New Transformations of Azacycles

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Abstract

New Transformations of Azacycles

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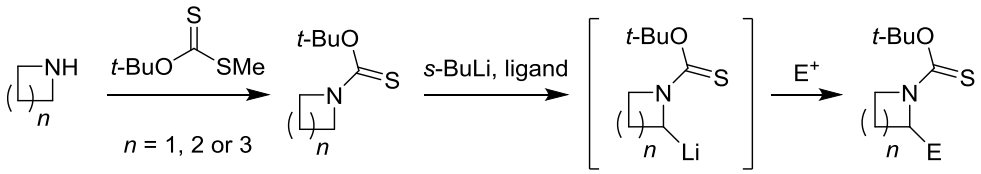
The work presented in this thesis involves new transformations of azacycles, focusing on the introduction of functionality α-to N. α-C-H functionalisation on an azetidine has been a long-standing challenge, with *N*-protecting/activating groups that work well in the higher and lower azacyclic systems not viable. A recent breakthrough in the Hodgson group showed the rarely used *N*-thiopivaloyl group was effective for α-deprotonation–electrophile trapping on azetidines, but was not without limitations concerning harsh removal conditions and scope for further substitutions. This thesis describes efforts to overcome these issues by development of a new protecting/activating group for N, *t*-butoxythiocarbonyl (Botc).



Investigation into suitable methods for introducing the Botc group onto commericially available azacycles is detailed; after considerable optimisation, aminolysis of a *t*-Bu xanthate ester was found to be effective. Notably, the Botc group could be deprotected under mild acid or thermal conditions, and selectively in the presence of *N*-Boc. Optimisation of and electrophile scope for α-lithiation–electrophile trapping of *N*-Botc-pyrrolidine and *N*-Botc-azetidine is discussed. Moreover, access to an asymmetric variant of this azetidine lithiation chemistry using chiral ligands has been explored, providing the best levels of enantioselectivity in azetidine α-substitution to date (up to 92:8 er).

Acknowledgements

Firstly, I would like to thank Prof David Hodgson for giving me the opportunity to work on this interesting project. I am extremely grateful for his support throughout, for excellent suggestions and advice on this project, and for his patience during our many long meetings.

I would also like to thank the CRL support staff, particularly Dr Barbara Odell and Prof Tim Claridge for patiently assisting me with all of my NMR woes and for calculating the rotational energy barriers from variable temperature NMR data. Additionally, I wish to thank Kelvin Jackson for providing useful computational support.

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Thanks also to the other members of the Hodgson group and to lab mates from the Anderson and Smith groups, for providing a fantastic lab atmosphere and for cheering me up during the tough times. Specific thanks go to Chris Pearson- my lab partner in crime from day one! I don't think I could have got this far without his friendship and our celebratory Chinese takeaway meals after every group presentation! I am also incredibly grateful to Craig Campbell for his invaluable advice and encouragement.

Finally, I would like to thank my wonderful family, and my fiancé Paul, for their love and support throughout.

Statement of Authorship

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

- Computational analyses and data (performed and provided by Kelvin Jackson).
- Variable temperature NMR analyses and data (performed and provided by Dr Barbara Odell and Prof Tim Claridge).
- Where reference is given to a published source.

Signature: Date:

Abbreviations

$( )_n$	number of repeat units
Δ	reflux
° C	degrees Celsius
~	approximately
% D	percentage deuteration
δ	chemical shift
µ	micro
Ac	acetyl
[Ag(fod)]	(2,2-dimethyl-6,6,7,7,8,8,8-heptafluoro-3,5-octanedionato) silver(I)
AIBN	azobisisobutyronitrile
aq	aqueous
Ar	aryl
atm	atmosphere
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
Botc	*tert*-butoxythiocarbonyl
Br	broad
brsm	based on recovered starting material
n-Bu	butyl
s-Bu	*sec*-butyl
t-Bu	*tert*-butyl
Bus	*tert*-butyl sulfonyl
calcd	calculated
cat.	catalytic
Cbz	carboxybenzoyl
cm^{-1}	wavenumber
COSY	correlation spectroscopy
d	day(s), doublet
DABCO	1,4-diazabicyclo-[2.2.2]octane
DBU	1,8-diazabicycloundec-7-ene
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	diethyl azodicarboxylate
dec.	decomposition
DEPT	distortionless enhancement by polarization transfer
DIANANE	2,5-diaminonorbornane
DIBAL-H	diisobutylaluminium hydride
DKR	dynamic kinetic resolution
DMAP	4-dimethylaminopyridine
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
dr	diastereomeric ratio

dtbbpy	di-*tert*-butyl-bipyridine
DTR	dynamic thermodynamic resolution
E/E^+	electrophile
e.g.	for example
epi	epimer
equiv	equivalent(s)
er	enantiomeric ratio
ESI	electrospray ionisation
Et	ethyl
FI	field ionisation
g	gram(s)
GC	gas chromatography
GCMS	gas chromatography–mass spectrometry
h	hour(s)
HCMV	human cytomegalovirus
Hex	hexyl
HPLC	high-performance liquid chromatography
HRMS	high resolution mass spectrometry
HSQC	heteronuclear single quantum coherence
Hz	hertz
IR	infrared
J	coupling constant
k	rate constant
K	kelvin
KHMDS	poatassium bis(trimethylsilyl) amide
L/L*	generic ligand/generic chiral ligand
LCMS	liquid chromatography–mass spectrometry
LDA	lithium diisopropyl amide
LHMDS	lithium bis(trimethylsilyl) amide
lit.	literature
LRMS	low resolution mass spectrometry
LTMP	lithium 2,2,6,6-tetramethylpiperidide
M	molar, parent mass
m	*meta*
m	milli, multiplet, medium
Me	methyl
MHz	megahertz
min	minute(s)
mol	mole(s)
mp	melting point
M.S.	molecular sieves
MTBE	methyl *tert*-butyl ether
m/z	mass to charge ratio

NMR	nuclear magnetic resonance
NOESY	nuclear Overhauser effect spectroscopy
Nu	nucleophile
o	*ortho*
p	*para*
p	page number
Pd/C	palladium on carbon
PG	protecting group
Ph	phenyl
piv	pivaloyl
pK_a	acid dissociation constant
pK_{aH}	pK_a of conjugate acid
pp	page numbers
ppm	part(s) per million
ppy	phenyl-pyridine
Pr	propyl
i-Pr	isopropyl
py	pyridine
q	quartet
quant	quantitative
quin	quintet
R	generic substituent
rac	racemic
R_f	retention factor
rt	room temperature
s	singlet, strong
sat.	saturated
S_E2	bimolecular electrophilic substitution
sept	septet
SET	single electron transfer
SFC	supercritical fluid chromatography
Si-gel	silica gel
SM	starting material
(−/+)-sp	(−/+)-sparteine
t	triplet
$t_{1/2}$	half life
TBAI	tetrabutylammonium iodide
TBDMS	*tert*-butyldimethylsilyl
TBHP	*tert*-butyl hydroperoxide
temp	temperature
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMEDA	*N*,*N*,*N*',*N*'-tetramethylethylenediamine
TMS	trimethylsilyl
TOF	time of flight
Tr	triphenylmethyl

Triton-B	benzyltrimethylammonium hydroxide	w	weak
		w/v	weight per unit volume
Ts	*para*-toluenesulfonyl		

Stereochemistry

Throughout this thesis, the schematic nomenclature shown in Figure 1 is used to differentiate between absolute and relative stereochemistry.[1]

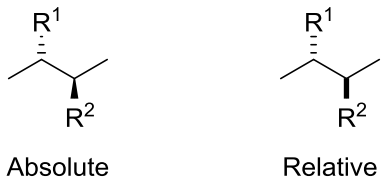


Figure 1. Stereochemical notation used.

For non-racemic stereocentres, with an undefined *R*:*S* ratio, the schematic nomenclature shown in Figure 2 is used.

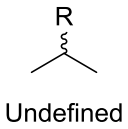


Figure 2. Schematic nomenclature used for undefined stereochemistry.

Contents

1. Introduction

The work presented in this thesis describes the design and development of a novel *N*-protecting/activating group for α-lithiation–electrophile trapping of azacycles, with a particular focus on an improved synthesis of substituted azetidines. The first part of this introductory chapter will outline the current approaches to substituted azetidines and the limitations of these methods. This will help to put our own work into context and highlight the value of our studies.

The second part of the introductory chapter will provide an overview of the available methods for C(sp^3)-H 'activation' adjacent to N in saturated azacycles. The main focus of this section will be to highlight the progress that has been made in α-lithiation–electrophile trapping of azacycles, and the importance of a suitable *N*-protecting/activating group. The design elements of an improved *N*-protecting/activating group for azetidine α-deprotonation and the main aims of the project will be explained.

1.1. Saturated azacycles

Heterocycles are abundant, being present in over 50% of all known organic compounds including drugs, herbicides, pesticides and dyes.[2] The most prevalent heterocycles are those containing N, O or S heteroatoms. Of these compound classes, saturated azacycles are becoming increasingly important templates for drug discovery and as chiral auxiliaries in organic synthesis; of the top 200 most commonly prescribed drugs in 2010 in the US, 33 contained small saturated cyclic amines (pyrrolidine or piperidine derivatives).[3] As a

result, the chemistry community is continuously striving to develop improved methods for the synthesis of such compounds.

1.2. Importance of azetidines

Azetidines are an important class of azacycles that have wide-ranging applications in the agrochemical and pharmaceutical industries.[4] The azetidine ring is also present in a small number of natural products such as penaresidins A and B (**1a**/**1b**) (Figure 3).[5] These sphingosine-derived azetidine alkaloids were isolated from marine sponge *Penares sp*., and possess potent actomyosin ATPase-activating activity. Other azetidine-containing natural products include a series of peptidyl polyoxins **2** and vioprolides, such as vioprolide A (**3**).[6,7] The peptidyl polyoxins **2** are useful antifungal antibiotics and their degradation products can be potent inhibitors of chitin synthetase. Vioprolides are metabolites from myxobacterium *Cystobacter violaceus* which exhibit both antifungal and cytotoxic activity.

Azetidine-2-carboxylic acid and related amino acid derivatives have numerous agrochemical applications.[6,8] For example, azetidine-2-carboxylic acid functions as a plant growth regulator and 3-methylazetidine-2-carboxylic acid is a sterilising agent for male plants. In addition, these amino acid analogues are often active pharmaceutical ingredients: 2,4-disubstituted-azetidine **4** acts as a metabotropic receptor agonist, whereas 2,3-disubstitued-azetidine **5** operates as both a kainate receptor agonist and a sodium-dependent glutamate uptake inhibitor (Figure 4).[9] Another interesting property of non-proteinogenic azetidine amino acids, in particular α-alkylated azetidine-2-carboxylic acids, is their ability to induce and stabilise particular conformations in short bioactive peptides.[10]

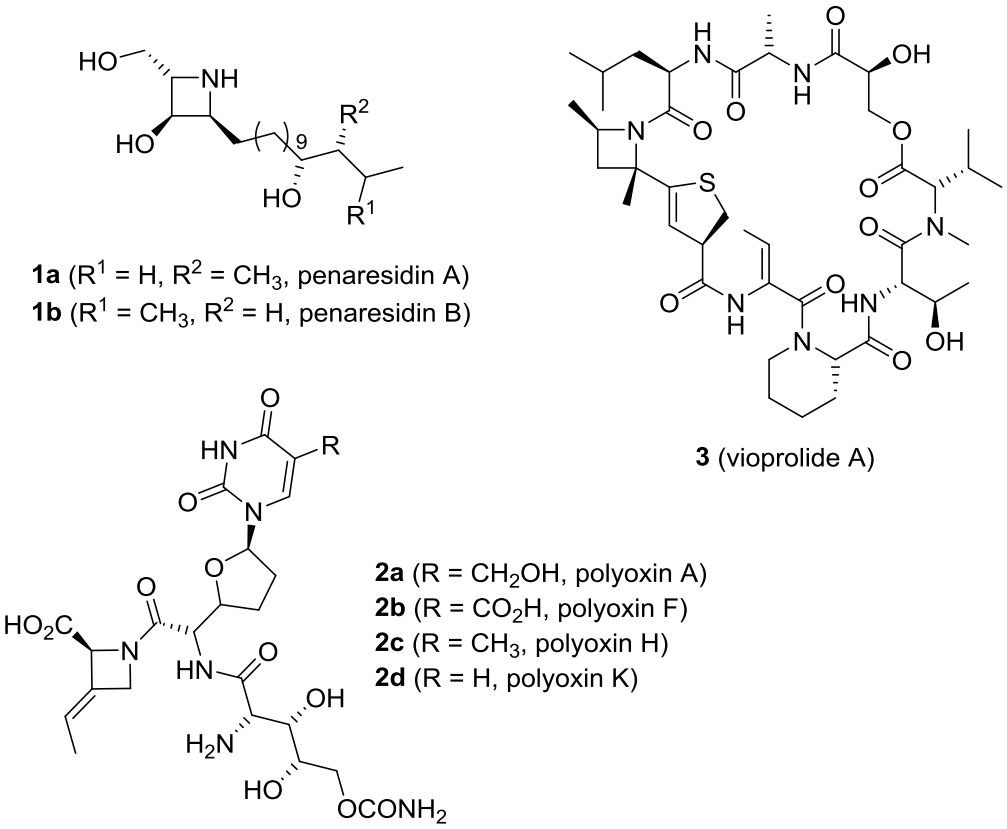


Figure 3. Azetidine-containing natural products.

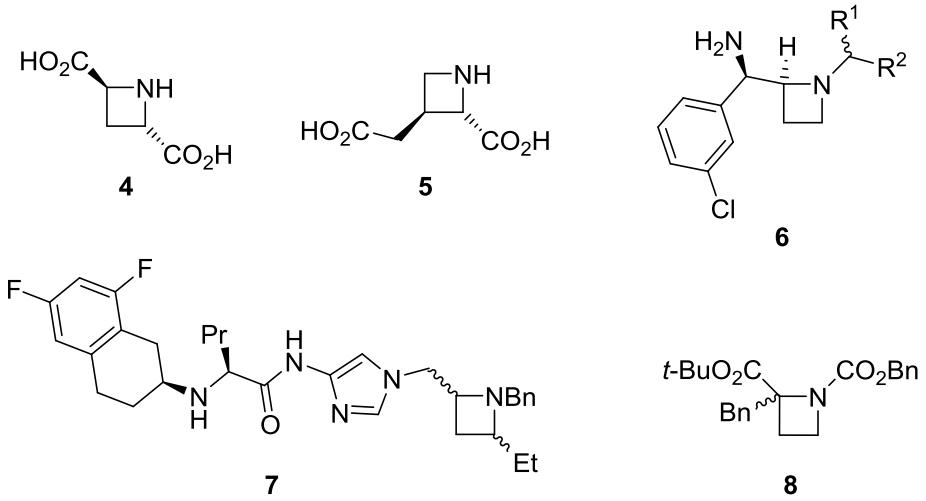
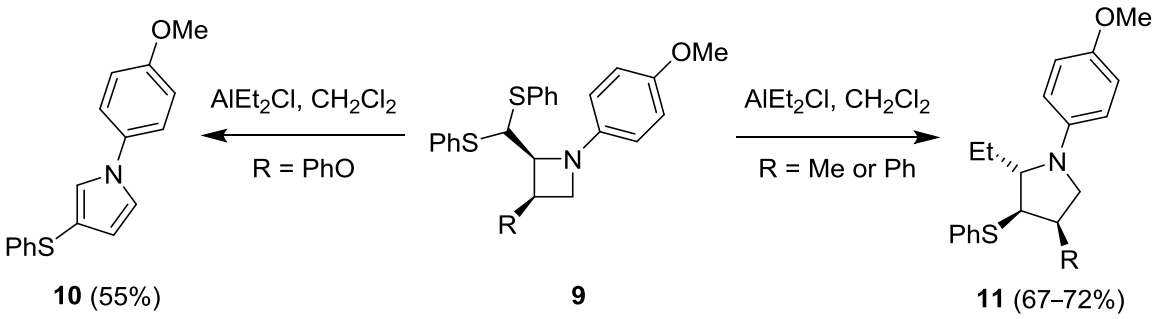


Figure 4. Azetidine-containing drug leads.

There are a plethora of potential uses for azetidines in the pharmaceutical field;[11] additional examples include G-protein receptor ligands **6**, Pfizer's γ-secretase inhibitor **7**, and anti-human cytomegalovirus (HCMV) lead **8** (Figure 4).[9]

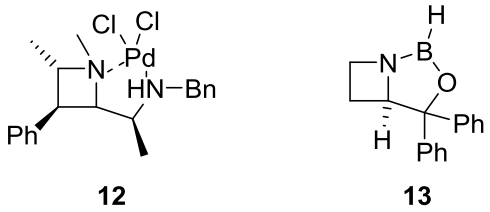
Azetidines are also valuable reagents in organic synthesis. Azetidine ring-strain is comparable to that of the smaller aziridine ring (25.2 and 27.3 kcal mol^{-1}, respectivity),[12] providing a useful driving force for ring-opening and ring-expansion reactions.[13] These reactions require activation of the nitrogen atom, typically by alkylation or reaction with Lewis or Brønsted acids, to create a better leaving group; this process occurs readily with azetidines due to the relative basicity of the nitrogen (pK_{aH} 11.29).[14] Ring-opening of azetidines has been demonstrated with a broad range of nucleophiles and has become a powerful tool for the stereoselective synthesis of acylic compounds.[15] Ring-expansion of azetidines can be used to generate larger saturated or unsaturated azacycles (Scheme 1)[9], up to 8-membered rings[16], or even those containing other heteroatoms.[17]



Scheme 1. Ring-expansion of azetidine **9** to give saturated and unsaturated products.

Additional synthetic uses of azetidines include their role as chiral auxiliaries,[18] or as ligands for metal catalysed reactions;[5,19] Pd-complex **12** functions as an efficient catalyst for Suzuki cross-coupling reactions of aromatic halides, while Corey reduction catalyst

analogue **13** operates as a catalyst for reduction of prochiral ketones with borane, providing excellent reactivity and enantioselectivity (Figure 5).



12 **13**

Figure 5. Azetidine-containing catalysts.

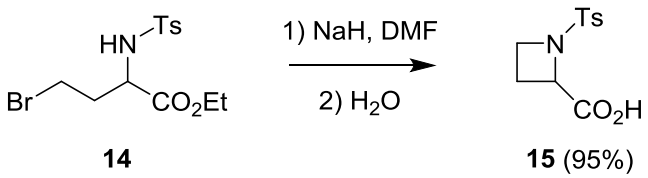
1.3. Current approaches to substituted azetidines

Despite their growing importance in the pharmaceutical and agrochemical industries, azetidines have received relatively little interest from the synthetic community compared to their higher (and lower) azacyclic homologs.[5] There is a particularly noticeable lack of methods for the enantioselective synthesis of substituted azetidines.[20] One reason for this may be attributed to the strained nature of the orthogonally twisted σ bonds,[21] which increases the difficulty in forming the azetidine ring. In fact, within the series of halo-amines, the rate of ring-closure is lowest for formation of the 4-membered azacycle (5>>3>4).[22] Nevertheless, cyclisation of amines is currently one of most reliable and widely used methods for generating substituted azetidines. A brief overview of this approach, along with the other key methods for azetidine synthesis,[4d,5,6,9,21,23] is presented below.

1.3.1. Ring-closure by C-N bond formation

One of the earliest methods for azetidine synthesis was ring-closure of γ-halo amines, which is now well established in the literature.[4d,23] Typically, a primary halide leaving

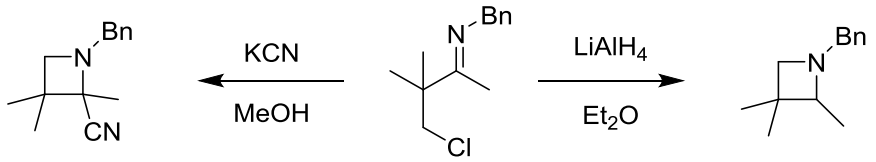
group and a sufficiently bulky substituent on the nitrogen are required for efficient cyclisation (Scheme 2).[24] Large *N*-substituents assist the reaction by setting up the correct conformation for cyclisation;[25] in most examples smaller *N*-substituents lead to low yields.[26] Another drawback with this approach is that it often suffers from considerable side-reactions such as elimination of the leaving group and dimerisation.



14 **15** (95%)

Scheme 2. Early synthesis of azetidine **15** from γ-halo amine **14**.

De Kimpe and co-workers showed that β-haloimines can also be useful substrates for cyclisation, resulting in fewer side-reactions than with γ-halo amines.[27] Various nucleophiles can be used for reduction of the imine, such as hydride, cyanide or alkoxides; the latter two providing an additional substituent on the resulting azetidine ring (Scheme 3).[28] Gem-disubstitution at C-3 in the starting imine was found to be essential, limiting this method to the synthesis of 3,3-substituted azetidines.

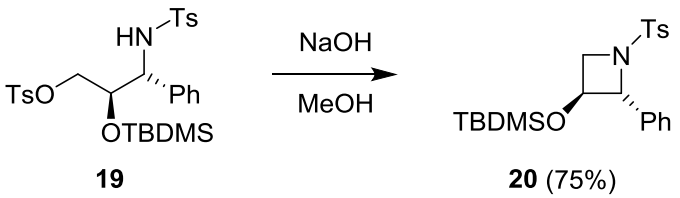


17 (76%) **16** **18** (95%)

Scheme 3. Cyclisation of β-haloimine **16** to give substituted azetidines **17**/**18**.

Cyclisation of amines is a particularly popular route to azetidines due to its viability with a wide variety of leaving groups.[23b] Activated 1,3-aminoalcohols, readily prepared in

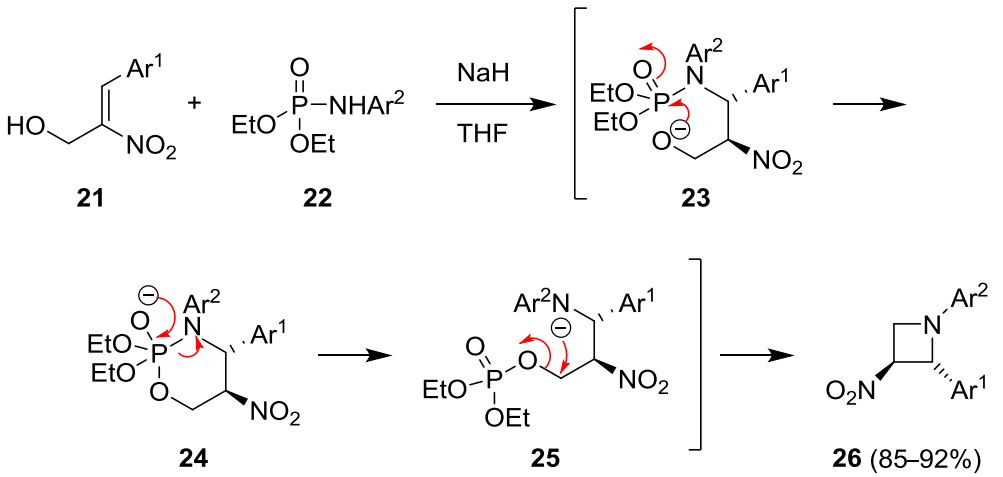
enantiomerically pure form, are most commonly used and can lead to azetidines in high yield and er (Scheme 4).[29] This method has been employed to synthesise the penaresidins natural products.[21] However, substituents on the ring and the relative stereochemistry of these substituents have a substantial influence on the ease of cyclisation, and can often lead to lower rates of ring-closure with concomitant formation of side-products.



19 **20** (75%)

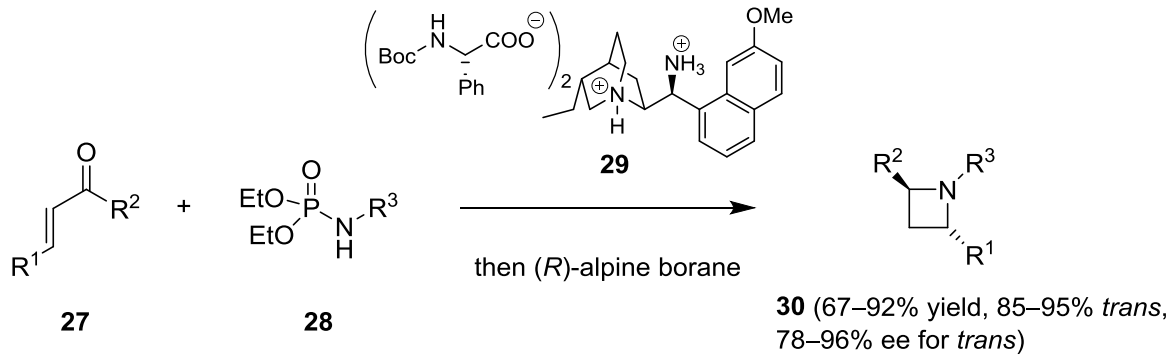
Scheme 4. Ring-closure of tosyl-protected amino alcohol **19**.

The Yadav group devised a clever way of accessing activated 1,3-aminoalcohols *in situ*, by a diastereselective aza-Michael addition of *N*-aryl phosphoramidates **22** to Baylis-Hillman adducts **21**, followed by anion-induced cyclisation to give azetidines **26** (Scheme 5).[30] Further development of this methodology led to the enantioselective generation of 1,2,4-trisubstituted azetidines **30** by an organocatalytic aza-Micheal addition of *N*-substituted phoshoramidates **28** to enones **27**, followed by intramolecular reductive cyclisation with (*R*)-alpine borane (Scheme 6).[31]



Ar^1 = Ph, 4-ClC_6H_4, 2-ClC_6H_4, 4-$MeOC_6H_4$, 3-furyl
Ar^2 = Ph, 4-FC_6H_4, Ts

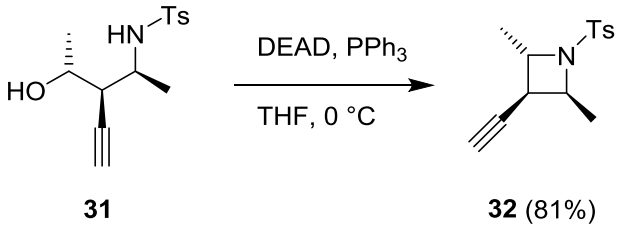
Scheme 5. Azetidines **26** from Baylis-Hillman adducts **21**.



R^1, R^2 = Ph, Me, Et, Bn, 4-ClC_6H_4
R^3 = Ts, Ph, 4-$MeOC_6H_4$, *o*-tolyl, Bn

Scheme 6. Yadav's synthesis of 1,2,4-trisubstituted-azetidines **30**.

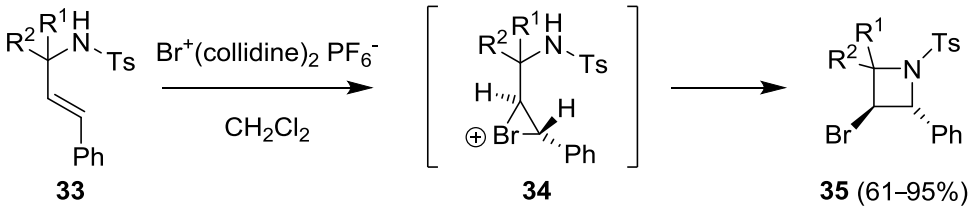
Ring-closure can also be carried out under Mitsunobu conditions,[32] with primary alcohols shown to be particularly suitable substrates. For example, enantiopure azetidine **32** was formed in excellent yield from reaction of alcohol **31** with DEAD and PPh_3 (Scheme 7).[33] Less common strategies to substituted azetidines include cyclisation of γ-amino epoxides using strong bases,[34] and intramolecular reductive alkylation of dinitriles with siloxanes.[35]



31 **32** (81%)

Scheme 7. Cyclisation of alcohol **31** under Mitsunobu conditions.

There are a limited number of examples of regioselective azetidine synthesis using allylic and homoallylic substrates, with the assistance of alkene-activating agents.[36] Electrophilic halogen sources are commonly used activating agents, resulting in the formation of halonium ion intermediates that are subsequently displaced by the amine in a ring-closure step; this is illustrated by the synthesis of azetidine **35** from allylic tosylamides **33** (Scheme 8).[37] For this reaction, the highest yield (95%) was achieved with a gem dimethyl group α to N ($R^1 = R^2$ = Me). Similar examples of ring-closure include hydrozirconation of chiral allylic amines,[38] iodine-mediated[39] or phenylselenyl halide-mediated[40] cyclisation of homoallylic amines, and Pd-catalysed cyclisation of β-amino allenes.[41]



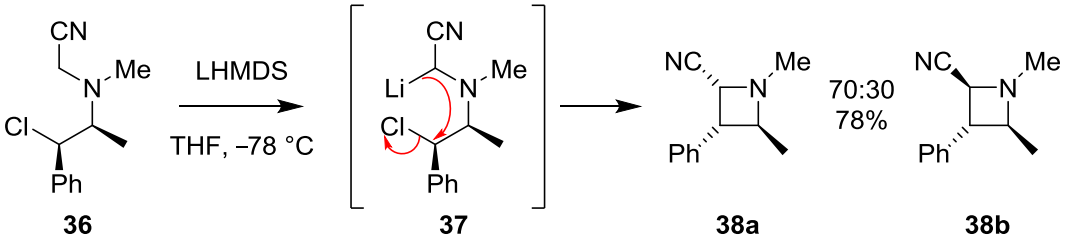
33 **34** **35** (61–95%)

Scheme 8. Alkene-activation of allylic tosylamide **33** to give azetidine **35**.

1.3.2. Ring-closure by C-C bond formation

More recently, a limited number of examples of ring-closure of amines by *C*-cyclisation have appeared in the literature.[23b] as alternatives to the above *N*-cyclisation approaches to azetidines. This strategy has been neglected for many years due to the instability of β-

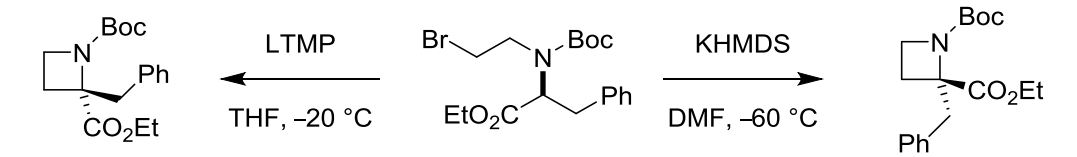
haloamines, which are known to undergo intramolecular substitution to give aziridinium ions.[14] However, substrates such as *N*-cyanomethyl β-chloroamine **36** were found to be surprisingly stable, undergoing α-lithiation followed by anionic cyclisation to give highly-substituted azetidines **38a/b** in good yield, albeit with modest diastereoselectivity (Scheme 9).[42]



36 **37** **38a** **38b**

Scheme 9. *C*-cyclisation of α-metallated β-chloroamine **37**.

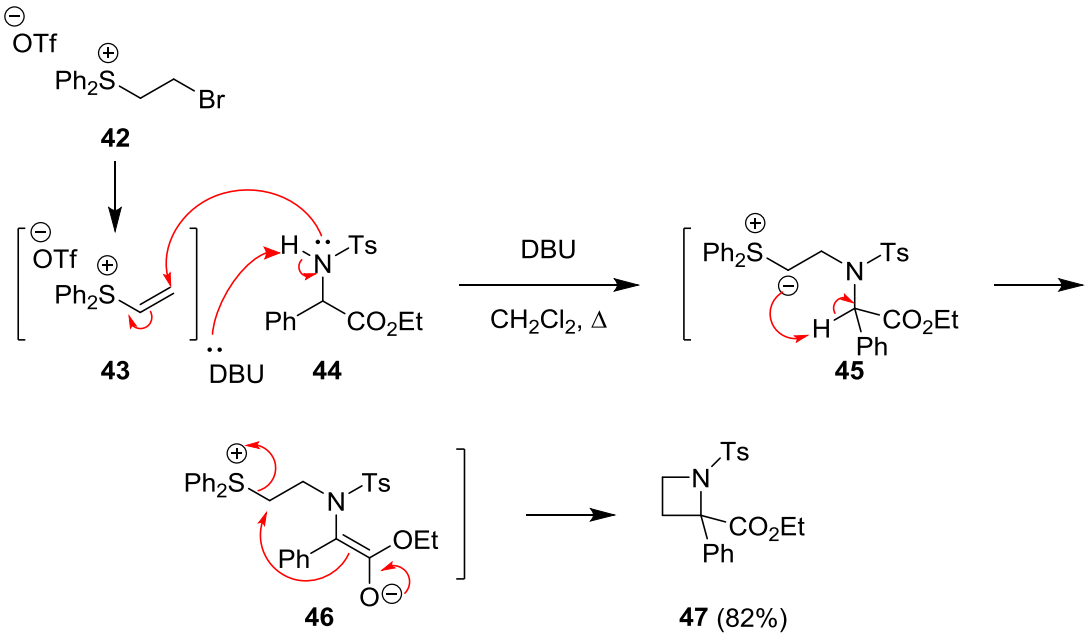
The nitrile group can be replaced by other anion-stabilising groups such as sterically hindered esters[43] and phosphonates[44]. Such *C*-cyclisations have been reported to take place with 'memory of chirality'[45]. in which a non-racemic enolate intemediate containing a chiral C-N axis plays an essential role in directing the stereochemical course of the reaction.[46] Using this approach, azetidines **40** and **41** were produced in high yield and er from enantiopure α-amino ester **39**, and the absolute stereochemistry of the product could be controlled by the choice of reactions conditions (Scheme 10).



40 (69%, 95:5 er) **39** **41** (61%, 97:3 er)

Scheme 10. Formation of azetidines **40**/**41** with 'memory of chirality'.

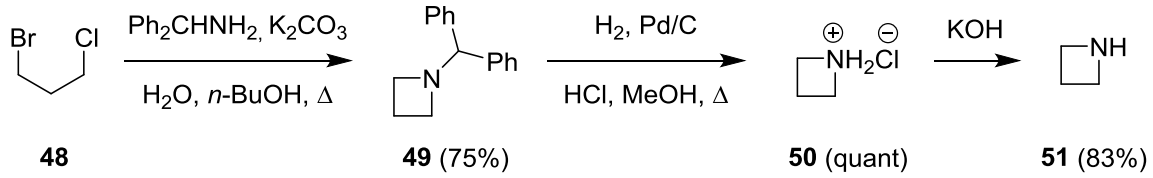
Other examples of azetidine synthesis through *C*-cyclisation include α-lithiation of *N*-benzylamino and *N*-allylamine epoxides,[47] photochemical cyclisation of α-amino ketones[48] and intramolecular Michael additions of α,β-unsaturated esters.[49] More recently, Aggarwal and co-workers reported an alternative annulation strategy, involving the generation of enolate intermediates such as enolate **46** which underwent *C*-cyclisation to give substituted azetidine **47** in high yield (Scheme 11).[50]



Scheme 11. Synthesis of substituted azetidine **47** from aryl glycine **44**.

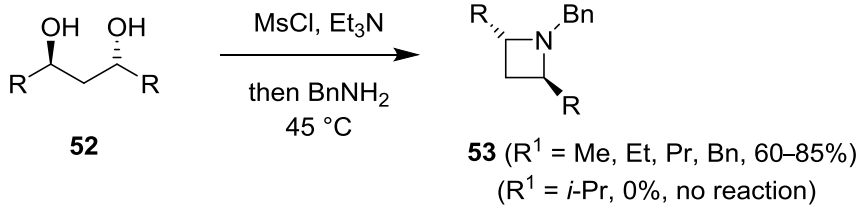
1.3.3. Addition of amines to 1,3-dielectrophiles

Direct addition of primary amines to 1,3-dihalo compounds is another very popular route to azetidines, and has been used to synthesise unsubsituted azetidine **51** on a kg scale (Scheme 12).[51] However, in more substituted cases, this methodology is prone to severe side-reactions such as double intermolecular amine addition, alkene generation by elimination of the leaving group in the starting material, and polymerisation, often resulting in poor yields of desired products.[6,23b]



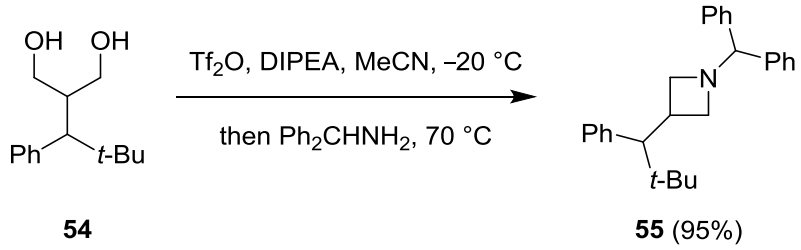
Scheme 12. Large-scale synthesis of unsubstituted azetidine **51**.

A variety of other leaving groups are also tolerated including mesylates, tosylates, sulfonic esters and triflates.[23d] Activation of 1,3-diols **52** to their 1,3-bis-sulfonate derivatives followed by reaction with amines such as benzylamine allows slightly larger substituents to be incorporated into the ring compared to the corresponding 1,3-dihalo substrates, and generally provides higher yields (Scheme 13).[52] However, this reaction failed when the ring substituents became more sterically demanding (R = *i*-Pr).



Scheme 13. Addition of benzylamine to 1,3-diols **52**.

1,3-Bis-triflates have been found to be the most successful substrates for reactions involving particularly bulky substituents. This is exemplified by formation of azetidine **55** in very high yield (95%) by bis-triflate activation of 1,3-diol **54** (Scheme 14); a much lower yield (20%) was achieved with bis-tosyl activation of the same substrate.[53]

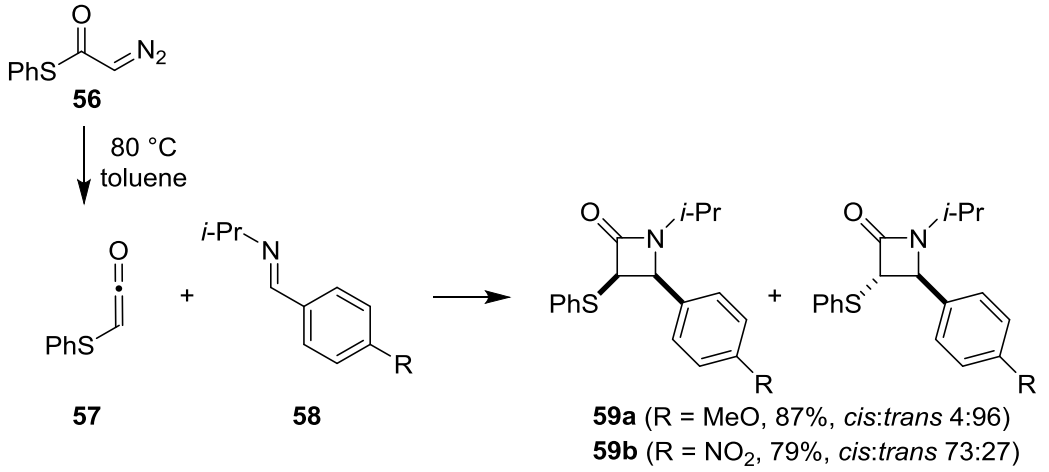


54 **55** (95%)

Scheme 14. Triflate activation of 1,3-diol **54** to give azetidine **55**.

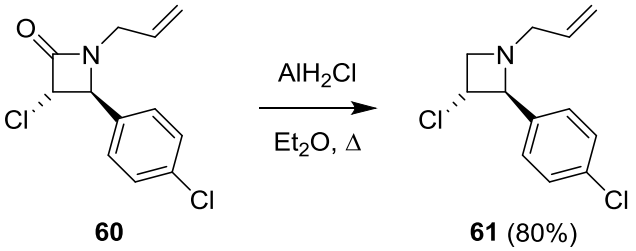
1.3.4. Reduction of β-lactams

Azetidines have received relatively little attention from the synthetic community compared with azetidine-2-ones (β-lactams). The latter have been extensively investigated due to their importance as a key structural motif in the most widely used family of antibiotics.[6,9,54] As a result, a wide array of methods have been developed for β-lactam synthesis,[5,55] the most common being the Staudinger cycloaddition of ketenes and imines (Scheme 15).[56] Similarly, concerted [2+2] cycloaddition of isocyanates with alkenes can be used to prepare β-lactams,[57] among other methods. It is therefore not surprising that reduction of β-lactams has become another key approach to substituted azetidines.



Scheme 15. Staudinger synthesis of β-lactams **59**.

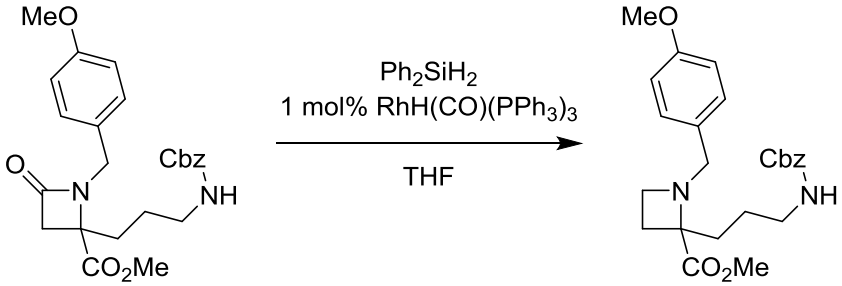
The main concern with this β-lactam reduction strategy is the potential for reductive ring cleavage, as well as unwanted reduction of other functional groups present on the substrate. Although a wide range of reducting agents have been employed (such as $LiAlH_4$, diborane or Raney Ni), DIBAL-H and chloroalanes were found to be far more efficient for clean reduction of β-lactams to azetidines.[5,58] Use of chloroalanes (AlH_2Cl or $AlHCl_2$) in 'Ojima's procedure'[59] has allowed the synthesis highly functionalised products such as azetidine **61** (Scheme 16).[60] However, many reduction-sensitive functional groups including esters, nitriles and azides were not tolerated under these conditions.



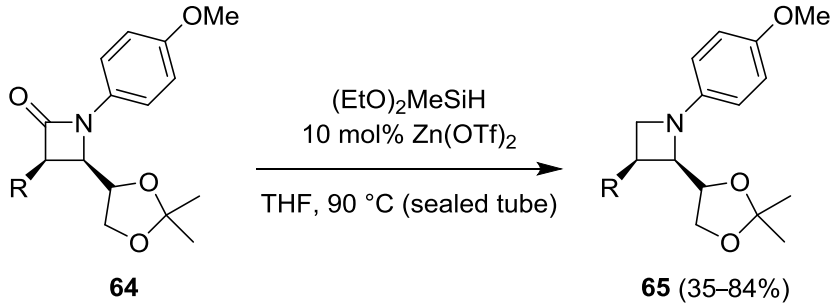
60 **61** (80%)

Scheme 16. Reduction of β-lactam **60** using dichloroalane.

Alternative conditions, using diphenylsilane with rhodium hydride catalysts, were developed by Gonzales-Muniz and co-workers for the reduction of ester-containing β-lactams (Scheme 17).[61] More recently, Alcaide and co-workers reported a silane-mediated zinc-catalysed reduction of β-lactams that can also tolerate reduction-sensitive functional groups, although yields of azetidines **65** were variable (Scheme 18).[62]



Scheme 17. Reduction of β-lactam **62** using diphenylsilane and a Rh hydride catalyst.



Scheme 18. Zinc-catalysed reduction of β-lactams **64**.

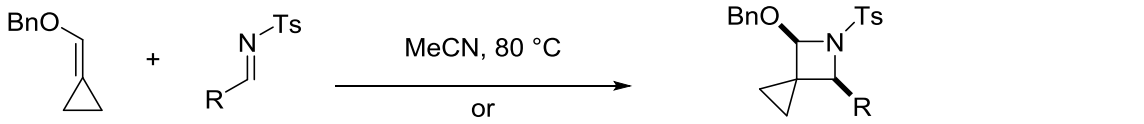
1.3.5. [2+2] cycloaddition

As noted above, the [2+2] cycloaddition of imines with ketenes is a successful route to β-lactams. On the other hand, there are only a small number of examples of the corresponding reaction of imines with alkenes to give azetidines, with limited substrate scope. Initially, this methodology required harsh conditions such as a high pressure and long reaction time (Scheme 19).[63]

66 **67** **68** (90%, 90:10 dr)

Scheme 19. Early example of a [2+2] cycloaddition to give substituted azetidine **68**.

Improved substrate scope and milder conditions were made possible using the strained cyclopropyl enol ether **69** for thermal or catalytic cycloadditions with a range of imines (Scheme 20).[64] Thus, heavily substituted azetidines **71** could be synthesised with high diastereoselectivities (up to 98:2 thermally, up to >99:1 catalytically) and good yields (up to 97% thermally, up to 94% catalytically), although the yields and diastereoselectivities were noticeably reduced when R = CO_2Et.



