad lines due to rotamers about the amide;*

^{13}C NMR (100 MHz, $CHCl_3$): δ = 139.8 (C3), 85.6 (C9), 79.9 (C2), 42.4 (C4), 28.4 (C1), 26.5 (C8), 25.1 (C10), 24.9 (C6), 24.4 (C7) ppm. *C5-not observed due to quadrupolar relaxation*;

^{11}B NMR (128 MHz, $CDCl_3$): δ = 16.0 ppm.

Data in accordance with that reported in the literature.[269]

(*S*)-4,4,5,5-Tetramethyl-2-(1-phenylethyl)-1,3,2-dioxaborolane (380)



Racemic: To a solution of $[RhCl(cod)]_2$ (50 mg, 0.10 mmol, 0.5 mol%), dppb (104 mg, 0.25 mmol, 1.25 mol%) and DMAP (30 mg, 0.25 mmol, 1.25 mol%) in 1,2-dichloroethane (21 mL) was added freshly distilled styrene (3.8 mL, 40.6 mmol, 1.00 eq.) and freshly distilled pinacolborane (7.1 mL, 48.7 mmol, 1.20 eq.) at RT.[270] The resulting solution was stirred at RT for 1.5 hrs, then filtered through a plug of silica gel with Et_2O (50 mL) and concentrated *in vacuo*. The crude residue was purified by column chromatography (4% Et_2O/hexane) to give racemic boronic ester **380** as a colourless oil (7.56 g, 80%).

(*S*)-enantiomer: A mixture of CuCl (6 mg, 0.06 mmol, 3 mol%), NaO^{t}Bu (12 mg, 0.12 mmol, 6 mol%) and (*R*)-DTBM-SEGPHOS ® (71 mg, 0.12 mmol, 3 mol%) in anhydrous toluene (0.8 mL) was stirred for 10 mins in a Schlenk tube under N_2. Pinacolborane (0.36 mL, 2.40 mmol, 1.20 eq.) was added to the reaction mixture and stirred for 10 mins at RT. Styrene (0.23 mL, 2.0 mmol, 1.00 eq.) was added, and the Schlenk flask was washed with further toluene (1.2 mL), sealed and stirred at RT, with progress monitored by TLC. The reaction mixture was filtered through a pad of Celite ® (~2 cm thick) and concentrated under reduced pressure. The product was purified by flash column chromatography (4% Et_2O/hexane) to give the desired product **380** as a colourless oil (425 mg, 92%, >95:5 *e.r.*).

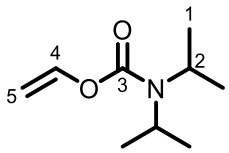
$\mathbf{R_f}$ = 0.57 (10% Et_2O/PE, *p*-anisaldehyde);

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.28 – 7.20 (4H, m, H2/H3), 7.13 (1H, m, H1), 2.43 (1H, q, J = 7.5 Hz, H5), 1.33 (3H, d, J = 7.5 Hz, H6), 1.21 (6H, s, H8), 1.20 (6H, s, H8) ppm;

^{13}C NMR (101 MHz, $CDCl_3$): δ = 145.1 (C4), 128.4 (C2), 127.9 (C3), 125.2 (C1), 83.4 (C7), 24.8 (C8), 24.7 (C8), 17.2 (C6) ppm. *C5 (next to boron) not observed due to quadrupolar relaxation.*

Data in accordance with that reported in the literature.[270–272]

Vinyl diisopropylcarbamate (381)



Following a modified procedure by Clayden *et al*.,[274,275] *n*BuLi (6.00 mL, 2.5 M in hexanes, 15 mmol) was added to THF (11 mL, 1.3 M) at RT. After 16 hrs, *N,N*-diisopropyl carbamoyl chloride (1.60 g, 10 mmol) was dissolved in DMPU (11 mL, 0.91 M) and added dropwise to a cooled solution (0 °C) containing the lithium ethenolate. The reaction was warmed to RT over 4 hrs. The reaction was quenched with saturated NH_4Cl and extracted with Et_2O (3 x 25 mL). The organic layer was washed with water and dried over Na_2SO_4. The solvent was removed *in vacuo* and purified by flash silica chromatography (33% EtOAc/hexane) to afford the desired product **381** as a colourless oil (975 mg, 83%).

$\mathbf{R_f}$ = 0.84 (50% EtOAc/hexane);

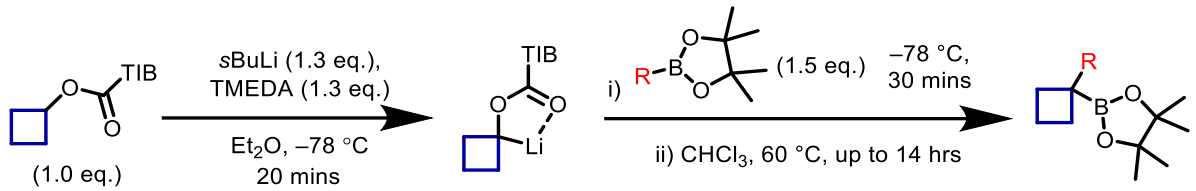
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.26 (1H, dd, J = 14.7, 5.6 Hz, H4), 4.77 (1H, dd, J = 14.0, 1.4 Hz, $H5_{trans\text{-}H4}$), 4.43 (1H, dd, J = 6.3, 1.4 Hz, $H5_{cis\text{-}H4}$), 4.07 (1H, br. s, H2), 3.86 (1H, br. s, H2), 1.25 (12H, d, J = 6.7 Hz, H1) ppm;

^{13}C NMR (101 MHz, $CDCl_3$): δ = 152.7 (C3), 142.3 (C4), 94.5 (C5), 46.7 (C2), 45.8 (C2), 20.4 (C1), 19.4 (C1) ppm.