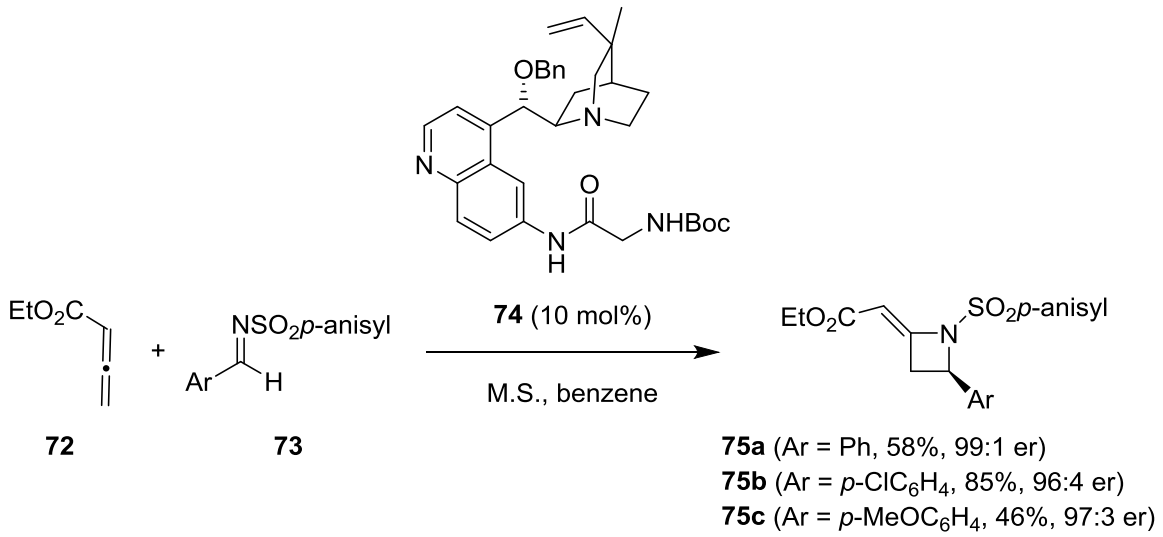
69 **70**

71a (R = Ph, 97%, 98:2 dr (thermal), 94%, >99:1 dr (cat.))
71b (R = CO_2Et, 57%, 55:45 dr (thermal), 45%, 97:3 dr (cat.))

Scheme 20. Thermal and catalytic [2+2] cycloadditions of cyclopropyl enol ether **69**.

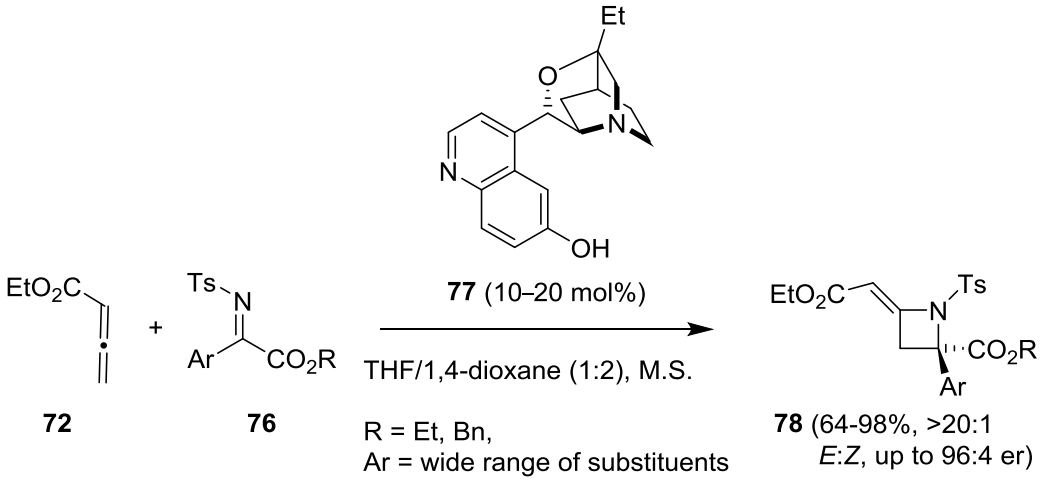
In 2003, Shi and co-workers developed a novel DABCO-catalysed regioselective synthesis of 2,4-disubstituted azetidines through a formal [2+2] cycloaddition of *N*-tosylimines with allenoates.[65] Since then, Zhu and co-workers have adapted this methodology for the synthesis of highly enantioenriched azetidines **75**, by replacing DABCO with cinchona alkaloid-derived catalyst **74** (Scheme 21).[66] The yield of this reaction was highly

dependent on the electronic properties of the substituents on the aromatic ring, being significantly reduced in the presence of strongly electron-donating groups.



Scheme 21. Formal [2+2] cycloaddition catalysed by cinchona alkaloid-derivative **74**.

More recently, Sasai and co-workers further extended this methodology to allow a formal [2+2] cycloaddition of allenoate **72** with less reactive *N*-tosyl α-ketimine substrates **76** (Scheme 22).[67] In this case, the optimal chiral organocatalyst was found to be β-isocupreidine **77**, providing azetidines **78** in high yield and stereoselectivity.

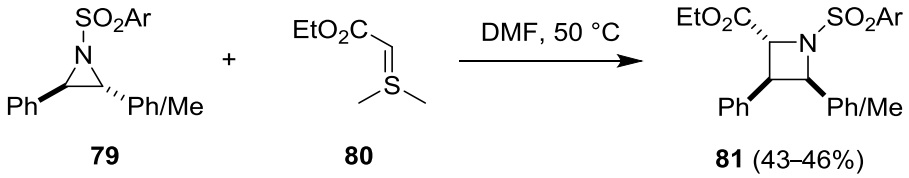


Scheme 22. Formal [2+2] cycloaddition of allenoate **72** with ketimines **76**.

1.3.6. Ring-expansion and ring-contraction

Another route to substituted azetidines is by ring-expansion of aziridines. Compared with azetidines, these smaller and more reactive azacycles have been investigated in more detail due to their presence in a range of biologically active compounds as well as their enormous value in synthetic organic chemistry.[68] Accordingly, numerous methods have been reported for aziridine synthesis, including cyclisation of amines, nitrene or carbene transfers and additions to azirines.[69]

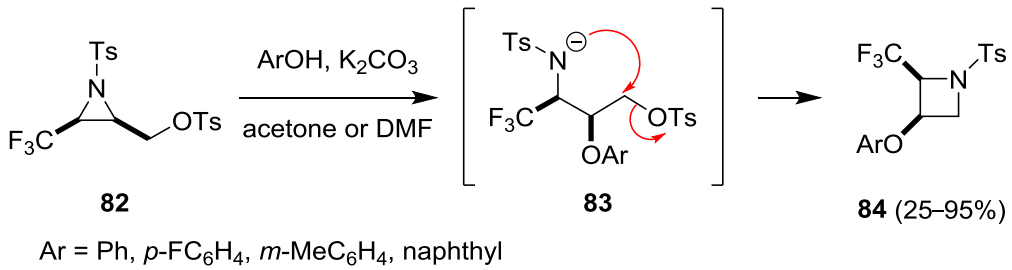
Ring-expansion of *N*-arylsulfonyl-aziridine **79**, by nucleophilic ring-opening with ylide **80** followed by ring-closure, generated substituted azetidines **81** in moderate yield (Scheme 23).[70] However, the substrate scope was extremely limited, and the reaction was unsuccessful with 2,3-dialkyl-aziridines.



79 **80** **81** (43–46%)

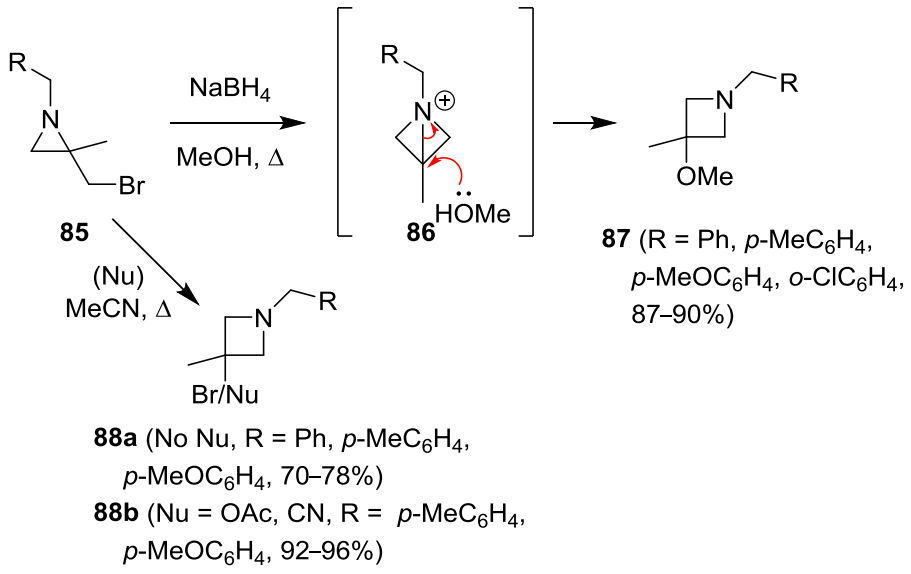
Scheme 23. Ring-expansion of aziridine **79** to form azetidine **81**.

De Kimpe and co-workers successfully incorporated a useful trifluoromethyl group into the azetidine ring by a stereospecific and regioselective ring-expansion of aziridine **82** (Scheme 24).[71] The yields of the resulting azetidines **84** were higher for reactions in DMF (56–95%) than in acetone (25–38%).



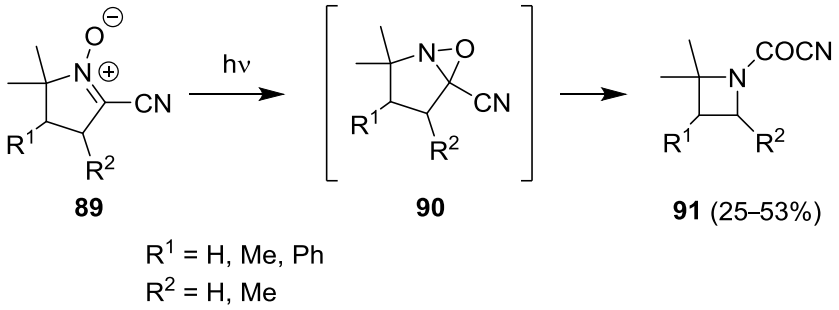
Scheme 24. Formation of trifluoromethyl-substituted azetidines **84**.

Ring-expansion of 2-(bromomethyl)-aziridines **85** was observed upon heating with $NaBH_4$ and MeOH, resulting in formation of azetidines **87** (Scheme 25).[72] The reaction occurs via bicyclic aziridinium intermediate **86**, which subsequently undergoes nucleophilic attack at the most substituted carbon atom.[73] The reactivity of the bicyclic azirdinium intermediate **86** with other nucleophiles such as NaOAc, KCN or the displaced bromide anion was explored, providing a straightforward route to 3,3-disubsituted-azetidines **88**.[74] The outcome of the reaction was found to be directly linked to the choice of solvent; azetidines **88** were obtained as the sole products in MeCN, whereas the corresponding aziridines, formed by nucleophilic attack at the less hindered carbon atom, were favoured in DMF.



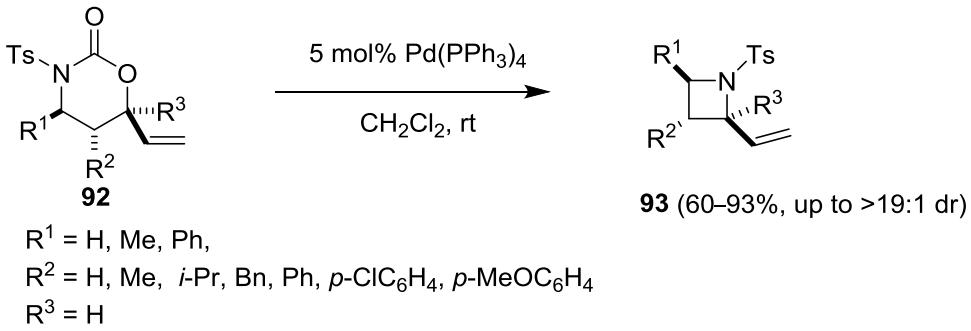
Scheme 25. Ring-expansion of aziridine **85** to give a range of 3,3-disubstituted-azetidines.

There is far less literature precedent for azetidine synthesis by ring-contraction of larger azacycles. One of the few examples is the photochemical rearrangement of pyrrolidine *N*-oxides **89** to give substituted azetidines **91** in low to moderate yields (Scheme 26).[75]



Scheme 26. Ring-contraction of pyrrolidine *N*-oxides **89**.

Disappointing yields have also been observed with ring-contraction of 6-membered azacycles, such as the reaction of perhydrooxathiazines with KOH/EtOH[76] and the LiCl-catalysed thermal decarboxylation of tetrahdro-1,3-oxazin-2-ones.[77] A more efficient decarboxylative ring-contraction was demonstrated in Pd-catalysed rearrangement of oxazin-2-ones **92** to give azetidines **93** in good yield with retention of stereochemistry (Scheme 27).[78] Whilst a range of R^1 and R^3 substituents were tolerated in this reaction, further substitution adjacent to the vinyl group ($R^3 \neq H$) led to dramatically lower yields (<5%).



Scheme 27. Pd-catalysed decarboxylative ring-contraction of oxazin-2-ones **92**.

1.3.7. Limitations of the ring-forming methodologies

Although good yields of substituted azetidines have been achieved with a number of the ring-forming approaches discussed above, the substrate scope is very limited. Some of the above methods require harsh reaction conditions, or suffer considerable side-reactions resulting in lower yields of azetidines. Furthermore, these methods generally involve exotic (often enantiopure) starting materials with the desired ring substituents already present, often requiring lengthy syntheses.

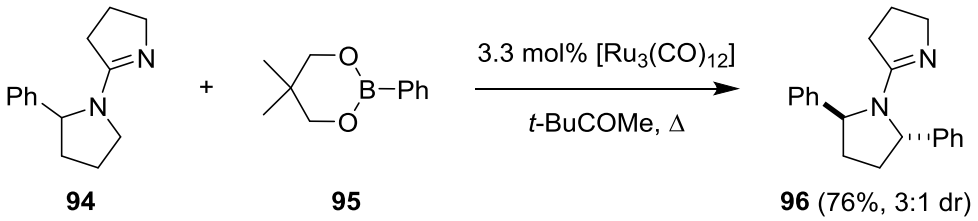
1.4. C(sp^3)-H activation adjacent to nitrogen

An alternative approach to substituted azacycles is to directly functionalise simple starting materials that already contain the core ring structure. This strategy allows late stage divergence which is particularly desirable in the drug discovery process, and avoids challenging syntheses of complex starting materials. Although direct functionalisation of azetidines is rare, there have been a number of successful C(sp^3)-H activation methods for the functionalisation of other azacycles α- to nitrogen.[3,79] A brief overview of the most significant methods is detailed below.

1.4.1. Transition-metal catalysed C(sp^3)-H activation

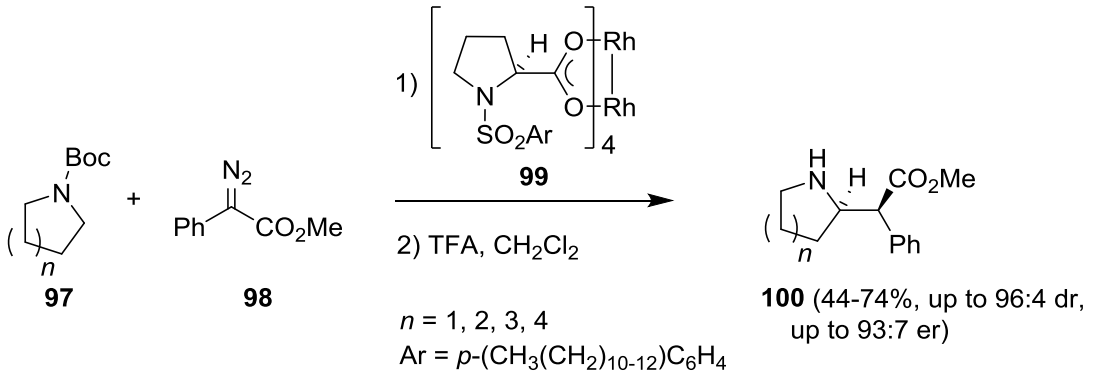
Whilst transition-metal catalysed C(sp^2)-H activation has received a great deal of attention from the synthetic community,[80] there have been only a very limited number of reports regarding transition-metal catalysed α-C(sp^3)-H activation in azacycles, mainly focused on pyrrolidines.[79] One approach involves the oxidative addition of an α-C-H bond to a transition-metal catalyst. This process generally requires a suitable *N*-activating group, such as py, to direct the catalyst to the α-C-H position. Examples include Ru-catalysed

coupling of *N*-py-azacycles with unactivated alkenes[81] and Rh-catalysed carbonylative coupling of *N*-heteroaryl-azacycles.[82] More recently, Ru-catalysed α-arylation of pyrrolidines and piperidines has been achieved using suitable *N*-activating groups (pyrroline and py, respectively) with boronic ester coupling partners (Scheme 28).[83]



Scheme 28. Direct α-arylation of pyrrolidine **94**.

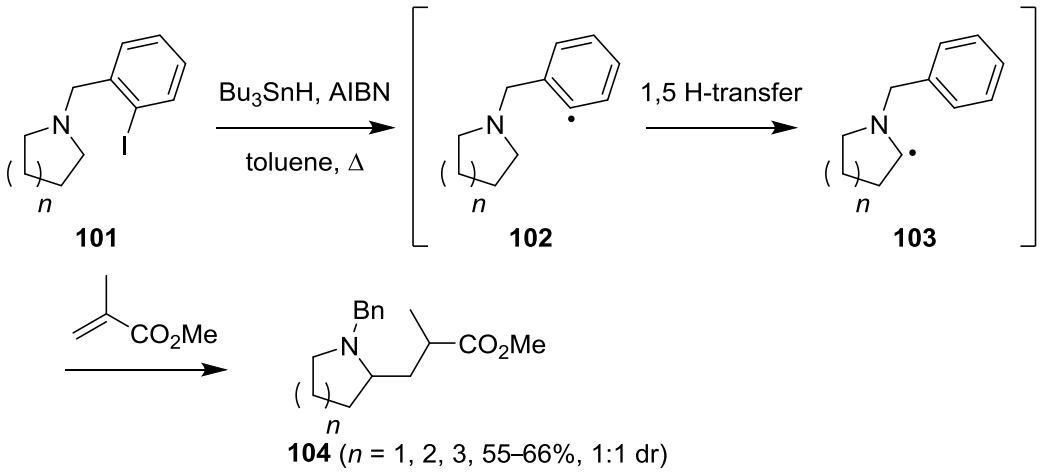
Another approach involves α-C-H insertion of *N*-protected azacycles with metal carbenes or nitrenes.[3,79] For example, Davies and co-workers reported the highly stereoselective C-H insertion of a range of aryldiazoacetates into *N*-Boc-protected-azacycles **97** using a chiral dirhodium catalyst **99** (Scheme 29).[84] Although this chemistry was very efficient with 5, 7 and 8-membered azacycles, and worked reasonably well for *N*-Boc-piperidine, attempted α-functionalisation of *N*-Boc-azetidine led to a complex mixture of products.



Scheme 29. Rh carbenoid induced C-H insertion of Boc-protected-azacycles.

1.4.2. Radical based C(sp^3)-H activation

Several groups have achieved C-H activation of *N*-protected saturated azacycles by the generation of α-amino radical intermediates.[85] For example, 2-(iodobenzyl)-protected-azacycles **101** were reacted under standard tin hydride radical-forming conditions to give benzyl radical **102**, which was converted to α-amino radical **103** by a 1,5-H-transfer and subsequently trapped with appropriate radical acceptors to provide substituted azacycles **104** (Scheme 30).[86] In this case, the 2-(iodobenzyl)-group was found to be a more suitable *N*-protecting group than the originally used 2-halobenzamides because it avoided issues of hindered rotation about the amide and could be readily deprotected by hydrogenolysis. Disadvantages with this methodology are that it fails with more complex heterocycles and uses toxic tin derivatives.



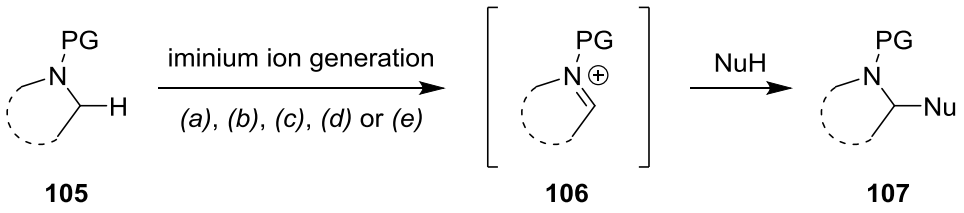
Scheme 30. Radical based synthesis of α-substituted azacycles **104**.

Recently, radical based C(sp3)-H activation has been extended to include more environmentally friendly variants: Nakamura and co-workers reported an iron-catalysed α-phenylation of *N*-(2-halo)benzylated-azacycles with organometallic reagents;[87] an alternative radical source, Et_3B/air, has been used to carry out radical hydroxyalkylation of

N-alkyl-azacycles;[88] α-cyanation of azacycles using non-toxic $PhCH_2CN$ as the radiophile was demonstrated;[89] metal-based photocatalysts have been employed,[90] including a cationic iridium complex for photoredox-catalysed C-H arylations;[91] visible-light-mediated reactions of α-amino radicals with a range of α,β-unsaturated reagents have been reported.[92] Despite these impressive developments, this approach to substituted azacycles is still restricted by the narrow substrate scope, and has so far not been used to synthesise substituted azetidines.

1.4.3. Oxidative C(sp^3)-H activation

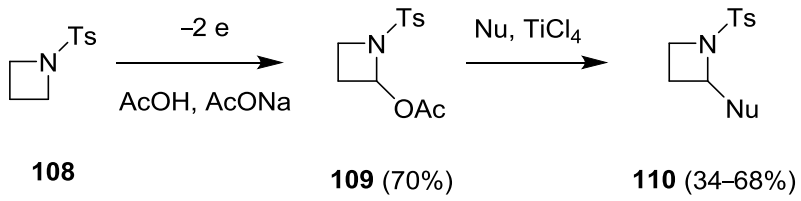
Oxidative C-H activation has become a powerful tool for direct functionalisation of *N*-substituted azacycles. A variety of methods have been used to generate the crucial iminium ion **106**, and this electrophilic intermediate can then react with a broad range of nucleophiles (Scheme 31).[3,79] Much of the research in this area has been focused on the α-functionalisation of *N*-substituted tetrahydroisoquinolines, with only a few examples of oxidative α-functionalisation of piperidines and pyrrolidines.



Scheme 31. Strategies for the formation of iminium ion intermediate **106**.

A rare example of direct functionalisation on an azetidine ring is the anionic oxidation of *N*-tosyl-azetidine **108** to give 2-acetylated-azetidine **109** in 70% yield (Scheme 32).[93]

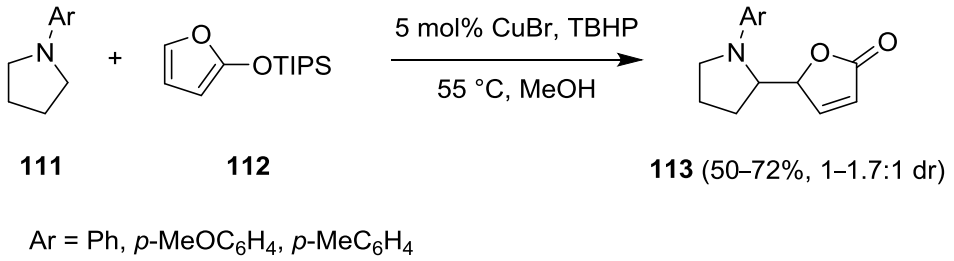
Further functionalisation was then achieved by displacement of the acetoxy group with a range of nucleophiles. Electrochemical oxidation has become an increasingly popular route to α-functionalised saturated azacycles since Yoshida and co-worker's development of the "cation pool" method.[94] This involves the use of electrolysis, usually at a low temperature, to generate and accumulate the iminium ion intermediate **106**, followed by reaction with nucleophiles such as allylic silanes, electron-rich aromatics and 1,3-dicarbonyls. A major limitation with this method is possible oxidation of the nucleophiles. Recent reports have illustrated a number of ways to tackle this problem, including the use of a polymer-supported nucleophile source.[95]



Scheme 32. Direct functionalisation of *N*-tosyl-azetidine **108** by oxidation.

Iminium ion **106** is most commonly generated by a transition-metal catalysed oxidation, usually requiring an external oxidant (e.g. *t*-BuOOH or O_2).[3] Cu-catalysed processes, developed by Li and co-workers,[96] are most frequently observed in the literature, and have been used with a wide-variety of nucleophiles such as alkynes, indoles, nitroalkanes, cyanides, activated and unactivated ketones and dialkyl malonates. This oxidative Cu-catalysed chemistry is still an active research topic, with recent reports focused on the use of chiral ligands for asymmetric functionalisation,[97] or on broadening the reaction scope. For example, Tan and co-workers recently reported the oxidative Cu-catalysed reaction of pyrrolidines **111** with siloxyfuran **112** (Scheme 33).[98] Other nucleophiles have also been

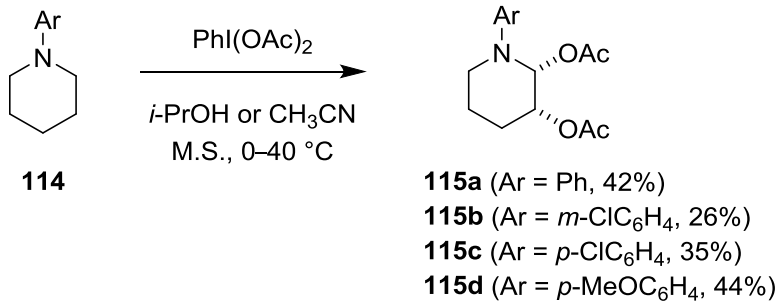
successfully α-incorporated into azacyclic rings, such as silylated enol ethers,[99] ketene acetals, aryl boronic acids,[100] fluorine-containing reagents,[101] and dialkyl phosphonates.[102]



Scheme 33. Cu-catalysed oxidative C-H activation with siloxyfuran **112**.

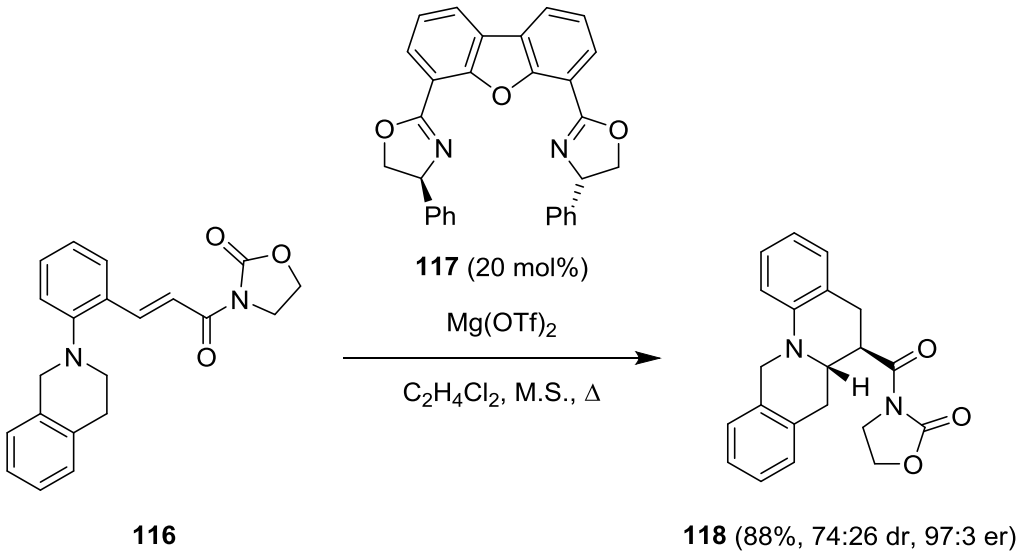
Fe-catalysed processes have also been developed alongside several of the corresponding Cu-processes, and many successful Fe-catalysed oxidative coupling reactions of *N*-substituted-azacycles have been reported.[3] A much smaller number of publications concern the use of alternative transition metals such as Ru, Au, Rh, Pd and V compounds for effective transition-metal catalysed generation of iminium ion intermediate **106**.[103]

A small number of examples of oxidative C-H activation using a stoichiometric oxidant without the assistance of a transition metal catalyst have been reported.[3] Direct functionalisation *N*-alkyl and *N*-aryl tetrahydroisoquinolines using chemical oxidation (benzoyl peroxide or DDQ) was possible with a very limited number of nucleophiles (Me_3SiCF_3 or nitroalkane).[104] A metal-free functionalisation of *N*-aryl-piperidines **114** with $PhI(OAc)_2$ was also reported to give 2,3-diacetylated products **115** in low to moderate yields (Scheme 34).[105] Whilst *p*- and *m*- substituents on the aromatic ring were tolerated in this reaction, *o*-substitution led to decomposition.



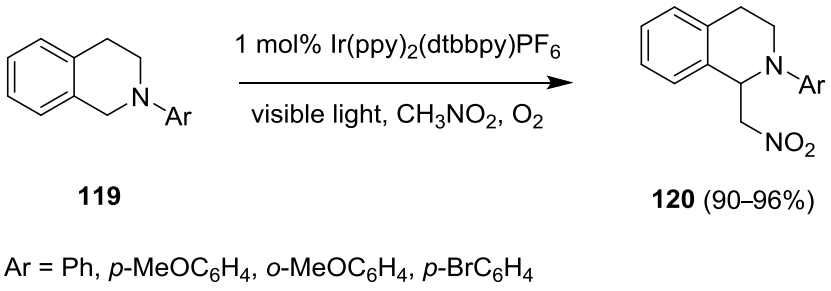
Scheme 34. Metal-free functionalisation of *N*-aryl-piperidines **114**.

Although the majority of methods to form iminium ion intermediate **106** involve transition metals and/or chemical oxidants, a number of ring-fused products have been produced by thermal oxidation.[3] This process is thought to proceed by an intramolecular 1,5- or 1,6-H transfer, which can be promoted by Brønsted or Lewis acids, followed by cyclisation. Enantioenriched fused-ring products have been generated in high er (up to 99:1) by a thermal and Lewis acid catalysed oxidation in the presence of a chiral ligand (Scheme 35).[106]



Scheme 35. Asymmetric synthesis of fused-ring system **118**.

A new method for the α-functionalisation of *N*-aryl tetrahydroisoquinolines involves a photocatalyst which is activated by visible-light. The activated photocatalyst is thought to oxidise the *N*-aryl tetrahydroisoquinoline to a radical species. An external oxidant is required to regenerate the photocatalyst and then convert the amino radical to the iminium ion intermediate **106** by α-H abstraction. Stephenson and co-workers have employed this method for the coupling of *N*-aryl tetrahydroisoquinolines **119** with nitroalkanes by an oxidative aza-Henry reaction (Scheme 36).[107] Although a variety of β-nitro tetrahydroisoquinolines **120** were formed in excellent yield, a much lower yield (27%) was observed with *N*-methyl pyrrolidine. Organophotocatalysts such as Rose Bengal and Eosin Y have also been used as successful alternatives to metal-based photocatalysts for visible-light-induced oxidation of *N*-aryl tetrahydroquinolines.[108]



Scheme 36. Visible-light-induced photocatalytic oxidation of tetrahydroisoquinolines **119**.

1.4.4. α-Lithiation–electrophile trapping methodology

The oldest method for direct α-functionalisation of azacycles is by α-lithiation with a strong base, followed by trapping of the resulting carbanion with electrophiles. Lithiation is usually achieved with a butyllithium/diamine complex,[79,109] although sterically hindered lithium amides such as LDA and LTMP have also been used successfully.[110] This methodology was significantly developed by Beak and co-workers, and is well established

for the functionalisation of suitably *N*-protected/activated pyrrolidines (and higher homologs to some extent).[111,112]

Direct α-lithiation of unprotected azacycles cannot occur due to destabilisation of the carbanion by the adjacent N atom lone pair of electrons.[113] This lone pair of electrons must be involved in conjugation with an activating functional group, such as a carbonyl, to allow formation of dipole-'stabilised' carbanion **122** (Figure 6). An additional benefit of such *N*-activating groups is their chelation to the lithium atom of the base to generate a prelithiation complex, which directs lithiation to the α-position; a process known as the complex-induced proximity effect.[114] In fact, it is thought that the major source of stabilisation of the carbanion **122** is due to chelation with the lithium atom.[115] Effective *N*-protecting/activating groups for α-lithiation include amide, phosphoramide, nitroso and carbamate groups.[79] The Boc protecting group is the most commonly used due to its effectiveness in combination with its ease of attachment and removal.[116] Another advantage is that the sterically demanding *t*-Bu group helps prevent attack of the base at the carbonyl position.

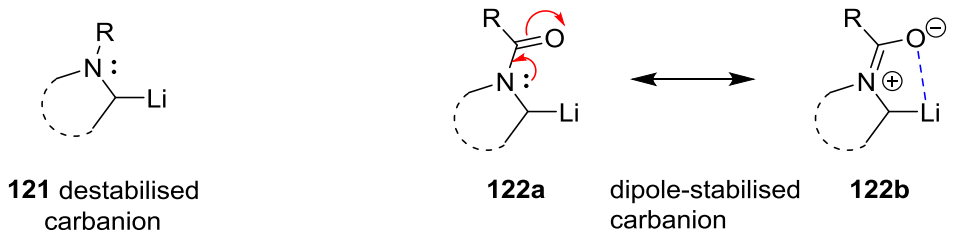
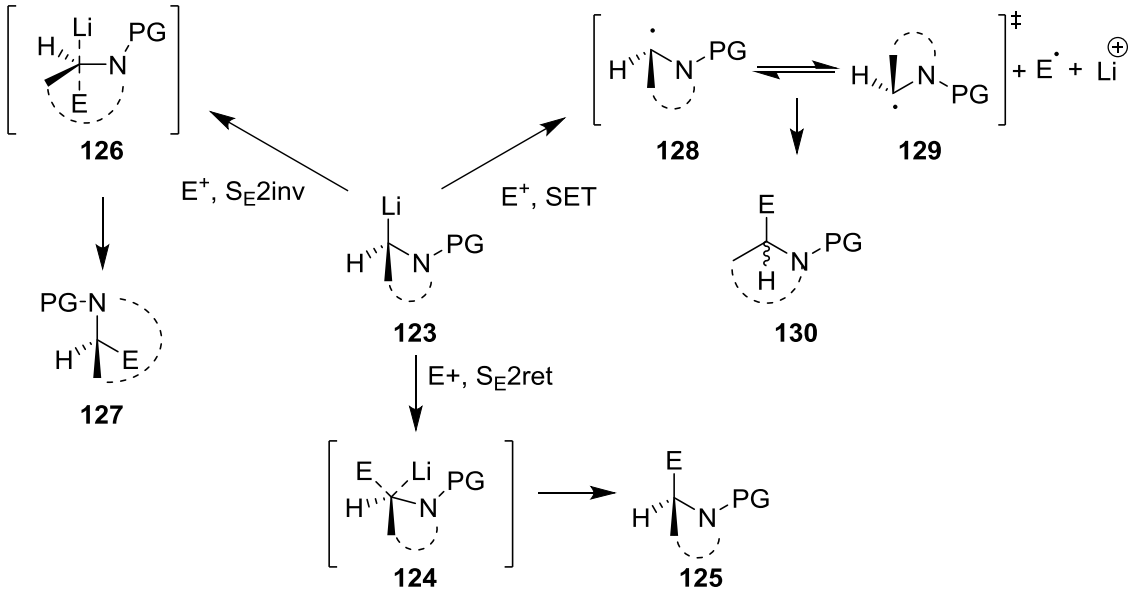


Figure 6. Destabilised and dipole-stabilised carbanions.

Once an α-lithioamine is formed it can then react with an electrophile in a bimolecular electrophilic substitution (S_E2) reaction.[115] Two reaction mechanisms are possible, radical

or polar, depending on the substrates involved (Scheme 37).[117] Either retention (S_E2ret) or inversion (S_E2inv) of stereochemistry can be observed through the polar mechanism, since both are allowed by orbital symmetry. Suitable electrophiles consist of alkyl halides, trialkylsilyl/stannyl halides, aldehydes, ketones, carbonic acid derivatives and Michael acceptors. Certain electrophiles, such as alkyl halides, are usually less efficient due to their tendency to undergo single electron transfer (SET), often increasing the number of side-reactions.[118] The SET pathway is also less desirable because the steric course of radical coupling is random, leading to racemic products.

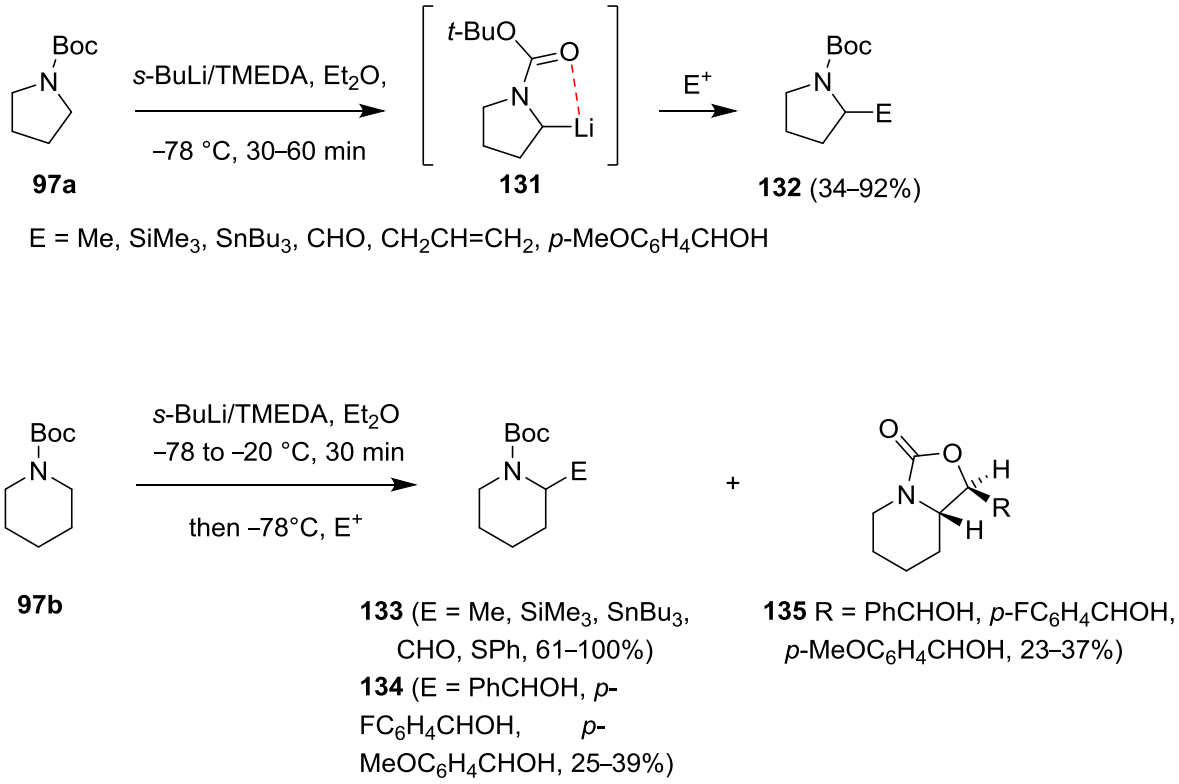


Scheme 37. Reaction mechanisms for bimolecular electrophilic substitution.

1.4.4.1. α-Functionalisation of pyrrolidines and piperidines

Early work by Beak and co-workers demonstrated the use of α-lithiation–electrophile trapping methodology for the direct funtionalisation of *N*-Boc-protected pyrrolidines and piperidines. α-Lithiation of the Boc-protected cyclic amines with *s*-BuLi and deaggregation ligand TMEDA at −78 °C followed by trapping with a range of electrophiles gave 2-substituted azacycles in good yields (Scheme 38).[111,116,119] Reactions

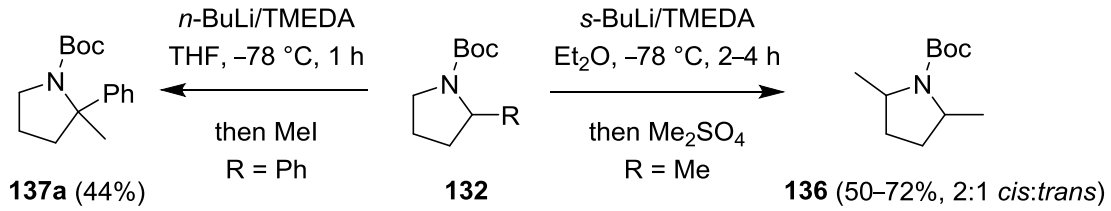
of either substrates with aromatic aldehydes gave 2-substituted products as a ~1:1 mixture of *syn* and *anti*- isomers, with selective cyclisation of the *syn*-isomer onto the Boc group being observed with the piperidine substrate.



Scheme 38. α-Functionalisation of Boc-protected pyrrolidine **97a** and piperidine **97b**.

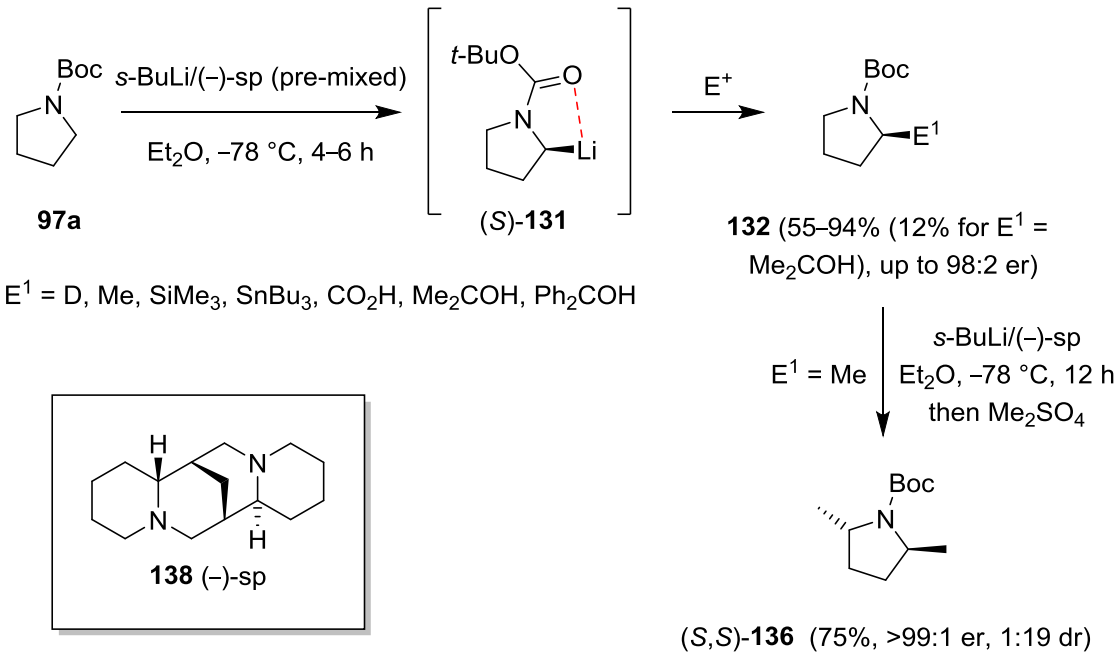
Furthermore, a second α′-deprotonation–electrophile trapping on the mono-substituted products could be carried out with longer lithiation times, generating 2,5-disubstituted-pyrrolidines as a mixture of *cis* and *trans* isomers (Scheme 39),[111] and 2,6-disubstituted-piperidines which strongly favoured the *trans* isomer. In contrast, Xiao and co-workers showed that 2,2-disubstituted products such as **137a** could be formed from a mono-substituted substrate containing an anion-stablilising phenyl substituent in the α-position.[120] This was notable because lithiation took place at the more sterically hindered

position and with milder reaction conditions (a less reactive base and shorter lithiation time).

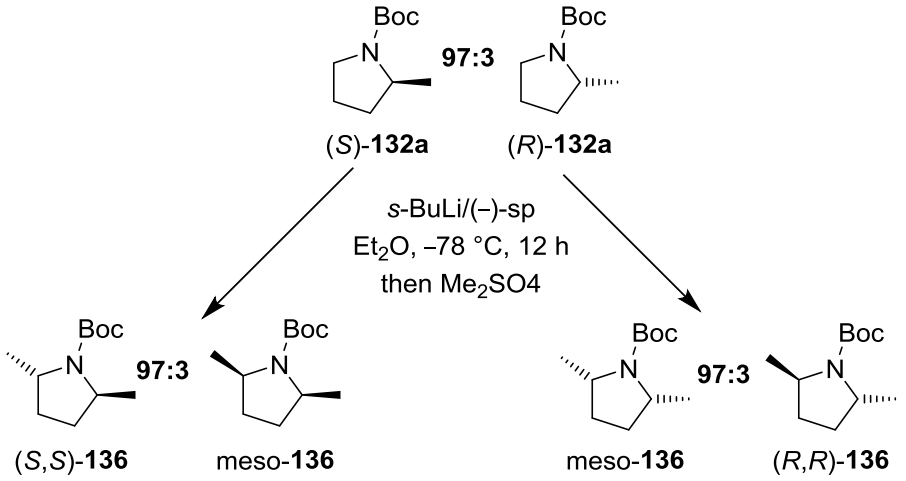


Scheme 39. Formation of disubstituted pyrrolidines.

By replacing the TMEDA ligand with a chiral diamine such as (−)-sparteine ((−)-sp) **138**, Beak and co-workers extended the α-deprotonation–electrophile trapping methodology to include asymmetric synthesis of 2-substituted *N*-Boc-pyrrolidines (Scheme 40).[112,121] Generally, good yields and a high enantioselectivity (up to 98:2 er) could be obtained with a modest range of electrophiles using this approach. The exceptionally low yield of 2-substituted-pyrrolidine from the reaction with acetone is thought to be caused by competing enolisation. Mechanistic studies indicated that selective deprotonation of the *pro-S* H occurs under kinetic control to give carbanion (*S*)-**131**, which is configurationally stable below −50 °C.[122] This was trapped then with electrophiles with retention of configuration. Further reaction of the enantioenriched 2-methyl-pyrrolidine (*S*)-**132a** generated 2,5-dimethylated-pyrrolidine (*S*,*S*)-**136** in both high enantioselectivity and high diastereoselectivity, which is in stark contrast to the poor selectivity observed with TMEDA. This is a good example of the use of a chiral substrate to amplify the enantioselectivity:[123] assuming that the second α′-deprotonation–electrophile trapping step occurs with the same enantioselectivity as the initial methylation step, the er is calculated to increase from 97:3 for starting material (*S*)-**132a** to 99.9:0.1 for 2,2-dimethylated product (*S*,*S*)-**136** (Scheme 41), which is consistent with the experimental result.