The spectral data corresponds to the literature values.[274,275]

3.3.3. General Procedure for the Lithiation-Borylation of Cyclobutyl Benzoates (GP4/ GP5)

GP4



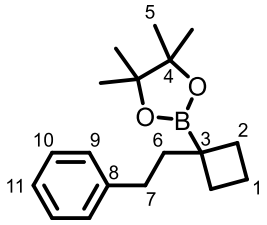
Under a N_2 atmosphere, TMEDA (1.30 eq.) was added to benzoate (1.00 eq.) dissolved in anhydrous Et_2O (0.2 M) in a flame dried Schlenk tube. After cooling to −78 °C, *s*BuLi (1.3 mmol mL^{-1} solution, 0.25 mL, 0.32 mmol, 1.30 eq.) was added dropwise and the brown/orange reaction mixture was left to stir for 20 mins. A solution of boronic ester (1.50 eq.) in dry Et_2O (1.0 M), made up in a flame dried flask, was added dropwise to the reaction mixture. After 30 mins the reaction was warmed to RT and the solvent exchanged to $CHCl_3$ or toluene* (2.5 mL) by removal of Et_2O under vacuum. The resultant mixture was heated to 60 °C for 16 hrs or until full consumption of the boronate complex was observed by ^{11}B NMR. The crude material was filtered through a silica plug and washed with Et_2O, concentrated *in vacuo*, and purified by flash column chromatography to afford the desired product. *All solvent exchange to toluene are explicitly stated, otherwise assume solvent exchange to $CHCl_3$.

GP5

As per **GP4** with oxidation of the boronic ester to the corresponding alcohol prior to column chromatography for ease of purification:

The reaction mixture was cooled down to 0 °C and THF (0.50 mL) was added. A 2:1 NaOH (2 M):H2O2 (33% $_{aq.}$) mixture (0 °C, 1 mL) was added dropwise. The reaction was warmed to RT and stirred until deemed complete by TLC analysis (typically 4–16 hrs). The reaction was dissolved in diethyl ether (10 mL) and washed with brine (5 mL). The aqueous phase was extracted twice with diethyl ether (5 mL). The combined organic phases were dried over $MgSO_4$ and the solvent removed *in vacuo* to afford the crude alcohol, which was then purified by column chromatography.

4,4,5,5-Tetramethyl-2-(1-phenethylcyclobutyl)-1,3,2-dioxaborolane (297)



297 was synthesised following **GP4** using cyclobutyl 2,4,6- triisopropylbenzoate (1.00 eq.) and 4,4,5,5-tetramethyl-2-phenethyl-1,3,2-dioxaborolane **294** (70 mg, 0.30 mmol, 1.50 eq.) as the starting boronic ester. The crude mixture was purified using flash column chromatography (15-30% CH_2Cl_2/pentane) to afford the title compound as a colourless oil (34 mg, 60%).

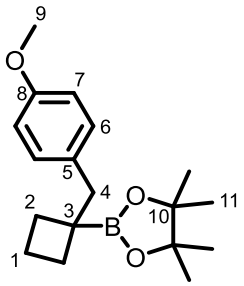
$\mathbf{R_f}$ = 0.30 (30% CH_2Cl_2/pentane, *p*-anisaldehyde);

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.31 – 7.13 (5H, m, H9/H10/H11), 2.49 (2H, m, H7), 2.16 (2H, m, H2), 1.95 (2H, m, H1), 1.85 (2H, m, H6), 1.78 – 1.69 (2H, m, H2), 1.29 (12H, s, H5) ppm;

^{13}C NMR (101 MHz, $CDCl_3$): δ = 143.4 (C8), 128.5 (C10), 128.4 (C9), 125.6 (C11), 83.2 (C4), 42.2 (C6), 33.4 (C7), 30.6 (C2), 24.9 (C5), 18.4 (C1) ppm.

Data in accordance with that reported in the literature.[233]

2-(1-(4-Methoxybenzyl)cyclobutyl)-4,4,5,5-tetramethyl-1,3,2- dioxaborolane (299)



299 was synthesised following **GP4** using cyclobutyl 2,4,6- triisopropylbenzoate (1.00 eq.) and 2-(4-methoxybenzyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane **372** (74 mg, 0.30 mmol, 1.50 eq.) as the starting boronic ester. The crude mixture was purified using flash column chromatography (5-10% Et_2O/PE) to afford the desired compound as a colourless oil (41 mg, 67%).

$\boldsymbol{R_f}$ = 0.30 (10% Et_2O/PE, *p*-anisaldehyde);

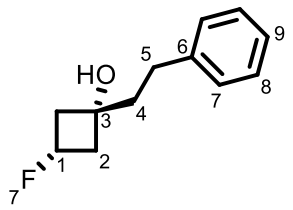
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.13 – 7.07 (2H, m, H7), 6.79 – 6.75 (2H, m, H6), 3.77 (3H, s, H9), 2.80 (2H, s, H4), 2.13 (2H, m, H2), 1.96-1.82 (4H, m, H1/H2), 1.18 (12H, s, H11) ppm;

^{13}C NMR (101 MHz, $CDCl_3$): δ = 157.8 (C8), 133.5 (C5), 130.1 (C6), 113.4 (C7), 83.2 (C10), 55.4 (C9), 44.2 (C4), 30.4 (C2), 24.8 (C11), 18.3 (C1) ppm. *C3 (next to boron) not seen due to quadrupolar relaxation;*

IR (ν_{max}/cm^{-1}, neat): 2975, 2855, 1611, 1511, 1380, 1302, 1244, 1140, 1037, 836, 686, 631;

HRMS (ESI) calc. for $[C_{18}H_{27}BO_3 + Na]^+$ 325.1949. Found 325.1967.

(1*s*,3*r*)-3-Fluoro-1-phenethylcyclobutan-1-ol (303)



303 was synthesised following **GP4** using (1s,3s)-3-fluorocyclobutyl 2,4,6-triisopropylbenzoate **302** (1.00 eq.) and 4,4,5,5-tetramethyl-2-phenethyl-1,3,2-dioxaborolane **294** (54 mg, 0.23 mmol, 1.50 eq.) as the starting boronic ester, followed by oxidation according to **GP5**. The oxidised crude mixture was purified using flash column chromatography (0-10% EtOAc/pentane) to afford the desired compound as a colourless oil (19 mg, 62%).