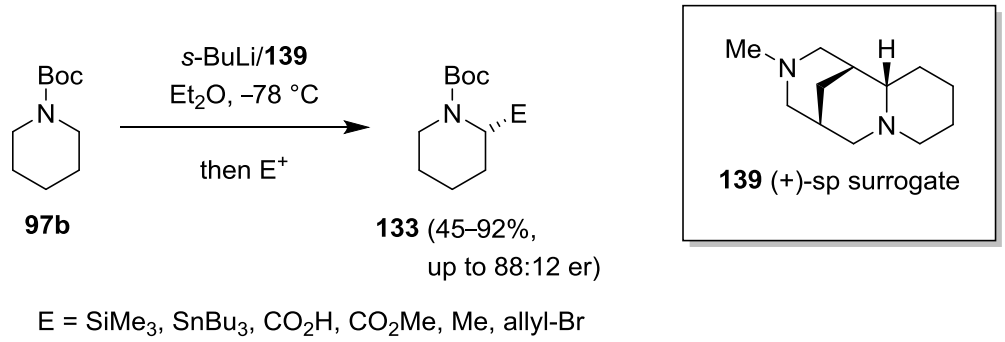
Scheme 40. Asymmetric α-lithiation–electrophile trapping on *N*-Boc-pyrrolidines.



Scheme 41. Calculated er amplification using an enantioenriched substrate.

Although the (−)-sp-mediated asymmetric deprotonation methodology could be successfully applied to a number of other azacycles,[124] poor yields were obtained with *N*-Boc-piperidine **97b**.[125] For example, attempted reaction of *N*-Boc-piperidine **97b** with *s*-BuLi/(−)-sp complex followed by trapping with Me_3SiCl gave the 2-silylated product in

only 8% yield. Another disadvantage was the comparative unavailability of (+)-sp compared to (−)-sp; historically, the latter was the only enantiomer that was commercially available. To overcome this problem, O'Brien and co-workers developed a readily accessible (+)-sp surrogate **139**,[126] which afforded enantioenriched substitution products with the opposite sense of asymmetric induction to those formed with (−)-sp. Pleasingly, the **139**/s-BuLi complex can even operate well with the less reactive *N*-Boc-piperidine substrate under optimised reaction conditions, providing 2-substituted-piperidines **133** in high yield and enantioenrichment (Scheme 42).[127] Since then, the availability of the natural products (−)-sp and (+)-sp has changed, and this issue will be further discussed in section 4.2. (p 140–141).



Scheme 42. First high-yielding asymmetric lithiation–electrophile trapping of *N*-Boc-piperidine **97b**.

A range of other chiral ligands (mostly diamines) have also been explored,[3,128] and many gave good results with *N*-Boc-pyrrolidine. O'Brien and co-workers carried out competition experiments between selected ligands and (−)-sp in order to construct a reactivity series for the asymmetric deprotonation of *N*-Boc-pyrrolidine (Figure 7).[129] The *s*-BuLi/(+)-sp surrogate **139** complex was found to be more reactive than the *s*-BuLi/(−)-sp, which is why it was more successful with the challenging *N*-Boc-piperidine substrate. Of the ligands examined in this report, bispidine ligand **145** formed the least reactive *s*-

BuLi/diamine complex. This less reactive ligand has been employed to act as an achiral 'bulk ligand' for ligand-exchange catalytic asymmetric deprotonation reactions with sub-stoichiometric quantities of (−)-sp.[130] This approach relies on a much faster deprotonation with the *s*-BuLi/(−)-sp complex compared to the *s*-BuLi/**145** complex and rapid ligand exchange, to generate enantioenriched products in high yield.

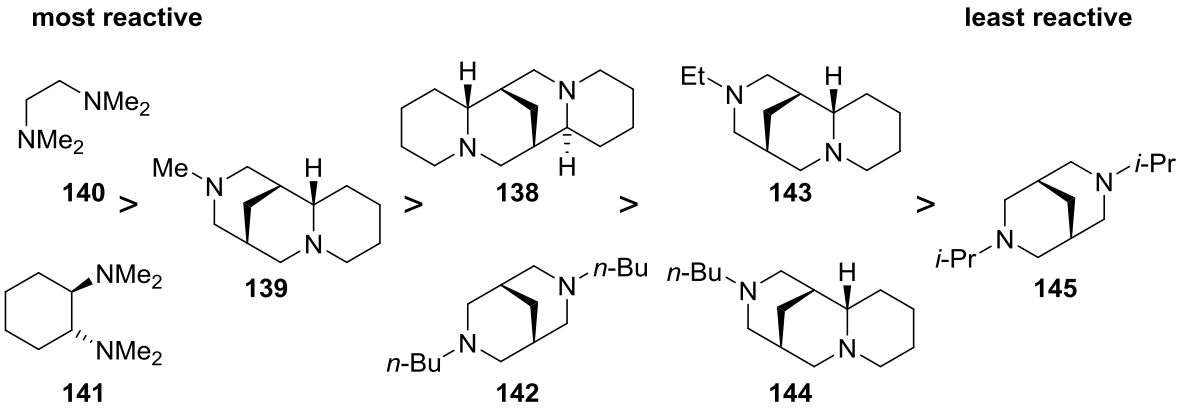
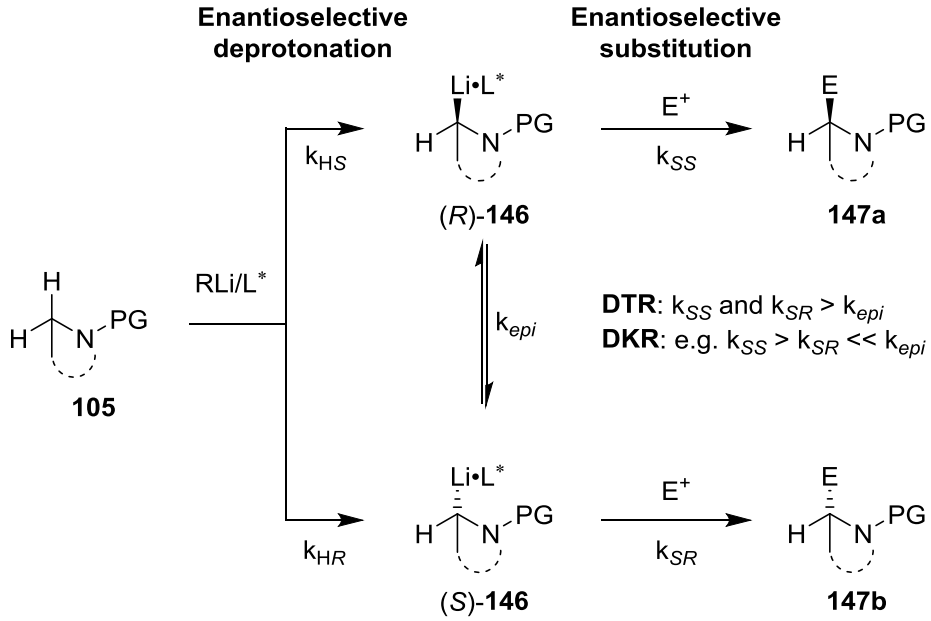


Figure 7. Most of the ligands from O'Brien's reactivity series for asymmetric deprotonation.

Another important development is the use of dynamic resolution for the asymmetric α-lithiation–electrophile trapping of *N*-protected azacycles.[3] Unlike the more traditional asymmetric approaches mentioned above, dynamic resolution relies on the generation of configurationally labile diastereomeric organolithium complexes (in the presence of a chiral ligand) (Scheme 43).[131] Since α-amino organolithium species are typically configurationally stable at very low temperatures, higher reaction temperatures are often required to reach equilibrium between the two diastereomeric complexes. The er of the product reflects the ratio of the two diastereomeric complexes if their interconversion rate is lower than the rate of electrophile trapping. High enantioselectivity can be achieved using appropriate conditions/chiral ligands to favour the formation of one of the

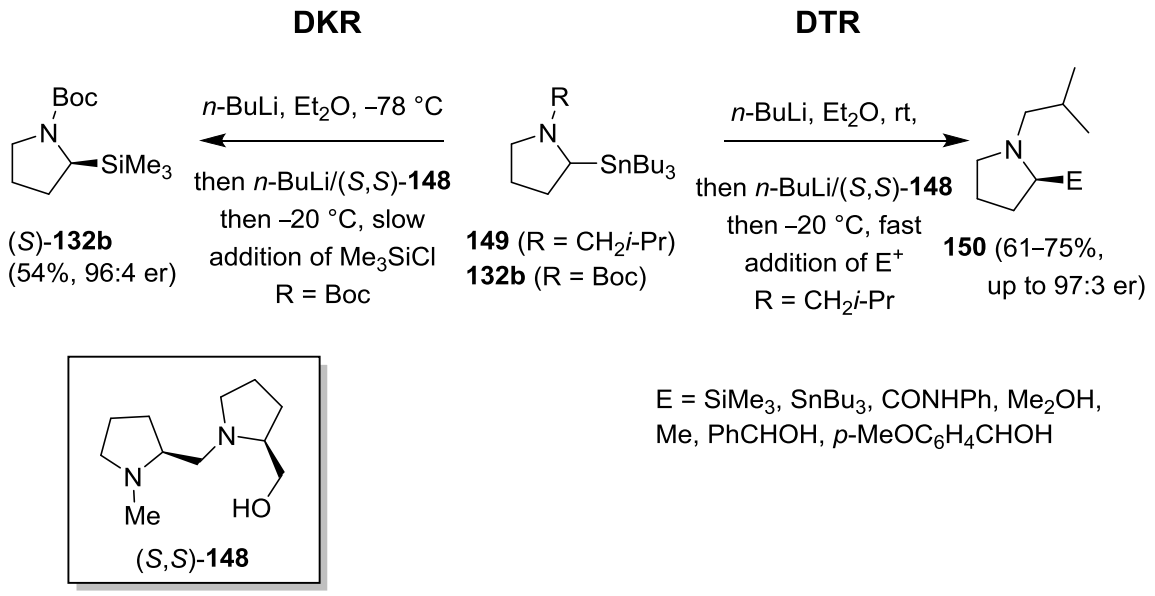
diastereomeric complexes. This process is known as dynamic thermodynamic resolution (DTR).[132] Alternatively, a dynamic kinetic resolution (DKR) can occur if interconversion of the diastereomeric complexes is faster than the electrophile trapping step and one of the diastereomeric complexes reacts more quickly with the electrophile.



Scheme 43. Pathways for chiral induction using a chiral ligand L*.

Coldham and co-workers discovered that the choice of *N*-protecting group was of high importance for dynamic resolution of pyrrolidines.[133] Treatment of *N*-alkyl-2-tributylstannyl-pyrrolidine **149** with 1.2 equiv *n*-BuLi in Et_2O for 1 h at rt, followed by addition of chiral ligand (*S*,*S*)-**148** (pre-treated with *n*-BuLi) and then trapping with electrophiles gave high levels of enantioselectivity by a DTR (Scheme 44).[134] The disadvantage of the *N*-isobutyl 'protecting group' is that it cannot be removed at the end of the synthesis. However, reaction of *N*-Boc-2-tributylstannyl-pyrrolidine **132b** under similar conditions led to poor enantioselectivity.[135] Studies by Gawley and co-workers have enabled the thermodynamic parameters to be calculated for enantiomeric inversion of

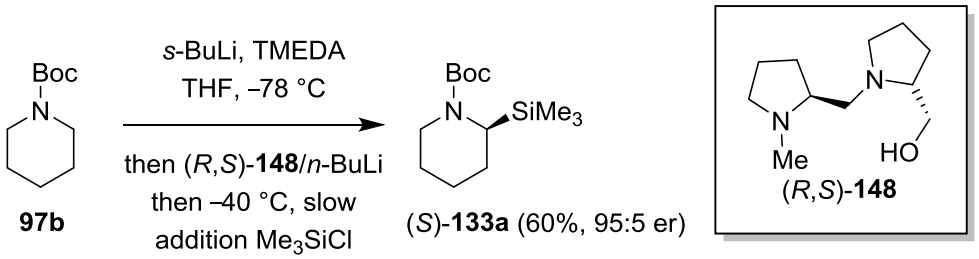
2-lithiopyrrolidines with different protecting groups.[136] These data revealed that the barrier for enantiomerisation is lower for the *N*-Boc-pyrrolidine substrate compared to *N*-alkyl-pyrrolidine derivatives, which implies that dynamic resolution should be possible at lower temperatures. In fact, excellent enantioselectivity was achieved with the *N*-Boc-2-tributylstannyl-pyrrolidine **132b** substrate by reaction with 10 equiv *n*-BuLi (to increase the rate of interconversion of the complexes) at −78 °C, followed by addition of chiral ligand (*S*,*S*)-**148** at −20 °C and then slow addition of Me_3SiCl. In this case, the improved enantioselectivity results from a DKR, with a faster Me_3SiCl-trapping of the (2*S*)-*N*-Boc-2-lithiopyrrolidine enantiomer compared to the (2*R*)-enantiomer.



Scheme 44. Dynamic resolution of *N*-protected 2-substituted pyrrolidines.

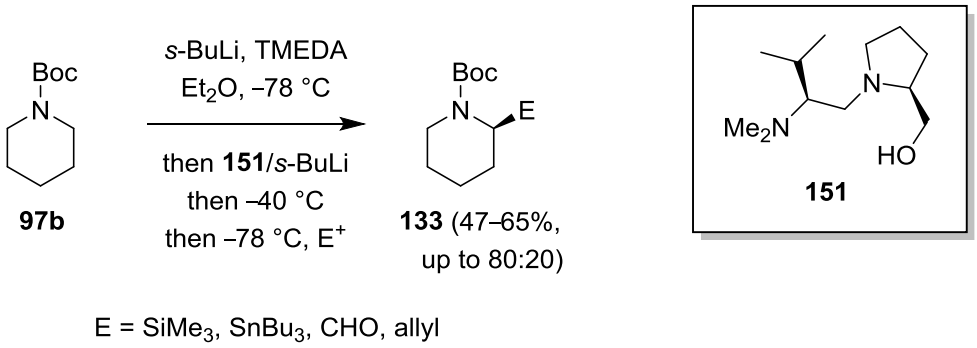
The dynamic resolution approach has also been successfully applied to the asymmetric synthesis of Boc-protected piperidines. α-Silylation of *N*-Boc-piperidine **97b** occurred smoothly under DKR conditions to give enantioenriched 2-silylated product (*S*)-**133a** in good yield (Scheme 45); as seen with the corresponding *N*-Boc-pyrrolidine system, the electrophile was limited to Me_3SiCl for high enantioselectivity.[137] To broaden the reaction

scope, the highly selective Me_3SiCl could be added in smaller amounts as a sacrificial electrophile, followed by the desired electrophile (Bu_3SnCl or Me_2SO_4), to give highly enantioenriched 2-stannylated or 2-methyl products (up to 99:1 er) in low yield (12–19%) with the opposite sense of enantioinduction to the 2-silylated product.



Scheme 45. DKR of *N*-Boc-2-silylated-piperidine **133a**.

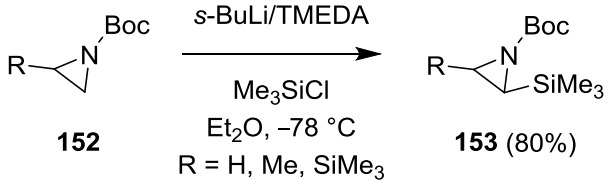
Further development of this chemistry by Coldham and co-workers gave rise to conditions for the dynamic resolution of 2-substituted *N*-Boc-piperidines under thermodynamic control (Scheme 46).[138] A limited range of electrophiles could be trapped using these conditions to give enantioenriched 2-substituted-piperidines in good yield. The enantioselectivity was found to be highly dependent on the structure of the chiral ligand; higher levels of selectivity were generally observed with ligands containing the rigid prolinol motif and steric bulk α- to the N. As with the previous *N*-protected pyrrolidine systems, studies to establish the thermodynamic parameters of the enantiomersiation of the diastereomeric complexes were also carried out for the *N*-Boc-piperidine substrate.[139] These studies highlighted the important role of the TMEDA additive in the rate of both enantiomersiation and DTR.



Scheme 46. DTR of *N*-Boc 2-substituted piperidines **133**.

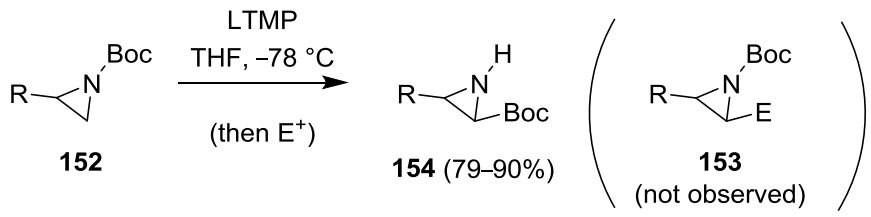
1.4.4.2. Previous work: α-functionalisation of aziridines

α-Deprotonation-electrophile trapping of the smaller aziridine substrate has been far less investigated. One of the aims in the Hodgson group has been to extend this α-functionalisation chemistry. Although Boc proved to be an efficient *N*-protecting/activating group for α-deprotonation–electrophile trapping on pyrrolidines, there is only one analogous example for a simple Boc-protected-aziridine (terminal aziridines **152**) in which the electrophile (Me_3SiCl) had to be present during the lithiation step (Scheme 47).[140]



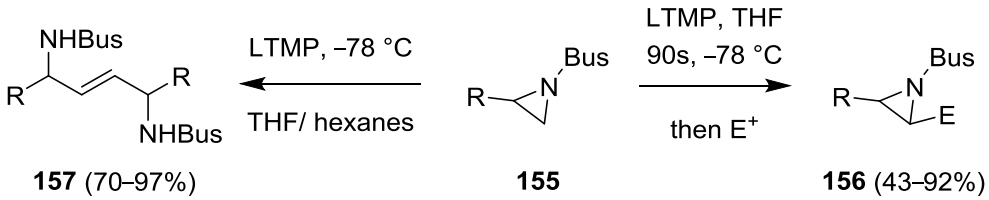
Scheme 47. Silylation of *N*-Boc-aziridines **152**.

Furthermore, studies within the Hodgson group revealed that the Boc protecting group undergoes an unexpected *N*- to *C*- migration following α-lithiation of terminal aziridines **152** with the bulky base LTMP (Scheme 48).[141]



Scheme 48. *N*- to *C*- migration in *N*-Boc-aziridines **152.**

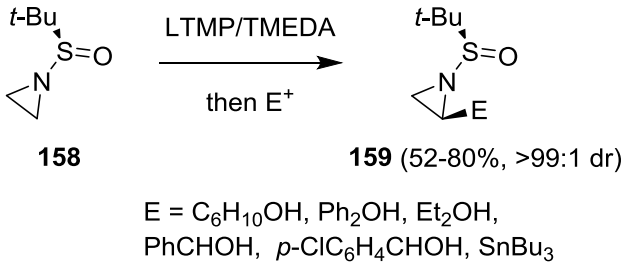
Earlier work showed that the *t*-butylsulfonyl (Bus) group is a more suitable *N*-protecting group for aziridines. Bus-protected terminal azirdines **155** reacted with a range of electrophiles, following a short lithiation time, to give the desired 2,3-disubstituted products **156** in good yield (Scheme 49).[142] Pleasingly, this methodology could also be applied to the *C*-unsubstituted *N*-Bus-aziridine substrate, providing a high yielding route to 2-substituted aziridines.[143] A major drawback to this approach is that *N*-Bus-aziridines can undergo a competing dimerisation to form 2-ene-1,4-diamines **157**.[141b,144] The best results for α-functionalisation of the unhindered *C*-unsubstituted azirdine were achieved by replacing LTMP with a combination of TMEDA, known to inhibit dimerization of α-lithiated epoxides,[145] and *s*-BuLi.



Scheme 49. Reactions of α-lithiated *N*-Bus-aziridines **155**.

Extension of this methodology to allow asymmetric synthesis of substituted aziridines was accomplished by employing the chiral *t*-butylsulfinyl group as an alternative *N*-protecting group (Scheme 50).[143] In this case, better yields were obtained using the less nucleophilic

base LTMP instead of *s*-BuLi, reducing the chance of unwanted attack at the sulfinyl group.



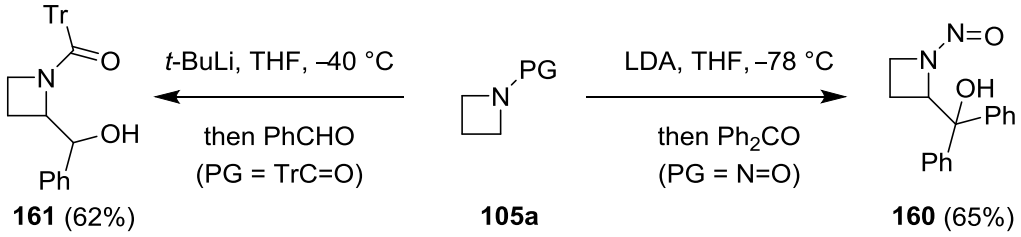
Scheme 50. Asymmetric synthesis of substituted aziridines.

1.4.4.3. Previous work: α-functionalisation of azetidines

Having successfully applied the α-lithiation–electrophile-trapping methodology for the direct funtionalisation of aziridines, the Hodgson group sought to tackle the more challenging azetidine substrate. As mentioned above, the azetidine ring has a similar, but lower, ring strain than the smaller aziridine system. It is well known that ring strain is alleviated by an increase in *s*-character of the C-H bonds in cyclic compounds;[146] therefore α-protons in azetidine are less acidic than those in aziridine. In addition, the greater ring strain of azetidine compared to that of pyrrolidine[12] means that charge transfer from the N atom to the *N*-activating group is more difficult for the 4-membered ring. These complications have resulted in much slower development of α-deprotonation–electrophile trapping methodologies on azetidine.

Until recently, there were only two isolated examples of α-deprotonation–electrophile trapping on azetidine.[147] These examples involved either a carcinogenic nitrosyl or high molecular weight triphenylacetyl *N*-protecting/activating group (Scheme 51). An

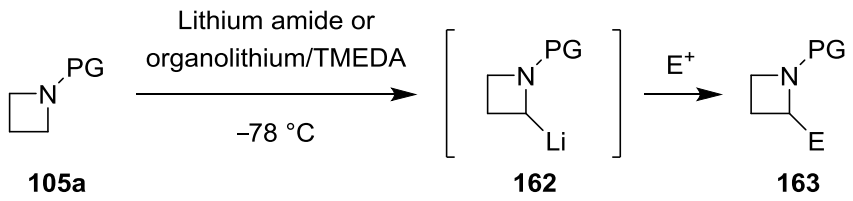
additional problem with the latter group is that a competing [1,3]-shift of the carbamoyl group occurs, following *o*-lithiation at the triphenyl acetyl group.



161 (62%) **105a** **160** (65%)

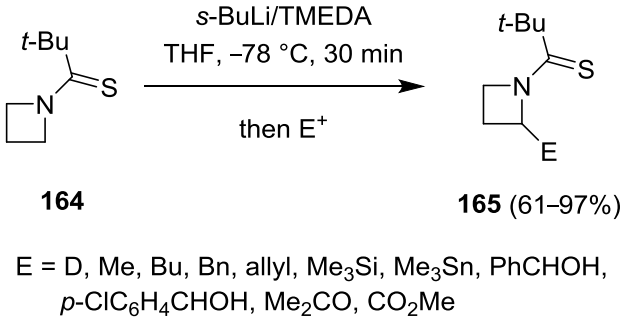
Scheme 51. Early examples of α-lithiation–electrophile trapping on azetidines.

The Hodgson group investigated a range of alternative *N*-protecting/activating groups for α-functionalisation of azetidine (Scheme 52).[148] Despite the good performance of the *t*-butylsulfinyl group for *N*-protection/activation of aziridines, reactions with *N*-*t*-butylsulfinyl-azetidine resulted in decomposition, thought to be due to attack at the sulfoxide group by the lithium base. Similarly, *N*-pivaloyl-azetidine suffered attack of *s*-BuLi at the carbonyl group and produced no desired product. *N*-Bus and *N*-(diethylphosphonyl)-azetidines also resisted α-lithiation, returning only starting materials. Although the Boc group works well for pyrrolidines, *N*-Boc-azetidine was shown to be unreactive to lithium amides (LDA and LTMP) and only generated a trace amount of desired product with *s*-BuLi/TMEDA. The rarely used thiopivaloyl group was the only *N*-protecting group in this study that was found to be effective for α-lithiation of azetidine. This was surprising as Seebach and co-workers had previously reported that out of several secondary amine-derived thiopivalamides, only the thiopivalamide derived from dimethylamine could be lithiated.[149]



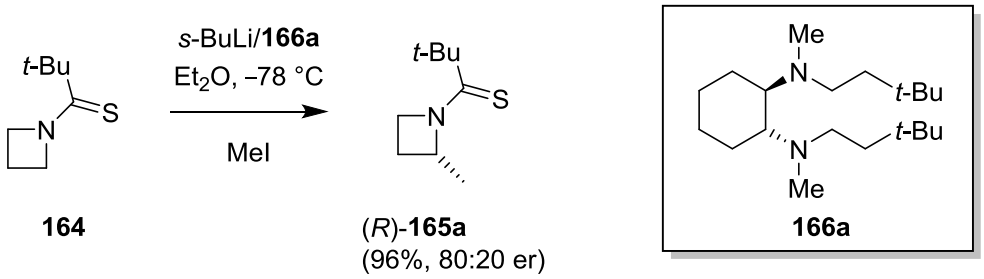
Scheme 52. Investigation of reaction conditions for the azetidine substrate.

Remarkably, *N*-thiopivaloyl-azetidine **164** underwent clean lithiation with *s*-BuLi/TMEDA in THF at −78 °C followed by electrophile trapping with a range of different electrophiles to give good to excellent yields of 2-substituted azetidines **165** (Scheme 53).[148] Furthermore, reactions with benzaldehyde and *p*-ClC_6H_4CHO generated trapped products as single diastereomers.



Scheme 53. α-Deprotonation–electrophile-trapping of *N*-thiopivaloyl-azetidine **164**.

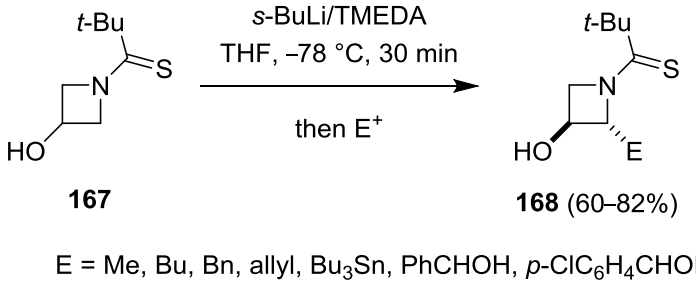
In order to develop an enantioselective variant of this methodology, Hodgson and co-workers tested a number of chiral ligands for asymmetric methylation of *N*-thiopivaloyl-azetidine **164**.[148] Although (−)-sp **138** led to poor enantioselectivity in several solvents (Et_2O, TBME and THF), a more promising er (72:28 *R*:*S*) was generated with this ligand in hexane. However, the ligand which showed the highest enantioselectivity was *trans*-cyclohexane-1,2-diamine **166a**, which gave methylated product (*R*)-**165a** in 80:20 er in Et_2O (Scheme 54).



164 (*R*)-**165a** (96%, 80:20 er) **166a**

Scheme 54. Asymmetric α-lithiation–methylation on *N*-thiopivaloyl-azetidine **164**.

More recently, Hodgson and co-workers have shown that the α-lithiation–electrophile trapping methodology can be applied to azetidines with a greater degree of substitution. *N*-Thiopivaloylazetin-3-ol **167** underwent trapping with a range of electrophiles to give the 2,3-disubstituted products **168**, with high *trans*-selectivity (Scheme 55).[150] An exception to this trend in selectivity was observed with protonation or deuteration, which was thought to be directed *cis* by the alkoxide.



167 **168** (60–82%)

E = Me, Bu, Bn, allyl, Bu_3Sn, PhCHOH, *p*-ClC_6H_4CHOH

Scheme 55. α-Functionalisation of *N*-thiopivaloylazetidin-3-ol **167**.

1.4.4.4. Limitations of the thiopivaloyl protecting group

Although *N*-thiopivaloyl-azetidine **164** could be successful α-deprotonated and trapped with a variety of electrophiles, the electrophile scope was limited (Figure 8).[151] Aromatic aldehydes with electron-donating substituents and electron-rich furfural gave mixtures of desired azetidines and unwanted alcohol side-products, whilst cinnamaldehyde,

benzophenone, enolisable aldehydes and ethyl chloroformate resulted in decomposition. Enolisable ketones (other than acetone), Mander's reagent, DMF and tosyl chloride also failed to produce the desired trapped products.

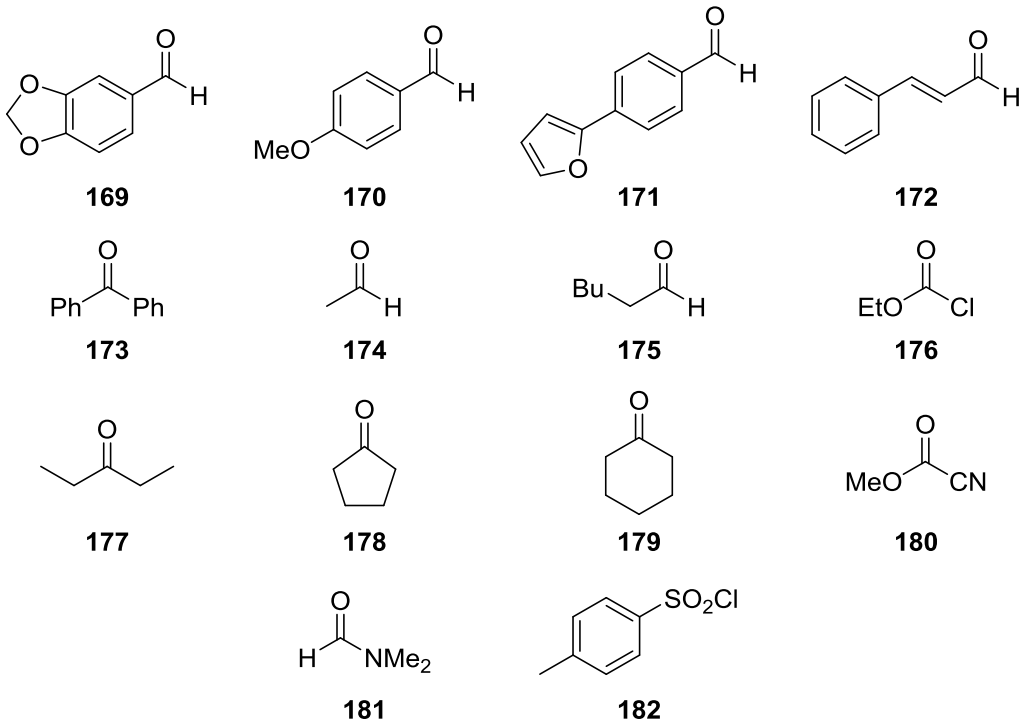
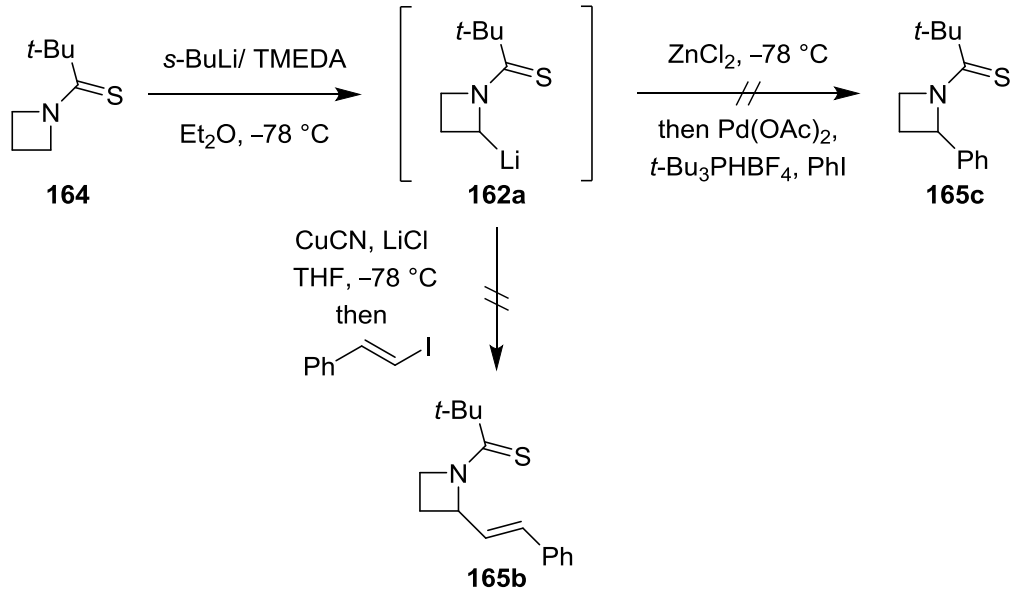


Figure 8. Unsuccessful electrophiles for α-functionalisation of *N*-thiopivaloyl-azetidine **164**.

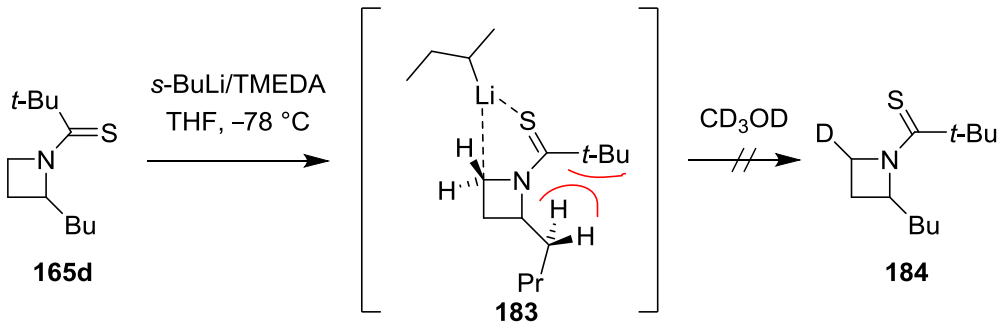
Further attempts to broaden the scope of α-functionalisation by transmetallation of α-lithiated *N*-thiopivaloyl-azetidine to the corresponding copper species followed by alkenylation to compound **165b**, using conditions that worked well for *N*-Boc-pyrrolidines,[152] was unsuccessful in preliminary studies (Scheme 56).[151] Likewise, transmetallation of the lithiated species to the corresponding zinc species followed by palladium-catalysed coupling with aryl bromides returned only starting materials when applied to *N*-thiopivaloyl-azetidine **164**, despite previous success with *N*-Boc-piperidines.[153] These disappointing results are thought to be due to some or all of the following: the high steric demand of the compound, the tendency of the starting materials

to undergo SET, and the incompatibility of the thioamide functionality with some of the reagent systems.



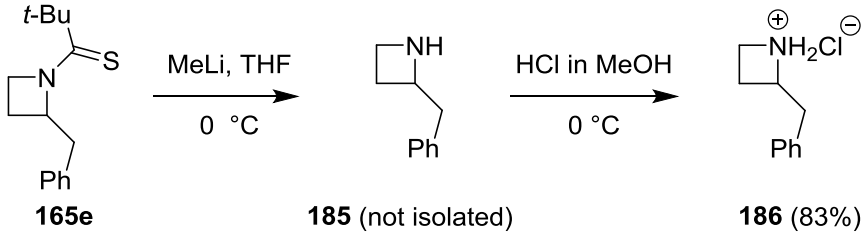
Scheme 56. Failed alkenylation and cross-coupling reactions.

One of the major limitations with using the thiopivialoyl protecting group for this chemistry is that it was found to inhibit the formation of 2,4-disubstituted-azetidines by a second α′-deprotonation–electrophile trapping on the mono-substituted products.[151] No reaction was observed when 2-butyl-azetidine **165d** was subjected to α-lithiation–electrophile trapping conditions, which at the time was attributed to steric hindrance between the bulky *t*-Bu group of the thioamide and the α-substitutent preventing formation of the correct rotamer for coordination of the sulfur atom to the organolithium (Scheme 57).



Scheme 57. Failed attempt to form 2,4-dibsubstiuted-azetidine **184**.

Another major drawback with the thiopivaloyl *N*-protecting/activating group is that harsh conditions (5 equiv. MeLi in THF at 0 °C for 5 h) were needed for deprotection (Scheme 58).[148] Alternative deprotection conditions have been reported by Lubosch and Seebach,[149c] involving reaction of the thiopivalamide with refluxing ethylene diamine; unfortunately deprotection of *N*-thiopivaloyl-azetidine **165e** was unsuccessful under these conditions.[151]



Scheme 58. Deprotection of *N*-thiopivaloyl-azetidine **165e**.

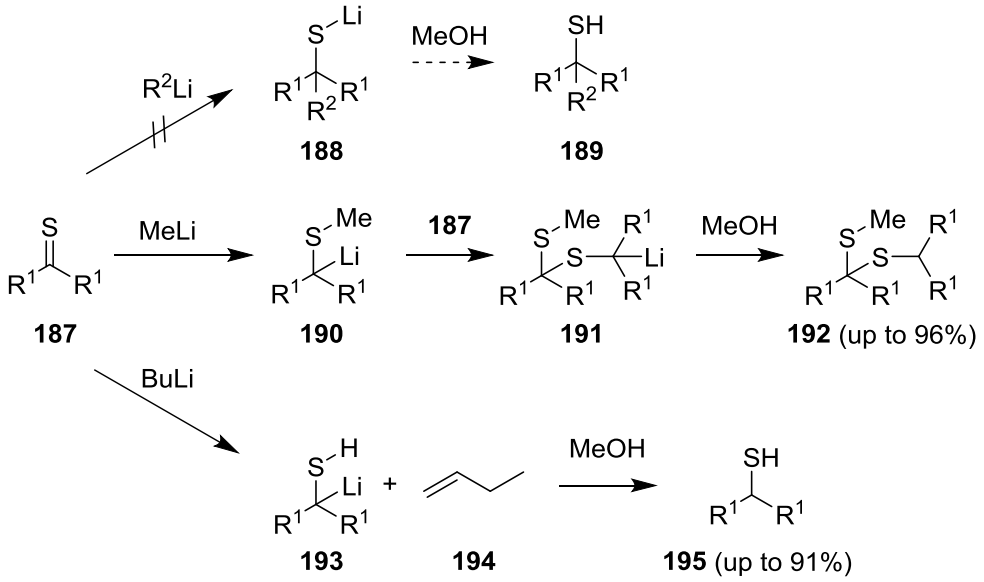
1.5. Proposed work

As discussed above, there is currently a lack of efficient methods for the synthesis of substituted azetidines, with many approaches involving complex starting materials with long syntheses. Since the parent unsubstituted azetidine (**51**) is commercially available and can be synthesised on kg scale,[51] protection of this substrate with a suitable *N*-protecting

group followed by α-lithiation–electrophile trapping, in initial studies, has been shown to be a potentially more convenient route to substituted azetidines. In an effort to overcome the previously mentioned issues with the thiopivaloyl protecting group, the overall aim of my studies was to develop a new *N*-protecting/activating group for the improved synthesis of 2-substituted and 2,4-disubstituted-azetidines, by α-lithiation–electrophile trapping, ultimately in an enantioselective fashion.

1.5.1. Design elements for a new *N*-protecting group

While use of the Boc and pivaloyl groups previously led to attack of *s*-BuLi at the carbonyl group in the azetidine system, *N*-thiopivaloyl-azetidine did not suffer in the same way (see section 1.4.4.3., p 42).[148] One simple explanation for the reduced propensity for attack of the base at the thiocarbonyl functionality is that S has a closer electronegativity to C, so the C=S bond is not strongly polarised and the C atom is less electron deficient than in the corresponding carbonyl functionality.[154] In fact, Bailey and co-workers have recently shown that alkyllithiums undergo fundamentally different reactions with thiocarbonyls than with carbonyls.[155] It is well known that tertiary alcohols can be readily generated from ketones by addition of alkyllithiums at the electrophilic carbonyl C. In contrast, the corresponding reactions with thioketones did not lead to tertiary thiols **189**; instead, sulfides **190** and **192** and secondary thiols **195** were formed by thiophilic addition or reduction reactions (Scheme 59).

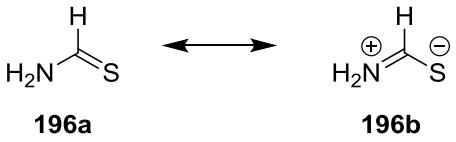


Scheme 59. Reactions of alkyllithiums with thioketones.

Computational modelling by Bailey and co-workers for addition of dimeric MeLi to the (thio)carbonyl C in acetone and thioacetone indicated that the two processes have very different transition state geometries;[155] the carbonyl C in acetone is well aligned for attack of the alkyllithium (calculated Li-O-C angle = 169.7°), whereas the thiocarbonyl C in thioacetone is in a less favourable alignment (calculated Li-S-C angle = 110.2°), resulting in a higher $\Delta G^{\ddagger}$ for the latter process. The above failure to produce tertiary thiols **189** (Scheme 59) was therefore attributed to a relatively high $\Delta G^{\ddagger}$ for this reaction. We therefore expected that by retaining thiocarbonyl functionality in a modified *N*-protecting group, attack of the organolithium at the thiocarbonyl C would remain unfavourable.

As mentioned above, the C=S bond is less polarised and has a less electron deficient C than the C=O bond. Despite this, thioformamide is known to have a larger rotational barrier than formamide.[154] One reason for this is because the O in C=O has a relatively large negative charge, so N to O charge transfer is less energetically favourable. In addition, the increased size of the S atom compared to O means that it can more readily

accommodate charge transfer from N (Figure 9). As mentioned in section 1.4.4. (p 29), successful α-lithiation of azacycles typically requires charge transfer from the N to an *N*-'activating' group in order to help stabilise the carbanion (and the transition state for deprotonation leading to it) and to direct the organolithium to react at the α-position ('complex-induced proximity effect'). We therefore considered that, to facilitate efficient azetidine α-lithiation, it was important to retain the thiocarbonyl functionality in the design of a modified *N*-protecting group.



196a **196b**

Figure 9. N to S charge transfer in thioformamide.

We decided to examine the sulfur analogue of the Boc group, the *t*-butoxythiocarbonyl (*t*-BuOC=S; Botc) group, on the basis that this would allow for mild deprotection by a similar mechanism to Boc deprotection. Additionally, we hoped that the oxygen 'spacer' might help to overcome the difficulty previously seen in the attempted synthesis of 2,4-disubstituted-azetidines (Scheme 57, p 47), by allowing access to the required rotamer that could direct lithiation to the 4-position. The key design elements for this novel *N*-protecting group are summarised in Figure 10.

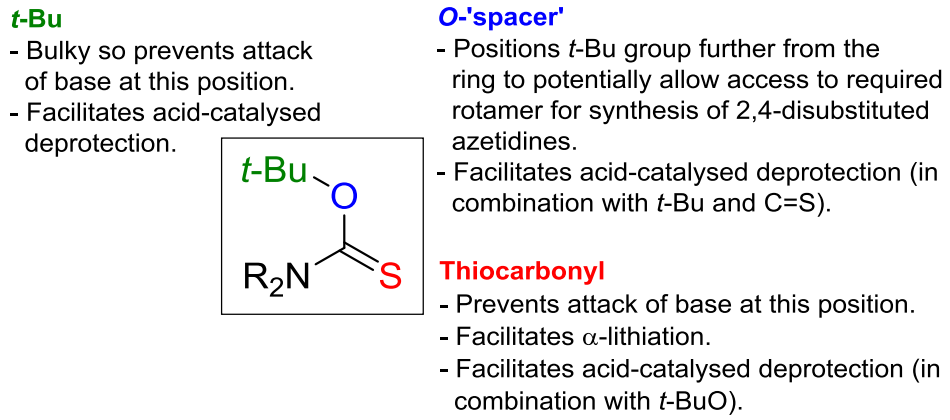
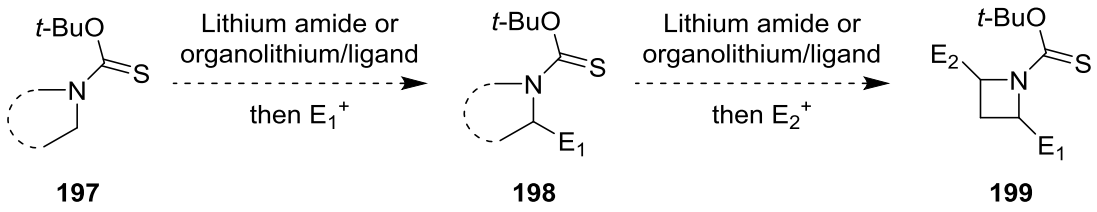


Figure 10. Key design elements for new *N*-protecting group.