$\mathbf{R}_f$ = 0.31 (3% EtOAc/pentane, *p*-anisaldehyde);

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.29 (2H, m, H8), 7.23-7.17 (3H, m, H7/H9), 4.75 (1H, dp, J = 55.8$_{JH\text{-}F}$, 6.6 Hz, H1), 2.71 (2H, m, H5), 2.65 (2H, dddd, J = 13.5, 9.0$_{JH\text{-}F}$, 6.6, 3.8 Hz, H2) 2.32 (2H, dddd, J = 25.7$_{JH\text{-}F}$, 13.5, 6.6, 3.8 Hz, H2), 1.81 (2H, m, H4) ppm;

^{13}C NMR (101 MHz, $CDCl_3$): δ = 141.7 (C6), 128.6 (C8), 128.3 (C7), 126.0 (C9), 80.8 (d, $J_{C\text{-}F}$ = 208.2 Hz, C1), 67.3 (d, $J_{C\text{-}F}$ = 17.9 Hz, C3), 44.8 (d, J = 19.5 Hz, C2), 42.8 (d, J = 3.4 Hz, C4), 30.2 (C5) ppm;

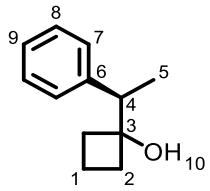
^{19}F NMR (376 MHz, $CDCl_3$): δ = -171.8 (dtt, $J_{H\text{-}F}$ = 55.8, 25.7, 9.0 Hz) ppm;

HRMS (ESI) calc. for $[C_{12}H_{15}OF + Na]^+$ 217.1025. Found 217.1033

IR (ν_{max}/ cm^{-1}, neat): 3403, 2987, 2938, 1454, 1274, 1261, 1143, 1028, 764, 750;

$[\alpha]_D^{24}$ +17.4 (c 0.86, $CHCl_3$).

(*R*)-1-(1-Phenylethyl)cyclobutan-1-ol (313)



313 was synthesised following **GP4** using (*S*)-4,4,5,5-tetramethyl-2-(1-phenylethyl)-1,3,2-dioxaborolane **313** (70 mg, 0.30 mmol, 1.50 eq.) as the starting boronic ester. S*olvent exchange to toluene was performed*, followed by oxidation using **GP5**. The oxidised crude mixture was purified using flash column chromatography (5-10% Et_2O/pentane) to afford the title compound as a colourless oil (19 mg, 56%, 96:4 *e.r.*).

$\mathbf{R_f}$ = 0.20 (10% Et_2O/pentane);

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35 – 7.27 (4H, m, H7/H8), 7.25 – 7.21 (1H, m, H9), 2.93 (1H, q, J = 7.2 Hz, H4), 2.25 (1H, m, H2), 2.14 (1H, m, H2), 2.02 (1H, m, H2), 1.86 (1H, dtt, J = 10.5, 9.4, 4.9 Hz, H1), 1.80 – 1.71 (1H, m, H2), 1.67 – 1.51 (1H, m, H1), 1.56 (1H, br.s, H10), 1.32 (3H, d, J = 7.2 Hz, H5) ppm;

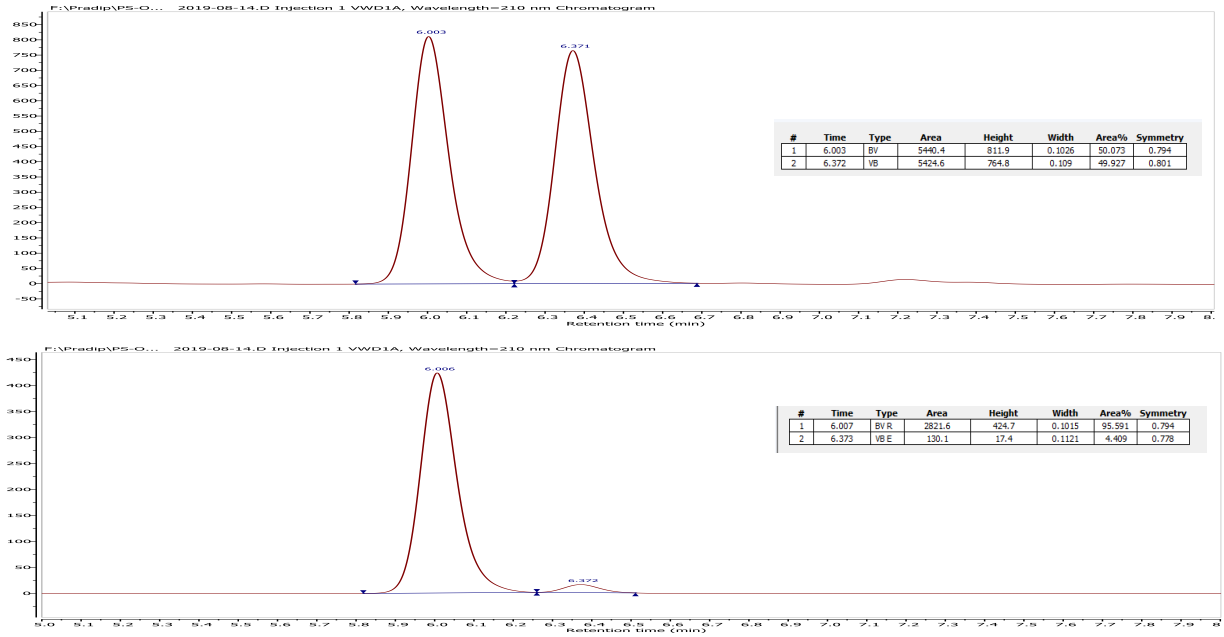
^{13}C NMR (101 MHz, $CDCl_3$): δ = 142.7 (C6), 128.7 (C8), 128.4 (C7), 126.7 (C9), 78.1 (C3), 47.2 (C4), 34.6 (C3), 34.3 (C2), 14.4 (C5), 12.6 (C1) ppm;

IR (ν_{max}/ cm^{-1}, neat): 2968 (br.), 1455, 1260, 1922, 799, 702;

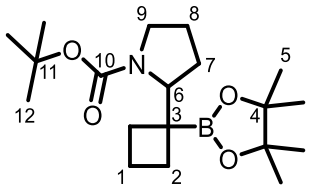
HRMS (ESI) calc. for $[C_{12}H_{16}O_2 + Na]^+$ 199.1099. Found, 199.1090;

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{24}}$ +12.2 (*c* 0.49, $CHCl_3$);

Chiral HPLC (IB with guard, 2% *i*PrOH/hexane, 0.7 mL/min, RT) T_R = 6.01 mins (major), 6.27 mins (minor).



***tert*-Butyl 2-(1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclobutyl)pyrrolidine-1-carboxylate (308)**



308 was synthesised following **GP4** using cyclobutyl 2,4,6- triisopropylbenzoate (1.00 eq.) and *tert*-butyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indole-1-carboxylate **377** (111 mg, 0.30 mmol, 1.50 eq.) as the starting boronic ester. The crude mixture was purified using flash column chromatography (5-15% Et_2O/PE) to afford the desired compound as a colourless oil (35 mg, 42%).

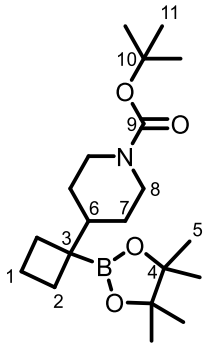
R_f = 0.13 (10% Et_2O/pentane);

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.89 (1H, br. s, H6), 3.48 (1H, br. m, H9), 3.17 (1H, br. s, H9), 2.15 – 1.73 (7H, m, H2/H7/H8), 1.70 – 1.54 (3H, m, H1/H2), 1.45 (9H, s, H12), 1.24 (12H, s, H5) ppm. *Many of the small vicinal couplings on the 6-membered ring were not resolved and gave broad lines;*

^{13}C NMR (101 MHz, $CDCl_3$): δ = 155.8 & 155.5 (C10), 83.0 & 82.5 (C4), 79.2 & 79.0 (C11), 63.2 & 62.3 (C6), 47.9 (C9), 30.7 & 30.2 (C2), 28.5 (C12), 26.2 (C8), 24.8 (C5), 24.3 & 23.9 (C7), 18.3 & 18.1 (C1) ppm. *Compound exists as 1:1 mixture of rotamers at RT;*
IR (ν_{max}/cm^{-1}, neat): 3675, 2973, 1687, 1381, 1260, 1066, 868, 764;

HRMS (ESI) calc. for $[C_{16}H_{34}BNO_4 + Na]^+$ 352.2654. Found, 352.2653;

***tert*-Butyl 4-(1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclobutyl)piperidine-1-carboxylate (311)**



311 was synthesised following **GP4** using cyclobutyl 2,4,6- triisopropylbenzoate (1.00 eq.) and *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)piperidine-1-carboxylate **378** (111 mg, 0.36 mmol, 1.50 eq.) as the starting boronic ester. The crude mixture was purified using flash column chromatography (5-15% Et_2O/pentane) to afford the desired compound (42 mg, 48%) as a clear oil.

$\mathbf{R_f}$ = 0.64 (15% Et_2O/pentane, anisaldehyde);

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.17 (2H, br. s, H8), 2.58 (2H, br. t, J = 11.1 Hz, H8), 2.08 (2H, br. t, J = 7.7 Hz, H2), 1.87-1.69 (4H, m, H1/H2), 1.56 (2H, br. d, J = 13.7 Hz, H7), 1.44 (9H, s, H11), 1.43 (1H, m, H6), 1.24 (12H, s, H5), 1.15 (2H, qd, J = 12.7, 4.4 Hz, H7) ppm. *Many of the small vicinal couplings on the 6-membered ring were not resolved and gave broad lines;*

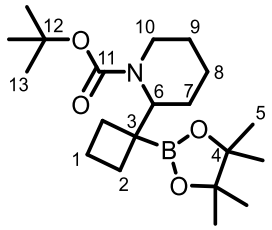
^{13}C NMR (101 MHz, $CDCl_3$): δ = 155.2 (C9), 83.2 (C4), 79.2 (C10), 46.4 (C6), 44.9 (br. s, C8), 29.1 (C2), 28.6 (C11), 28.2 (C7), 24.9 (C5), 18.1 (C1) ppm. *C4 (next to boron) not observed due to quadrupolar relaxation, C8 broadened due to nitrogen quadrupolar relaxation;*

^{11}B NMR (96 MHz): δ = 32.9 ppm;

HRMS (ESI) calc. for $[C_{20}H_{36}BNO_4 + H]^+$ 366.2810. Found 366.2804;

IR (ν_{max}/cm^{-1}, neat): 3675, 2975, 2930, 1693 (C=O), 1466, 1364, 1275, 1142, 966, 868, 764;

***tert*-Butyl 2-(1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclobutyl)piperidine-1-carboxylate (312)**



312 was synthesised following **GP4** using cyclobutyl 2,4,6- triisopropylbenzoate (1.00 eq.) and *tert*-butyl 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)piperidine-1-carboxylate **379** (111 mg, 0.36 mmol, 1.50 eq.) as the starting boronic ester. *Solvent exchange to toluene was performed*. The crude mixture was purified using flash column chromatography (5-15% Et_2O/pentane) to afford the desired compound (40 mg, 46%) as a clear oil.

R_f = 0.38 (10% Et_2O/PE, *p*-anisaldehyde);

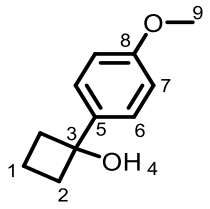
^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.03 (1H, br. s, H6), 3.79 (1H, br. s, H10), 3.09 (1H, br. s, H10), 2.11 – 1.93 (3H, m, H2/H7), 1.90 – 1.70 (4H, m, H1/H2), 1.69 – 1.52 (3H, m, H8/H9), 1.43 (9H, s, H13), 1.47 – 1.39 (2H, m, H7/H8), 1.24 (12H, s, H5) ppm. *Many of the small vicinal couplings on the 6-membered ring were not resolved and gave broad lines;*

^{13}C NMR (101 MHz, $CDCl_3$): δ = 155.9 (C11), 82.9 (C4), 79.3 (C12), 42.0 (br. s, C10), 29.9 (C9), 29.2 (C2), 28.6 (C13), 25.8 (C7), 24.9 (C5), 20.9 (C8), 18.4 (C1) ppm. *C3 (next to boron) not observed due to quadrupolar relaxation. C6 (next to nitrogen) broadened* and *not observed due to nitrogen quadrupolar relaxation*;

HRMS (ESI) calc. for $[C_{20}H_{36}BNO_4 + H]^+$ 366.2809. found 366.2812;

IR (ν_{max}/ cm^{-1}, neat): 2979, 2924, 2830, 1683 ($C{=}O_{amide}$), 1368, 1232, 1143, 1025, 867.