1.5.2. Project aims

The first aim of this project was to develop a synthetic route to Botc-protected-azacycles, and to determine whether deprotection of these novel substrates could be achieved under mild reaction conditions. The ability of the Botc group to allow efficient α-lithiation–electrophile trapping on azacycles, particularly azetidines, would then be tested (Scheme 60). If successful, we planned to thoroughly explore the electrophile scope of the reaction and find out if the Botc protecting group could also be used for synthesis of 2,4-disubstituted-azetidines **199** by a second α′-lithiation–electrophile trapping of the mono-substituted products.



Scheme 60. Proposed novel *N*-protecting/activating group for α-deprotonation–electrophile trapping of azacycles.

If the above aims were accomplished, we planned to investigate the propensity of the Botc protecting group to allow access to an asymmetric variant of this azetidine lithiation chemistry using chiral ligands. Finally, we hoped to apply this methodology to the synthesis of a natural product containing the 2,4-disubstituted-azetidine motif, potentially one of the penaresidins (see Figure 3, p 3).

2. Results and Discussion: Synthesis and utility of a new *N*-protecting group

Selective reaction at one site in a multifunctional molecule requires appropriate protecting groups to block any other reactive sites, such as amino groups.[156] The disadvantage with the use of protecting groups is that they add additional steps to synthetic sequences, but they cannot often be avoided; even the synthesis of relatively simple molecules is usually dependant on a protection strategy. In fact, introduction and removal of different protecting groups is the most frequently carried out transformation in the synthesis of multifunctional molecules. Synthesis of molecules of ever-increasing complexity calls for on-going development of a wider variety of new protecting groups.

A number of considerations should be taken into account when designing a new protecting group.[156] The protecting group must be easy to synthesise from inexpensive starting materials, and be stable to chromatography and a wide range of reaction conditions. The ideal protecting group will be easily characterised and contain no chiral centres. In addition, it should be readily and selectively removed under mild conditions. The by-products from the deprotection reaction should be separable from the substrate.

2.1. *N*-Protecting groups

A large number of *N*-protecting groups have been developed, the most important being amides and carbamates.[156] The carbonyl functionality in these protecting groups is essential for conjugation with the *N* atom lone pair, lowering the nucleophilicity of the reactive amino group. Protection of amino groups as amides, formed from acid chlorides

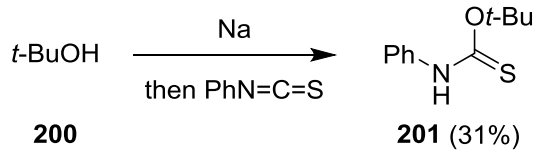
or anhydrides, is most abundant in the syntheses of alkaloids and nucleotides. However, hydrolytic removal of acyl groups requires considerable force, often heating in strongly acidic or strongly basic conditions. On the other hand, carbamates can be deprotected by a range of techniques (depending on the substrate), and have become the dominant protecting group for N. Carbamates can be generated from a variety of reagents, but chloroformates are most often used. They have been particularly successful *N*-protecting groups for minimising base-catalysed racemisation in peptide and protein synthesis

The Cbz group, which can be cleaved by catalytic hydrogenolysis,[156] was first introduced as a protecting group for peptide synthesis in 1932.[157] It has since become one of the most widely used *N*-protecting groups, along with the Boc group. The advantage of the Boc group is its ease of deprotection by acidic hydrolysis, producing gaseous by-products. Importantly, the Boc group contains a bulky *t*-Bu moiety which inhibits nucleophilic attack at the carbonyl and prevents base-catalysed hydrolysis.

2.1.1. The *t*-butoxythiocarbonyl (Botc) group

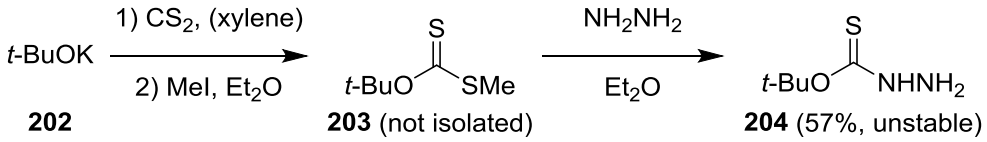
In 1961, Carpino and co-workers suggested the *t*-butoxythiocarbonyl (Botc) group as 'promising and highly selective blocking function' for nitrogen.[158] Their preliminary studies indicated that the Botc group was more acid-labile than even the Boc group; instantaneous deprotection of *N*-Botc aniline **201** was observed with 48% aq HF whereas cleavage of the analogous Boc-protected substrate was slow under these conditions. However, this potential *N*-protecting group has not been further examined,[159] which may be due the perceived instability of the unoxidised sulfur, as well as a lack of practical methods for introducing this blocking function. The synthesis of thiocarbamate **201** was

limited to reaction of *t*-BuOH with an isothiocyanate, giving a low yield of Botc-protected product (Scheme 61).[160]



Scheme 61. Low-yielding synthesis of thiocarbamate **201**.

An alternative method, involving an unstable xanthate **203** intermediate, was reported for the Botc-protection of hydrazine (Scheme 62).[158a,161] The authors note that purification of xanthate **203** was not possible as visible decomposition to 2-methylpropene via a Chugaev reaction occurred at temperatures above 55 °C.[162] Reaction of the crude xanthate **203** with hydrazine generated unstable thiocarbohydrazide **204**, which decomposed on standing.

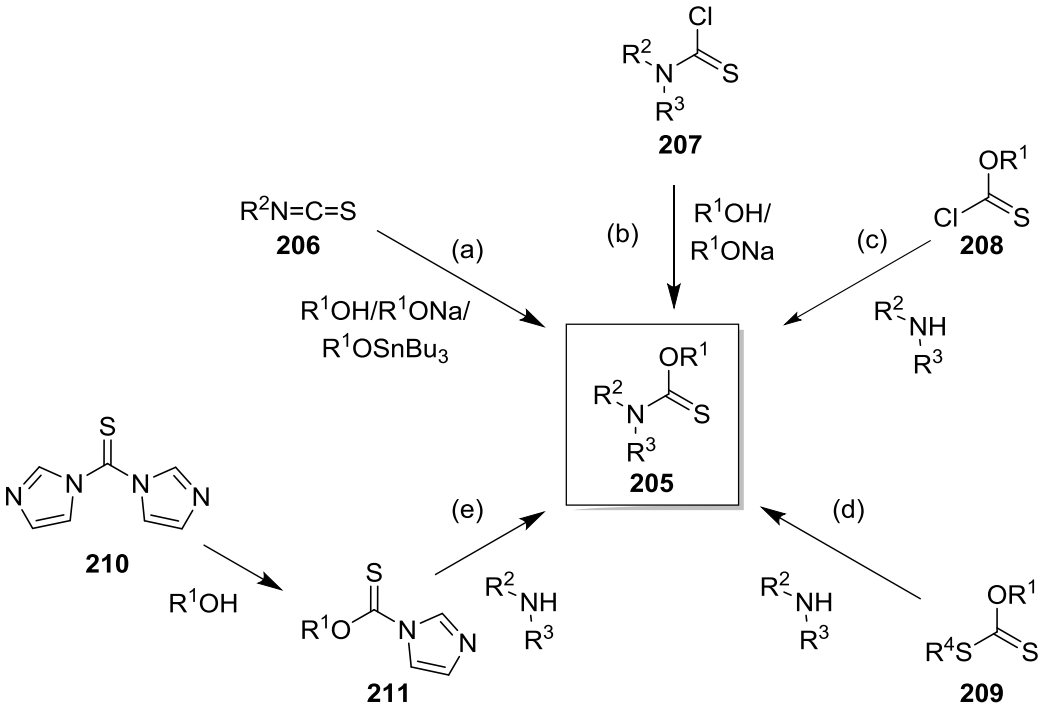


Scheme 62. Attempted Botc-protection of hydrazine.

As discussed in section 1.5.1. (p 48–50), we anticipated that the Botc group would be an effective *N*-protecting group for α-lithiation–electrophile trapping on the azetidine system. Therefore, the first priority of this project was to find suitable conditions for Botc-protection of azacycles.

2.2. Synthesis of *O*-alkyl-thiocarbamates

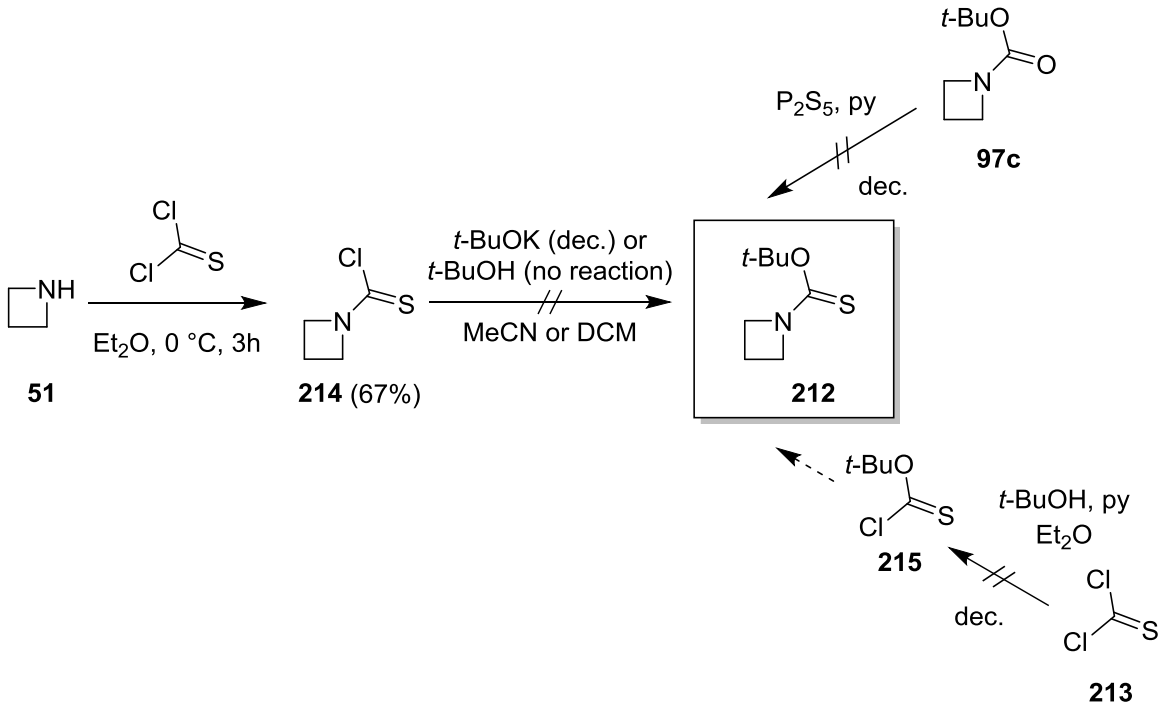
There are a limited number of routes to *O*-alkyl-thiocarbamates (Scheme 63).[163] The most common approach is the reaction of isothiocyanates **206** with alcohols, alkoxides or tin alkoxides (method a), although reactions of thiocarbamoyl chloride derivatives **207** with alcohols or alkoxides can also produce thiocarbamates in high yield (method b). The vast majority of examples employ primary or secondary alcohols or phenols for these methodologies. Alternatively, chlorothioformates **208** (R^1 = alkyl or aryl) can be formed from thiosphosgene, leading to the desired thiocarbamates upon reaction with primary or secondary amines (method c). Thiocarbamates can also be formed from xanthate esters **209**, usually derived from primary or secondary alcohols (method d). Thiocarbonyldiimidazole **210** was found to be another effective thiocarbonyl transfer reagent, reacting with alcohols or phenols to give thiocarbamate **211**, which can undergo further reaction with amines to generate a wider range of thiocarbamates (method e).



Scheme 63. Key approaches to *O*-alkyl thiocarbamates.

2.2.1. Previous work: attempted synthesis of *N*-Botc-azetidine

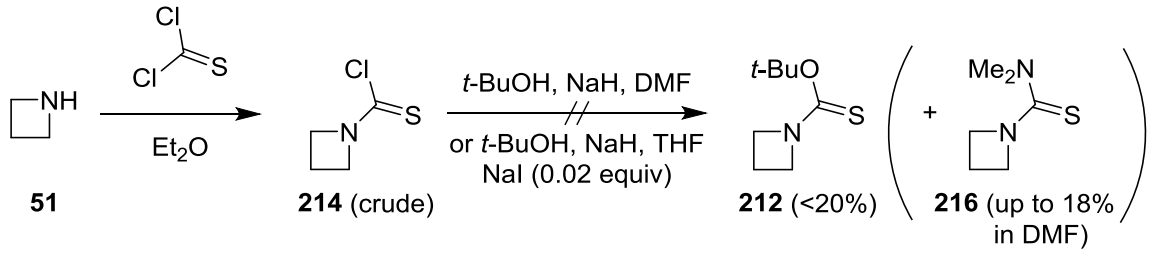
Formation of thiocarbamates from secondary amines such as azetidines is not possible from isothiocyanates. Alternative routes to *N*-Botc-azetidine **212** were previously investigated in the Hodgson group, but without success (Scheme 64).[151] Whilst the reaction of the parent azetidine **51** with thiophosgene **213** did generate the desired thiocarbamoyl chloride intermediate **214** in good yield, further reaction of this intermediate returned only starting materials (with *t*-BuOH) or led to decomposition (with *t*-BuOK). Similarly, attempted preparation of *t*-Bu-chlorothionoformate **215** was unsuccessful, which was unsurprising given the reported instability of the *i*-Pr analogue.[164] Direct thionylation of the *N*-Boc-azetidine **97c**, using conditions that were previously established for formation of *N*-thiopivaloyl-azetidine **164** from the corresponding *N*-pivaloyl-azetidine, also resulted in decomposition.



Scheme 64. Previous attempts to synthesise *N*-Botc-azetidine **212**.

2.3. Studies towards *N*-Botc-azacycles

Although reaction of thiocarbamoyl chloride **214** with either *t*-BuOH or *t*-BuOK was previously unsuccessful in the Hodgson group (see section 2.2.1.), Newman and Hetzel reported a high-yielding preparation of a number of *O*-alkyl dimethylthiocarbamates by reaction of dimethylthiocarbamoyl choride and the corresponding sodium alkoxides in DMF.[165] These reaction conditions were tested on thiocarbamoyl chloride **214**, which was synthesised from azetidine **51** using our established conditions[151] and taken on without purification (Scheme 65). Disappointingly, a low yield (<20%) of very impure *N*-Botc-azetidine **212** was generated during this reaction, with or without heating to 60 °C, along with a number of unknown decomposition products. One side-product which could be identified was thiourea **216**, which was produced in up to 18% yield under these conditions.



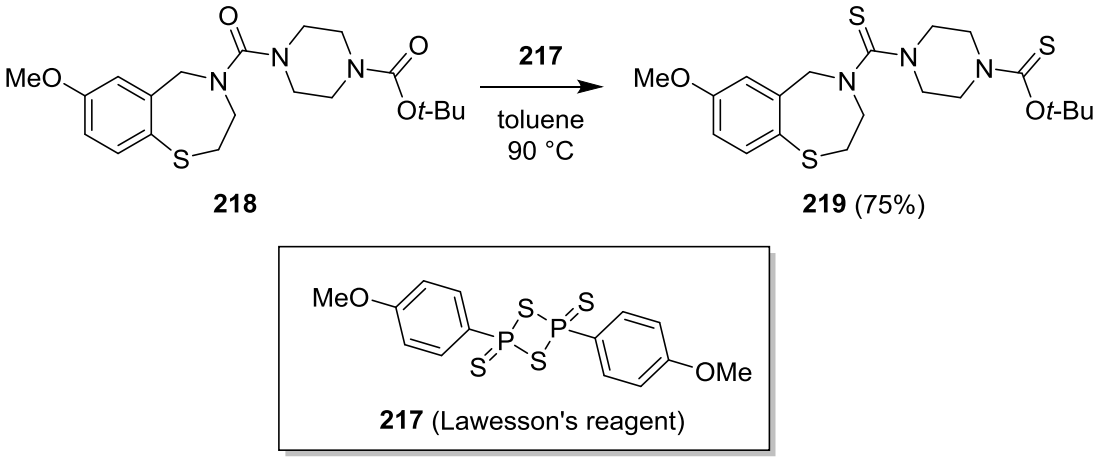
Scheme 65. Attempted synthesis of *N*-Botc-azetidine **212** from thiocarbamoyl chloride **214**.

Falck and co-workers reported the synthesis of several *N*,*N*-dimethylthiocarbamates from primary alcohols using dimethylthiocarbamoyl chloride, NaH and catalytic NaI in THF.[159] Unfortunately, application of these conditions to the reaction of thiocarbamoyl chloride **214** with tertiary alcohol *t*-BuOH was unsuccessful, resulting in decomposition (Scheme 65). Less than 8% yield of impure *N*-Botc-azetidine **212** was isolated from this reaction.

We therefore decided to explore alternative routes to Botc-protected-azacycles (see below).

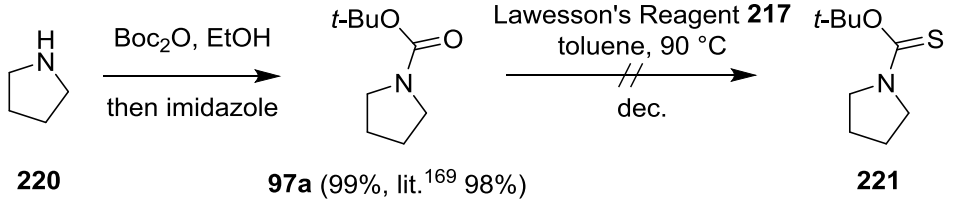
2.3.1. Attempted thionation with Lawesson's reagent

As mentioned above, attempted thionation of *N*-Boc-azetidine using P_2S_5 was previously unsuccessful. Lawesson's reagent **217** is an increasingly popular alternative for high yielding thionation of carbonyl-containing compounds such as ketones, esters, lactones, amides and lactams.[166] A few examples have also been reported for the conversion of *O*-ethyl carbamates to the corresponding thiocarbamates using Lawesson's reagent **217**, with heating under reflux in a high boiling solvent (xylene).[167] High reaction temperatures were required for ring-opening of Lawesson's reagent **217**, generating two reactive dithiophosphine ylides which can then react with carbamates in a Wittig-type reaction. An isolated example in a patent was apparently reported for the synthesis of an *O*-*t*-butyl thiocarbamate **219** from the corresponding Boc-protected substrate **218** by reaction with Lawesson's reagent in toluene at 90 °C (Scheme 66).[168]



Scheme 66. Purported synthesis of *O*-*t*-butyl thiocarbamate **219** using Lawesson's reagent.

We hoped that *N*-Botc-azacycles could be synthesised from the corresponding *N*-Boc-azacycles using these conditions. Owing to the relatively high commercial cost of the parent azetidine **51**, it was decided that this approach would first be tested on the inexpensive pyrrolidine **220** starting material, which was Boc-protected in high yield using literature[169] conditions (Scheme 67). Unfortunately, attempts to react this intermediate with Lawesson's reagent **217** in toluene at 90 °C only resulted in decomposition.

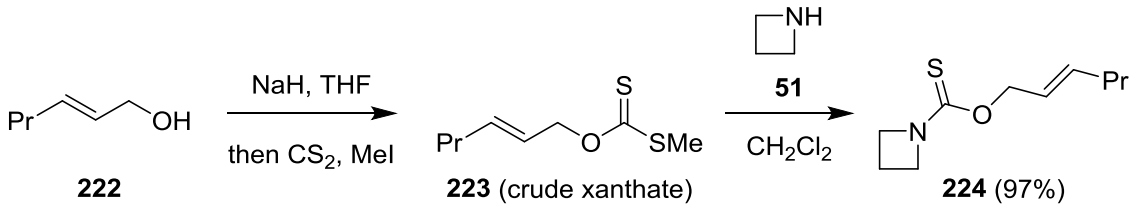


Scheme 67. Attempted thionation of *N*-Boc-pyrrolidine **97a** with Lawesson's reagent.

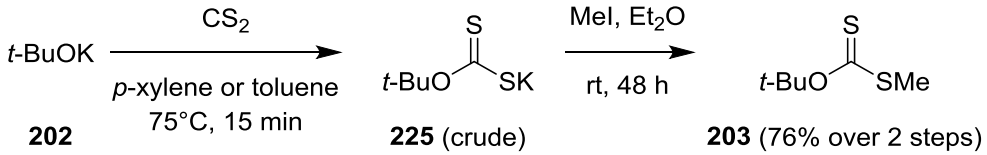
2.3.2. Botc-protected-azacycles from an *O*-*t*-butyl xanthate

Overman and co-workers reported another approach to azetidine carbothioates, such as azetidine **224**, via a xanthate ester intermediate (Scheme 68).[170] However, applying these conditions to the synthesis of desired *t*-butyl xanthate **203** resulted in very impure product. For this reaction, the THF solvent was removed under reduced pressure at 40 °C. As mentioned above (section 2.1.1., p 55), xanthate **203** decomposes via a Chugaev reaction at elevated temperatures,[162] so we considered switching to a lower-boiling solvent which could be removed more readily under reduced pressure at room temperature. Xanthate **203** was synthesised in high yield and much greater purity using conditions reported by Barany and Mott,[171] involving reaction of potassium salt **225** in Et_2O (Scheme 69). Only one (initially unknown) impurity peak (singlet at δ_H = 2.77 ppm) was detected in the crude ^1H NMR spectrum of xanthate **203**, which integrated to 1 proton relative to product signals.

The results were unaffected by switching the solvent from *p*-xylene to toluene in the first step.



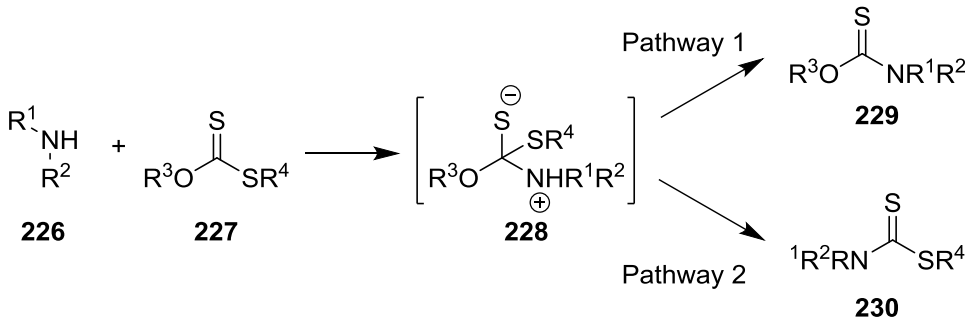
Scheme 68. Overman's synthesis of azetidine carbothioate **224**.



Scheme 69. Synthesis of xanthate **203**.

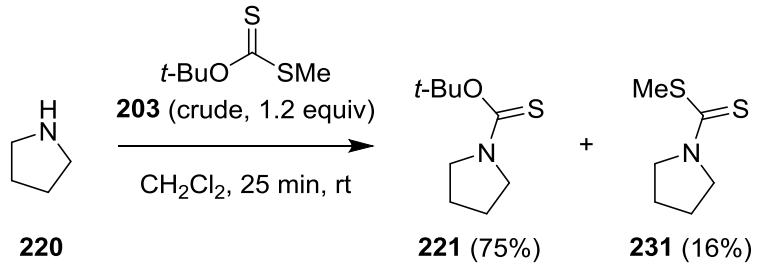
In 1972, Barrett and Martins proposed that the aminolysis of xanthates **227** involves a zwitterionic tetrahedral intermediate **228**, which can collapse by one of two pathways (Scheme 70).[172] Pathway 1 involves expulsion of the better leaving group, and is regarded as a high-yielding route to thiocarbamates **229** from xanthates derived from primary or secondary alcohols (see section 2.2., p 56). However, they reported that *t*-butyl xanthates **227** (R^3 = *t*-Bu) mainly react by Pathway 2, in which expulsion of the bulky *t*-butoxy-group is apparently preferred to give dithiocarbamates **230**. Yields for dithiocarbamates **230** were higher with secondary amines than with primary amines, which suggests that the reaction pathway may be determined by steric factors. In fact, as shown above (section 2.1.1.), reaction of primary amine hydrazine with xanthate **203** gave thiocarbamate **204** in moderate yield as the only product (Scheme 62, p 55).[161] On the other hand, Barrett and Martins claimed that the aminolysis of xanthate **203** with secondary cyclic amine

piperidine **244** resulted in exclusive formation of the piperidine dithiocarbamate **246** (71%). This latter research indicated that aminolysis of xanthate **203** was unlikely to be a successful route to Botc-protected-azacycles.



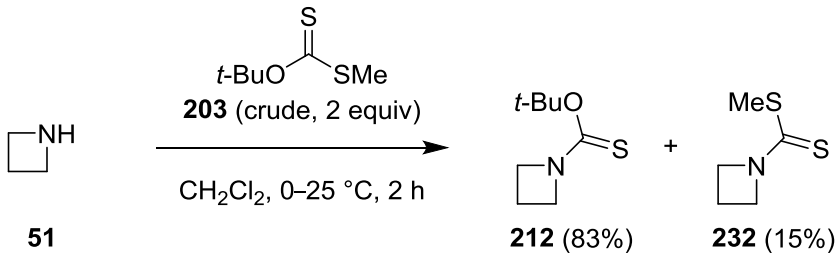
Scheme 70. Two competing reaction pathways in the aminolysis of xanthates **227**.

Surprisingly, reaction of xanthate **203** with the smaller azacycle pyrrolidine **220** in CH_2Cl_2 at rt gave a mixture of pyrrolidine thiocarbamate **221** and pyrrolidine dithiocarbamate **231**, both in 26% yield. We believed that these unexpected results may be due to the more 'tied-back' nature of the substituents on the nitrogen in this smaller cyclic amine, reducing the steric demands present in the tetrahedral intermediate **228** and allowing both reaction pathways to occur. A slightly better ratio of products was observed by reducing the reaction temperature to 0 °C, but a more substantial improvement in the yield of pyrrolidine thiocarbamate **221** (75%) was achieved by increasing the concentration of the reaction mixture from 0.15 M to 3.00 M (Scheme 71). Unfortunately, pyrrolidine dithiocarbamate **231** was still generated in low yield (16%) in this reaction, which made purification by column chromatography more challenging due to the similar R_f values of the 2 products. Attempts were made to directly convert the unwanted pyrrolidine dithiocarbamate **231** to the desired pyrrolidine thiocarbamate **221** by reaction with *t*-BuOH, with or without addition of a base (NaH), in either CH_2Cl_2 or THF. Unfortunately, these reactions were unsuccessful, returning only starting material.



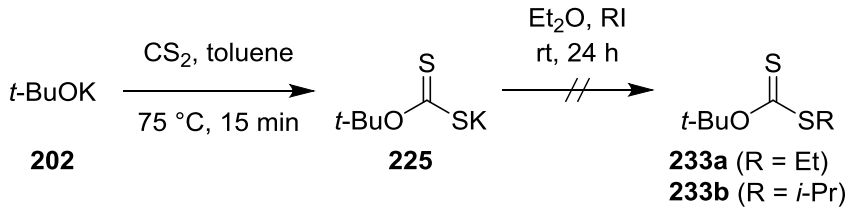
Scheme 71. Botc-protection of pyrrolidine **220**.

Attempted Botc-protection of azetidine **51** under the same conditions resulted in a much lower yield (43%) of the desired azetidine thiocarbamate **212**, as well as 16% yield of the unwanted azetidine dithiocarbamate **232**. Increasing the reaction time from 25 min to 2 h, with warming to rt, gave better results (65% yield of thiocarbamate **212**, 7% yield of dithiocarbamate **232**) with this substrate. However, the yield of Botc-azetidine **212** was still unsatisfactory as it meant that a significant amount of the azetidine precursor **51** was wasted. No additional improvement was observed by further increasing the reaction time to 3 h, or by carrying out the entire reaction at rt. Since the crude xanthate **203** contained an unknown impurity, and was too unstable for purification by column chromatography or distillation, the exact number of moles added was unknown and may have been less than 1 equiv. Pleasingly, a considerably higher yield (83%) of azetidine thiocarbamate **212**, along with unwanted azetidine dithiocarbamate **232** in 15% yield, was generated when the reaction was repeated with a greater excess of xanthate **203** (Scheme 72).



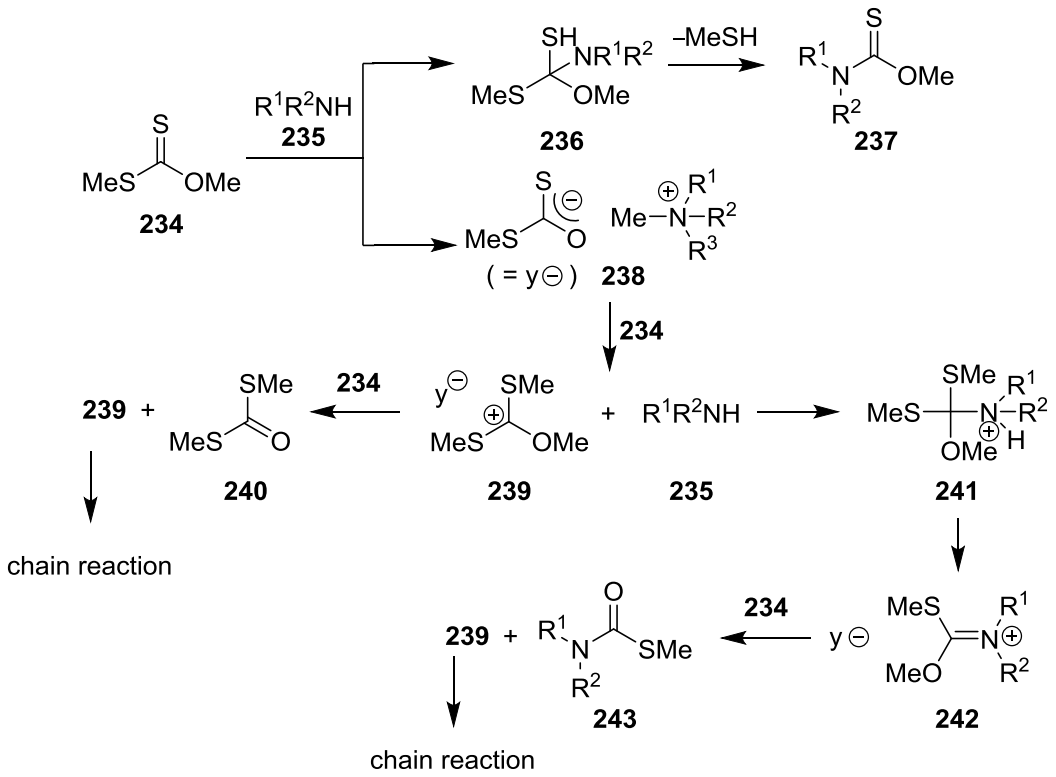
Scheme 72. Botc-protection of azetidine **51**.

It was hoped that the thioester functionality on the xanthate starting material could be modified to provide a better leaving group, in order to further promote pathway 1 and increase the preference for the desired thiocarbamate product. We considered increasing the steric bulk of the thioester functionality of xanthate **203**. Synthesis of *S*-ethyl xanthate **233a** and *S*-*i*-propyl xanthate **233b** was attempted using the previously established conditions for xanthate synthesis,[171] by replacing MeI with EtI or *i*-PrI (Scheme 73). Unfortunately, decomposition occurred in both cases, and neither product could be obtained by this route.



Scheme 73. Attempted synthesis of *S*-alkyl xanthates **233**.

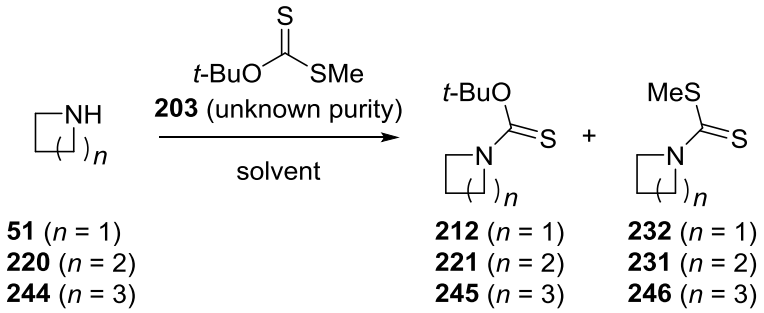
In 2009, Fochi and co-workers proposed a detailed mechanism for aminolysis of *S*-Me xanthate esters **234** (Scheme 74).[173] Their work suggests that as well as formation of desired thiocarbamate **237**, salt **238** may also be synthesised competitively, leading to formation of unwanted side-products **240** and **243** by chain reactions. Fochi and co-workers discovered that product **237** could be formed exclusively if water was present in the reaction mixture, because salt **238** is water-soluble. They also observed a higher ratio of desired thiocarbamate **237** when the reaction was carried out at lower temperatures.



Scheme 74. Fochi's proposed mechanism for aminolysis of xanthate esters.

This work prompted us to investigate the importance of solvent in our own studies on the aminolysis of xanthate **203** (Table 1). The synthesis of *N*-Botc-azetidine **212** was tested in a range of solvents. The ratio of products was dramatically altered when CH_2Cl_2 was replaced by H_2O, giving azetidine thiocarbamate **212** in 21% yield and azetidine dithiocarbamate **232**, now as the major product, in 39% yield. On the other hand, if a smaller quantity of water was present (40% aq solution of azetidine **51** added to neat xanthate **203**), there was little change in the result compared to the previous reaction in CH_2Cl_2. Carrying out the reaction neat still favoured the formation of the desired azetidine thiocarbamate **212** (75% yield), although a significant amount of azetidine dithiocarbamate **232** was also formed (25%). Lee and co-workers calculated that the activation barrier for acyl transfers with (thio)carbonyls is always higher in the presence of a solvent, and is highest with protic solvents.[174] This is because solvation stabilisation is greater with the

reactants than on the route to the tetrahedral intermediate (due to charge dispersion in the transition state, together with a decrease in dipole moment on intermediate formation), which seemed to explain why the highest combined yield of products **212** and **232** was achieved with no solvent, whilst the lowest combined yield was seen in H_2O.



Solvent	Isolated Yield/%					
	n = 1		*n* = 2		*n* = 3	
	212	**232**	**221**	**231**	**245**	**246**
H_2O	21	39	-	-	15	35
50% aq dioxane	-	-	-	-	6	40
CH_2Cl_2	83	15	76	16	36	32
neat	75	25	59	33	57	29
cyclohexane	-	-	65	35	65	26
pentane	96	4	73	27	91	0

Table 1. Investigating the effect of solvent on the aminolysis of xanthate **203**.

Attempts were made to repeat Barrett and Martins' reaction of xanthate **203** with piperidine, mentioned above (section 2..3.2., p 61–62), which was reported to give piperidine dithiocarbamate **246** as the sole product in 71% yield.[172] Since the experimental section for this work is rather vague and no solvent was mentioned,[175] it was assumed that the reagents were originally mixed together neat in a 1:1 ratio. Surprisingly, in my hands,

these conditions led to a significantly higher yield of piperidine thiocarbamate **245** (57%) than the expected piperidine dithiocarbamate **246** (29%) (Table 1). More experimental detail was given for their reaction of xanthate **203** with amino acids such as *L*-proline; long reaction times were used (12–24 h), no ice-bath cooling was required and the reactions were carried out in 50% aq dioxane. Remarkably, piperidine dithiocarbamate **246** was formed almost exclusively in 50% aq dioxane, albeit in lower yield (40%) than reported in the literature[172] Piperidine dithiocarbamate **246** was formed in lower yield (35%) in H_2O, but was still the major product as piperidine thiocarbamate **245** was isolated in just 15% yield. In contrast to the aminolysis of xanthate **203** with azetidine and pyrrolidine, reaction with piperidine in CH_2Cl_2 showed no selectivity for piperidine thiocarbamate **245**, instead both products were formed in similar yields (32–36%). Switching to non-polar solvent cyclohexane resulted in a much higher selectivity for piperidine thiocarbamate **245** (65% yield) compared to piperidine dithiocarbamate **246** (26% yield). Furthermore, piperidine thiocarbamate **245** was formed exclusively in pentane in excellent yield (91%).

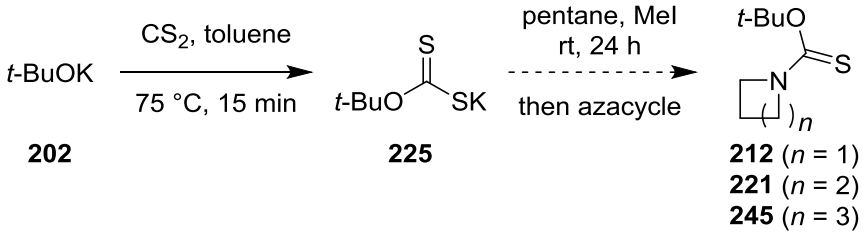
Douglas and Alborz used isostructural plots to compare the relative nucleofugalities of RO^- and RS^- from the conjugate bases of acetoacetate esters and fluorene esters.[176] Their results showed that at the isobasic point, RO^- is a better nucleofuge than RS^-. This is thought to be due to a difference in solvation energies. This gives one explanation as to why dithiocarbamates **232** and **246** were the major products in the above reactions in protic solvents. However, this is a reversal of the normal order of nucleofugality, since the pK_a difference works in opposition and is usually the major factor, as observed in the above reactions in non-polar solvents.

Castro's studies on the aminoloysis of thioesters and dithioesters show that the mechanism of these reactions can either be stepwise or concerted, depending on the stability of tetrahedral intermediate.[177] In our case, it seemed likely that the reactions in protic solvents go through a stepwise mechanism as these solvents would stabilise the zwitterionic tetrahedral intermediate **228** (Scheme 70). Steric factors then become more important as the secondary amine and *t*-butoxy groups would be held in close proximity in intermediate **228**. This supports Barrett and Martin's argument that steric relief from loss of the bulky *t*-butoxy group outweighs the opposing pK_a difference between the two leaving groups.[172] On the other hand, non-polar solvents (e.g. pentane) may destabilise tetrahedral intermediate **228**, promoting a concerted mechanism. Since the bulky secondary amine and *t*-butoxy groups would be further apart in the transition state, the order of nucleofugality would then be determined by the difference in pK_a, which seemed to explain why piperidine thiocarbamate **245** was the dominant product in cyclohexane and pentane.

Pleasingly, repeating the reaction of azetidine **51** and xanthate **203** in pentane delivered azetidine thiocarbamate **212** in excellent yield (96%), whilst the yield of azetidine dithiocarbamate **232** was minimised (4% yield) (Table 1). Since Botc-protected azetidine **212** and piperidine **245** were formed in highest yields in pentane, we were disappointed with the lower yield of *N*-Botc pyrrolidine **221** (73%) formed in this solvent, along with a significant quantity of pyrrolidine dithiocarbamate **231** (27%). On the other hand, aminolysis of xanthate **203** with pyrrolidine **220** in cyclohexane or in the absence of solvent gave very similar results to the corresponding reactions with piperidine **244**.

We envisaged that our route to Botc-protected-azacycles could be shortened by carrying out the last two steps in one-pot in pentane (Scheme 75). However, methylation of

potassium salt **225** in pentane instead of Et_2O resulted in a significant reduction in the yield of xanthate **203** from 76% to just 49%. For this reason, this approach was abandoned as it was likely to give a lower overall yield of *N*-Botc-azacycles than with our current 2-step 2-solvent process from potassium salt **225**.

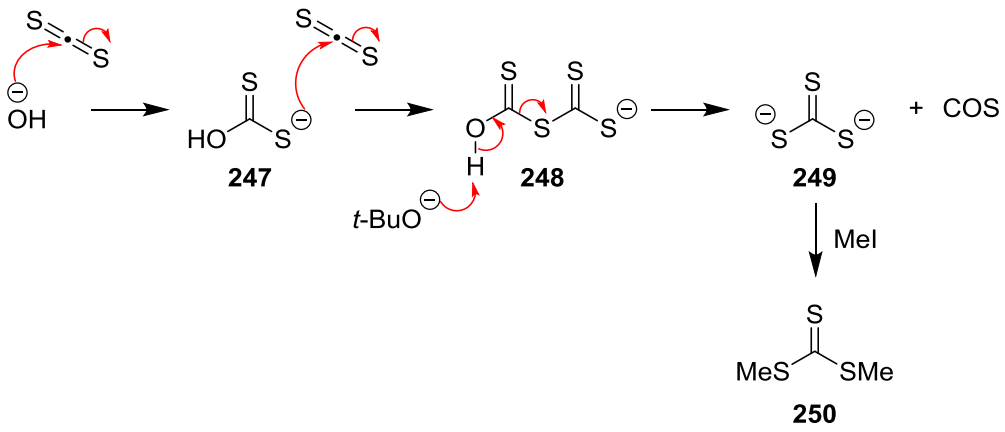


Scheme 75. Proposed shorter route to *N*-Botc-azacycles.

Although the results in Table 1 appeared to highlight a correlation between the choice of solvent and the ratio of thiocarbamate:dithiocarbamate formed, further investigation revealed an alternative explanation for these results. The aminolysis of xanthate **203** with piperidine **244** was repeated several times in H_2O and 50% aq dioxane and gave varying ratios of products, often favouring piperidine thiocarbamate **245** over piperidine dithiocarbamate **246**. The overall yields of these reactions were always low (<60%), implying that the reproducibility issues were caused by the poor solubility of the xanthates in protic solvents. In addition, the ratio of thiocarbamate **245**:dithiocarbamate **246** was noticeably higher in the crude material (determined from the crude ^{1}H NMR spectra) compared to the ratio of isolated products, which suggests that piperidine thiocarbamate **245** is more susceptible to losses on silica.

As mentioned above, the crude xanthate **203** used in the above aminolysis reactions contained an unknown impurity, giving a singlet signal in the crude ^{1}H NMR spectrum (at δ_H = 2.77 ppm), as well as two small impurity signals in the ^{13}C NMR spectrum (at δ_C =

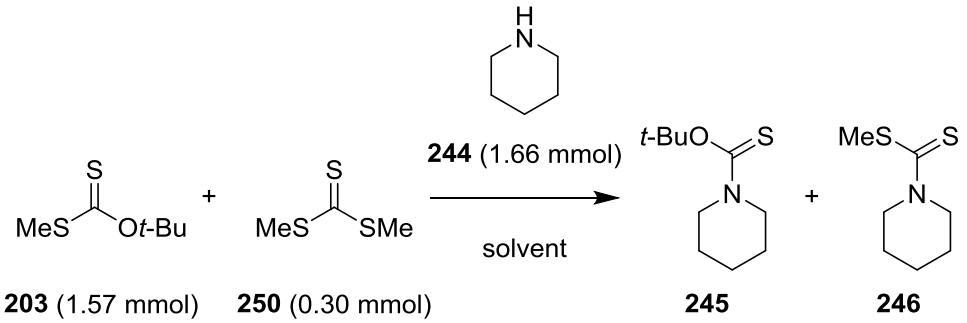
225.8 and 20.1 ppm). On further inspection of the literature, we discovered that these impurity signals were consistent with the NMR spectra of a known compound, dimethyl trithiocarbonate **250**,[178] which is often formed from the corresponding trithiocarbonate dianion **249**.[179] Leung and co-workers have shown that symmetrical trithiocarbonates can be synthesised from the reaction of alkyl halides, KOH and CS_2 in the absence of a phase-transfer catalyst.[180] Therefore, the most plausible mechanism for the formation of dimethyl trithiocarbonate **250** is initiated by reaction of CS_2 with hydroxide (Scheme 76), derived from moisture in the (old bottle of) *t*-BuOK used.



Scheme 76. Proposed mechanism for the formation of dimethyl trithiocarbonate **250**.

Since dimethyl trithiocarbonate **250** was formed in variable quantities (% molar ratio typically 7–16%, as calculated from the crude ^{1}H NMR spectra), and is known to undergo reactions with amines,[181] it is likely that the ratios of products in Table 1 were affected by the quantity of this side-product present in the reaction mixture. To gain a better understanding of the effect of solvent on the aminolysis of xanthate **203**, the reactions with piperidine **244** were repeated with a single batch of xanthate **203** of a known purity (84% pure) (Table 2). The yield of piperidine dithiocarbamate **246** was fairly consistent, whereas the yield of the desired thiocarbamate **245** decreased in protic solvents, likely due to poor

solubility. These results suggest that piperidine dithiocarbamate **246** is formed entirely from the less sterically hindered dimethyl trithiocarbonate **250**, which is believed to be the more reactive starting material.

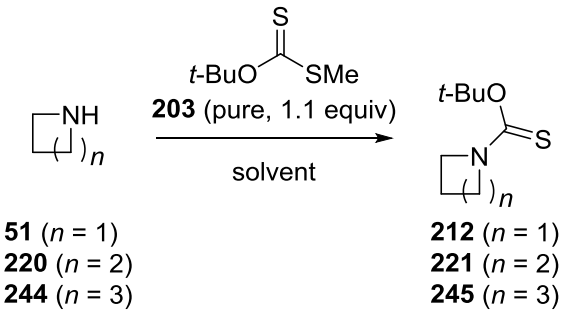


Entry	Solvent	**245**:**246** molar ratio from crude	% yield **245**	% yield **246**	Overall yield
1	H_2O	57:43	18	13	31
2	50% aq dioxane	55:45	12	11	23
3	CH_2Cl_2	68:32	40	14	54
4	neat	82:18	61	14	75
5	pentane	80:20	59	14	73

Table 2. Aminolysis of xanthate **203** of known purity (84%).