1-(4-Methoxyphenyl)cyclobutan-1-ol (321)



321 was synthesised following **GP4** using 2-(4-methoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane **373** (88 mg, 0.30 mmol, 1.50 eq.) as the starting boronic ester, followed by oxidation using **GP5**. The oxidised crude mixture was purified using flash column chromatography (10-20% Et_2O/pentane) to afford the title compound as a colourless oil (26 mg, 66%).

R_f = 0.30 (20% Et_2O/pentane);

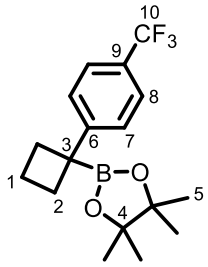
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.42 (2H, d, J = 8.8 Hz, H6), 6.90 (2H, d, J = 8.8 Hz, H7), 3.81 (3H, s, H9), 2.53 (2H, m, H2), 2.35 (2H, m, H2), 1.97 (1H, dtt, J = 11.1, 9.6, 5.0 Hz, H1), 1.64 (1H, m, H1) ppm;

^{13}C NMR (101 MHz, $CDCl_3$): δ = 158.8 (C8), 138.6 (C5), 126.5 (C6), 113.8 (C7), 76.8 (C3), 55.4 (C9), 37.0 (C2), 13.0 (C1) ppm;

IR (ν_{max}/cm^{-1}, neat): 3397 (br. OH), 2938, 2836, 1611, 1512, 1464, 1299, 1132, 1108, 1068, 957, 731;

Data in accordance with that reported in the literature.[276]

4,4,5,5-Tetramethyl-2-(1-(4-(trifluoromethyl)phenyl)cyclobutyl)-1,3,2-dioxaborolane (322)



322 was synthesised following **GP4** using cyclobutyl 2,4,6- triisopropylbenzoate (1.00 eq.) and 4,4,5,5-tetramethyl-2-(4-(trifluoromethyl)phenyl)-1,3,2-dioxaborolane **374** (101 mg, 0.37 mmol, 1.50 eq.) as the starting boronic ester. The crude mixture was purified using flash column chromatography (0-10% Et_2O/pentane) to afford the desired compound (40 mg, 46%) as a white solid.

R_f = 0.54 (5% Et_2O/pentane);

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.50 (2H, d, J = 7.9 Hz, H8), 7.20 (2H, d, J = 7.9 Hz, H7), 2.57 (2H, m, H2), 2.27 (2H, m, H2), 2.08 (1H, m, H1), 1.85 (1H, m, H1), 1.19 (12H, s, H5) ppm;

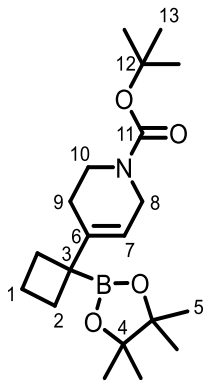
^{13}C NMR (101 MHz, $CDCl_3$): δ = 153.5 (C9), 144.9 (C6), 125.9 (C7), 125.0 (q, $^3J_{C\text{-}F}$ = 3.8 Hz, C8), 123.4 (C10), 83.8 (C4), 32.2 (C2), 24.6 (C5), 18.9 (C1) ppm;

IR (ν_{max}/cm^{-1}, neat): 2935, 1611, 1512, 1463, 1299, 1135, 731;

M.P: 99-101°C (EtOAc);

HRMS (ESI) calc. for $[C_{17}H_{22}BF_3O_2 + Na]^+$ 349.1607. Found 349.1601.

***tert*-Butyl 4-(1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclobutyl)-3,6-dihydropyridine-1(2H)-carboxylate (325)**



325 was synthesised following **GP4** using cyclobutyl 2,4,6- triisopropylbenzoate (1.00 eq.) and *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate **376** (117 mg, 0.38 mmol, 1.50 eq.) as the starting boronic ester. The crude mixture was purified using flash column chromatography (5-10% EtOAc/pentane) to afford the desired compound (39 mg, 43%) as a clear oil.

R_f = 0.38 (30% Et_2O/pentane, *p*-anisaldehyde);

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.21 (1H, br. s, H7), 3.88 (2H, br. s, H8), 3.42 (2H, br. s, H10), 2.18 (2H, m, H2), 2.03–1.94 (4H, m, H2/H9), 1.90 (1H, m, H1), 1.71 (1H, m, H1), 1.45 (9H, s, H13), 1.23 (12H, s, H5) ppm. *Many of the small vicinal couplings on the 6-membered ring were not resolved and gave broad lines;*

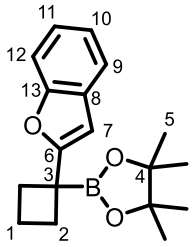
^{13}C NMR (101 MHz, $CDCl_3$): δ = 155.2 (C11), 141.9 (C6), 114.6 & 114.0 (C7), 83.5 (C4), 79.4 (C12), 43.8 & 43.2 (C7), 41.2 & 40.1 (C8), 29.6 (C2), 28.5 (C13), 26.1 (C9), 24.6 (C5), 18.0 (C1) ppm. *C3 (next to boron) not observed due to quadrupolar relaxation. Some peaks are doubled due to the presence of rotamers;*

^{11}B NMR (96 MHz): δ = 34.4 ppm;

HRMS (ESI) calc. for $[C_{20}H_{34}BNO_4 + Na]^+$ 386.2477. Found 386.2476;

IR (ν_{max}/ cm^{-1}, neat): 3675, 2973, 2901, 1693, 1394, 1260, 1066;

2-(1-(Benzofuran-2-yl)cyclobutyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (323)



323 was synthesised following **GP4** using cyclobutyl 2,4,6- triisopropylbenzoate (1.00 eq.) and 2-(benzofuran-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane **375** (92 mg, 0.38 mmol, 1.50 eq.) as the starting boronic ester. The crude mixture was purified using flash column chromatography (5-10% Et_2O/pentane) to afford the desired compound (38 mg, 53%) as a colourless oil.

$\boldsymbol{R_f}$ = 0.50 (10% Et_2O/pentane, *p*-anisaldehyde);

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.47 (1H, m, H9), 7.41 (1H, m, H12), 7.20 – 7.13 (2H, m, H10/H11), 6.44 (1H, d, J = 0.9 Hz, H7), 2.55-2.42 (4H, m, H2), 2.08 (2H, m, H1), 1.30 (12H, s, H5) ppm;

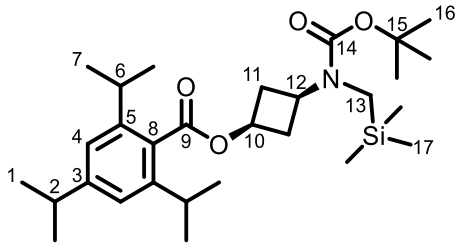
^{13}C NMR (101 MHz, $CDCl_3$): δ = 164.1 (C6), 155.0 (C13), 129.5 (C8), 122.9 (C11), 122.3 (C10), 120.3 (C9), 110.9 (C12), 100.4 (C7), 84.0 (C4), 30.1 (C2), 24.8 (C5), 18.9 (C1) ppm. *C3 (next to boron) not observed due to quadrupolar relaxation*;

^{11}B NMR (96 MHz): 33.4 ppm;

HRMS (ESI+): mass ion not observed.

IR (ν_{max}/ cm^{-1}, neat): 3675, 2987, 2901, 1614, 1325, 1262, 1067;

(1s,3s)-3-((*tert*-Butoxycarbonyl)((trimethylsilyl)methyl)amino)cyclobutyl 2,4,6-triisopropylbenzoate (346)



346 was synthesised following **GP4** using 3-((*tert*-butoxycarbonyl)(methyl)amino)cyclobutyl 2,4,6-triisopropylbenzoate **344** (1.00 eq.) and trimethylsilyl chloride (49 μL, 0.39 mmol, 2.00 eq.) as the electrophile. The crude mixture was purified using flash column chromatography (5-10% Et_2O/pentane) to afford the desired compound (39 mg, 43%) as a clear oil.

$\mathbf{R_f}$ = 0.60 (10% Et_2O/pentane, *p*-anisaldehyde);

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.96 (2H, s, H4), 5.20 (1H, app. t, *J* = 7.0 Hz, H10), 4.76 (1H, pent., *J* = 8.5 Hz, H12), 2.84 (1H, hept., *J* = 6.9 Hz, H2), 2.83 (2H, hept., *J* = 6.9 Hz, H6), 2.66 (2H, s, H13), 2.65 (2H, m, H11), 2.38 (2H, dddd, *J* = 12.7, 6.3, 3.4, 1.4 Hz, H11), 1.40 (9H, s, H16), 1.21 (12H, d, *J* = 6.9 Hz, H7), 1.19 (6H, d, *J* = 6.9 Hz, H1), 0.00 (9H, s, H17) ppm;

^{13}C NMR (101 MHz, $CDCl_3$): δ = 170.8 (C9), 155.2 (C14), 150.4 (C3), 145.0 (C5), 130.4 (C8), 120.0 (C4), 79.6 (C15), 67.9 (C10), 50.6 (C12), 36.0 (C11), 34.6 (C2), 31.6 (C6), 28.7 (C13), 28.6 (C16), 24.3 (C7), 24.1 (C7), -1.40 (d, $J_{C\text{-}Si}$ = 1.6 Hz, C17) ppm;

HRMS (ESI) calc. for $[C_{29}H_{49}NO_4Si + Na]^+$ 526.3309. Found, 526.3303;

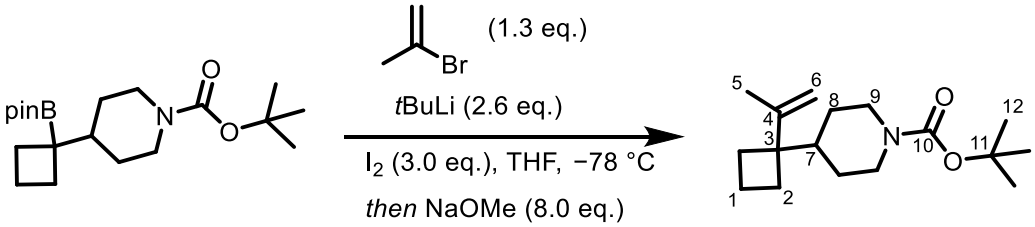
IR (ν_{max}/cm^{-1}, neat): 2962, 1723 (C=O_{ester}), 1699 (C=O_{amide}), 1460, 1364, 1251, 1148, 1078;

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{22}}$ 0 (*c* 1.0, $CHCl_3$), starting material showed no optical rotation.

3.3.4. Boronic Ester Functional Group Interconversions

tert-Butyl 4-(1-(prop-1-en-2-yl)cyclobutyl)piperidine-1-carboxylate (329)

Zweifel olefination



Freshly distilled 2-bromopropene (21 mg, 0.18 mmol, 1.3 eq.) was dissolved in THF (2 mL). The solution was cooled to -78 °C and a freshly titrated *tert*-butyllithium solution (0.29 mL, 0.54 mmol, 1.9 M in pentane, 2.6 eq.) was added dropwise. After stirring at -78 °C for 1 hr, a solution of boronic ester **311** (50 mg, 0.14 mmol in 1.4 mL of THF, 1.0 eq.) was added dropwise at the same temperature. The reaction was stirred 5 mins at -78 °C, then warmed up to RT and stirred for 1 hr. The reaction was cooled down to -78 °C and a solution of iodine (106 mg in 0.7 mL THF, 3.0 eq.) was added dropwise. The solution was stirred 15 mins at -78 °C, followed by further 15 mins at RT. The solution was cooled down again to -78 °C and NaOMe (59 mg, 1.12 mmol, 8.0 eq.) was added under N_2 flow, followed by anhydrous methanol (1.0 mL). The reaction was stirred 10 minutes at -78 °C followed by 1 hr at RT. The reaction was diluted with pentane (15 mL), washed with a sat. $Na_2S_2O_3$ solution (5 mL) and brine (5 mL). The organic phase was dried over magnesium sulfate and the solvent evaporated. The residue was passed through a Pasteur/silica plug (~6 cm) using pure pentane as eluent. Next, the solvent was evaporated to afford the title compound **329** as a colourless oil (30 mg, 80%).