The quantity of unwanted dimethyl trithiocarbamate **250** produced could be greatly reduced (% molar ratio lowered to just 3%) by repeating the synthesis of xanthate **203** with freshly sublimed *t*-BuOK. Furthermore, pure xanthate **203** could be synthesised using new bottles of *t*-BuOK and CS_2, with no dimethyl trithiocarbonate **250** side-product detected by NMR analysis. This supports the rationalisation that moisture (hydroxide) was the origin of the problem in our case (Scheme 76). Pleasingly, aminolysis of pure xanthate **203** led to exclusive formation of Botc-protected-azacycles, with no trace of the unwanted dithiocarbamates in the crude NMR spectra, regardless of the solvent used (Table 3). The

best results were observed for the reactions in non-polar solvents cyclohexane and pentane, providing a straightforward and high-yielding route to Botc-protected-azacycles.

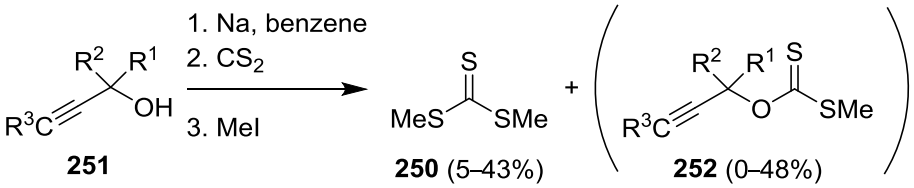


Solvent	Isolated yield of thiocarbamate/%		
	212 (*n* = 1)	**221** (*n* = 2)	**245** (*n* = 3)
H_2O	81	59	61
50% aq dioxane	87	60	30
CH_2Cl_2	73	84	64
neat	87	-	81
cyclohexane	90	89	87
pentane	88	89	90

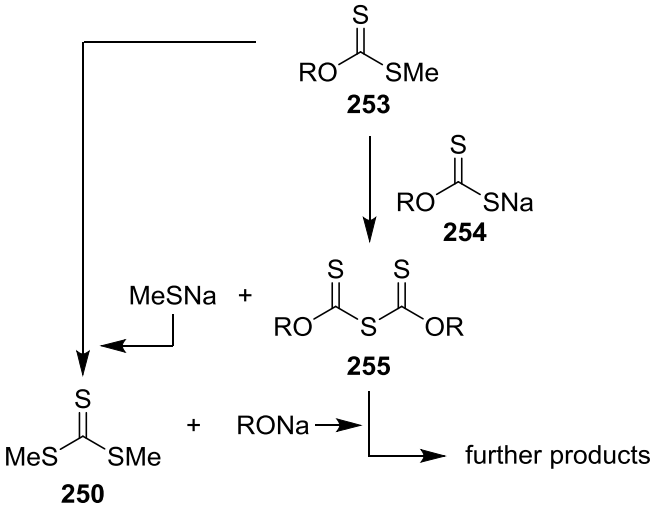
Table 3. Aminolysis of pure xanthate **203** in a range of solvents.

The results in Table 3 for the reactions of xanthate **203** with piperidine **244** are in stark contrast to the work of Barrett and Martins, who reportedly formed piperidine dithiocarbamate **246** in high yield as the sole product.[172] We suspected that dimethyl trithiocarbonate **250** may have been formed in large quantities during their synthesis of xanthate **203**, which involved the formation of the sodium *t*-butoxide in Et_2O.[175] However, on obtaining the relevant pages of Martins' thesis we discovered that the reported preparation specified that *t*-BuOH was thoroughly dried by refluxing for 6 h over Na metal before use, so no hydroxide would be present. Similar conditions were employed by

Tomita and Nagano in 1968 for the formation of xanthates **252** from α-acetylenic alcohols.[182] Interestingly, dimethyl trithiocarbonate **250** was reported to be a major by-product, or even the only product, for the reactions with secondary and tertiary alcohols **251** (Scheme 77). Having carried out further studies on this process, Tomita and Nagano proposed a 'hydroxide-free' mechanism for the formation of dimethyl trithiocarbonate **250** (Scheme 78).[183]



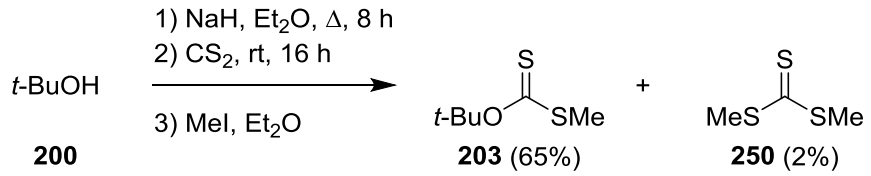
Scheme 77. Tomita and Nagano's attempted synthesis of xanthates **252**.



Scheme 78. Tomita and Nagano's proposed mechanism for formation of trithiocarbonate **250**.

However, another graduate student in the Hodgson group recently followed Martins' experimental section closely,[175] producing xanthate **203** in high purity, with only a trace of the inseparable side-product dimethyl trithiocarbonate **250** (Scheme 79). It is unlikely that

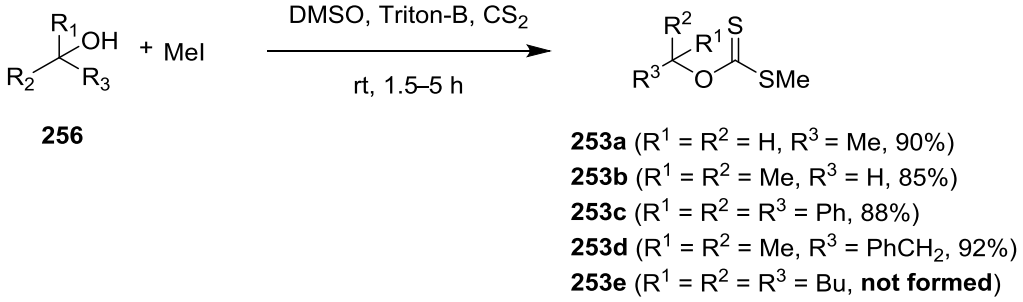
this by-product was responsible for the high yield of piperidine dithiocarbamate **246** reported. Therefore, the discrepancy between Martins' results for aminolysis of xanthate **203** (with piperidine **244**) and our own results remains unresolved.



Scheme 79. Preparation of xanthate **203** using literature[175] conditions.

2.3.2.1. Triton-B-catalysed synthesis of xanthates

Chaturvedi and Ray have published an alternative, one-pot, benzyltrimethylammonium hydroxide (Triton-B) catalysed synthesis of xanthates **253** from their corresponding alcohols **256** (Scheme 80).[184] High yields (78–98%) and short reaction times (1–5 h) were reported, and this methodology was shown to be successful with a range of primary, secondary and tertiary alcohols. We anticipated that the closely related xanthate **203** could be synthesised using these conditions.



Scheme 80. Chaturvedi and Ray's synthesis of xanthates **253**.

Triton-B is commercially available as a 40 wt. % solution in MeOH or water. We were informed through e-mail correspondence with Chaturvedi that Trition-B was apparently used as a solution in both MeOH and water in their studies.[184] However, attempting this reaction with *t*-BuOH, using a methanolic solution of Triton-B, led to formation of an *O*-methyl xanthate instead of the desired *O*-*t*-butyl xanthate **203**. This result is logical, since MeOH is a less sterically hindered nucleophile than *t*-BuOH. The reaction was repeated using dry DMSO and *t*-BuOH (freshly distilled over CaH_2), but no improvement was observed. Synthesis of xanthate **203** was also attempted using an aqueous solution of Triton-B, but no product was detected by analysis of the NMR spectra. It is possible that *t*-BuOH is too sterically hindered to react effectively under these conditions. In fact, Chaturvedi and Ray's noted that a more bulky xanthate **253e** could not be formed by this route (Scheme 80).

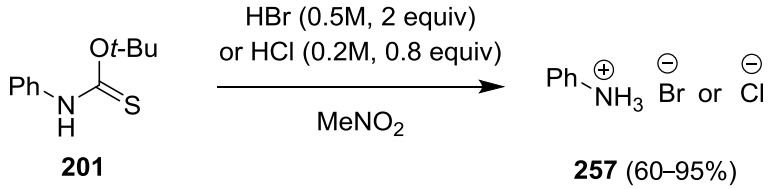
Repeating Chaturvedi and Ray's synthesis[184] of xanthate **253b** in my own hands, using a methanolic solution of Triton-B, did not lead to the expected product. Instead, the *O*-methyl xanthate was again the major product. In an effort to obtain anhydrous Triton-B, the methanolic solution was concentrated under reduced pressure and recrystallisation of the resulting hygroscopic gum was attempted from CH_2Cl_2. However, this resulted in an anion exchange to form unwanted benzyltrimethylammonium chloride, as detected by ^1H NMR analysis in which the chemical shifts were consisted with literature[185] values. Therefore, the methanolic solution of Triton-B was then treated in accordance with a literatuer[186] procedure for purification: the solution was decolourised with charcoal and was then concentrated under reduced pressure with final drying at 75 °C at 2 mbar. Unfortunately, the resulting pale yellow gum was extremely hygroscopic which made

handling and storage more difficult. In addition, it was not soluble in DMSO, which meant that it could not easily be weighed out and added to the reaction mixture.

A closer inspection of the literature revealed that tetraalkylammonium salts, similar in structure to Triton-B, catalyse the 'hydrolysis' of *O*-*t*-butyl xanthates to their corresponding alkanethiols and isobutene.[187] This work implies that Chaturvedi and Ray's methodology is unsuitable for synthesis of the desired *O*-*t*-butyl xanthate **203**, so it was no longer considered as a viable route.

2.4. Deprotection of the Botc group

As mentioned above (section 2.1.1., p 54), early studies by Carpino and co-workers showed that the Botc group can be readily removed in acidic conditions, as demonstrated by the instantaneous cleavage of *N*-Botc aniline **201** by hydrogen halides in nitromethane (Scheme 81).[158a] We anticipated that similar conditions would be suitable for deprotection of Botc-protected-azacycles.

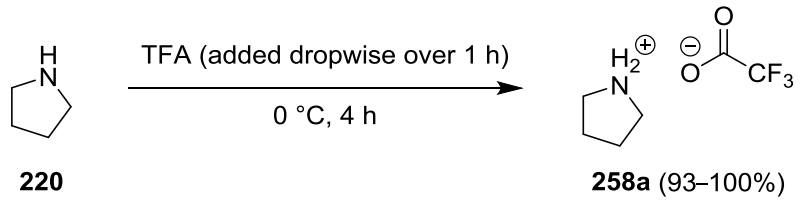


201 **257** (60–95%)

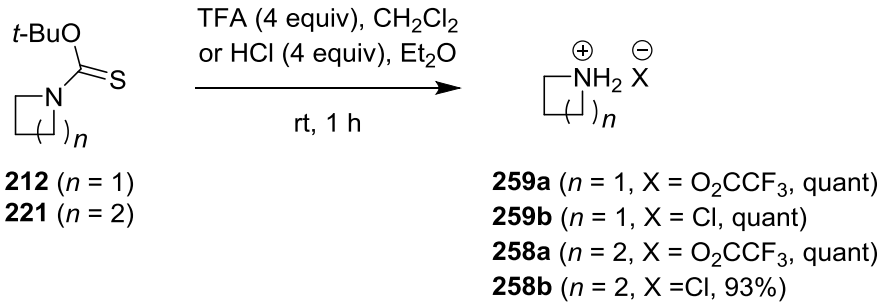
Scheme 81. Acid-catalysed deprotection of *N*-Botc aniline **201**.

Deprotection of *N*-Botc-pyrrolidine **221** was first attempted with excess TFA in CH_2Cl_2 at rt; TLC analysis indicated that no starting material remained after 1 min, although the isolated yield of pyrrolidium trifluoroacetate **258a** was disappointing (54%) after this time. Research by Anouti and co-workers showed that a long reaction time is required to

produce pyrrolidium trifluoroacetate **258a** in excellent yield from pyrrolidine **220** and TFA (Scheme 82).[188] Therefore, deprotection of *N*-Botc-pyrrolidine **221** with TFA was repeated with longer reaction time of 30 min, resulting in a higher yield of product (82%). A quantitative yield of pyrrolidium trifluoroacetate **258a** was achieved by further increasing the reaction time to 1 h (Scheme 83). A similar result was obtained using HCl in Et_2O as alternative deprotection conditions. Pleasingly, *N*-Botc-azetidine **212** also underwent facile deprotection under acidic conditions (Scheme 83). Deprotection of *N*-Botc-azetidine **212** was still observed in quantitative yield after 1 h at rt when the amount of TFA was reduced from 4 to 2 equiv. However, addition of only 1 equiv TFA resulted in just 50% deprotection, even after 12 h at rt. This result suggests that the salt formation step is more rapid than the deprotection step.



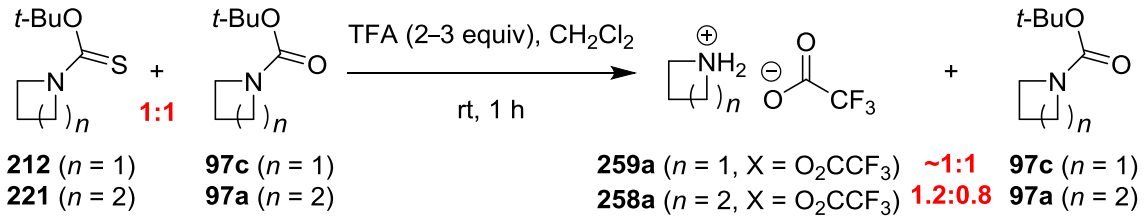
Scheme 82. Formation of pyrrolidium trifluoroacetate **258a**.



Scheme 83. Acid-catalysed deprotection of *N*-Botc-azacycles.

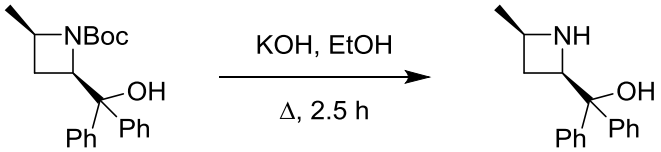
To determine the minimum acid strength required for deprotection of the Botc group, a number of TLC-monitored reactions were carried out: neat acid (4 equiv) was added to a 0.27 M solution of *N*-Botc-pyrrolidine **221** in CH_2Cl_2, and the reaction mixture was stirred at rt until complete disappearance of the starting material was witnessed. No reaction was observed with acetic acid, whereas complete disappearance of starting material was seen after 24 h with chloroacetic acid, or after 1 h with dichloroacetic acid or trichloroacetic acid. The reaction using dichloroacetic acid was repeated with *N*-Boc-pyrrolidine **97a**, and complete disappearance of this substrate was also seen by TLC analysis after 1 h.

As mentioned above (section 2.1.1., p 54), early research by Carpino and co-workers indicated that the Botc *N*-protecting group is more acid labile than the Boc group.[158] To study this aspect, TFA (3 equiv) was added to a 1:1 mixture of *N*-Botc-azetidine **212** and *N*-Boc-azetidine **97c** in CH_2Cl_2, resulting in a ~1:1 mixture of salt **259a** and *N*-Boc-azetidine **97c** (Scheme 84). This ratio was calculated by analysis of the crude ^{1}H NMR spectrum, which showed a clean mixture of salt **259a** and *N*-Boc-azetidine **97c** with no ring-opening side-products. The *N*-Boc-azetidine **97c** substrate was prepared in high yield (96%) by analogy to a literature[169] procedure for *N*-Boc-pyrrolidine. A similar result was obtained with a 1:1 mixture of *N*-Botc-pyrrolidine **221** and *N*-Boc-pyrrolidine **97a** and 2 equiv TFA. These pleasing results illustrate the greater acid lability of *N*-Botc compared to *N*-Boc. An excess of TFA (at least 2 equiv) was required for complete deprotection of the Botc-protected-azacycles after 1 h at rt.



Scheme 84. Selective acid-catalysed deprotection of *N*-Botc in the presence of *N*-Boc.

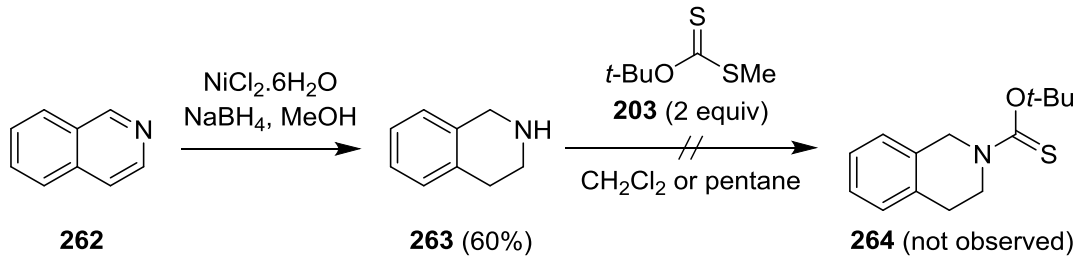
We also wanted to establish whether selective deprotection of the Botc group was possible under basic conditions. Guanti and Riva demonstrated the successful deprotection of 2,4-disubstituted *N*-Boc-azetidine **260** in 95% yield under basic conditions (Scheme 85).[189] However, TLC analysis showed that a significant amount of starting material still remained after 2.5 h under reflux when these conditions were applied to *N*-Botc-pyrrolidine **221** and *N*-Boc-pyrrolidine **97a** substrates. These reactions were heated to reflux for a further 5 h, and after this time no starting material was recovered from the reaction involving the Botc-protected-pyrrolidine **221**, whereas 51% of the *N*-Boc-pyrrolidine **97a** was recovered. No pyrrolidine **220** was observed from the crude NMR spectra for either reaction, but due to the volatility of this product, we could not determine whether deprotection was successful or if the substrates underwent decomposition under these conditions.



260 **261** (95%)

Scheme 85. Deprotection of 2,4-disubstituted *N*-Boc-azetidine **260** under basic conditions.

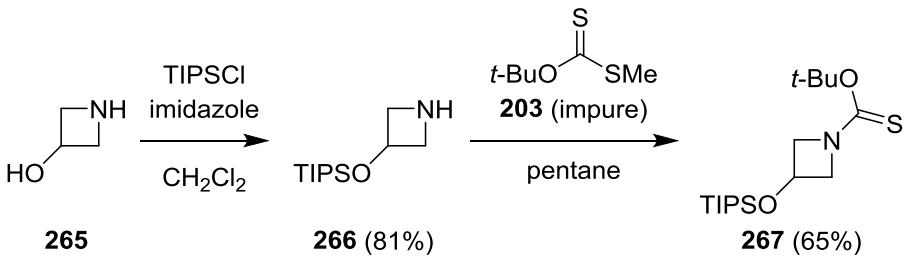
Further investigation of this methodology required a substrate which would generate a less volatile free amine, such as 1,2,3,4-tetrahydroisoquinoline (**263**), which has previously been used by Weinreb and co-workers for a similar purpose.[190] Isoquinoline (**262**) was successfully reduced to 1,2,3,4-tetrahydroisoquinoline (**263**) using literature[191] conditions (Scheme 86). Further reaction of this amine with xanthate **203** to form the desired *N*-Botc-tetrahydroisoquinoline **264** was attempted in CH_2Cl_2 and pentane, but unfortunately no product was observed in the crude NMR spectra. Amine **263** is larger than the previous azacycles tested, so it is likely that the rate of nucleophilic substitution was reduced. Therefore, the reaction was repeated at a higher temperature (25 °C throughout) over a longer time period (24 h), with and without the addition of pyridine. These alterations led to the formation of three unknown products with very similar R_f values, which could not be isolated and characterised. The crude NMR spectra showed that a large amount of both starting materials remained after this time, but no product signals were observed.



Scheme 86. Attempted synthesis of *N*-Botc tetrahydroisoquinoline **264**.

Amine **266** was considered as an alternative non-volatile substrate due to the known stability of the high molecular weight TIPS protecting group to basic conditions[192]. Silylation of 3-hydroxy-azetidine **265** was attempted using literature[193] conditions: a mixture of TIPSCl (2.2 equiv) and imidazole (6 equiv) in DMF was added and the reaction mixture was stirred at rt for 3 d. Although the hydroxyl group was successfully TIPS-

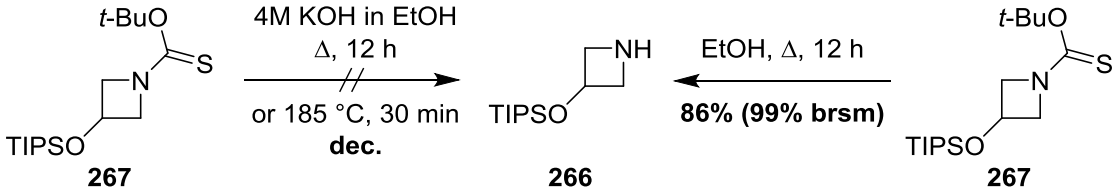
protected, the free amine reacted with DMF to give an unwanted *N*-formylated product in 65% yield. Literature[194] precedent for formation of the TIPS group in CH_2Cl_2 was discovered; replacing DMF with CH_2Cl_2 led to a high yield of TIPS-protected amine **266**, which was further reacted with xanthate **203** in pentane to give the desired thiocarbamate **267** (Scheme 87). At this stage, we had not yet determined that the crude xanthate contained the dimethyl trithiocarbonate **250** impurity (see p 70); signals consistent with the unwanted dithiocarbamate side-product were present in the crude ^{1}H NMR spectra, although this was not isolated. It is likely that a higher yield of thiocarbamate **267** would be formed using pure xanthate **203**.



Scheme 87. Preparation of a higher molecular weight Botc-protected substrate **267**.

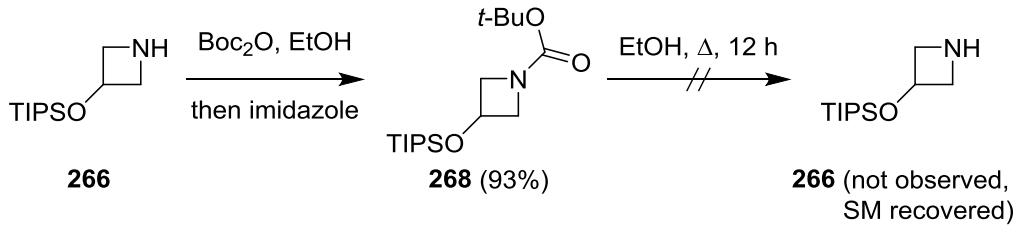
To assess the stability of the Botc group, thiocarbamate **267** was subjected to basic[189] and thermal[195] deprotection conditions previously established for deprotection of the Boc group. Addition of 4M KOH in EtOH to thiocarbamate **267** followed by heating under reflux for 12 h or heating neat thiocarbamate **267** to 185 °C for 30 min resulted in decomposition, with only a trace of starting material remaining in the crude NMR spectra (Scheme 88). Although the TIPS group is relatively stable in basic conditions, there is literature[196] precedent for removal of this group by 40% KOH in MeOH with heating to reflux for 18 h. Therefore, cleavage of the TIPS group under such harsh basic conditions may have occurred in our case, contributing to the observed decomposition. We were

particularly frustrated by the failed deprotection of thiocarbamate **267** under thermal conditions because *O*-alkyl thiocarbamates containing a β-hydrogen typically undergo pyrolysis by a similar mechanism to the Chugaev reaction.[165,197] Pleasingly, clean pyrolysis of the Botc group was achieved by heating an ethanolic solution of thiocarbamate **267** under reflux for 12 h, providing free amine **266** in high yield (Scheme 88).

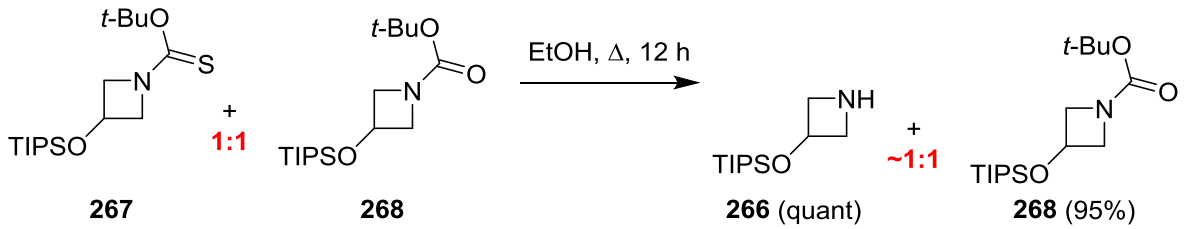


Scheme 88. Investigation of alternative deprotection conditions for the Botc group.

In contrast, thermal deprotection was not possible with the corresponding Boc-protected substrate **268**, which was synthesised in high yield (93%) from amine **266** using previously established conditions (Scheme 89). Selective deprotection of *N*-Botc in the presence of *N*-Boc under thermal conditions was demonstrated by heating a 1:1 mixture of *N*-Botc-azetidine **267** and *N*-Boc-azetidine **268** in EtOH to reflux for 12 h, producing a ~1:1 mixture of free amine **266** and *N*-Boc-azetidine **268** (Scheme 90).



Scheme 89. Preparation and attempted thermolyisis of *N*-Boc-azetidine **268**.



267 **268** **266** (quant) **268** (95%)

Scheme 90. Preferential elimination of *N*-Botc compared to *N*-Boc under thermal conditions.

2.5. Summary

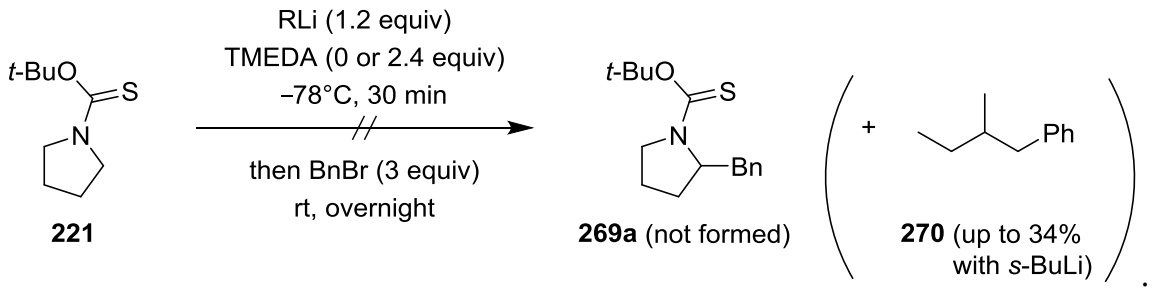
As originally envisaged by Carpino and co-workers more than half a century ago,[158] the *t*-butoxythiocarbonyl (Botc) group has shown great promise as a novel *N*-protecting group. The Botc group was efficiently introduced onto saturated azacycles from the corresponding *O*-*t*-butyl xanthate ester **203**, despite literature[172] indicating that only the corresponding dithiocarbamates would be formed. Notably, the Botc group could also be removed under mild acid or thermal conditions, and selectively in the presence of *N*-Boc.

3. Results and Discussion: α-Deprotonation–electrophile trapping reactions

With an efficient route to Botc-protected-azacycles in hand, we were now in a position to probe the ability of this novel *N*-protecting/activating group to promote α-lithiation–electrophile trapping reactions. Although our main interest was the synthesis of substituted azetidines, our initial studies were carried out on the less expensive pyrrolidine analogue.

3.1. *N*-Botc-pyrrolidine substrate

Most organolithiums are surprisingly soluble in hydrocarbon solvents (e.g. hexanes), and several simple alkyllithiums are commercially available as stable solutions in these solvents in which they tend to form aggregates, commonly tetramers and hexamers.[113] Lithiation chemistry is primarily carried out in the presence of coordinating solvents such as THF or Et_2O, allowing entropically favoured aggregates to form with a lower degree of aggregation, potentially enhancing the reactivity of the organolithium.[198] A drawback to using these solvents is their tendency to themselves undergo reaction with the organolithiums, usually limiting the reaction temperature to 0 °C or below. *N*-Botc-pyrrolidine **221** was initially subjected to reaction conditions previously reported for benzylation of *N*-thiopivaloyl-azetidine **164**:[148] lithiation with *s*-BuLi (1.2 equiv)/TMEDA (2.4 equiv) in THF at −78 °C followed by quenching with BnBr. The expected product, 2-benzyl-pyrrolidine **269a**, was a desirable substrate for our deprotection studies (see section 2.4.), since the corresponding free amine can be readily isolated by distillation.[199] Disappointingly, these lithiation conditions simply led to decomposition (Table 4 , entry 1).



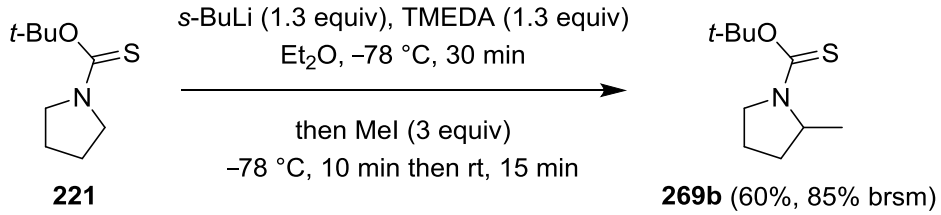
Entry	RLi	Solvent	TMEDA added?	Result
1	*s*-BuLi	THF	Yes	dec.
2		Et_2O		multiple products, not isolated
3	*t*-BuLi			impure SM
4			No	multiple products, not isolated

Table 4. Attempted lithiation–benzylation of *N*-Botc-pyrrolidine **221**.

Switching the solvent to Et_2O, a more stable solvent to organolithiums,[113] resulted in the formation of multiple side-products with similar R_f values (Table 4, entry 2). The only product that could be isolated by column chromatography was (2-methylbutyl)benzene **270**,[200] generated in 34% yield by a nucleophilic substitution reaction of *s*-BuLi and BnBr. α-Lithiation of *N*-Botc-pyrrolidine **221** was also attempted with a potentially more reactive organolithium (*t*-BuLi), with and without addition of TMEDA, but this did not improve the outcome (Table 4, entries 3–4).

Since the above reactions with BnBr proved challenging, we decided to try MeI as the electrophile, as this is generally more popular/successful with 'dipole-stabilised' α-amino lithiums. Pleasingly, lithiation of *N*-Botc-pyrrolidine **221** with *s*-BuLi/TMEDA at −78 °C followed by trapping with MeI resulted in methylated product **269b** in 60% yield (Scheme 91). Addition of TMEDA was found to be essential to promote the lithiation step, as no lithiation occurred in Et_2O in the absence of this diamine ligand. TMEDA is often

considered to have a better ability to coordinate to and increase the reactivity of organolithiums compared to typical solvents Et_2O and THF,[113] and is widely used as a co-solvent for reactions involving *s*-BuLi.[109,111] However, research by Collum suggests that relative affinities of diamine ligands and THF for lithium may be substrate-dependent.[201] O'Brien and co-workers have recently reported a diamine-free protocol for *s*-BuLi-mediated lithiation of *N*-Boc-heterocycles in THF, using a shorter lithiation time of just 10 min together with a higher lithiation temperature of −30 °C.[202] These conditions were also tested for α-lithiation–methylation of *N*-Botc-pyrrolidine **221**, but resulted in a lower yield (40%) of methylated product **269b**.



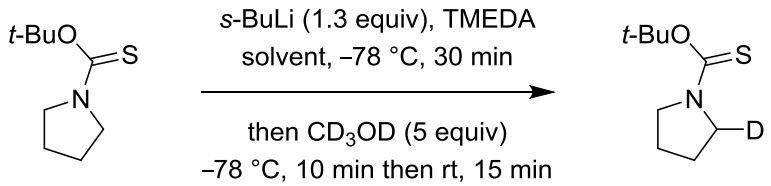
221 **269b** (60%, 85% brsm)

Scheme 91. α-Lithiation–methylation of *N*-Botc pyrroldine **221**.

3.1.1. Deuteration studies

We were encouraged by the successful α-lithiation–electrophile trapping reaction above with MeI, particularly since Beak and co-workers had shown that MeI was an unsuitable electrophile for α-lithiation–methylation of the *N*-Boc-pyrrolidine **97a** and *N*-Boc-piperidine **97b** substrates, resulting in low yields or no dectectable methylated product.[111,112] Before the electrophile scope could be further explored, extensive optimisation and investigation of the lithiation step was carried out using test deuteration reactions, in which the lithiated species was quenched by addition of 5 equiv of CD_3OD. Deuteration was used for this purpose due to ease of purification and direct calculation of % D by integration of the relevant signals (protons α- to N) in the ^{1}H NMR spectra.

α-Lithiation–deuteration was initially tested under similar conditions to the above methylation: lithiation of *N*-Botc-pyrrolidine **221** with 1.3 equiv of both *s*-BuLi and TMEDA at −78 °C for 30 min, followed by trapping with CD_3OD. A high level of D incorporation (up to 100% D) was observed for the reaction in Et_2O, which was not significantly changed (within experimental error) by increasing the amount of TMEDA to 2.4 equiv (Table 5, entries 1–2). For several reactions in Et_2O, 100% D was calculated by ^1H NMR analysis: the 2 multiplets observed for the 4 protons α to N in starting material **221** at δ_H = 3.69–3.66 and 3.48–3.45, transformed into a multiplet at δ_H = 3.72–3.39, which integrated to 3 protons. Furthermore, ^{13}C NMR analysis showed the following signals for the C-2 carbons: δ_C = 51.2, 50.9 (T, J = 22 Hz), 48.3 and 48.0 (T, J = 22 Hz), with the expected ^{13}C-D coupling. Doubling of resonances was observed in the ^{13}C NMR spectrum due to rotamers, caused by slow rotation of the NC(S) bond on the NMR timescale.



221 **269c**

Entry	Solvent	TMEDA/equiv	% Yield	% D[a]
1	Et_2O	2.4	100	96–100
2		1.3	98	92–100
3		0.1	94	8
4		0	86	0
5	THF	2.4	94	25
6		1.3	96	19
7		0	98	19

a) Calculated by analysis of the ^1H NMR spectra.

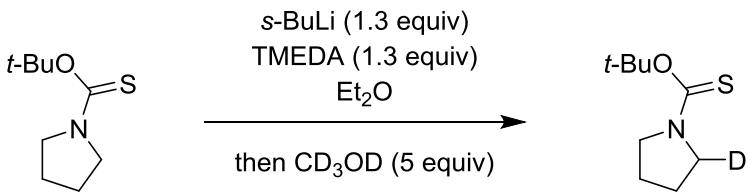
Table 5. Optimisation using test deuteration reactions.

α-Lithiation–deuteration of *N*-Botc-pyrrolidine **221** with 1.3 equiv TMEDA in Et_2O was carried out several times to assess the reproducibility of this reaction. Frustratingly, the results varied dramatically (0–100% D), even for reactions carried out in parallel under the same conditions. Slightly higher yields were generally observed when care was taken to ensure that the reaction flask and solvent were dry; glassware was flame-dried and the solvent was degassed, dried over activated alumina and distilled over sodium with benzophenone indicator. The results were unaffected by varying the reaction concentration (0.13 M or 0.38 M), so the more dilute reaction concentration (0.13 M) was favoured, to aid stirring. There was also no change in the results by increasing the lithiation time from 30 min to 45 min. Ultimately, the speed of addition of *s*-BuLi was found to be the most crucial factor, and a consistently high level of deuteration (>96% D) could only be achieved if *s*-BuLi was added very slowly dropwise (~200 μL/min) (Table 5, entry 1). Slightly lower yields (82–94% D) were obtained when the amount of *s*-BuLi was reduced from 1.3 to 1.0 equiv. It was thought that a faster addition of *s*-BuLi caused an increase in the reaction temperature, accounting for the anomalously lower yields (<<80% D) that had been observed for certain reactions.

As seen for the above methylation reactions (section 3.1.), addition of TMEDA was required for α-lithiation–deuteration of *N*-Botc-pyrrolidine **221** to occur in Et_2O. No D incorporation was observed in the absence of this ligand, whilst addition of 0.1 equiv TMEDA led to just 8% D, indicating that the reactivity of *s*-BuLi in Et_2O is greatly enhanced by formation of a (likely 1:1) complex with TMEDA (Table 5, entries 3–4). On the other hand, varying the number of equiv of TMEDA had no effect on the results for reactions carried out in THF, which all gave a consistently low level of deuteration (Table

5, entries 5–7). These results suggest that THF may be a more strongly coordinating ligand than TMEDA in this case.

Although the above deuteration reactions with 1.3 equiv TMEDA in Et_2O indicated that α-deprotonation of *N*-Botc-pyrrolidine **221** was complete after 30 min at −78 °C, attempted trapping of the resulting lithiated species with BnBr previously led to decomposition (see section 3.1.). It was hoped that decomposition could be prevented if the α-lithiation–benzylation reaction was maintained at a lower temperature. However, a test deuteration reaction showed that *N*-Botc-pyrrolidine **221** could not be fully lithiated/deuterated at −98 °C (Table 6, entry 1). On the other hand, fully deuterated product **269c** could be generated without the need to warm to rt before addition of NH_4Cl in the work-up stage (Table 6, entry 2).



221 **269c**

Entry	Lithiation temp (time)	CD_3OD stirring temp (time)	Work-up temp	% Yield	% D[a]
1[a]	−98 °C (40 min)	−98 °C (40 min)	−98 °C	quant	36–44
2	−78 °C (30 min)	−78 °C (10 min)	−78 °C	92–98	80–100
3	−78 °C (3 h)	−78 °C (10 min) then rt (15 min)	rt	98	100
4	−78 °C (30 min) then −40 °C (15 min)			quant	100
5	−78 °C (30 min) then rt (24 h)			66–82	0

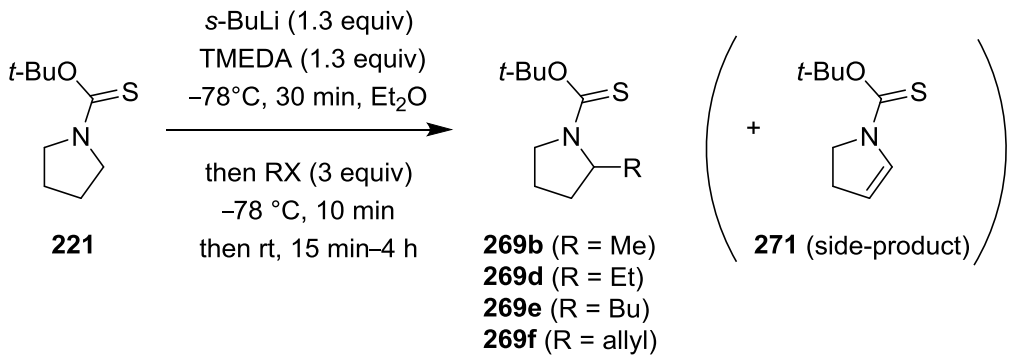
a) Calculated by analysis of the ^1H NMR spectra.

Table 6. Investigation of reaction temperature and time.

To investigate the chemical stability of the pyrrolidine anion, the lithiated species was stirred for a further 2.5 h at −78 °C, or 15 min at −40 °C, before addition of CD_3OD at −78 °C (Table 6, entries 3–4). In both cases, 100% D incorporation was observed, demonstrating complete stability of the lithiated species under these conditions. In contrast, warming the lithiated species to rt for 24 h before addition of CD_3OD led to slightly impure non-deuterated *N*-Botc-pyrrolidine **221** (Table 6, entry 5). As expected, the lithiated species was unstable at rt, and was likely protonated by the Et_2O solvent or TMEDA ligand,[203] allowing starting material **221** to re-form.

3.1.2. Electrophile scope: alkyl halides

As detailed above, an initial good yield (60%) of methylated product **269b** was formed by α-lithiation–methylation of *N*-Botc-pyrrolidine **221** with 1.3 equiv TMEDA (Scheme 91, p 86). However, repeating the methylation reaction with 2.4 and 1.3 equiv TMEDA in parallel gave disappointing yields (33% and 42%, respectively), even with slow addition of *s*-BuLi. A significant quantity of white precipitate was generated in these reactions on addition of MeI, preventing efficient stirring. This white solid was suspected to be LiI, which may not be soluble in Et_2O at −78 °C; MeI itself was found to be readily soluble in Et_2O at this temperature. Methylation of *N*-Botc-pyrrolidine **221** with 1.3 equiv TMEDA was repeated with dropwise addition of MeI, which reduced the quantity of white precipitate formed and provided a more pleasing yield (68%) of methylated product **269b** (Table 7, entry 1). Decreasing the amount of MeI added (from 3 to 2 equiv) resulted in a slightly lower yield (60%).



Entry	RX	% Yield		
		Product **269**	Side-product **271**	SM **221**
1	MeI	68	1	7
2	EtI	25	25	22
3	BuI	21	20	15
4	allyl Br	34	7	28

Table 7. Alkylation of *N*-Botc-pyrrolidine **221**.

Attempted alkylation with more sterically hindered alkyl halides (EtI, BuI and allyl Br) led to lower yields (21–34%) of the desired alkylated products **269d–f**, which could not be separated from a side-product with an identical R_f value (Table 7, entries 2–4). A large amount of starting material was also recovered at the end of these reactions, indicating that the electrophile trapping step had not gone to completion. The side-product was identified as enecarbamate **271** (7–25% yield), as its ^{1}H and ^{13}C NMR signals were in close correlation with those known for enecarbamate **272**[204] (Figure 11). In the previous methylation reaction, the enecarbamate **271** side-product was generated in a much lower yield (1%), and was separable from the methylated product **269b** by column chromatography.

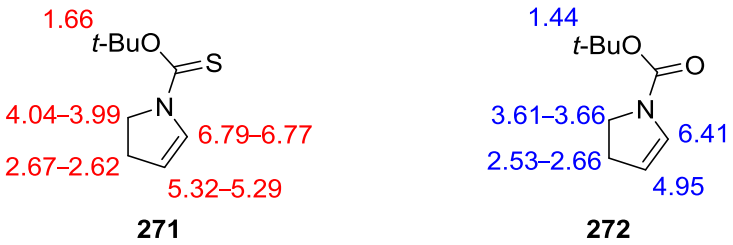
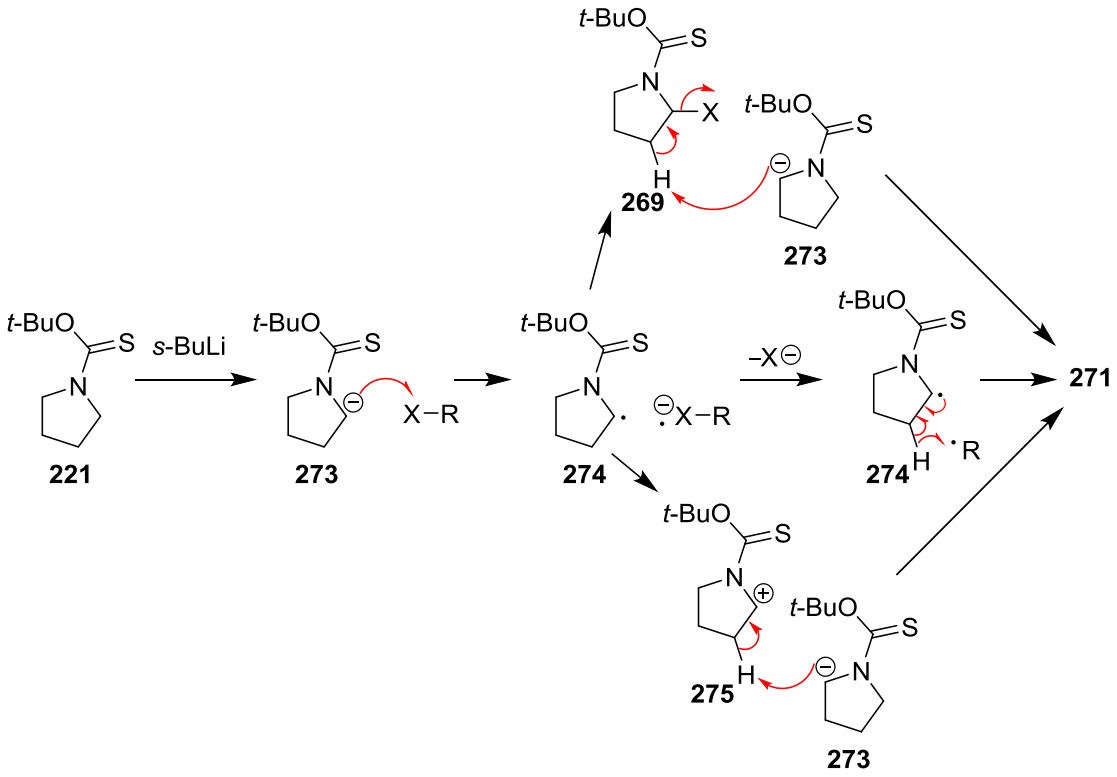
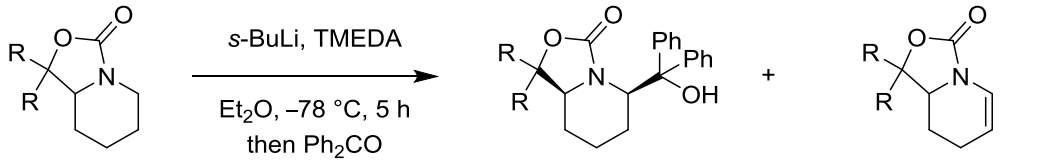


Figure 11. ^{1}H NMR chemical shifts of side-product **271** and known enecarbamate **272**.

Alkyl halides are often less efficient electrophiles in α-lithiation–electrophile trapping reactions as they have a greater tendency to undergo single electron transfer (SET);[118] a process which may be responsible for the formation of unwanted side-product **271** (Scheme 92). Gross and Beak reported the formation of a similar olefin side-product **278** in the α-deprotonation-electrophile trapping of bicyclic carbamates **276** with benzophenone, supporting the notion that side-products such as these are formed by a SET process (Scheme 93).[205]



Scheme 92. Possible mechanism for formation of side-product **271**.