R_f = 0.42 (5% Et_2O/pentane, *p*-anisaldehyde);

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.87 (1H, app. pent., J = 1.5 Hz, H6), 4.63 (1H, br. s, H6), 4.17 (2H, br. s, H9), 2.60 (2H, br. t, J = 12.2 Hz, H9), 2.03-1.94 (4H, m, H2), 1.71 (2H, pent., J = 7.3 Hz, H1), 1.62 (2H, m, H8), 1.60 (3H, s, H5), 1.48 (1H, tt, J = 12.1, 3.0 Hz, H7), 1.45 (9H, s, H12), 1.16 (2H, dq, J = 12.6, 4.5 Hz, H8) ppm. *Many of the small vicinal couplings on the 6-membered ring were not resolved and gave broad lines;*

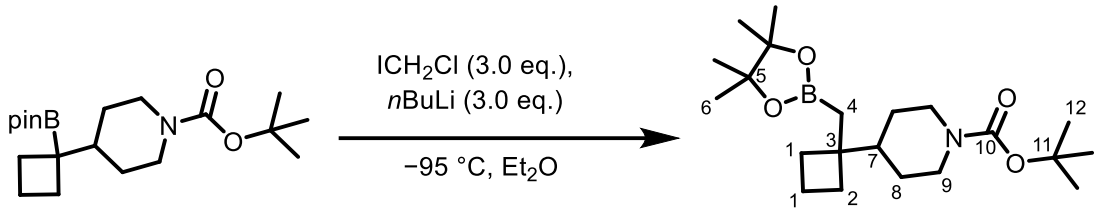
^{13}C NMR (101 MHz, $CDCl_3$): δ = 155.0 (C10), 150.3 (C4), 110.9 (C6), 79.3 (C11), 50.6 (C3), 44.7 (br. s, C9), 41.8 (C7), 28.6 (C12), 28.5 (C2), 27.0 (C8), 19.0 (C5), 15.2 (C1) ppm;

HRMS (ESI) calc. for $[C_{17}H_{29}NO_2 + Na]^+$ 302.2090. Found, 302.2089;

IR (ν_{max}/ cm^{-1}, neat): 3675, 2973, 2901, 1692, 1451, 1415, 1276, 1066, 890, 764.

tert-Butyl 4-(1-((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl)cyclobutyl)piperidine-1-carboxylate (330)

Matteson Homologation



According to a literature procedure,[177] boronic ester **311** (50 mg, 0.14 mmol, 1.0 eq.) and iodochloromethane (30 µL, 0.41 mmol, 3.0 eq.) were dissolved in diethyl ether (1 mL) and cooled to -95 °C (methanol/liquid N_2 cooling bath). *n*BuLi (0.39 mL, 0.63 mmol, 1.6 M solution in *n*hexane, 2.95 eq.) was added dropwise and the solution was stirred 10 minutes at -95 °C, followed by additional 1 hr at RT. The whole mixture was passed through a thin layer of silica and eluted with Et_2O. Solvents were evaporated to afford the crude boronic ester, containing impurities of starting material and overhomologated product. The crude mixture was purified silica column chromatography, eluting with 5-15% EtOAc/pentane, afforded the title compound **330** (33 mg, 63%) as a colourless oil.

$\mathbf{R_f}$ = 0.38 (10% EtOAc/pentane, *p*-anisaldehyde);

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.15 (2H, br. d, J = 13.3 Hz, H9), 2.58 (2H, td, J = 12.8, 2.5 Hz, H9), 1.92-1.78 (5H, m, H1/H2), 1.72 (2H, m, H1), 1.57 (2H, br. d, J = 12.8 Hz, H8), 1.44 (9H, s, H12), 1.40 (1H, tt, J = 12.1, 3.1 Hz, H7), 1.24 (12H, s, H6), 1.17-1.01 (2H, dq, J = 12.5, 4.5 Hz, H8), 0.89 (2H, s, H4) ppm. *Many of the small vicinal couplings on the 6-membered ring were not resolved and gave broad lines;*

^{13}C NMR (101 MHz, $CDCl_3$): δ = 155.0 (C10), 83.0 (C5), 79.2 (C11), 46.5 (C7), 44.7 (C9), 42.6 (C3), 31.2 (C2), 28.6 (C12), 26.4 (C8), 25.1 (C6), 19.7 (br. s, C4), 14.7 (C1) ppm;

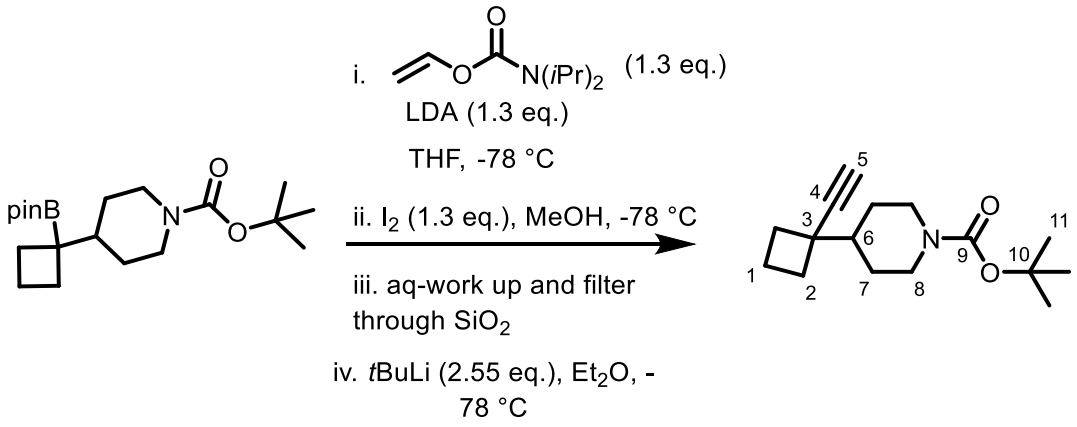
^{11}B NMR (96 MHz): 34.0 ppm;

HRMS (ESI) calc. for $[C_{21}H_{39}BNO_4 + Na]^+$ 380.2971. Found, 380.2978;

IR (ν_{max}/ cm^{-1}, neat): 3675, 2974, 1693, 1410, 1364, 1275, 1144, 1057, 891, 764.

tert-Butyl 4-(1-ethynylcyclobutyl)piperidine-1-carboxylate (332)