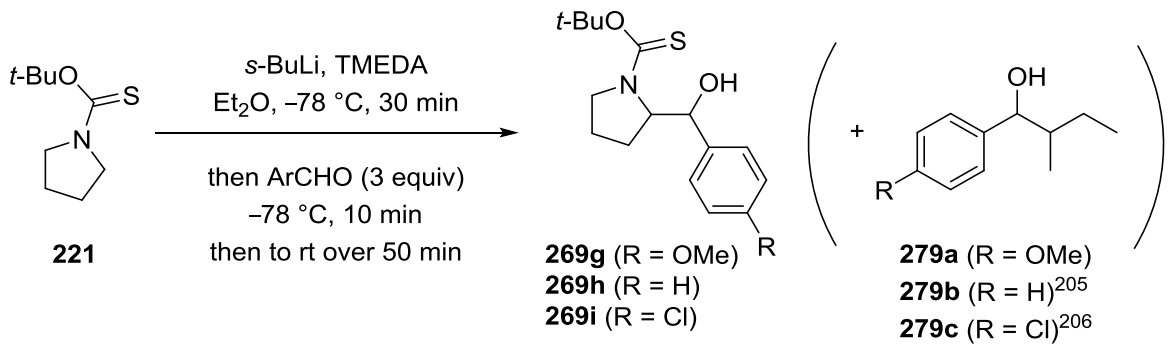


276a (R = *i*-Pr) **277a** (R = *i*-Pr, 59%) **278a** (R = *i*-Pr, 8%)
276b (R = *t*-Bu) **277b** (R = *t*-Bu, 62%) **278b** (R = *t*-Bu, 10%)

Scheme 93. Gross and Beak's reactions with benzophenone.

3.1.3. Electrophile scope: aromatic aldehydes

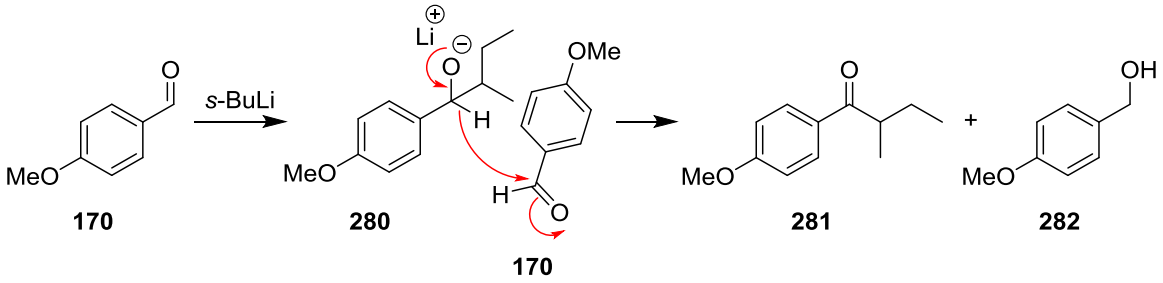
α-Lithiation–electrophile trapping of *N*-Botc-pyrrolidine **221** with aromatic aldehydes using our optimised conditions led to good yields (69–70%) of the desired alcohols **269g–i**, as a mixture of diastereomers (Table 8). We were pleased to observe that both electron-withdrawing and electron-donating substituents were tolerated on the aromatic ring. While the major diasteromers were readily isolated by column chromatography, the minor diastereomers could not be separated from side-products **279**,[206,207] formed in 11–17% yield by reaction of the aromatic aldehyde and *s*-BuLi, the latter being added in slight excess (1.3 equiv). It was thought that the side-product may be formed during the warming stage, as the reaction mixture was warmed to rt after addition of the electrophile. Therefore, the reaction with *p*-anisaldehyde was repeated under modified conditions: the reaction mixture was stirred for 3 h at −78 °C after addition of the electrophile, and was then quenched with sat aq NH_4Cl at this temperature. Under these conditions, formation of the unwanted side-product **279a** was minimised (2% yield), but the yield of the desired alcohol **269g** was also greatly reduced to just 20%, isolated as a single diastereomer.



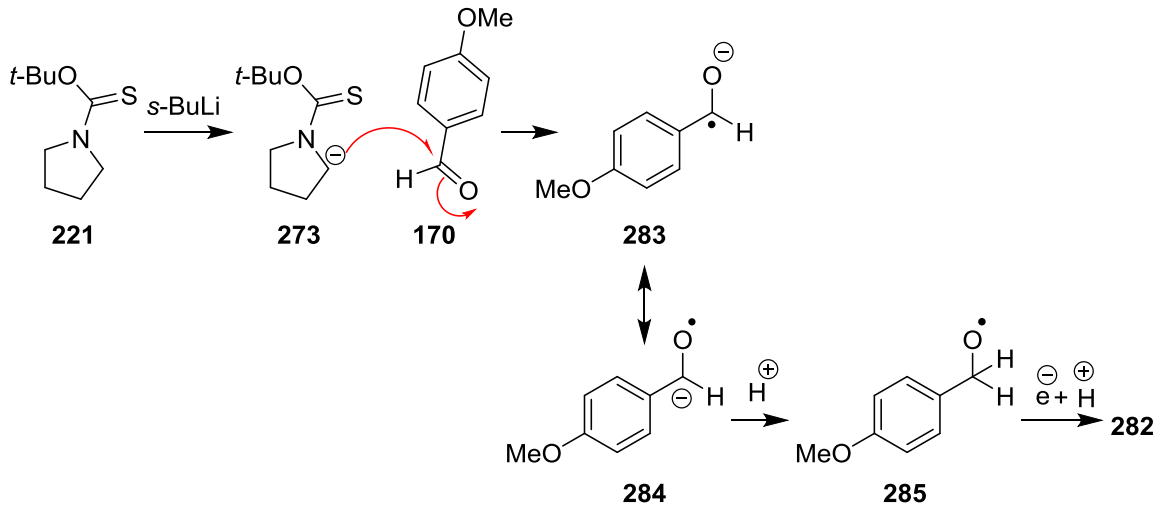
Entry	E^+	1.3 equiv *s*-BuLi		1.0 equiv *s*-BuLi	
		% Yield of product **269** (dr)	% Yield of **279**	% Yield of product **269** (dr)	% Yield of **279**
1	*p*-$MeOC_6H_4CHO$	69 (77: 23)	17	65% (72:28)	0
2	PhCHO	70 (77:23)	11	74% (72:28)	0
3	*p*-ClC_6H_4CHO	70 (69:31)	17	60% (67:33)	5

Table 8. Electrophile trapping with aromatic aldehdyes.

TLC analysis of the crude reaction mixture showed that a number of other side-products were also formed in the above reactions with aromatic aldehydes. For the reaction with *p*-anisaldehyde and 1.3 equiv of *s*-BuLi, two known side-products, ketone **281** (10% yield based on *s*-BuLi)[208] and alcohol **282** (22% yield based on *p*-anisaldehyde),[209] were successfully isolated. It was initially thought that ketone **281** may have been formed from the corresponding carboxylic acid, since Yus and co-workers reported that a similar product (*s*-butyl phenyl ketone) can be synthesised from benzoic acid and *s*-BuLi (formed in situ) in the presence of an electrophile.[210] However, *p*-anisaldehyde was purified by distillation before use, and NMR analysis showed that it contained no 4-methoxybenzoic acid impurity. It is perhaps more likely that side-products **281** and **282** were formed by an alternative mechanism involving lithium salt intermediate **280** (Scheme 94). Alternatively, alcohol **282** may have been generated by a SET process (Scheme 95).



Scheme 94. Proposed mechanism for formation of side-products **281** and **282**.

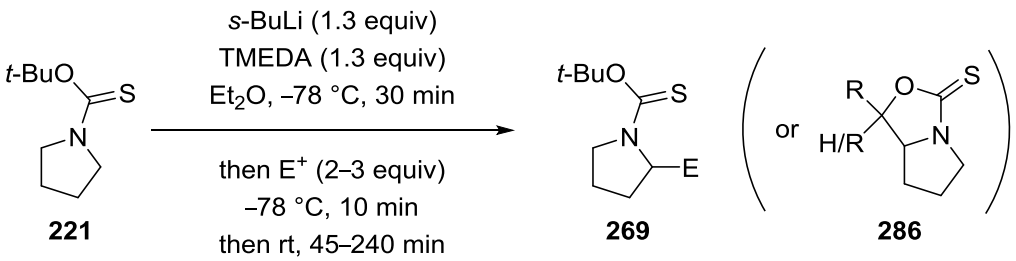


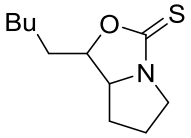
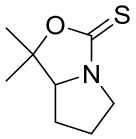
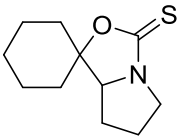
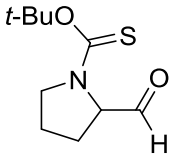
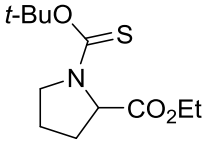
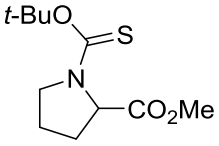
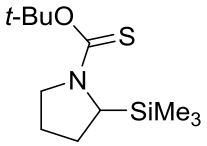
Scheme 95. Proposed formation of alcohol **282** by a Bouveault-Blanc reduction.

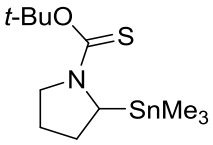
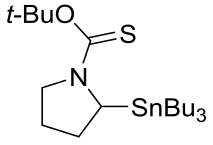
Previous deuteration studies had revealed that reducing the amount of *s*-BuLi from 1.3 to 1.0 equiv causes only a slight decrease in the extent of lithiation, with the level of deuteration dropping from 100% D to 82–94% D (see section 3.1.1., p 88). Pleasingly, side-products **279a** and **279b** were not formed when reactions with *p*-anisaldehyde and benzaldehyde were repeated with only 1 equiv. of *s*-BuLi, allowing both diastereomers of the desired alcohols **269g** and **269h** to be successfully isolated with no significant change in the dr (Table 8, entries 1–2). A substantial improvement was also seen in the reaction of 4-chlorobenzaldehyde under the same conditions, although side-product **279c** was still produced in 5% yield and was inseparable from the minor diastereomer of product **269i** (Table 8, entry 3).

3.1.4. Electrophile scope: other electrophiles

The above successful α-lithiation–electrophile trapping reactions of *N*-Botc-pyrrolidine **221** with MeI and with aromatic aldehydes prompted further investigation of the electrophile scope. In contrast to the above reactions with aromatic aldehydes, which gave non-cyclised products, trapping with an aliphatic aldehyde (hexanal) led to a high yield (78%) of cyclised product **286a** as a 1:1 mixture of diastereomers (Table 9, entry 1). Reaction with enolisable ketones acetone and the more sterically hindered cyclohexanone also led to cyclised products, albeit in lower yields (Table 9, entry 2–3). Due to the high % yields brsm, it seems likely that these electrophile-trapping reactions were affected by competing enolisation reactions. Pleasingly, α-lithiation–electrophile trapping went very cleanly with DMF, producing trapped product **269j** in high yield and purity, avoiding the need for further purification (Table 9, entry 4). This was particularly fortunate since trapped aldehyde **269j** was found to decompose on silica, and would therefore be unsuitable for purification by column chromoatography. Following this success, it was envisaged that the ketone functionality could be incorporated into the pyrrolidine ring using *N*,*N*-dimethylacetamide as the electrophile. Unfortunately, only a trace of the desired ketone (2% yield) was generated, and a large amount of starting material **221** (45%) was recovered at the end of this reaction.



Entry	Electrophile	Product Structure	% Yield (brsm)
1	hexanal	 **286a**	78[a] (95)
2	acetone	 **286b**	51 (84)
3	cyclohexanone	 **286c**	25 (~100)
4	DMF	 **269j**	88
5	ethyl chloroformate	 **269k**	38 (54)
6	Mander's reagent	 **269l**	15 (21)
7	Me_3SiCl	 **269m**	74 (93)

8	Me_3SnCl	 **269n**	69
9	Bu_3SnCl	 **269o**	70 (73)

a) 1:1 dr.

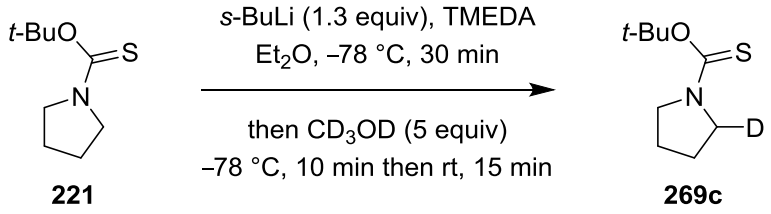
Table 9. Electrophile scope with *N*-Botc-pyrrolidine **221**.

In order to install the ester functionality in a single step, trapping with ethyl chloroformate was attempted. This very reactive electrophile led to the desired ester **269k** in 38% yield, along with a number of unidentified side-products and a high recovery of starting material **221** (31%) (Table 9, entry 5). In an effort to improve the yield, this reaction was repeated under modified conditions: after addition of ethyl chloroformate, the reaction mixture was stirred at −78 °C for 4 h, then at −40 °C for 30 min, and then at rt for 30 min before being quenched by sat aq NH_4Cl. Although slightly less starting material was recovered (22%) after this reaction, the yield of desired ester **269k** was also reduced to just 27%. It was hoped that the ester functionality would be more readily accessed with a less reactive electrophile, Mander's reagent, but this led to an even lower yield of the desired ester **269l** (Table 9, entry 6).

Silylation and stannylation proceeded well, giving high yields of trapped products (Table 9, entries 7–9). It was thought that these reactions may be promoted by LiCl, formed in situ; Collum and co-workers have previously shown that addition of just 0.5 mol % LiCl can substantially accelerate ortholithiations of arenes by LDA.[211] For the reaction with Me_3SiCl, although silylated product **269m** was obtained in 74% yield, a significant amount of starting material (21%) was also recovered. Since previous deuteration studies indicated

that lithiation was complete under these conditions (see section 3.1.1., p 87), it was assumed that the electrophile-trapping step had not gone to completion. The reaction was repeated under modified conditions: after addition of Me_3SiCl, the reaction mixture was stirred at −78 °C for 2 h, then at −40 °C for 30 min, before being quenched by addition of sat aq NH_4Cl. Although these conditions resulted in a lower recovery of starting material (8%), no significant improvement in the yield of silylated product **269m** (76%) was observed. Surprisingly, reaction of the lithiated species with Me_3SiCl for just 15 min at −78 °C followed by addition of either CD_3OD or MeI led to silylated product **269m** (83–84% yield) and unsubstituted starting material **221** (10%), implying that it was the lithiation step that had not gone to completion.

The above results suggest that, for deuteration studies, % D incorporation cannot be accurately calculated by integration of signals in the ^1H NMR spectra. Test deuterations with 2.4 and 1.3 equiv TMEDA were repeated in parallel, and while NMR analysis indicated almost complete lithiation in both cases (96–100% D), analysis by high resolution mass spectrometry revealed a slightly lower % D value for the reaction with 1.3 equiv TMEDA (Table 10). Therefore, analysis of the FI mass spectra became our preferred method for calculating % D incorporation.



Entry	TMEDA/equiv	% D		% Yield
		From ^{1}H NMR signal integration	From FI mass spectra analysis	
1	2.4	100	98	100
2	1.3	96	88	98

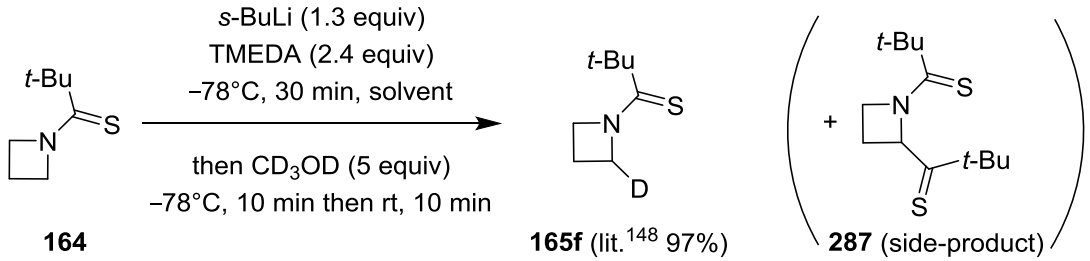
Table 10. NMR vs. FI mass spectrometry analysis for % D calculation.

3.2. *N*-thiopivaloyl-azetidine substrate

The successful studies above on *N*-Botc pyrroldine **221** demonstrated that the Botc group is an efficient *N*-activating group for electrophile incorporation into the pyrrolidine system. We were now keen to determine whether this novel *N*-protecting group would also allow α-lithiation–electrophile trapping on the more challenging azetidine system. Before the Botc group was further investigated, I hoped to increase my practical knowledge of α-lithiation of azetidines by repeating some of the Hodgson group's preliminary reactions on the *N*-thiopivaloyl-azetidine **164**,[148] on which my own research builds upon.

Frustratingly, in my hands, lithiation–deuteration of *N*-thiopivaloyl-azetidine **164** in THF gave a much lower yield (51%) of deuterated product **165f** than reported in the literature[148] (Table 11, entry 1). The yield of deuterated product **165f** was further reduced by switching the solvent from THF to Et_2O (Table 11, entry 2). Decreasing the amount of TMEDA (to 1.3 or 0 equiv) had no significant effect on the results in either THF or Et_2O. Non-polar side-product 2-thiopivaloyl-azetidine **287** was consistently observed in 11–16% yield, and was thought to be formed by attack of the lithiated species at the thiocarbonyl group of another *N*-thiopivaloyl-azetidine species, followed by loss of the azetidine group. Since the speed of addition of *s*-BuLi was found to be of great importance in the above reactions with *N*-Botc-pyrrolidine **221**, deuteration of *N*-thiopivaloyl-azetidine **164** was tested with a

slower rate of addition of *s*-BuLi (~100 µL/min). Surprisingly, yield of side-product **287** increased considerably and the formation of deuterated product **165f** was inhibited under these conditions (Table 11, entries 3–4). These intriguing results prompted a closer inspection of Seebach and Lubosch's original report on the lithiation of thiopivalamides.[149c] For the metallation of the *N*,*N*-dimethylthiopivalamide, the experimental section stated that '*s*-BuLi zugespritzt', suggesting that the *s*-BuLi was 'squirted' or 'injected' into the reaction mixture in this case. In stark contrast to our previous results, rapid addition of *s*-BuLi in 1 portion (typical rate of 1 mL in <2 s) resulted in good yields of deuterated product **165f**, with no side-product **287** observed (Table 11, entries 5–6).



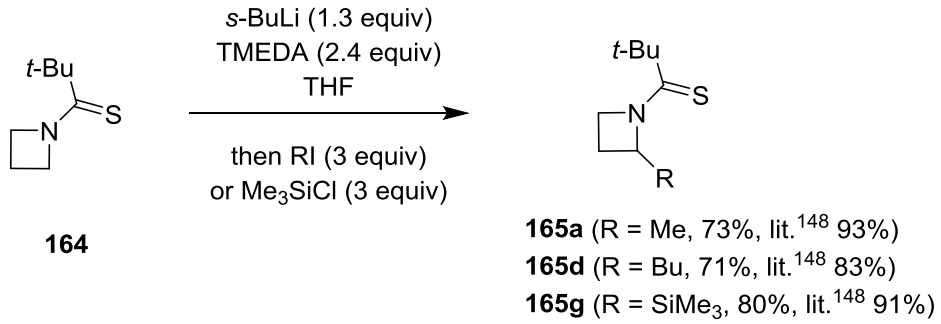
164 **165f** (lit.[148] 97%) **287** (side-product)

Entry	*s*-BuLi addition speed	Solvent	% D[a]	% Yield	% side-product **287**
1	dropwise (~200 µL/min)	THF	98–100	51	16
2		Et_2O		24	11
3	slow dropwise (~100 µL/min)	THF		8	66
4		Et_2O		0	39
5	fast (1 portion)	THF		74	0
6		Et_2O		75	

a) Determined by analysis of the FI mass spectra.

Table 11. Deuteration of *N*-thiopivaloyl-azetidine **164**.

Pleasingly, methylation, butylation and silylation of *N*-thiopivaloyl-azetidine **164** could also be carried out successfully with rapid addition of *s*-BuLi, giving reasonably similar yields of α-substituted products **165** to the reported literature[148] values (Scheme 96).



Scheme 96. α-Lithiation–electrophile trapping of *N*-thiopivaloyl-azetidine **164**.

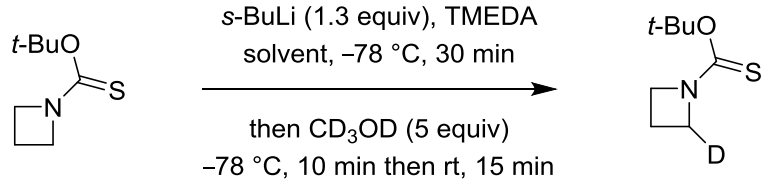
3.3. *N*-Botc-azetidine substrate

As discussed in section 1.5.1 (p 48–50), it was envisaged that the acid-labile Botc group would be a more suitable *N*-protecting group than the thiopivaloyl group for efficient α-lithiation–electrophile trapping on the azetidine system. Test deuteration reactions of *N*-Botc-azetidine **212** were initially used to validate the use of this *N*-protecting group for azetidine α-lithiation and to optimise the reaction conditions.

3.3.1. Deuteration studies

α-Lithiation–deuteration of *N*-Botc-azetidine **212** was first tested using conditions that worked well for *N*-Boc-pyrrolidine **97a**, employing Et_2O as the solvent and TMEDA as a ligand for *s*-BuLi. Although a high level of D incorporation could be generated with 1.3 or 2.4 equiv TMEDA, the yield of isolated product **288a** was disappointing, and a number of unknown decomposition products were also produced (Table 12, entries 1–2). For the

reaction with 2.4 equiv TMEDA, increasing the lithiation time (to 1 h) or the lithiation temperature (to −50 °C) led to numerous impurities but no recovery of starting material or product. An extremely low % D incorporation was observed in this solvent in the absence of TMEDA (Table 12, entry 3). No improvement in the results could be seen by switching the solvent to *t*-BuOMe (Table 5, entry 4). In contrast to the above studies on *N*-Botc-pyrrolidine **221**, deuteration of *N*-Botc-azetidine **212** in THF provided highly deuterated product **288a** in excellent yield with 1.3 or 2.4 equiv TMEDA (Table 12, entries 5–6). Calculation of the % D by analysis of the FI mass spectra, previously shown to be a more accurate method than analysis of the ^{1}H NMR spectra, revealed that 2.4 equiv TMEDA was required to achieve almost complete lithiation. A significantly lower level of lithiation occurred in the absence of TMEDA (Table 12, entry 7).

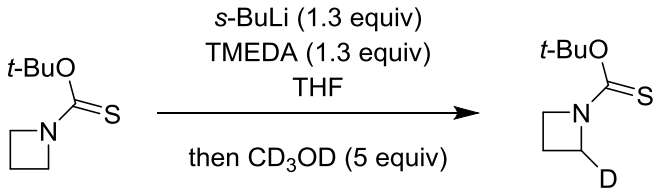


212 **288a**

Entry	Solvent	TMEDA/equiv	% Yield	% D	
				From ^{1}H NMR spectra	From FI mass spectra
1	Et_2O	2.4	40	92	-
2		1.3	58	94	-
3		0	89	22	14
4	*t*-BuOMe	2.4	48	111	98
5	THF	2.4	83–93	101–111	94–98
6		1.3	85–98	95–98	79–83
7		0	88	80	67

Table 12. Optimisation using test deuteration reactions.

The chemical stability of the azetidine anion was investigated by varying the lithiation time and temperature. Only 1.3 equiv TMEDA was used in these deuteration experiments because we had not yet finished our above optimisation studies. The lithiated species was found to be relatively stable for 2.5 h at −78 °C (Table 13, entry 1), but rapidly decomposed at −40 °C; a much lower yield and slightly reduced % D of deuterated product **288a** was observed after just 15 min at this temperature (Table 13, entry 2). To prevent decomposition and formation of unwanted side-products, we aimed to carry out α-lithiation–electrophile trapping studies at lower temperatures and with shorter reaction times. Lithiation for 30 min at −78 °C led to highly deuterated product **288a** in excellent yield, even without a warming stage, indicating that the deuteration step is rapid at −78 °C (Table 13, entry 3). Deuteration of *N*-Botc-azetidine **212** with a shorter lithiation time (15 min or 5 min) resulted in significantly reduced % D incorporation (Table 13, entries 4–5), suggesting that complete lithiation is only achieved after 30 min at −78 °C.



212 **288a**

Entry	Lithiation temp (time)	Work-up temp	% Yield	% D[a]
1	−78 °C (2.5 h)	rt	75	96
2	−78 °C (30 min) then −40 °C (15 min)	rt	25	84
3	−78 °C (30 min)	−78 °C	95	90
4	−78 °C (15 min)	rt	80	68

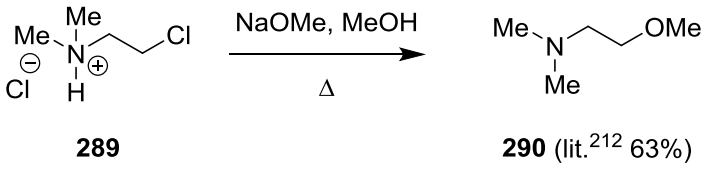
5	−78 °C (5 min)		83	42

a) Calculated by analysis of the ^{1}H NMR spectra.

Table 13. Investigation of reaction temperature and time.

3.3.2. Investigation of a hemi-labile ligand

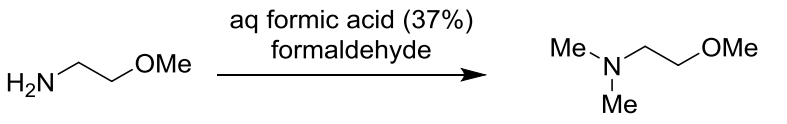
Ramírez and Collum have shown that hemi-labile ligands such as **290**, which chelate lithium only at the rate limiting transition structures, can help to increase the reaction rates in organolithium chemistry.[212] Lillocci and co-workers previously synthesised hemi-labile ligand **290** by reaction of 2-chloro-*N*,*N*-dimethylethylamine hydrochloride (**289**) and NaOMe under reflux in MeOH (Scheme 97).[213] However, in my hands, no desired product **290** was formed by this method. The reaction was attempted with solid NaOMe, which did not dissolve effectively in MeOH, and also with 0.5 M solution of NaOMe in MeOH; no product was observed in the crude NMR spectra in either case.



289 **290** (lit.[212] 63%)

Scheme 97. Lillocci and co-worker's synthesis of ligand **290**.

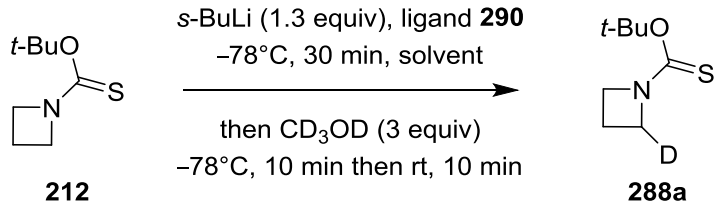
Hemi-labile ligand **290** was successfully synthesised by an alternative route, involving a known Eschweiler-Clark methylation of the free-amine **291** (Scheme 98).[214]



291 **290** (40%, lit.[213] 40%)

Scheme 98. Eschweiler-Clark methylation of amine **291**.

With hemi-labile ligand **290** in hand, it was then tested in α-lithiation–electrophile-trapping reactions on *N*-Botc-azetidine **212** (Table 14, entries 1–4). Disappointingly, ligand **290** did not perform as well as TMEDA in test deuteration reactions, generating similar yields of deuterated product **288a** but with a lower level of deuteration than previously seen for the corresponding reactions with TMEDA (Table 12, entries 1–2 and 5–6).



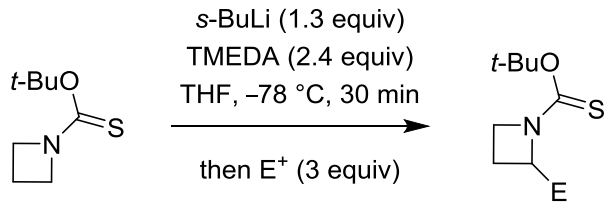
Entry	Solvent	Ligand **290** equiv	% Yield	% D[a]
1	Et_2O	2.4	41	46
2		1.3	63	81
3	THF	2.4	91	49
4		1.3	77	67

a) Calculated by analysis of the FI mass spectra.
Table 14. Test deuteration reactions using hemi-labile ligand **290**.

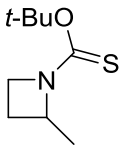
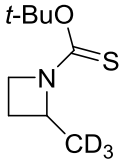
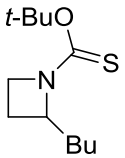
3.3.3. Electrophile scope

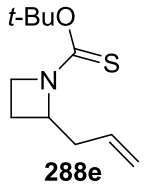
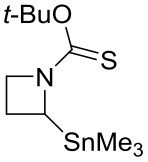
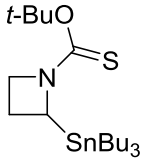
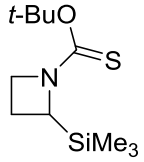
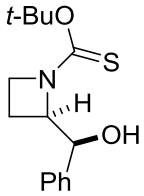
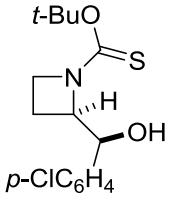
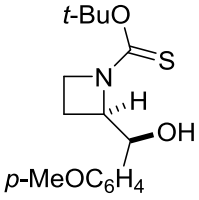
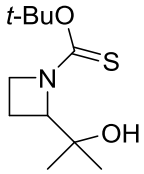
Having optimised reaction conditions for α-lithiation of *N*-Botc-azetidine **212**, we were keen to explore electrophile scope. Pleasingly, the lithiated species could be successfully trapped with MeI, providing methylated product **288b** in high yield (Table 15, entry 1). A small amount of unreacted starting material **212** was recovered; most likely due to incomplete lithiation since addition of excess CD_3OD 30 min after addition of the MeI led to only a trace of deuteration detected (1% D by analysis of the FI mass spectrum). Also,

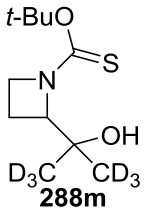
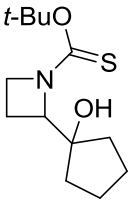
no deuteration of the recovered starting material was observed for the corresponding reaction with CD_3I (Table 15, entry 2), indicating that unreacted lithiated material was not quenched by protons from the electrophile. The yield of methylated product **288b** was only slightly reduced by decreasing the amount of TMEDA to 1.3 or 0 equiv (75% and 70% yields, respectively). Alkylation with BuI and allyl Br was also successful, leading to high yields of trapped products **288d** and **288e** (Table 15, entries 3–4). Butylation of *N*-Botc-azetidine **212** was repeated with a longer stirring time with BuI (12 h at −78 °C), but no improvement in the yield of butylated product **288d** was observed. Unlike previous alkylation reactions with *N*-Botc-pyrrolidine **221** (which we carried out in Et_2O, p 91), alkylation of the analogous azetidine substrate did not give rise to an unwanted (and, in this case, strained) enamine (azetidine) side-product.



212 **288**

Entry	Electrophile	Product Structure	% Yield (brsm)
1	MeI	 **288b**	79 (83)
2	CD_3I	 **288c**	73 (76)
3	BuI	 **288d**	77 (86)

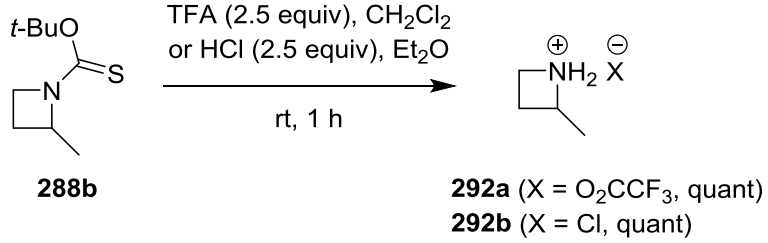
4	allyl Br	 **288e**	53 (59)
5	Me_3SnCl	 **288f**	72 (86)
6	Bu_3SnCl	 **288g**	75
7	Me_3SiCl	 **288h**	76[a] (84)
8	PhCHO	 **288i**	74[b,c] (80)
9	*p*-ClC_6H_4CHO	 **288j**	69[b,c] (80)
10	*p*-$MeOC_6H_4CHO$	 **288k**	57[b,c] (76)
11	Me_2CO	 **288l**	65 (90)

12	$(CD_3)_2CO$	 **288m**	70 (86)
13	cyclopentanone	 **288n**	44 (74)

a) *N*-Botc-2,2-disilylazetidine **293a** also formed in 5% yield, and was separable. *b*) *s*-BuLi reduced to only 1.0 equiv. *c*) 70:30 dr, major (*R**,*S**) diastereomer shown.

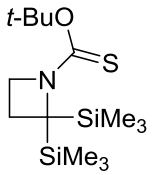
Table 15. Electrophile scope with *N*-Botc-azetidine **212**.

Having previously established that unsubstituted *N*-Botc-azetidine **212** could be readily deprotected under acidic conditions (see section 2.4.), we were pleased to find that deprotection of an α-substituted *N*-Botc-azetidine could also be achieved under these conditions, in quantitative yield from methylated-azetidine **288b** (Scheme 99).



Scheme 99. Acid-catalysed deprotection of α-methylated *N*-Botc-azetidine **288b**.

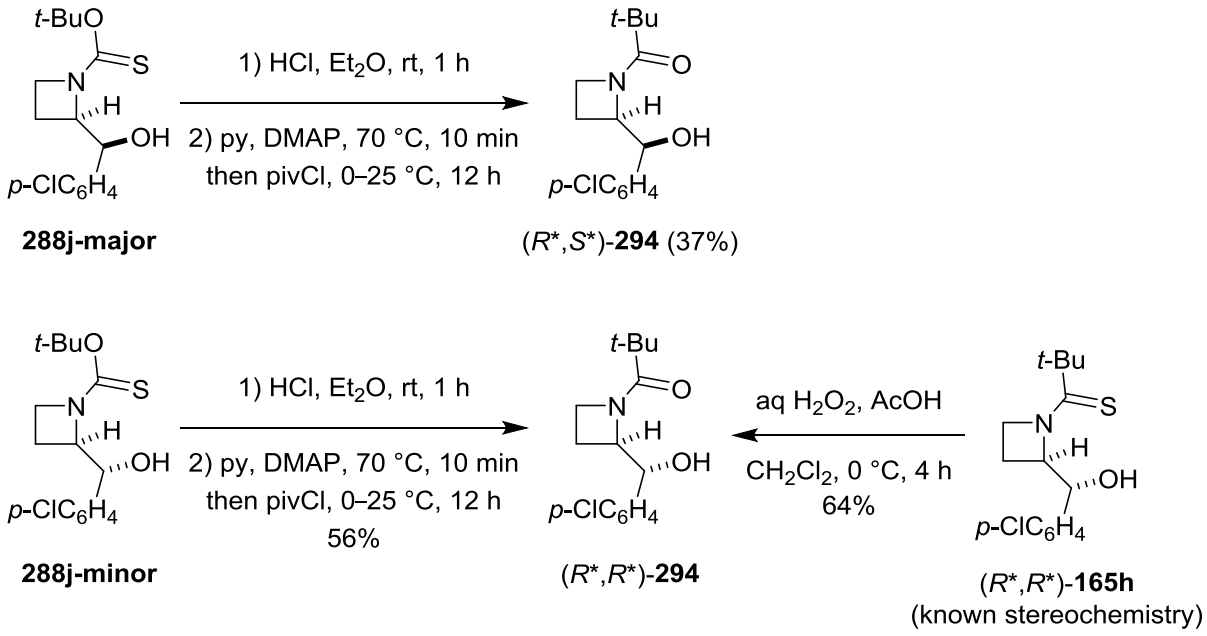
Stannylation of *N*-Botc-azetidine **212** was also successful, giving high yields of stannanes **288f** and **288g** (Table 15, entries 5–6), which offer potential for further functionalisation by cross-coupling. A high yield of silylated product **288h** could be generated by reaction with Me_3SiCl (Table 15, entry 7), although *N*-Botc-2,2-disilylazetidine **293a** was also isolated in 5% yield (Figure 12). A similar yield of the doubly silylated side-product **293** was obtained when only 1 equiv of Me_3SiCl was added, whilst the yield of desired mono-silyated product **288h** was reduced to 59%.



293a

Figure 12. *N*-Botc-2,2-disilylazetidine **293a**; a minor side-product from silylation.

Reactions with aromatic aldehydes and acetone initially resulted in numerous unknown side-products, preventing successful isolation of the desired trapped products. However, these electrophiles proved viable under slightly modified conditions: the reaction mixture was stirred for 2–3 h at −78 °C after addition of the electrophile, and was then quenched with sat aq NH_4Cl at −78 °C (no warming stage). Aromatic aldehydes could then be trapped in high yield, in 70:30 dr, with only a slight lowering in yield seen for the more electron-rich *p*-anisaldehyde (Table 15, entries 8–10). This electrophile had previously failed to produce any trapped product with *N*-thiopivaloyl-azetidine **164**.[151] As formed for the corresponding reactions of *N*-Botc-pyrrolidine **221** with aromatic aldehydes (see section 3.1.3.), reduction in the amount of *s*-BuLi from 1.3 to 1.0 equiv was also necessary to prevent the formation of side-products. The stereochemistry of the major and minor diastereomers **288j-major** and **288j-minor** was determined by conversion to the corresponding *N*-piv-azetidines (*R**,*R**)-**294** and (*R**,*S**)-**294**, and comparing characterisation data to that of an authentic sample of (*R**,*R**)-**294** (Scheme 100). An authentic sample of (*R**,*R**)-**294** was synthesised from *N*-thiopivaloyl-azetidine (*R**,*R**)-**165h**,[148] and the stereochemistry of the latter had previously been determined in the Hodgson group by X-ray crystallography. The stereochemistry of the major and minor diastereomers of **288i** and **288k** were determined by analogy to **288j**.



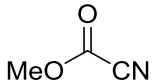
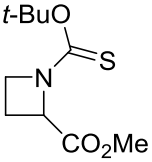
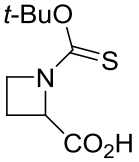
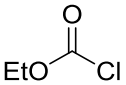
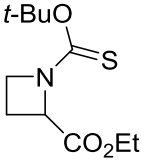
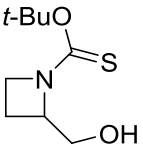
Scheme 100. Stereochemistry determination of **288j-major** and **288j-minor**.

In contrast to previous results for *N*-Botc-pyrrolidine **221**, non-cyclised products were formed from reaction of *N*-Botc-azetidine **212** with enolisable ketones (likely due to increased ring strain with this substrate). Trapping with acetone led to a reasonable yield of the desired alcohol **288l** with no warming stage, despite suffering from a competing enolisation reaction (Table 15, entry 11): trapping with acetone-D_6 led to a similar yield (70%) of trapped product **288m**, along with 20% yield of recovered starting material with 35% D incorporation, as determined by analysis of the FI mass spectrum (Table 15, entry 12). It was also possible to obtain trapped product **288n** using the more sterically hindered ketone, cyclopentanone, albeit in lower yield (Table 15, entry 13).

3.3.4. Unsuccessful electrophiles

Although a range of electrophiles performed well in α-lithiation–electrophile trapping reactions, less pleasing results were seen with a number of carbonyl-based electrophiles. Attempts to incorporate an ester group using Mander's reagent or ethyl chloroformate led

to poor yields of the resulting esters (<20% yield), which could not be cleanly isolated from the numerous unknown side-products (Table 16, entries 1–2). A similar result was observed with the aliphatic aldehyde hexanal (Table 16, entry 3), despite the previous success with aromatic aldehydes. For the reaction with ethyl chloroformate, 2 of the side-products were isolated and characterised: dimer **295**, formed by attack of the lithiated species at the carbonyl group in the desired product **288p**, was isolated in 11% yield and 2,2-disubstituted-azetidine **293b** was formed in 5% yield (Figure 13). Since cyclopentanone could be trapped in 44% yield, it was hoped that a higher yield could be achieved with the less enolisable ketone cyclohexanone; however, the trapped product could not be separated from unknown side-products in this reaction (Table 16, entry 4).

Entry	Electrophile	Expected product	**Entry**	Electrophile	Expected product
1		 **288o**	**7**	CO_2	 **288u**
2		 **288p**	**8**		 **288v**

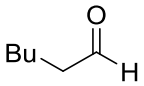
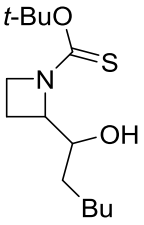
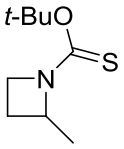
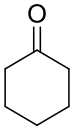
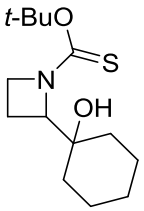
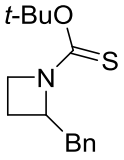
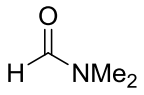
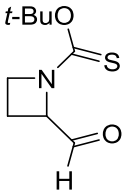
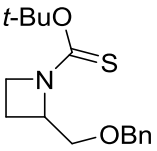
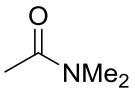
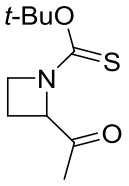
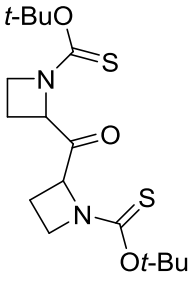
3		 **288q**	**9**	MeOTf	 **288b**
4		 **288r**	**10**	BnBr	 **288w**
5		 **288s**	**11**	$BnOCH_2Cl$	 **288x**
6		 **288t**			

Table 16. Unsuccessful electrophiles in α-lithiation–electrophile trapping.


295

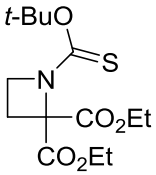
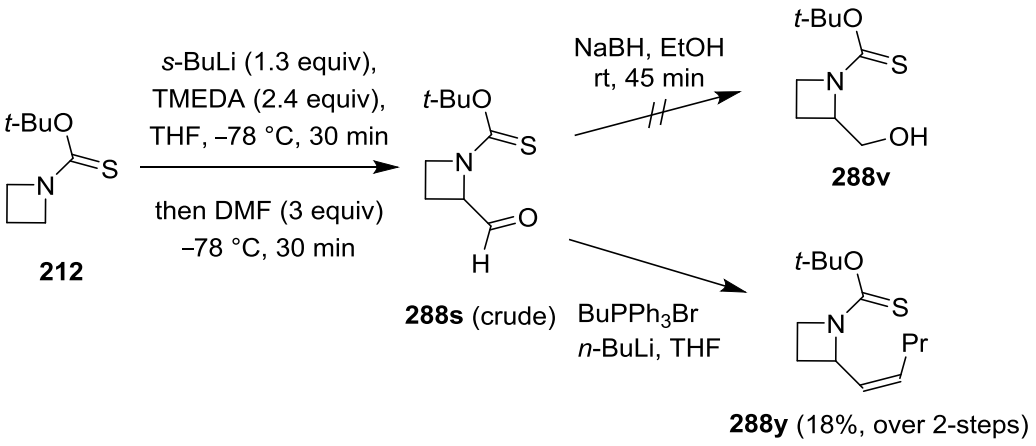

293b

Figure 13. Isolated side-products from reaction with ethyl chloroformate.

Contrary to our previous result with *N*-Botc-pyrrolidine **221**, *N*-Botc-azetidine **212** could not be cleanly trapped with DMF (Table 16, entry 5). Although possible product peaks were observed in the crude ^{1}H NMR spectrum [several peaks in the range δ_H = 9.88–9.54 (HC=O), singlet at δ_H = 9.88 ($C(CH_3)_3$)], the desired product **288s** was found to be

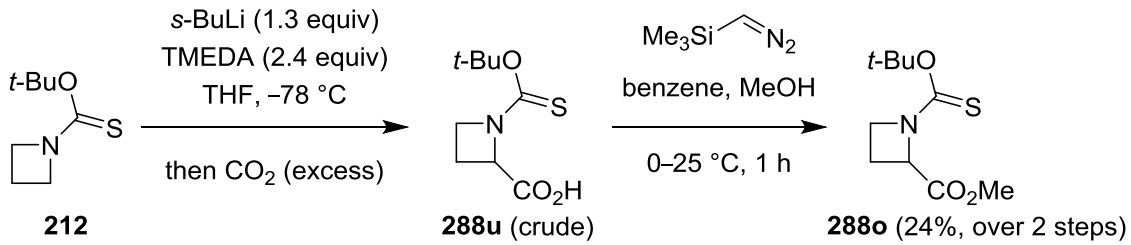
unstable on silica and could not be successfully isolated by column chromatography. Attempted reduction of the crude product with $NaBH_4$ in EtOH led to decomposition, whereas subjecting the crude product to a Wittig reaction only resulted in formation of alkene **288y** in very low yield (Scheme 101). Since an unstablised ylide was used in this case, it was assumed that alkene **288y** was formed as the *Z*-isomer; the analogous Wittig reaction with *N*-Boc-2-formyl-pyrrolidine was previously reported by Beak and co-workers to give the corresponding alkene as a 10:1 mixture of *Z*:*E* isomers.[111] Likewise, no trapped product could be formed using dimethyl acetamide as the electrophile (Table 16, entry 6).



Scheme 101. Attempted formation and further reaction of aldehyde **288s**.

Trapping with CO_2 was of particular interest as this would provide concise access to a novel azetidine amino acid (Table 16, entry 7). However, treatment of the lithiated species with CO_2 gas, followed by methylation with TMS-diazomethane gave methyl ester **288o** in low yield (Scheme 102). In this procedure, CO_2 gas from dry-ice was passed through a drying tube ($CaCl_2$) and then bubbled through the reaction mixture containing the lithiated azetidine species for 0.5–3.5 min at −78 °C, then 30 min at rt. Attempts to purify the crude product **288u** by column chromatography were unsuccessful, with or without addition of a

small amount of formic acid to the eluent. Employing solid CO_2 (dry ice) as the electrophile led to formation of impure product **288u** in very low yield (<11%), and 25% mass recovery of starting material **212**.



Scheme 102. Attempted formation and methylation of carboxylic acid **288u**.

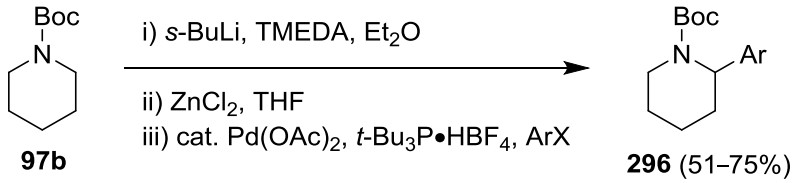
Trapping with formaldehyde was also unsuccessful, leading to a low yield of alcohol **288v** (14%), along with a large quantity of recovered starting material **212** (38%) (Table 16, entry 8). In this case, paraformaldehyde and *p*-toluenesulfonic anhydride were heated at 85 °C,[215] and the resulting formaldehyde gas was passed through the reaction mixture containing the lithiated species with a strong flow of Ar. Unfortunately, after less than 10 min, a blockage caused by re-polymerisation of solid paraformaldehyde inhibited the flow of formaldehyde into the reaction mixture. This problem also occurred when paraformaldehyde cracking was carried out by heating paraformaldehyde to 180 °C, providing no trapped product **288v**. No reaction occurred when solid paraformaldehyde was added as the electrophile: 89% of starting material being recovered from this latter reaction.

Although α-alkylation of *N*-Botc-azetidine **212** was successful with a range of alkyl halides including MeI, methylation with the potentially more reactive electrophile methyl triflate led to a greatly diminished yield of methylated product **288b** (14–21%), along with numerous unknown side-products (Table 16, entry 9). In addition, reaction with BnBr or

benzyl chloromethyl ether resulted in numerous side-products and disappointing yields (9% and 31%, respectively) of the desired trapped product (Table 16, entries 10–11).

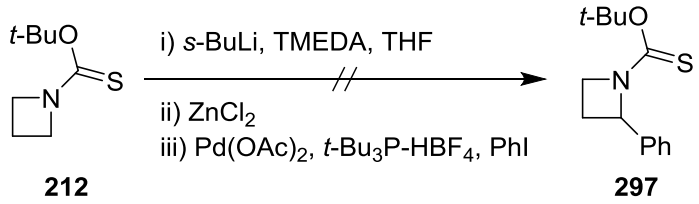
3.3.5. Attempted arylation

Coldham and Leonori have reported the synthesis of 2-aryl-piperidines **296** by α-lithiation of *N*-Boc-piperidine **97b** followed by transmetallation–Negishi coupling (Scheme 103).[153]



Scheme 103. Coldham and Leonori's arylation of *N*-Boc-piperidine **97b**.

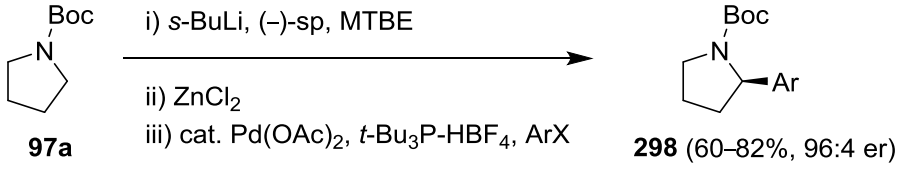
Disappointingly, these conditions could not be extended to our *N*-Botc-azetidine **212** substrate; only impure starting material was recovered from attempted coupling with PhI (Scheme 104). In this case, for successful α-lithiation of this substrate with *s*-BuLi/TMEDA, it was required that the solvent was switched from Et_2O to THF (see section 3.3.1., p 102–104).



Scheme 104. Attempted synthesis of 2-phenyl-azetidine **297**.

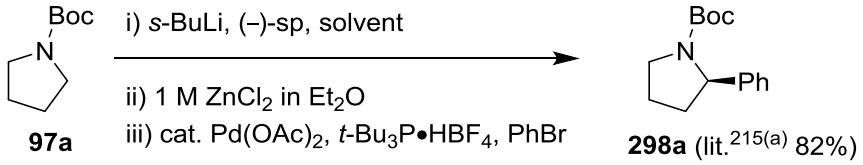
Campos and co-workers had previously shown that this strategy was suitable for the synthesis of chiral 2-aryl-pyrrolidines **298**, using the chiral ligand (−)-sp **138** with MTBE

as solvent (Scheme 105).[216] However, recent studies by O'Brien and co-workers revealed that TMEDA is not a suitable ligand for transmetalation–Negishi coupling of *N*-Boc-pyrrolidines, since yields of 2-aryl-pyrrolidines were greatly reduced when the ligand was changed from (−)-sp to TMEDA.[217] We therefore decided to test this methodology on the *N*-Botc-azetidine **212** substrate using (−)-sp as the diamine ligand instead of TMEDA.



Scheme 105. Campos' asymmetric arylation of *N*-Boc-pyrrolidine **97a**.

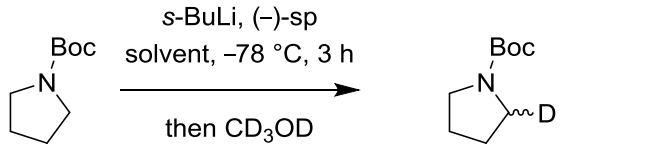
Before continuing our studies on the azetidine substrate, arylation of *N*-Boc-pyrrolidine **97a** using the established literature[216(a)] procedure was carried out in my own hands to test the quality of the reagents used (Table 17, entry 1). 2-Phenyl-pyrrolidine **298a** was formed successfully under these conditions, using a new bottle of $ZnCl_2$, albeit in a lower yield (41%) than expected. This chemistry was found to be very sensitive to the quality of $ZnCl_2$ added, since the yield of 2-phenyl-pyrrolidine **298a** was significantly reduced (to 17%) when an older bottle of this reagent was used. A lower yield of product was also observed by switching the solvent from MTBE to Et_2O (Table 17, entry 2). Test deuteration reactions resulted in a high level of D incorporation in both Et_2O and MTBE, indicating that lithiation was not the problematic step (Scheme 106). Although reproducing the literature yield proved challenging for this sensitive chemistry, a more satisfactory yield of 2-phenyl-pyrrolidine **298a** (51%) was achieved by reducing the transmetallation time (Table 17, entry 3).



97a **298a** (lit.[215(a)] 82%)

Entry	Solvent	Transmetallation conditions	% Yield	% SM
1	MTBE	30 min (−78 °C) then 45 min (rt)	41	31
2	Et_2O		28	39
3	MTBE	30 min (−78 °C) then 15 min (rt)	52	25

Table 17. Attempted synthesis of 2-phenyl-pyrrolidine **298a**.

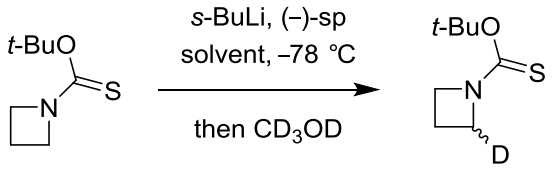


97a **132c**
(In MTBE: 94%, 95% D)
(In Et_2O: 80%, 87% D)

Scheme 106. Test deuteration reactions of *N*-Boc-pyrrolidine **97a**.

Test deuteration reactions on *N*-Botc-azetidine **212** revealed that this substrate could be fully lithiated within 1 h with *s*-BuLi (dropwise addition) and (−)-sp in either MTBE or Et_2O (Table 18, entries 2 and 4). In contrast, analogous reactions using TMEDA or hemi-labile ligand **290** previously required THF as solvent for a high level of lithiation (see Table 12, p 103–104 and Table 14, p 106). The resulting lithiated species was found to be stable for at least 3 h at −78 °C in MTBE (Table 18, entry 1). Additional test deuteration

reactions showed that pre-forming the *s*-BuLi/ligand complex before addition to the azetidine thiocarbamate substrate was unnecessary, and in fact led to a slightly lower % D incorporation (Table 18, entries 3 and 5).



212 **288a**

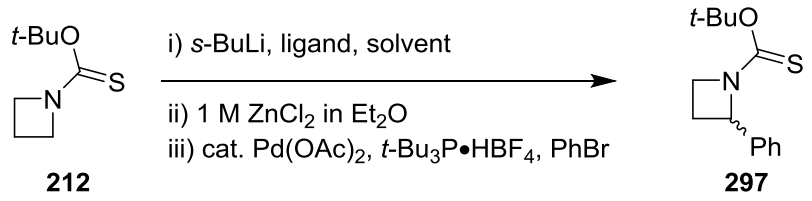
Entry	Solvent	Lithiation time/ h	Pre-form complex?	% Yield	% D[a]
1	MTBE	3	No	86	>99
2		1		82	>99
3			Yes	98	80
4	Et_2O		No	80	>99
5			Yes	88	73

a) Calculated by analysis of the ^{1}H NMR spectra.

Table 18. Deuteration of *N*-Botc-azetidine **212** using (−)-sp ligand.

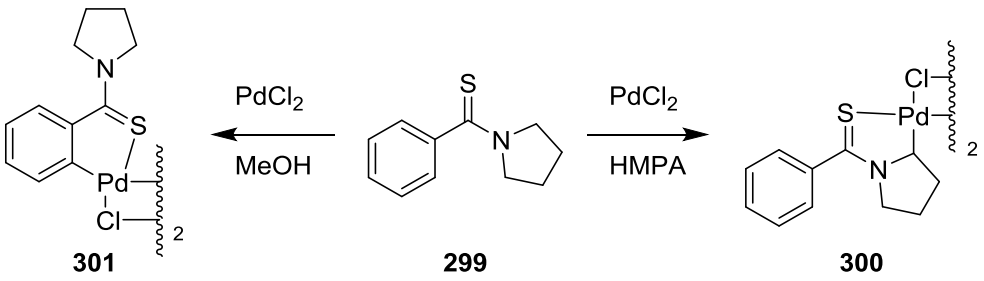
With suitable lithiation conditions in hand, arylation of the *N*-Botc-azetidine **212** substrate could then be attempted using the above optimised conditions. Unfortunately, no 2-arylated product **297** was obtained in either MTBE or Et_2O; instead a large amount of starting material was recovered from the reaction mixture (Table 19, entries 1–2). No improvement in the results was observed with a longer transmetallation time, with or without a warming step (Table 19, entries 3–4). In addition, no 2-phenyl-azetidine **297** was generated in either MTBE or Et_2O by replacing the (−)-sp ligand with TMEDA (Table 19, entries 5–6). The lack of success in this area may be attributed to the presence of the thiocarbonyl functionality in this substrate. Studies by Yoshida and co-workers showed that heating thioamides with $PdCl_2$ can lead to formation of stable *N*-

palladiomethylthioamides in polar solvents (Scheme 107).[218] In our case, formation of a similar stable palladocycle intermediate would have resulted in catalyst inhibition, preventing cross-coupling with PhBr.



Entry	Solvent	Ligand	Lithiation time/h	Transmetallation time (temp)	% Yield	% SM
1	MTBE	(−)-sp	1	45 min (−78 °C) then 15 min (rt)	0	66
2	Et_2O					56
3	MTBE			3 h (−78 °C)		64
4				3 h (−78 °C) then 30 min (rt)		70
5		TMEDA	0.5	45 min (−78 °C) then 25 min (−40 °C) then 15 min (rt)		16
6	Et_2O					8

Table 19. Attempted arylation of *N*-Botc-azetidine **212**.



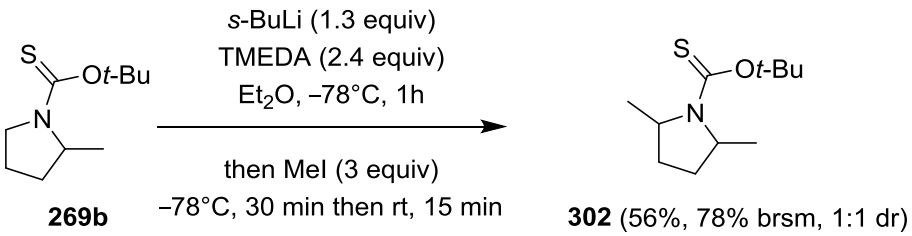
Scheme 107. Formation of stable *N*-palladiomethylthioamides.[218]

3.4 Synthesis of disubstituted-azacycles

Having established that Botc was an effective *N*-protecting group for α-lithiation–electrophile trapping on pyrrolidines and azetidines with a range of electrophiles, our next aim was to determine whether this methodology could be extended to allow the formation of disubstituted azacycles, particularly 2,4-disubstituted-azetidines.

3.4.1. Synthesis of 2,5-disubstituted-pyrrolidines

Test reactions on the pyrrolidine system were encouraging: a second α′-lithiation–methylation of 2-methyl-pyrrolidine **269b** was found to be possible, although 2,5-dimethylated product **302** was produced in only 29% yield (39% brsm) as a mixture of diastereomers (1:1 dr). However, Beak and co-workers have previously reported that in the case of *N*-Boc-pyrrolidines, a relatively long lithiation time was required to synthesise *N*-Boc-2,5-dimethyl-pyrrolidine **136** in good yield from the corresponding mono-methylated substrate (Scheme 39, p 32).[111] Pleasingly, a higher yield (56%) of *N*-Botc-2,5-disubstituted product **302** could be achieved by increasingly the lithiation time from 30 min to 1 h (Scheme 108).



269b **302** (56%, 78% brsm, 1:1 dr)

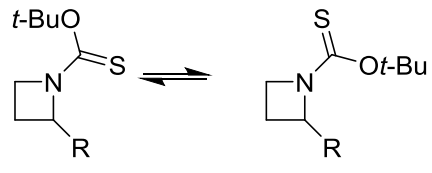
Scheme 108. Synthesis of 2,5-dimethylated-pyrrolidine **302**.

3.4.2. Synthesis of 2,4-disubstituted-azetidines

As discussed in section 1.4.4.4., a major limitation with the thiopivaloyl *N*-protecting group was that it inhibited the attempted synthesis of 2,4-disubstituted azetidines (Scheme 57, p 47).[151] It was anticipated that the Botc *N*-protecting group may be used to alleviate this problem (see section 1.5.1., p 48–50).

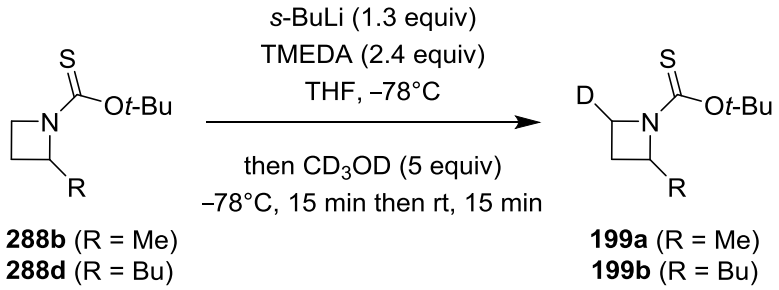
3.4.2.1. *N*-Botc-2-methyl-azetidine substrate

Test deuteration reactions on 2-methyl-azetidine **288b** were carried out to determine the whether α′-lithiation of mono-subsituted azetidines was feasible using this *N*-protecting group. Pleasingly, 59% D incorporation at the 4-position was achieved with a lithiation time of 30 min, with no deuteration observed at the 2-position (Table 20, entry 1). As expected, the rate of lithiation was slower with this more sterically hindered α-methylated substrate than with the previous unsubstituted azetidine **212**, requiring a longer lithiation time of 1 h to obtain a high level of deuteration (76% D) (Table 20, entry 2). However, 2-methyl-azetidine **288b** could not be fully lithiated at −78 °C, even by further increasing the lithation time, suggesting that the *N*-Botc rotamers **288-major** and **288-minor** may not interconvert at this temperature (Figure 14, R = Me); further evidence for this is given below (see section 3.5.). Analysis of the ^{1}H NMR spectrum revealed that 2-methyl-azetidine **288b** is present as a 2.5:1 mixture of rotamers (at rt, in $CDCl_3$). Since lithiation is proposed to be directed by the thiocarbonyl moiety, the above experimental results suggest that the major rotamer is likely to be **288-major** (Figure 14, R = Me).



288-minor **288-major**

Figure 14. Botc rotamer interconversion.



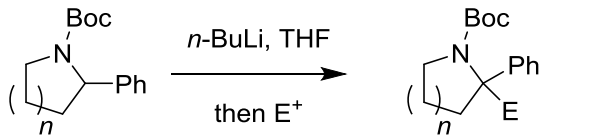
Entry	R	Lithiation time/min[a]	% Yield	% D[b]
1	Me	30	94	59
2		60	97	76
3		30 (−78 °C) then 15 (−40 °C)	50	91
4	Bu	30	96	58
5		60	96	59

a) Lithiation temperature is −78 °C unless otherwise stated.
b) Calculated by analysis of the FI mass spectra.

Table 20. Test deuteration reactions on 2-alkyl-azetidines **288b** and **288d**.

O'Brien and Coldham and co-workers experienced similar difficulties in their recent studies on α-lithiation–substitution of *N*-Boc-2-phenyl-pyrrolidines **298a** and piperidines **296a** (Scheme 109).[219] They were able to monitor the rate of lithiation using *in situ* IR spectroscopy, which showed that lithiation of the more reactive rotamer of *N*-Boc-2-phenyl-pyrrolidine **298a** (C=O *syn* to Ph) was complete within 2 min, but no further lithiation took place at −78 °C due to slow rotamer interconversion. In situ IR monitoring was possible because the starting material exhibited a $\nu_{C=O}$ peak at 1696 cm^{-1}, which was shifted to 1644 cm^{-1} in the lithiated species. O'Brien and Coldham and co-workers also carried out ^{1}H NMR spectroscopic studies in THF-D_8 to monitor rotamer interconversion.

They were able to achieve complete lithiation of *N*-Boc-2-phenyl-pyrrolidine **298a** by raising the lithiation temperature to 0 °C. Therefore, deuteration of 2-methyl-azetidine **288b** was repeated with a slightly higher lithiation temperature to hopefully aid rotamer interconversion (Table 20, Entry 3). Although lithiation was virtually complete (91% D) under these conditions, raising the lithiation temperature to −40 °C for just 15 min had a detrimental effect on the mass recovery, and a greater number of unknown impurities seen by TLC analysis of the crude material. We were not surprised to discover this chemical instability of the lithiated species at −40 °C, since a similar result was previously seen with the unsubstituted substrate **212** (see section 3.3.1., p 104).



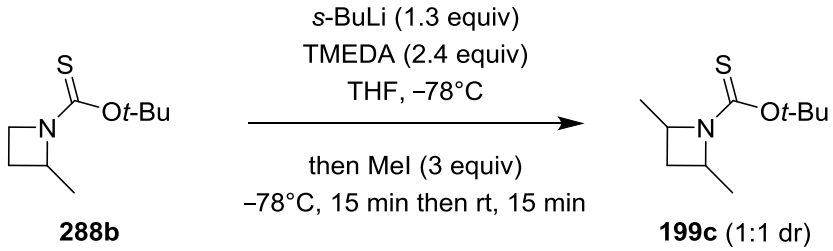
298a (*n* = 1)
296a (*n* = 2)

137 (*n* = 1, 67–98%)
303 (*n* = 2, 75–91%)

Scheme 109. α-Lithiation–substitution of *N*-Boc-2-phenyl-pyrrolidines **298a** and piperidines **296a**.

Having estabilished that α′-lithiation of 2-substituted-azetidines was possible using the Botc *N*-protecting group, a second α′-lithiation–methylation of 2-methyl-azetidine **288b** was attempted with a 30 min lithiation time, generating 2,4-dimethyl-azetidine **199c** in 55% yield (93% brsm) as a 1:1 mixture of diastereomers (Table 21, entry 1). Addition of excess CD_3OD 30 min after addition of the MeI led to no deuteration detected in the recovered starting material, indicating that the methylation was complete. Repeating this reaction with CD_3I as the electrophile resulted in a similar yield of 2,4-disubstituted product (58%), with only a trace of deuteration observed in the recovered starting material (32% mass recovery, 3% D); this implies that the lithiated azetidine species is not

quenched by protons from the electrophile. To ensure that the lithiation step had gone to completion, methylation was repeated with longer lithiation times: while no significant change in the yield of 2,4-dimethyl-azetidine **199c** was observed with a lithiation time of up to 2 h (Table 21, entries 2–3), decomposition of the lithiated species appeared to occur after 4 h at −78 °C, as indicated by a lower yield of product **199c** (30%) along with a number of unknown side-products (Table 21, entry 4).



Entry	Lithiation time[a]/h	% Yield (% brsm)
1	30	55 (93)
2	60	52 (77)
3	120	55 (72)
4	240	30 (37)
5	30 (−78 °C) then 10 (−60 °C)	53 (96)
6	30 (−78 °C) then 10 (−50 °C)	50 (84)
7	30 (−78 °C) then 30 (−60 °C)	33 (39)

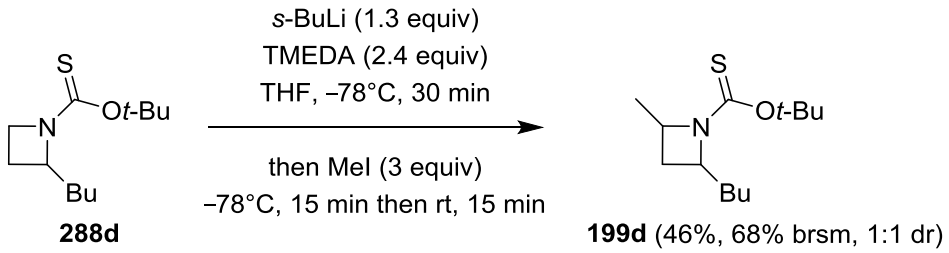
a) Lithiation was carried out at −78 °C unless otherwise stated.
Table 21. Synthesis of 2,4-dimethylated-azetidine **199c**.

In an attempt to accelerate rotamer interconversion and improve the yield of the 2,4-disubstituted-azetidine product, methylation of 2-methyl-azetidine **288b** was also repeated with higher lithiation temperatures. Allowing the lithiated species to warm to −60 °C or −50 °C for 10 min did not significantly change the result (Table 21, entries 5–6), whereas decomposition of the lithiated species occurred after 30 min at −60 °C (Table 21, entry 7).

Since the lithiation time or temperature could not be raised high enough to allow rotamer interconversion without causing decomposition of the azetidine anion, we were unable to improve the yield of 2,4-dimethylated azetidine **199c** above 55% (93% brsm).

3.4.2.2. *N*-Botc-2-butyl-azetidine substrate

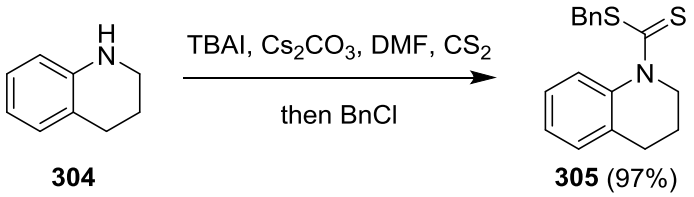
α′-Lithiation–electrophile trapping of the more hindered 2-butyl-azetidine **288d** was also found to be possible, giving a similar level of deuteration to the 2-methyl-azetidine **288b** substrate with a 30 min lithiation time (Table 20, entry 4, p 124). Analysis of the ^{1}H NMR spectrum showed that 2-butyl-azetidine **288d** is present as a 2.6:1 mixture of rotamers (at rt, in $CDCl_3$). The above experimental results suggest that the major rotamer is likely to be **288-major** (Figure 14, p 123, R = Bu). However, in this case, the extent of lithiation could not be improved by increasing the lithiation time to 1 h (Table 20, entry 5, p 124). Methylation of 2-butyl-azetidine **288d** with a 30 min lithiation time gave 2,4-disubstited product **199d** in moderate yield (46%), as a 1:1 mixture of diastereomers (Scheme 110). Once again, no change in the yield of 2,4-disubstited product **199d** was observed by increasing the lithiation time from 30 min to 1 h, although the quantity of recovered starting material was reduced (from 33% to 10%).



Scheme 110. α′-Lithiation-methylation of 2-butyl-azetidine **288d**.

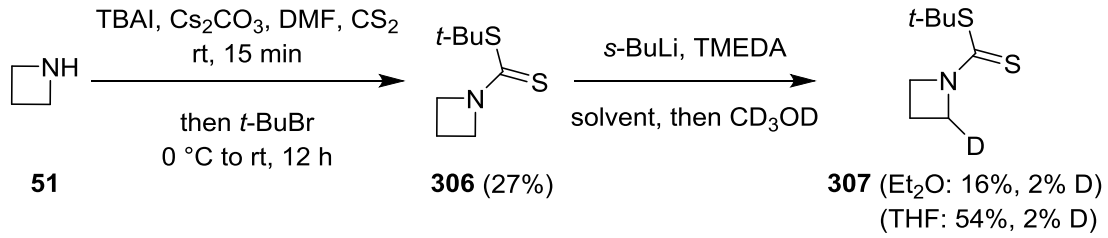
3.4.2.3. Investigation of a dithiocarbamate-based *N*-protecting group

It was considered that replacing the O atom of the Botc group with S might allow a faster rotamer interconversion due to increased bond lengths, positioning the *t*-Bu group further away from the ring. Jung and co-workers have previously reported an efficient thiocarbamation of secondary amines using CS_2 with alkyl halides in the presence of Cs_2CO_3 and tetrabutylammonium iodide (TBAI) (Scheme 111).[220] These conditions were applied to the formation of the desired dithiocarbamate **306**, generating an understandably low yield of product (27%), since a tertiary alkyl halide was required for the substitution reaction (Scheme 112). The yield of dithiocarbamate **306** was unchanged by increasing the quantity of the reagents added (CS_2, TBAI, Cs_2CO_3 and *t*-BuBr) from 1.1 to 2 equiv, or by increasing the reaction time of the first step from 15 to 60 min. Restricting the reaction temperature of the first step to 0 °C also resulted in no significant improvement in yield of product (28%). Nonetheless, enough dithiocarbamate **306** had been accumulated to test in α-deprotonation–electrophile-trapping reactions. Disappointingly, deuteration of this substrate was unsuccessful (only 2% D) in both Et_2O and THF, instead leading to formation of numerous unknown side-products (Scheme 112). This protecting group is therefore unsuitable for use in this methodology, and was not further investigated.



304 **305** (97%)

Scheme 111. Jung's thiocarbamation of a secondary amine.[220]

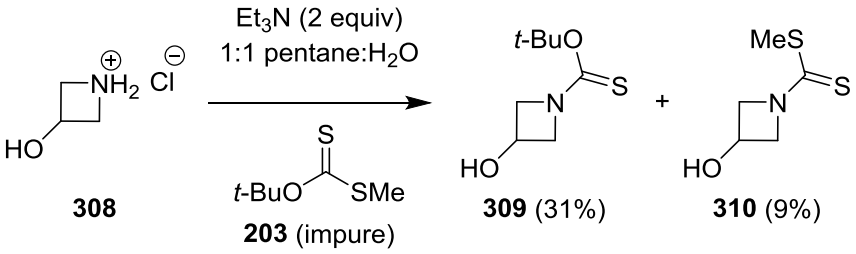


Scheme 112. Formation and deuteration of dithiocarbamate **306**.

3.4.3. Synthesis of 2,3-disubstituted-azetidines

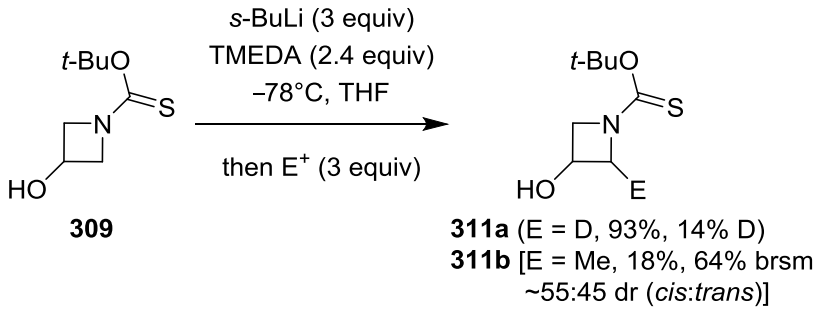
As mentioned in section 1.4.4.3, the Hodgson group has recently reported the synthesis of 2-substituted-3-hydroxy-azetidines **168** by α-lithiation–electrophile trapping using the thiopivaloyl *N*-protecting/activating group (Scheme 55, p 44).[150] Since there are a number of limitations with the thiopivaloyl group, including harsh deprotection conditions (see section 1.4.4.4.), we were keen to test the Botc group for use in this lithiation chemistry.

Aminolysis of crude xanthate **203** with commercially available azetidin-3-ol hydrochloride **308** gave the desired *N*-Botc-azetidin-3-ol **309** in low yield (31%), along with dithiocarbamate **310** in extremely low yield (9%) (Scheme 113). At this time, we had not yet discovered that crude xanthate **203** contained the dimethyl trithiocarbonate **250** impurity (see p 70), which accounted for the formation of the dithiocarbamate side-product **310**. Although earlier studies on the aminolysis of xanthate **203** with azacycles showed that higher yields of thiocarbamates are generally obtained in non-polar solvents (see section 2.3.2.), addition of H_2O was necessary in this case to aid solubility of the more polar substrate; the disappointing yield of *N*-Botc-azetidin-3-ol **309** may therefore be due to poor mixing of the reagents in the biphasic mixture.



Scheme 113. Synthesis of *N*-Botc-azetidin-3-ol **309**.

With *N*-Botc-azetidin-3-ol **309** in hand, we could then test this substrate for use in α-lithiation–electrophile trapping reactions. Initial results were encouraging: attempted deuteration and methylation reactions led to the desired 2,3-disubsituted product in both cases, albeit in low yield (Scheme 114). The presence of the free alcohol functionality meant that a higher number of equiv of *s*-BuLi was required compared to previous substrates. Since other areas of work were prioritised, no further work has yet been carried out on this substrate. Optimisation of lithiation conditions for this substrate (by varying the base, solvent and lithiation time) may be attempted in the Hodgson group in the future, which we hope will provide a more convenient route to 2,3,4-trisubstituted azetidines.

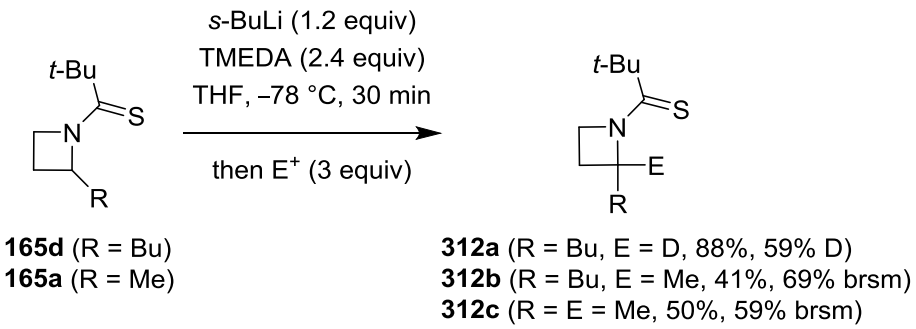


Scheme 114. Attempted α-lithiation-electrophile trapping of *N*-Botc-azetidin-3-ol **309**.

3.4.4. Synthesis of 2,2-disubstituted-azetidines

As mentioned in section 1.4.4.4., an initial attempt to carry out a second α′-lithiation–trapping on *N*-thiopivaloyl-2-butyl-azetidine **165d** was previously unsuccessful in the

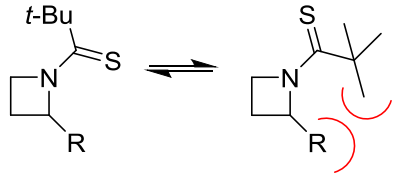
Hodgson group; it was reported that no 2,4-disubstituted product **184** was detected by GCMS and the ^{1}H NMR spectrum was consistent with clean starting material (Scheme 57, p 47).[151] However, by repeating this deuteration reaction in my own hands, 59% D incorporation was observed by analysis of the high resolution FI mass spectrum. Surprisingly, analysis of the ^{1}H and ^{13}C spectrum revealed that, in this case, deuteration had occurred at the more sterically hindered 2-position, generating 2,2-disubstituted-azetidine **312a** as the sole product (Scheme 115). Similarly, methylation of *N*-thiopivaloyl-2-butyl-azetidine **165d** was directed to the 2-position, giving 2,2-disubstituted-azetidine **312b** in 41% yield. A slightly higher yield of 2,2-disubstituted product was obtained by α-lithiation–methylation of the less hindered substrate, *N*-thiopivaloyl-2-methyl-azetidine **165a**, providing 2,2-dimethyl-azetidine **312c** in 50% yield. Analysis of the ^{1}H NMR spectra showed that *N*-thiopivaloyl-2-butyl-azetidine **165d** is present as a 10:1 mixture of rotamers and *N*-thiopivaloyl-2-methyl-azetidine **165a** is present as a 6:1 mixture of rotamers (at rt, in $CDCl_3$). The above experimental results suggest that the major rotamers are likely to be **165-major** (Figure 15, R = Bu or Me). As no 2,4-disubstituted products were formed in these reactions, and essentially no rotamer interconversion occurs at −78 °C on the reaction timescale (see section 3.5.), it is likely that the minor rotamers **165-minor** were not favourably orientated for lithiation, or the C-4 lithiated species rapidly decomposes. Future work may involve repeating the above reactions with a longer lithiation time, in the hope that this will allow higher yields of 2,2-disubstituted azetidines to be formed.



165d (R = Bu)
165a (R = Me)

312a (R = Bu, E = D, 88%, 59% D)
312b (R = Bu, E = Me, 41%, 69% brsm)
312c (R = E = Me, 50%, 59% brsm)

Scheme 115. Synthesis of *N*-thiopivaloyl-2,2-disubstituted-azetidines **312**.



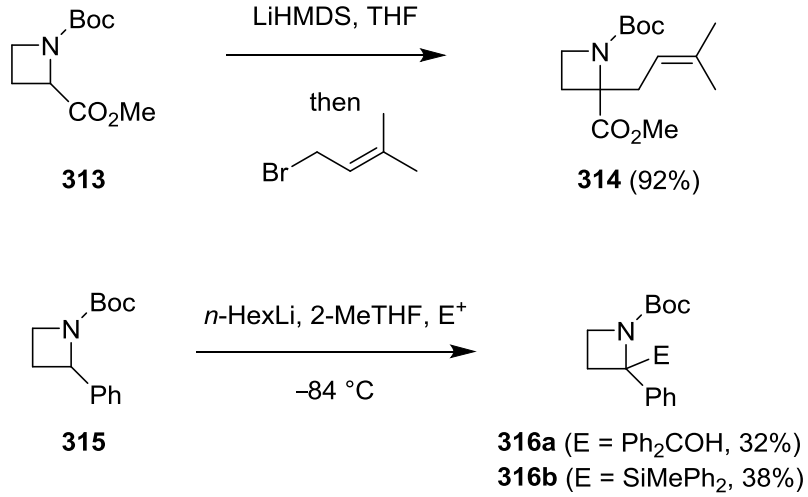
165-major **165-minor**

Figure 15. Thiopivaloyl rotamer interconversion.

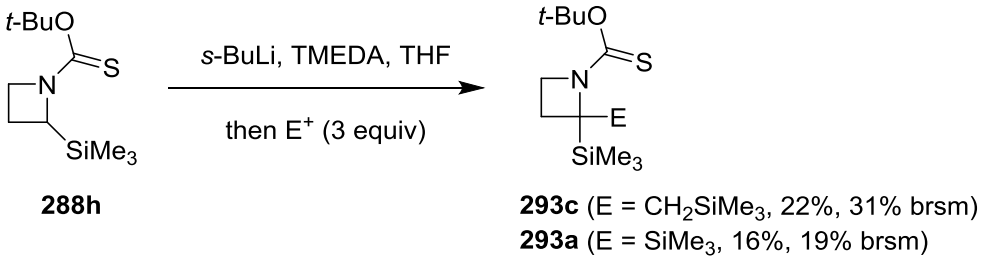
These results are in stark contrast to the corresponding reactions with the Botc *N*-protecting group, in which 2,4-disubstituted-azetidines were formed instead of 2,2-disubstituted-azetidines (see sections 3.4.2.1. and 3.4.2.2.); the regioselectivity of the reaction can therefore be simply controlled by the choice of *N*-protecting group. As mentioned above, for the thiopivaloyl-protected substrates, the major rotamer is likely to be **165-major** (Figure 15), in which the position of the thiocarbonyl functionality helps to direct lithiation to the 2-position. In this case, access to the minor rotamer **165-minor** is likely restricted by unfavourable steric interactions between the α-substitutent and the bulky *t*-bu group.

Formation of 2,2-disubstituted-azacycles using α-lithiation–electrophile trapping methodology previously relied on the presence of an anion-stabilising α-substituent to help to direct the α-lithiation to the 2-position.[219,221] For example, α-substituents such as an ester or aryl group have been employed for the regioselective synthesis of 2,2-

disubstituted-azetidines (Scheme 116).[222] However, introduction of aryl or carbonyl groups to the α-position of *N*-Botc-azetidine using α-lithiation-electrophile trapping methodology has proven difficult thus far (see sections 3.3.4. and 3.3.5.). Silyl groups are also known to act as anion-stabilising groups,[223] and there are a number of examples of the successful use of the TMS group to promote the regioselective synthesis of *N*-Boc-2,2-substituted-pyrrolidines.[224] A second α-lithiation–electrophile trapping of *N*-Botc-2-silyl-azetidine **288h** was therefore attempted, resulting in formation of 2,2-disubstituted products **293a** and **293c**, albeit in very low yield. Analysis of the ^{1}H NMR spectrum revealed that 2-silyl-azetidine **288h** is present as a 3.5:1 mixture of rotamers (at rt, in $CDCl_3$) (Figure 14, p 123, R = $SiMe_3$), but from these results we cannot be certain which is the favoured rotamer. Switching the electrophile to MeI or Me_3SnCl was unsuccessful, generating numerous unknown products that could not be isolated by column chromatography.



Scheme 116. Regioselective α-lithiation of Boc-protected azetidines.[222]

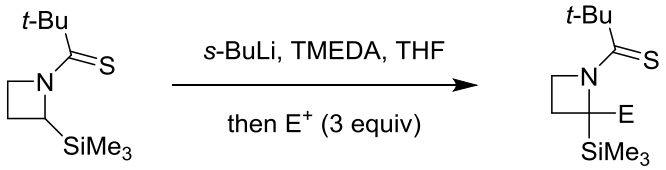


288h

293c (E = CH_2SiMe_3, 22%, 31% brsm)
293a (E = $SiMe_3$, 16%, 19% brsm)

Scheme 117. α-Deprotonation-electrophile trapping of *N*-Botc-2-silyl-azetidine **288h**.

On the other hand, α-lithiation–electrophile trapping of *N*-thiopivaloyl-2-silyl-azetidine **165g** was far more effective, cleanly generating 2,2-disubstituted azetidines **312d–g** in excellent yields (Scheme 118). These results, along with the lack of rotamers observed in the ^{1}H NMR spectrum of *N*-thiopivaloyl-2-silyl-azetidine **165g**, suggest that this substrate is present entirely as **165-major** (Figure 15, p 131, R = $SiMe_3$).



165g

312d (E = CH_2SiMe_3, 75%)
312e (E = Me, quant)
312f (E = $SiMe_3$, quant)
312g (E = $SnMe_3$, 78%)

Scheme 118. α-Deprotonation–electrophile trapping of *N*-thiopivaloyl-2-silyl-azetidine **165g**.

3.5. Rotational barrier studies

At the start of this project, when considering Botc as a potential alternative to the thiopivaloyl *N*-protecting group for α-lithiation chemistry, we envisaged that the oxygen 'spacer' might allow faster rotation around the thioamide N-C bond for 2-substituted azetidine substrates (see section 1.5.1., p 48–50). In-house variable temperature ^{1}H NMR

studies and line-shape analysis have been used to give approximate activation parameters ($\Delta H^{‡}$ and $\Delta S^{‡}$) for rotation with a range of azetidine substrates (see Appendix, section 7.2., p A3–A17);[225] from these values, activation energy ($\Delta G^{‡}$) and half-life ($t_{1/2}$) of rotation could be determined (Table 22). Unsubstituted substrates *N*-thiopivaloyl-azetidine **164** and *N*-Botc-azetidine **212** were found to have relatively similar $\Delta G^{‡}$ values (79.6 and 74.5 kJ mol^{-1}, respectively, at −78 °C), with half-lives of rotation indicating that essentially no rotation occurs at −78 °C (Table 22, entries 1–2). On the other hand, a significantly lower rotational barrier ($\Delta G^{‡}$ = 63.5 kJ mol^{-1} at −78 °C) was calculated for *N*-Boc-azetidine **97c** (Table 22, entry 3). These results are consistent with an earlier in-house rotational barrier study, in which *N*-thiopivaloyl-azetidine **164** was found to have a higher rotational barrier than the corresponding *N*-pivaloyl-azetidine.[226] The difference in activation energies of rotation for thioamides compared to amides is thought to be due to the greater polarizability of S, allowing a greater charge transfer from N to S[154] (Figure 9, p 50).

Entry	Substrate	NMR[a] $\Delta G^{‡}$/kJ mol^{-1}		$t_{1/2}$		Calculated[b] $\Delta G^{‡}$/kJ mol^{-1} at 25 °C
		−78 °C	25 °C	−78 °C	25 °C	
1	*N*-thiopivaloyl-azetidine **164**	79.6	76.8	11.4 years	3.2 s	80.8
2	*N*-Botc-azetidine **212**	74.5	75.0	178.9 d	1.6 s	83.2
3	*N*-Boc -azetidine **97c**	63.5	58.5	4.9 h	0.002 s	60.7
4	2-methyl-*N*-thiopivaloyl-azetidine **165a** (major rotamer)	67.3	70.7	2.1 d	0.3 s	72.4
5	2-methyl-*N*-thiopivaloyl-azetidine **165a** (minor rotamer)	63.2	64.5	4.0 h	0.02 s	-
6	2-methyl-*N*-Botc-azetidine **288b** (major rotamer)	76.1	76.4	1.3 years	2.8 s	78.3

7	2-methyl-*N*-Botc-azetidine **288b** (minor rotamer)	74.4	73.8	168.2 d	1.0 s	-

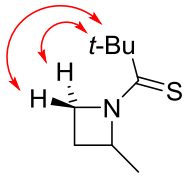
a) Calculated from a variable temperature ^{1}H NMR study by B. Odell and T. D. W. Claridge.[225] *b*) Results obtained from a DFT study by Kelvin Jackson.[227]

Table 22. Results for rotational barrier studies.

For 2-methylated substrates 2-methyl-*N*-thiopivaloyl-azetidine **165a** and 2-methyl-*N*-Botc-azetidine **288b**, population differences between the 2 rotamers (12.5:1 and 2.8:1, respectively, by analysis of ^{1}H NMR spectra in toluene-D_8 at rt) were used in the rotational barrier calculations to determine activation energies of rotation for both the major and minor rotamer about the thioamide N-C bond (Table 22, entries 4–7). Surprisingly, rotational barriers for these substrates were found to be significantly lower than for the corresponding unsubstituted substrates, despite increased intramolecular steric clashing between the α-Me groups and the bulky *t*-Bu substituent of the *N*-protecting groups. However, the calculated half-lives of rotation at −78 °C for the major and minor rotamers of 2-methyl-*N*-thiopivaloyl-azetidine **165a** ($t_{1/2}$ = 2.1 d and 4.0 h, respectively) and 2-methyl-*N*-Botc-azetidine **288b** ($t_{1/2}$ = 1.3 years and 168.2 d, respectively) again suggested that essentially no rotation occurred during the above lithiation–substitution reactions with these substrates (see section 3.4.2.1. and section 3.4.4.).

In-house DFT studies[227] on the above substrates carried out by Kelvin Jackson generated activation energies of rotation that were in good agreement with those obtained from the variable temperature NMR study (Table 22, right-hand side column). The generally lower rotational barriers observed for the 2-methylated substrates compared to the unsubstituted substrates were thought to be due to ground state destabilisation, reflected by a higher degree of pyramidalisation at N for the 2-methylated substrates. During this study, analysis of the lowest energy ground state structures for the 2-methyl-*N*-thiopivaloyl-azetidine

165a indicated that the major rotamer is **165-major** (Figure 15, R = Me, p 131), with a conformational free energy difference of 6.3 kJ mol^{-1}; this corresponds to a rotamer ratio of ~12.7:1 at 25 °C, which is consistent with the experimentally determined rotamer ratio (12.5:1 by ^{1}H NMR in toluene-D_8). Minor rotamer **165-minor** (Figure 15, R = Me, p 131) was found to be a less favourable conformer due to significant intramolecular steric clashing between the bulky *t*-Bu group and the α-Me group. The major rotamer **165-major** (R = Me) was also supported by NOESY (Figure 16): irradiation of the major *t*-Bu signal (singlet at δ_H = 1.3 ppm) gave enhancements at the NCH_2 signals (multiplets at δ_H = 4.59–4.51 and 4.44–4.37 ppm), with no enhancement at the CHMe signal, indicating that the *t*-Bu group is *anti* to the α-Me substituent in the major species.