Alkynylation



According to a literature procedure,[185] to a stirred solution of vinyl diisopropylcarbamate **381** (30 mg, 0.18 mmol, 1.3 eq.) and boronic ester **311** (50 mg, 0.14 mmol, 1.0 eq.) in THF (0.5 mL) under N_2 at –78 °C was added freshly prepared LDA (0.86 M in THF, 0.21 mL, 0.18 mmol, 1.3 eq.) dropwise at a rate of approximately 10 µL every 10 secs. The resulting solution was stirred for 1 hr at –78 °C before the addition of a solution of I_2 (45 mg, 0.18 mmol, 1.3 eq.) in MeOH (0.5 mL) dropwise over 5 mins. The reaction was stirred for 5 mins at –78 °C before warming to RT and stirred for 1 hr. The reaction was quenched by the addition of 20% $Na_2S_2O_3$ (5 mL) and the aqueous phase extracted with Et_2O (2 × 7.5 mL). The combined organic phases were washed with water (7.5 mL), dried over $MgSO_4$, filtered through a short pad of silica gel (~1 cm) and concentrated *in vacuo*. The crude product was then re-dissolved in Et_2O (1.5 mL) cooled to –78 °C and *t*BuLi (0.21 mL, 1.7 M, 0.36 mmol, 2.55 eq.) was added. The reaction was then transferred to a 0 °C bath and stirred for 30 min before the addition of saturated $NH_4Cl_{(aq.)}$ (5 mL). The aqueous phase was extracted with Et_2O (2 × 7.5 mL) and the combined organic phases dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product purified by flash column chromatography on silica gel (0-10% Et_2O/pentane) to give the desired product **332** as a colourless oil (31 mg, 83%).

$\mathbf{R_f}$ = 0.53 (10% Et_2O/pentane, $KMnO_4$);

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.16 (2H, br. d, J = 13.3 Hz, H8), 2.61 (2H, td, J = 13.4, 2.6 Hz, H8), 2.23 – 2.07 (4H, m, H1/H2/H5), 2.01 (2H, m, H2), 1.81 (1H, m, H1), 1.58 (2H, br. d, J = 11.7 Hz, H7), 1.47 (1H, tt, J = 11.6, 3.3 Hz, H6), 1.44 (9H, s, H11), 1.31 (2H, dq, J = 12.5, 4.5 Hz, H7) ppm. *Some of the small vicinal couplings on the 6-membered ring were not resolved and gave broad lines;*

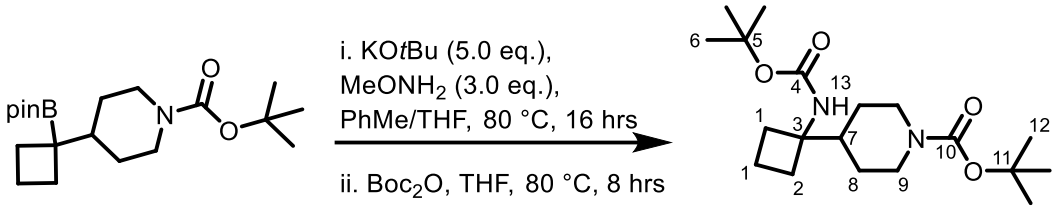
^{13}C NMR (101 MHz, $CDCl_3$): δ 155.0 (C9), 89.2 (C4), 79.4 (C10), 70.5 (C5), 45.3 (C6), 44.2 (br. s, C8), 40.6 (C3), 33.1 (C2), 28.6 (C11), 26.5 (C7), 16.4 (C1) ppm;

HRMS (ESI) calc. for $[C_{16}H_{25}NO_2 + Na]^+$ 286.1777. Found, 286.1786;

IR (ν_{max}/ cm^{-1}, neat): 3675, 3305, 2973, 2106, 1688, 1412, 1276, 1066, 868, 764.

tert-Butyl 4-(1-((tert-butoxycarbonyl)amino)cyclobutyl)piperidine-1-carboxylate (331)

Amination



According to a literature procedure outlined by Morken,[277] boronic ester **311** (50 mg, 0.14 mmol, 1.00 eq.), potassium *tert*-butoxide (77 mg, 0.70 mmol, 5.00 eq.) and *O*-methylhydroxylamine (0.19 mL, 19 mg, 0.42 mmol, 3.00 eq.) in anhydrous toluene (0.61 mL) and anhydrous THF (0.07 mL) were heated to 80 °C for 16 hrs. Following this, the reaction was cooled to ambient temperature and di-*tert*-butyl dicarbonate (0.08 mL, 0.35 mmol, 2.50 eq.) in THF (0.50 mL) was added concurrently with a solution of saturated aqueous $NaHCO_3$ (0.50 mL). The reaction was then reheated to 80 °C and stirred for a further 8 hrs before cooling to ambient temperature, adding water (10 mL) and extracting with EtOAc (3 × 10 mL). The combined organic fractions were then dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a crude residue, which was purified by silica column chromatography (0-20% EtOAc/pentane) to afford the desired amine **331** (29 mg, 60%) as a colourless oil.

R_f = 0.59 (20% EtOAc/pentane, ninhydrin);

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.56 (1H, br. s, H13), 4.12 (2H, br. d, J = 12.8 Hz, H9), 2.64 (2H, td, *J* = 13.0, 2.5 Hz, H9), 2.13 (4H, m, H2), 1.96 (1H, m, H1), 1.85 (1H, m, H7), 1.78-1.59 (3H, m, H1/H8), 1.45 (9H, s, H6), 1.43 (9H, s, H12), 1.17 (2H, dq, *J* = 12.7, 4.4 Hz, H8) ppm. *Many of the small vicinal couplings on the 6-membered ring were not resolved and gave broad lines;*

^{13}C NMR (101 MHz, $CDCl_3$): δ = 159.9 (C4), 155.0 (C10), 79.5 (C5/C11), 59.3 (C3), 44.3 (C9), 42.7 (C7), 29.8 (C2), 28.6 (C12), 28.5 (C6), 26.2 (C8), 14.9 (C1) ppm;

HRMS (ESI) calc. for $[C_{19}H_{34}N_2O_4 + Na]^+$ 377.2411. Found, 377.2411;

IR (ν_{max}/ cm^{-1}, neat): 3674, 3346, 2973, 1694, 1408, 1394, 1275, 1066, 869, 750;

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