165a

Figure 16. NOESY carried out on 2-methyl-*N*-thiopivaloyl azetidine **165a**.

In stark contrast, the DFT studies[227] showed that **288-major** (Figure 14, R = Me, p 123) is the major rotamer for 2-methyl-*N*-Botc-azetidine **288b**, with a lower conformational free energy difference of just 2.6 kJ mol^{-1}; this corresponds to a rotamer ratio of ~2.9:1 at 25 °C, which again is consistent with the experimentally determined rotamer ratio (2.8:1 by ^{1}H NMR in toluene-D_8). Since the bulky *t*-Bu group is further away from the ring compared to the thiopivaloyl-protected substrate, steric interaction with the 2-Me substituent is a less important factor in dictating the favoured conformational isomer. In this case, the major rotamer could not be confirmed experimentally by NOESY; the two Me signals were very close together in the ^{1}H NMR spectra, leading to inconclusive

results. The DFT-computed lowest energy ground state rotamers were found to have a H on the α-Me group pointing towards either the O atom (in major rotamer) or the S atom (in the minor rotamer), with interatomic distances calculated to be 2.68 and 3.06 Å, respectively. It is therefore likely that the observed orientations of the 2 rotamers are affected by H-bonding interactions.

3.6. Summary

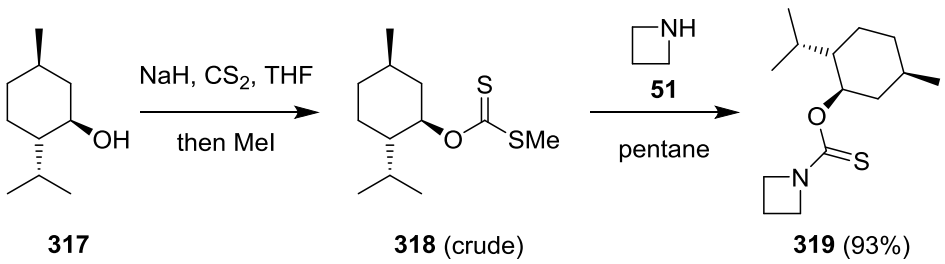
These studies have shown that the novel *N*-protecting group, Botc, can facilitate α-lithiation–electrophile trapping of azacycles, generating 2-substituted pyrrolidines and azetidines in generally high yield. Futhermore, Botc allows the synthesis of 2,4-disubstuted azetidines by a second α′-lithiation–electrophile trapping reaction. In contrast, further functionalisation of thiopivaloyl-protected 2-substituted azetidines resulted in the formation of 2,2-disubsituted products; the regionselectivity could therefore be conveniently controlled by the choice of *N*-protecting group. The different reactivity profile of these two substrates has been rationalised by the opposite orientation of their ground state conformational isomers, as supported by in-house DFT calculations.

4. Results and Discussion: Asymmetric α-Deprotonation–electrophile trapping reactions

Having established a convenient route to substituted azetidines using the novel Botc protecting group, our next aim was to develop this α-lithiation–electrophile trapping methodology to allow the synthesis of enantioenriched products.

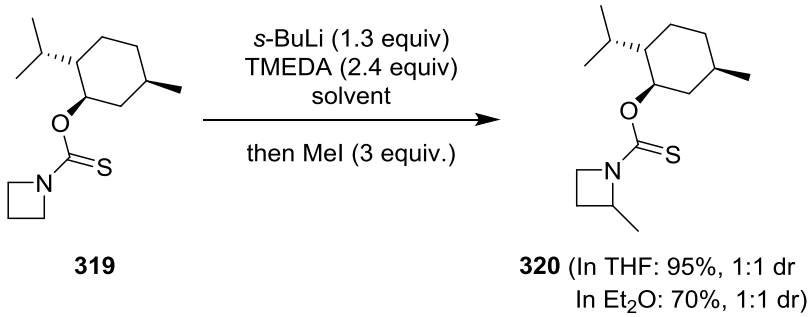
4.1. Chiral auxillary

We initially sought to render the α-lithiation–electrophile trapping process asymmetric using a chiral auxiliary approach. Previously, this approach was independently developed by Meyers and by Gawley for asymmetric alkylation of chiral dipole-stabilised organolithiums using chiral formamidines.[228] In an attempt to 'block' one face of the azetidine ring, the Botc *N*-protecting group was significantly modified. Formation of unstable xanthate **318**[220,229] from inexpensive available (L)-menthol **317** was achieved in high yield (~95%, Scheme 119) using conditions[170] reported by Overman and co-workers for construction of a similar xanthate. Aminolysis of crude xanthate **318** with azetidine **51** generated the desired (L)-menthol-derived substrate **319** in excellent yield (93%). It was expected that this chiral auxiliary could be cleaved using $NaIO_4$, as described by Falck and co-workers.[159]



Scheme 119. Synthesis of (L)-menthol-derived-azetidine **319**.

(L)-Menthol-derived substrate **319** was then subjected to our standard α-lithiation–alkylation conditions, in both THF and Et_2O, generating methylated **320** in good yield in both cases (Scheme 120). These results show that an *N*-protecting group derived from a secondary alcohol is also a viable option for this methodology, able to withstand the lithiation conditions; however, NMR analysis revealed that methylated product **320** was formed as a 1:1 mixture of diastereomers, in both reactions.



Scheme 120. Lithiation–methylation of (L)-menthol-derived-azetidine **319**.

4.2. Initial investigations with (−)-sparteine

Replacement of TMEDA with a chiral ligand was viewed as a more attractive option to provide access to an asymmetric variant of this α-lithiation–electrophile trapping methodology, as previously achieved with larger azacycles (e.g., Scheme 40, p 33).[112] Lupin alkaloid (−)-sp **138** was chosen for our initial studies, as this diamine is the most well-known naturally occurring chiral ligand for asymmetric organolithium chemistry,[230] with proven effectiveness for lithiation α- to N.[128,231] (−)-sp **138** can be readily extracted from papilionaceous plants such as Scotch broom, and for a long period of time was commercially available. Furthermore, (−)-sp can often be recovered after a reaction by acid-base extraction and re-used.[232] Although (+)-sp **321** is also a natural product, this enantiomer has a much lower natural abundance and, until recently, was not commercially

available. To overcome previous supply issues, O'Brien and co-workers developed a more accessible (+)-sp surrogate **139** (Figure 17).[126] Significantly, the *s*-BuLi/(+)-sp surrogate **139** complex has been found to perform better than *s*-BuLi/(−)-sp **138** for lithiation α- to N with some substrates (see section 1.4.4.1.).[127] As mentioned in section 1.4.4.1., the availability of these compounds has recently changed: (+)-sp **321** is now available from commercial vendors whilst (−)-sp **138** has become more difficult to obtain. Fortunately, O'Brien and co-workers have very recently reported a short and high-yielding route to their enantiomeric (−)-sp surrogate **322**.[233]

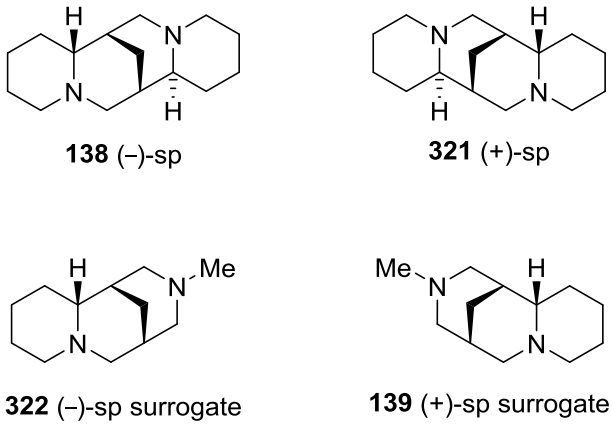
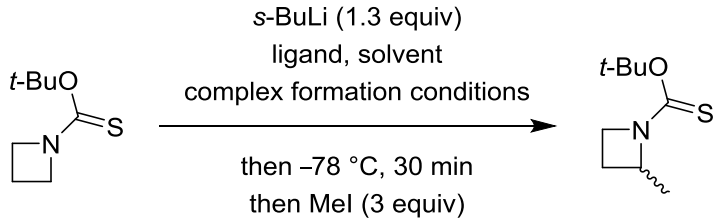


Figure 17. Naturally occurring alkaloids (−)-sp and (+)-sp and easily accessible surrogates.

Although our earlier studies had shown that THF was required as the solvent for *N*-Botc-azetidine **212** to react cleanly in the presence of TMEDA (Table 12, p 103–104), (−)-sp is more commonly used in combination with the less strongly coordinating solvent Et_2O in organolithium chemistry. Asymmetric methylation of *N*-Botc-azetidine **212** was first attempted with (−)-sp in Et_2O using conditions established earlier for *N*-thiopivaloyl-azetidine **164** (previously giving 61:39 er with the latter substrate):[148] a solution of the diamine ligand and *s*-BuLi in solvent was warmed to rt over 10 min, stirred at rt for 15 min, and then re-cooled to −78 °C before addition of the substrate ('Method A').

Disappointingly, only starting material and very polar unknown impurities were recovered under these conditions, with either (−)-sp or TMEDA as ligand (Table 23, entries 1–2). Repeating the methylation reaction with TMEDA in THF (which previously provided racemic 2-methyl-azetidine **288b** in 79% yield under our standard racemic conditions with no warming stage) was also unsuccessful (Table 23, entry 3). This result, along with the observed colour change from bright yellow to colourless in these reactions, suggested that the *s*-BuLi/(−)-sp complex decomposes during the warming stage.



212 **288b**

Entry	Conditions for *s*-BuLi/ligand complex formation	Solvent	Ligand (equiv)	% Yield	er (*R*:*S*)[a]	% SM
1	25 min (rt)	Et_2O	(−)-sp (1.3)	0	-	66
2			TMEDA (2.4)		-	71
3		THF			-	88
4	15 min (rt)	Et_2O	(−)-sp (1.3)	38	52:48	61
5		hexane		28	52:48	41
6[b]				<7 (impure)	-	56
7	15 min (0 °C)	Et_2O		76	51:49	>5
8			TMEDA (2.4)	0	-	84
9			none	8	-	66

a) For er determination method, see section 4.2.1. *b*) *s*-BuLi/ligand complex transferred by cannula to a pre-cooled solution of *N*-Botc-azetidine **212** in hexane.

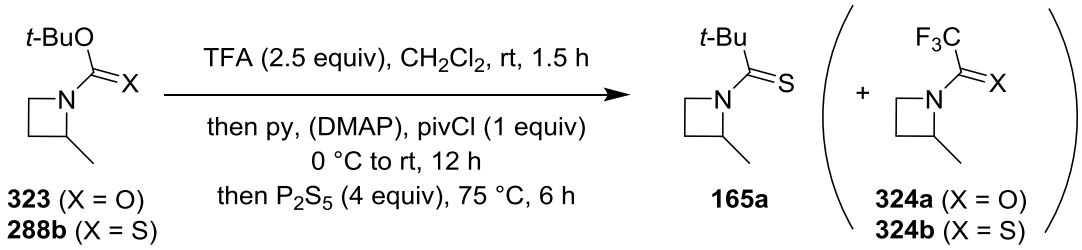
Table 23. Attempted asymmetric methylation using 'Method A'.

Asymmetric methylation with (−)-sp was therefore attempted with a shorter warming time of 15 min, generating a low yield of essentially racemic methylated product **288b** (Table 23, entry 4). Switching the solvent to hexane or changing the order of addition of the reagents had a detrimental effect on the results (Table 23, entries 5–6). By lowering the temperature for formation of the *s*-BuLi-ligand complex to 0 °C, methylated azetidine **288b** could be formed in good yield (Table 23, entry 7); unfortunately this product was found to be racemic. In Et_2O, the reaction was inhibited in the absence of a ligand or by replacing (−)-sp with TMEDA (Table 23, entries 8–9), indicating that a competitive ligand-free reaction did not contribute to the poor enantioselectivity observed with (−)-sp.

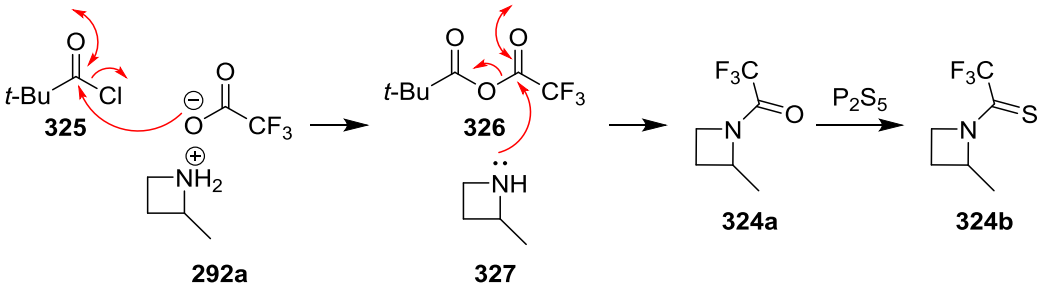
4.2.1. Determination of er

The er of the above methylated products **288b** could not be determined by chiral-HPLC (CHIRALCEL OD, CHIRALPAK AD-H and CHIRALPAK AS-H columns tested with a range of eluents), since the enantiomer peaks could not be adequately resolved. Although chiral-GC had previously been used in the Hodgson group to calculate the er of 2-methyl-*N*-thiopivaloyl-azetidine **165a**, this method led to decomposition of Botc-protected-azetidine substrate **288b**. Therefore, conversion of the protecting group from Botc to thiopivaloyl was considered as an option for er determination. Previously, in the Hodgson group, *N*-Boc-azetidine **323** was successfully converted to *N*-thiopivaloyl azetidine **165a**, in one-pot via the TFA-salt **292a** (Scheme 121, 63%).[151] However, a low yield of product (14%) was observed when these conditions were applied to the *N*-Botc-azetidine substrate **288b**, and significant quantities of inseparable side-products were formed; the crude NMR spectra[234] showed peaks that were consistent with amide/thioamide **324** (doubling of signals in the crude ^{1}H, ^{13}C and ^{19}F NMR spectra suggested that both side-products **324a**

and **324b** were obtained). A proposed mechanism for the formation of these side-products is shown in Scheme 122.

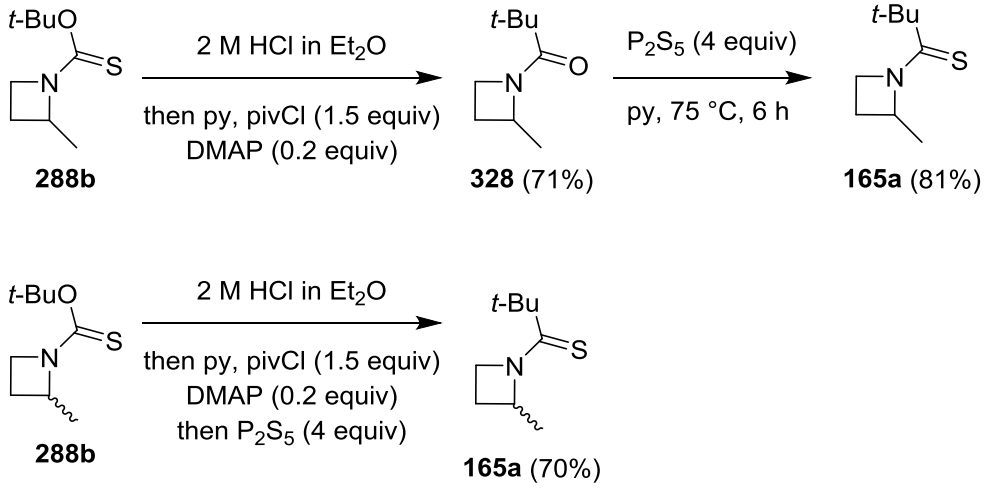


Scheme 121. Attempted conversion of the protecting group via TFA-salt **292a**.



Scheme 122. Suggested mechanism for formation of side-products **324a** and **324b**.

Pleasingly, the above side-reactions could be avoided by employing an alternative acid for the deprotection step. *N*-Botc-azetidine **288b** was successfully converted to *N*-pivaloyl-azetidine **328** by an HCl-mediated deprotection followed by reaction with pivCl (Scheme 123). Subsequent thionation with P_2S_5 led to the desired *N*-thiopivaloyl-azetidine **165a** in high yield (81%). Furthermore, direct conversion of *N*-Botc-azetidine **288b** to *N*-pivaloyl-azetidine **165a** could be carried out in good yield (70%) by a one-pot procedure. This product could then undergo chiral-GC analysis (column: β-cyclodextrin) to determine the er. The predominant sense of asymmetric induction was established by comparision with an authentic sample of (*R*)-**165a**, synthesised previously in the Hodgson group.[148]

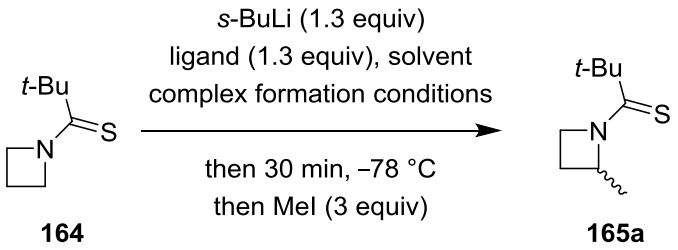


Scheme 123. Successful conversion of the protecting group via HCl-salt **292b**.

4.2.2. *N*-Thiopivaloyl-azetidine substrate

While the above initial investigations on asymmetric methylation of *N*-Botc-azetidine **212** with (−)-sp were unsuccessful, more promising results had previously been observed with the *N*-thiopivaloyl-azetidine **164** substrate (99% coversion by GC analysis, 61:39 (*R*:*S*) er in Et_2O; 72:28 (*R*:*S*) er in hexane).[148] However, as a check of quality of reagents, repeating the asymmetric methylation of *N*-thiopivaloyl-azetidine **164** in hexane in my own hands resulted in an extremely low yield of product **165a**, with a lower than expected er (Table 24, entry 1). In contrast to our earlier studies with achiral ligand TMEDA (Table 11, p 101–102), varying the speed of addition of *s*-BuLi did not have a significant effect on the outcome. Reducing the reaction time for formation of the *s*-BuLi/ligand complex, in an attempt to prevent decomposition, resulted in a lower recovery of SM but gave very little improvement in the yield of product **165a** (Table 24, entry 2). A test deuteration reaction under these conditions but in the absence of a ligand gave a low level of D incorporation (31% D, 86% mass recovery), implying that a competitive ligand-free reaction could be contributing to the poor enantioselectivity observed with (−)-sp in hexane. A higher yield

of methylated product could be achieved by switching the solvent to Et_2O, although the products were found to be essentially racemic (Table 24, entries 3–4).



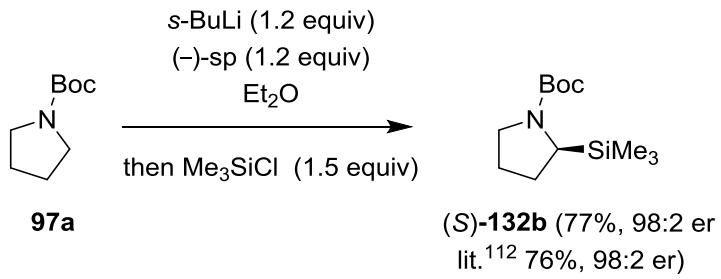
164 **165a**

Entry	Ligand	Conditions for *s*-BuLi/ligand complex formation	Solvent	% Yield	er (*R*:*S*)[a]	% SM
1	(−)-sp **138**	25 min (rt)	hexane	5	61:39	58
2		15 min (rt)		11		10
3			Et_2O	41	45:55	16
4		15 min (0 °C)		51		8
5	diamine **166a**	15 min (rt)		8	44:56	61
6		15 min (0 °C)		24	57:43	45

a) er determined by chiral-GC analysis

Table 24. Attempted asymmetric methylation of *N*-thiopivaloyl-azetidine **164** using 'Method A'.

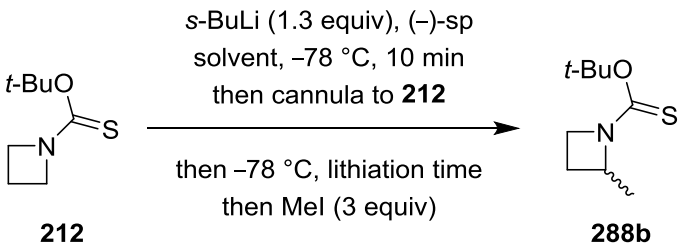
The above difficulties in reproducing the literature results for asymmetric methylation of the thiopivaloyl-protected substrate led us to become concerned about the quality of the ligand used. However, a well-established procedure for asymmetric silylation of *N*-Boc-pyrrolidine **97a** with (−)-sp was repeated in my own hands (Scheme 124), generating silylated-pyrrolidine (*S*)-**132b** in a similar yield and er to the literature[112] This result suggests that the (−)-sp used was of good quality.



Scheme 124. Asymmetric silylation of *N*-Boc-pyrrolidine **97a**.

4.2.3. Alternative conditions

Discouraged by the above results, and concerned that 'Method A' conditions resulted in decomposition of the s-BuLi/ligand complex during the warming stage, we decided to test alternative conditions established by Beak for asymmetric deprotonation of *N*-Boc pyrrolidines:[112] a solution of *s*-BuLi and ligand in solvent at −78 °C was transferred to a solution of the substrate in solvent at −78 °C, and the reaction mixture was stirred for 4 h at this temperature before addition of MeI ('Method B'). Attempted asymmetric methylation of *N*-Botc-azetidine **212** with (−)-sp in Et_2O under these conditions resulted in a high yield (78%) of methylated product **288b** (Table 25, entry 1); disappointingly, this adduct was determined to be essentially racemic. In an attempt to improve enantioselectivity, variation of solvent, equiv of (−)-sp and lithiation time were examined and the key results are summarised in Table 25.



Entry	Solvent	(−)-sp/equiv	Lithiation time/h	% Yield	er (*R*:*S*)[a]	% SM
1	Et_2O	1.3	4	78	52:48	5
2		2.4		87	53:47	2
3[b]				74	52:48	4
4		0		56	-	24
5			1	26		65
6		1.3		91	52:48	5
7	hexane		4	94	55:45	6
8		2.4		70	56:44	
9		1.3	1	85	54:46	8
10		0	4	0	-	65
11[c]	pentane	1.3	1	17	50:50	75

a) For er determination method, see section 4.2.1. *b*) 2 equiv s-BuLi used.
c) Lithiation carried out at −100 °C.

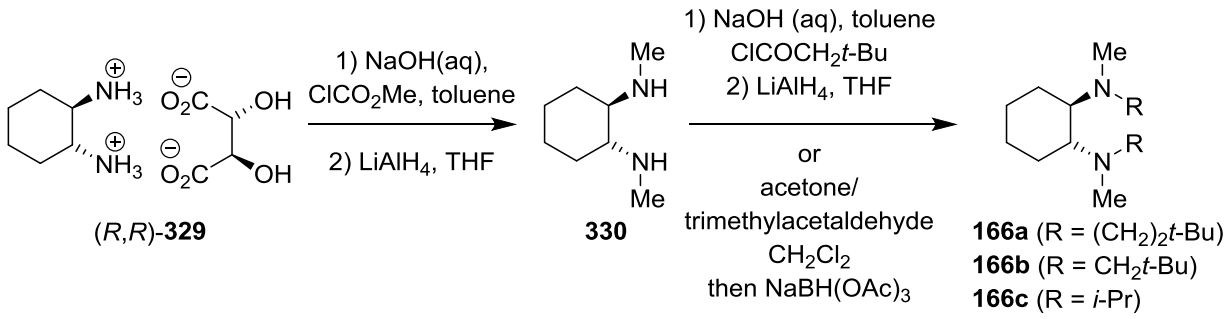
Table 25. Attempted asymmetric methylation using 'Method B'.

No significant improvement was observed by increasing the quantity of *s*-BuLi or (−)-sp added, suggesting that the active lithiating species is a 1:1 *s*-BuLi/(−)-sp complex (Table 25, entries 2–3). Since methylated product **288b** was formed in 56% yield in the absence of a ligand (Table 25, entry 4), the low er observed for the reaction with (−)-sp may have been adversely affected by a competing ligand-free reaction. However, a high yield (91%) of essentially racemic methylated product **288b** was produced with (−)-sp with a shorter lithiation time of 1 h, despite a lower yield (26%) observed for the ligand-free reaction after this time (Table 25, entries 5–6). In addition, although no ligand-free reaction

occurred in hexane even with a 4 h lithiation time, only a very marginal improvement in enantioselectivity was observed for the reactions with (−)-sp in this solvent (Table 25, entries 7–10). Furthermore, decreasing the lithiation temperature from −78 °C to −100 °C (pentane as solvent) had a detrimental effect on the yield of product **288b**, and gave no asymmetric induction.

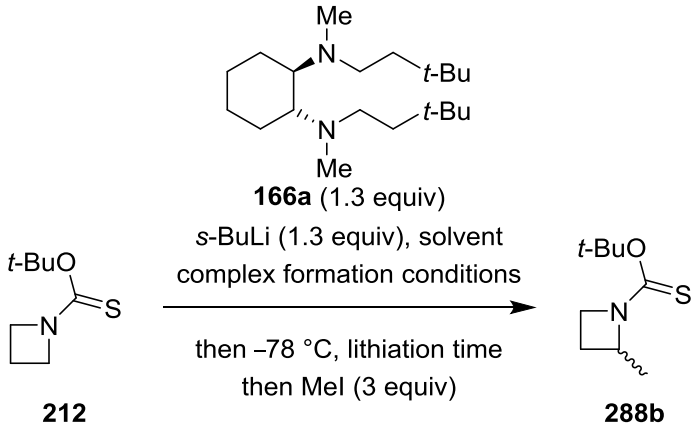
4.3. Chiral ligand screen

Since our extensive studies with (−)-sp did not provide good asymmetric induction, alternative chiral ligands were considered. Whilst (−)-sp was previously found to give the best enantioselectivity for methylation of *N*-thiopivaloyl-azetidine **164** in hexane (by a previous member of the Hodgson group), *trans*-cyclohexane-1,2-diamine **166a** was more effective in ethereal solvents (up to 80:20 er in Et_2O).[148] Diamine ligands such as **166a–c** were originally introduced by Alexakis and co-workers for asymmetric addition of MeLi to an imine; differently substituted tertiary amino groups in the ligand allowed the nitrogens to become stereocentres in the putative reactive complex.[235] O'Brien and co-workers have shown that diamine **166a** is also an effective chiral ligand for asymmetric α-lithiation–electrophile trapping of *N*-Boc-pyrrolidine.[236] An important feature of these ligands is that they can be easily prepared in either enantiomeric forms [by resolution with (−)- or (+)-tartaric acid] from inexpensive starting materials, and the groups at N can be readily modified to aid ligand optimisation (Scheme 125).



Scheme 125. Known synthesis of diamine ligands **166a–c**.[236]

Disappointingly, attempts to reproduce the asymmetric methylation of *N*-thiopivaloyl-azetidine **164** with diamine **166a** in my own hands were unsuccessful, generating methylated product **165a** in significantly lower yields and ers than the literature[148] (Table 24, entries 5–6. p 146). However, attempted asymmetric methylation of *N*-Botc-azetidine **212** with this ligand in Et_2O gave methylated product **288b** in slightly higher er than previously seen with (−)-sp (up to 60:40 *R*:*S*) (Table 26, entries 1–2). Optimisation of the reaction conditions was attempted, with key results shown in Table 26 (entries 3–6). As observed with (−)-sp, a high yield of product **288b** could only be generated if the chiral ligand diamine **166a** and *s*-BuLi were pre-mixed (at −78 °C) before addition to the substrate ('Method B'), to allow complex formation. No significant change in yield or er was observed by increasing the number of equiv of *s*-BuLi or diamine **166a**; the active lithiating species is therefore likely to be a 1:1 ligand:*s*-BuLi complex. There was also no significant change in the results when the lithiation time was reduced from 4 h to 1 h (Table 26, entries 3–4), potentially indicating that the lithiated species with this ligand is configurationally stable over several hours at −78 °C. In contrast to the previous reactions with (−)-sp, switching the solvent from Et_2O to hexane led to a slightly lower enantioselectivity (Table 26, entries 5–6).



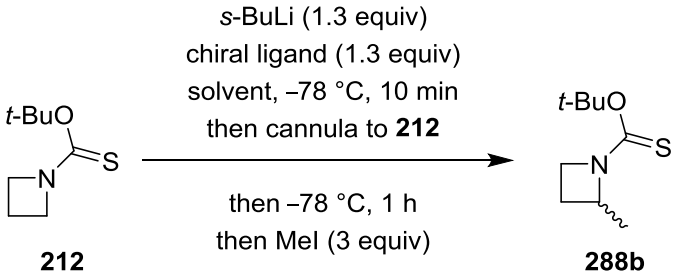
Entry	Solvent	Conditions for *s*-BuLi/ligand complex formation	Lithiation time/h	% Yield	er (*R*:*S*)[a]	% SM
1	Et_2O	15 min (0 °C)	0.5	33	60:40	41
2			4	29	56:44	
3		10 min (−78 °C)		83	58:42	6
4			1	75	59:41	11
5	hexane		4	81	52:48	9
6			1	79	53:47	11

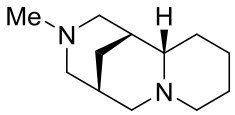
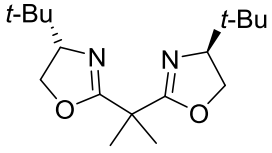
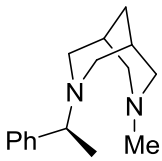
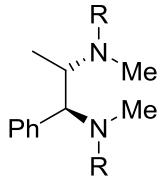
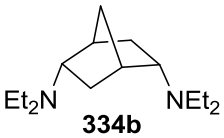
a) For er determination method, see section 4.2.1.

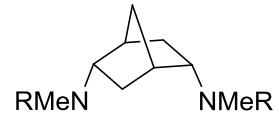
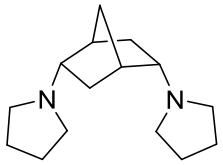
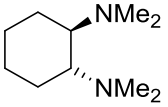
Table 26. Attempted asymmetric methylation with diamine **166a**.

In our above asymmetric methylation studies, the enantioselectivity was most affected by varying the chiral ligand structure, although the choice of solvent was another important factor. In contrast, changing other variables such reagent quantities and lithiation time had no significant effect on the results. Therefore, we decided to test a wider range of chiral ligands in Et_2O and hexane using 'Method B' conditions (no warming of the s-BuLi/ligand complex) with a 1 h lithiation time. The majority of ligands previously employed for organolithium-mediated α-deprotonation of cyclic amines were recently reviewed by Maes and co-workers.[3] These chiral ligands were considered, along with those more recently reported, and a structurally diverse range was selected to be tested with our *N*-Botc-azetidine substrate **212** (Table 27). Pleasingly, it was found that the er of the methylated

products **288b** also could be determined directly using chiral-SFC (carried out by the analytical team at Novartis Institutes for Biomedical Research, Horsham), without the need to convert to thioamide **165a** for chiral-GC analysis. The predominant sense of asymmetric induction was initially established by comparison of the $[\alpha]_D^{20}$ values with earlier results.



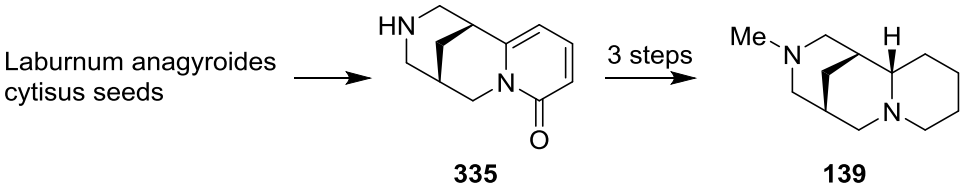
Entry	Solvent	Ligand	% Yield	er (*R*:*S*)[a]	%SM
1	Et_2O	 **139** (+)-sp surrogate	48	48:52	21
2	hexane		60	51:49	5
3	THF		16	52:48	45
4	Et_2O	 **331**	>0.5	-	89
5	Et_2O	 **332**	0		
6	hexane		0		87
7	Et_2O	 **333** (R = CH_2CH_2t-Bu)	58	47:53	25
8	hexane		73	58:42	73
9	Et_2O	 **334a**	64	56:44[b]	12
10	hexane		73	69:31	3
11	Et_2O	 **334b**	<15	-	36
12	hexane		0		90

13	Et_2O	 **334c** (R = CH_2CH_2t-Bu) **334d** (R = CH_2CH_2OMe)			78–90
14	hexane				61–90
15	Et_2O	 **334e**			100
16	hexane		7		73
17	Et_2O	 **141**	35	43:57	3
18	hexane		53	46:54	4

a) er determined by chiral-SFC analysis. *b*) er was determined by chiral-SFC anlysis and by conversion to thioamide **165a** followed by chiral-GC analysis. Both methods gave the same er result.

Table 27. Ligand screen for asymmetric methylation.

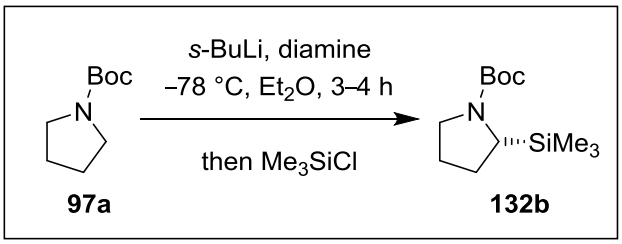
(+)-sp surrogate **139** was synthesised using a literature[237] procedure, starting from (−)-cystine (**335**), which was extracted from *Laburnum anagyroides cytisus* seeds (Scheme 126). Although a reasonable yield of methylated product **288b** was obtained with (+)-sp surrogate **139** in Et_2O or hexane, the products were essentially racemic (Table 27, entries 1–2). O'Brien and co-workers showed that (+)-sp surrogate **139** can provide high levels of enantioselectivity for deprotonation-electrophile trapping of *N*-Boc-pyrrolidine **97a** even in THF.[238] In our case, this ligand resulted in a poor yield of essentially racemic methylated product **288b** in THF (Table 27, entry 3).

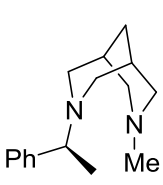


335 **139**

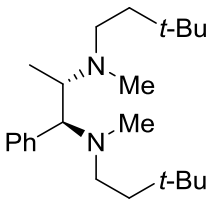
Scheme 126. Synthesis of (+)-sp surrogate **139**.

No methylated product **288b** could be formed with commercially available chiral ligand bisoxazoline **331** (Table 27, entry 4). Since a higher yield (26%) was previously achieved in the absence of a ligand (Table 25, entry 5, p 148), bisoxazoline **331** appears to be inhibiting either the lithiation or the electrophile trapping step. Similar results were observed with chiral bispidine ligand **332** (Table 27, entries 5–6), a ligand previously reported by Beak and co-workers to achieve a good er for α-lithiation–silylation of *N*-Boc-pyrrolidine **97a** (Scheme 127).[128] Synthesis of chiral bispidine ligand **332** was attempted using the literature[128] procedure: construction of the ketobispidine intermediate **338** by a double Mannich reaction was successful (Scheme 128), but conversion of this intermediate to the desired product **332** was inadequately described. Therefore, a Wolff-Kishner reduction of intermediate **338** was first attempted using solvent-free conditions previously established in the Hodgson group for a similar substrate,[239] unfortunately resulting in decomposition. O'Brien and co-workers previously used similar conditions, but with ethylene glycol as a solvent, to reduce closely-related ketone substrates.[240] Ketobispidine intermediate **338** was successfully reduced to chiral bispidine ligand **332** in 59% yield under these conditions (Scheme 128).

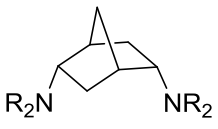




332 (55%, 87:13 er)[128]

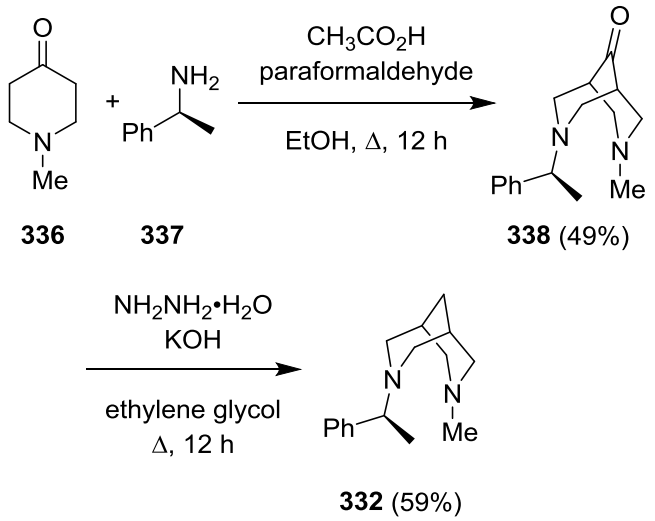


333 (100% conv, 94:6 er)[239]



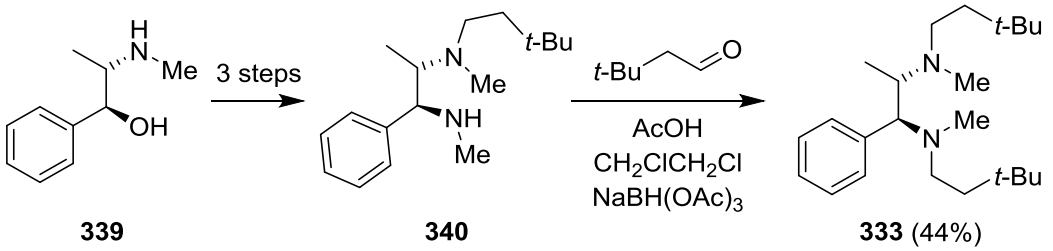
334a (R = Me, >99% conv, 85:15 er)[239]
334b (R = Et, 24% conv, racemate)[239]

Scheme 127. Asymmetric α-lithiation–silylation of *N*-Boc-pyrrolidine **97a**.



Scheme 128. Synthesis of chiral bispidine ligand **332**.

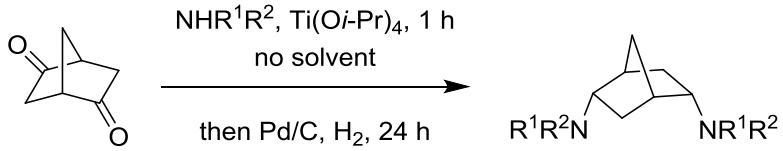
Alexakis and co-workers discovered that chiral 1,2-diamines bearing neohexyl substitutents, such as pseudo-ephedrine derivative **333**, are particularly effective ligands for asymmetric α-deprotonation of *N*-Boc-pyrrolidine **97a** (Scheme 127).[241] Pseudo-ephedrine-derived intermediate **340** was synthesised in 3 steps by a route established by Alexakis and Perron (Scheme 129).[242] Although the reported procedure for reductive amination of this crude diamine was carried out with $NaBH_3CN$, the less toxic reducing agent $NaBH(OAc)_3$ was also found to be suitable for synthesis of the desired chiral ligand **333**, albeit in lower yield (44%). In my hands, a lengthy purification process (bulb-to-bulb distillation, followed by prep-LCMS, followed by passing through an isolute SCX-2 column) was required to provide pure ligand **333**, which is thought to have had a detrimental effect on the yield. Attempted asymmetric methylation of *N*-Botc-azetidine **212** with pseudo-ephedrine-derived ligand **333** led to a good yield of methylated product **288b** in either solvent, although the reaction in Et_2O gave essentially racemic product **288b** (Table 27, entry 7, p 152–153); a more promising er (58:42) was achieved in hexane (Table 27, entry 8, p 152–153).



339 **340** **333** (44%)

Scheme 129. Synthesis of pseudo-ephedrine derivative **333**.

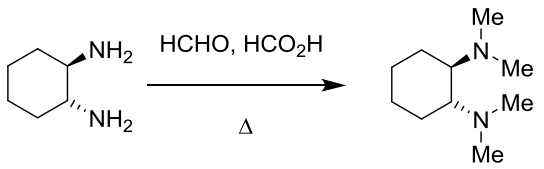
Alexakis and co-workers also recently examined 2,5-diaminonorbornanes (DIANANEs,) for enantioselective transformations involving organolithiums, including asymmetric α-lithiation–silylation of *N*-Boc-pyrrolidine **97a**, where the highest er (85:15) was achieved with tetramethyl-DIANANE **334a** (Scheme 127).[241] This chemistry was found to be extremely sensitive to the nature of substituents on the N atoms on the ligand, with tetraethyl-DIANANE **334b** providing no enantioselectivity. A major benefit of this class of chiral ligands is that they can be readily synthesised as either enantiomer from the corresponding commercially available norbornane-2,5-dione **341** (~£150/4 mmol for either enantiomeric form) (Scheme 130). Use of tetramethyl-DIANANE **334a** for methylation of *N*-Botc-azetidine **212** proved encouraging in hexane, giving methylated product **288b** in 73% yield, with a higher er (69:31) achieved than with previous ligands (Table 27, entry 10, p 152–153). Choice of solvent was found to be important, with a much lower er (56:44) generated in Et_2O (Table 27, entry 9, p 152–153). The DIANANE ligand was modified in an attempt to improve the enantioselectivity, but larger substituents on the N atoms were not tolerated, inbititing formation of product **288b** (Table 27, entries 11–16, p 152–153).



(*S*,*S*)-**341** **334**

Scheme 130. Synthesis of DIANANEs.[241]

Since the most effective DIANANE ligand contained methyl substituents on the N, we decided to consider tetramethyl-*trans*-cyclohexane-1,2-diamine **141**, which was synthesised in good yield from (*R*,*R*)-diamine **342** using Eschweiler-Clarke methylation conditions (Scheme 131).[243] However, tetramethyl-diamine ligand **141** was found to be unsuitable for enantioselective α-deprotonation–methylation of *N*-Botc-azetidine **212**, producing methylated product **288b** in disappointing yield and er (Table 27, entries 17–18, p 152–153).

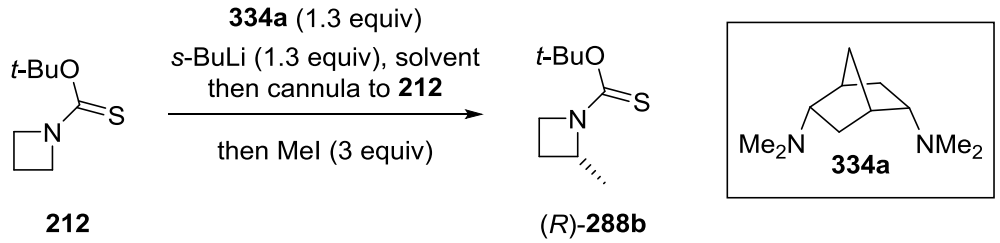


342 **141** (71%)

Scheme 131. Synthesis of tetramethyl-diamine ligand **141**.

4.4. Asymmetric Methylation Optimisation

From our above chiral ligand screen, tetramethyl-DIANANE **334a** was the most promising, providing the highest er (69:31) of methylated product **288b** (Table 27, entry 10, p 152–153). Therefore, reaction conditions for asymmetric methylation of *N*-Botc-azetidine **212** with this ligand were thoroughly examined in an attempt to gain a greater understanding of this reaction and improve the enantioselectivity; key results are displayed in Table 28.



Entry	Solvent	Lithiation time (temp)	Methylation time (temp)	% Yield	er (*R*:*S*)[a]	% SM
1	hexane	4 h (−78 °C)	30 min (−78 °C) then 30 min (rt)	55	59:41	10
2[b]		1 h (−78 °C)		73	69:31	3
3[c]				12	58:42	38
4		1 h (−78 °C) then 10 min (−40 °C)		36	70:30	20
5[b]		5 min (−78 °C)		71	74:26	8
6[c]				7	75:25	50
7			1 h (−78 °C)	65	75:25	27
8[b]		1 h (−78 °C)	30 min (−78 °C)	34	73:27	40
9			4 h (−78 °C)	55	66:34	28
10	pentane	1 h (−98 °C)	30 min (−98 °C) then 20 min (rt)	54	75:25	34
11[b]			1 h (−98 °C)	45	**91:9**	46
12[b]		3 h (−98 °C)	1 h (−98 °C) then 1 h (rt)	60	67:33	12
13[b]			1 h (−98 °C)	67	70:30	21
14[b]			3 h (−98 °C)	68	66:34	13

a) er determined by chiral-SFC analysis. *b*) Reaction carried out at least twice and results were found to be reproducible. *c*) 0.5 equiv MeI.

Table 28. Conditions for asymmetric methylation with tetramethyl-DIANANE **334a**.

A study on the effect of varying lithiation time gave rise to the following trend: as the lithiation time was reduced, a slight improvement in the enantioselectivity was observed (up to 74:26 er) (Table 28, entries 1, 2 and 5). The yield of methylated product **288b** remained high (71%) even with a lithiation time of just 5 min (Table 28, entry 5). A test deuteration reaction confirmed that lithiation of *N*-Botc-azetidine **212** with *s*-

BuLi/DIANANE **334a** in hexane was almost complete after 5 min at −78 °C, generating a high level of D incorporation (90% D, 100% mass recovery). A tentative interpretation of the above apparent trend is that asymmetric induction might be a result of enantioselective deprotonation (see Scheme 43, p 36), and that the resulting lithiated species is not entirely configurationally stable at −78 °C. Although entries 2 and 5 were repeated a number of times and gave consistent results, we could not make any firm conclusions based on these results due to the relatively small differences in the ers obtained.

Allowing the lithiated species to warm to −40 °C for 10 min (before re-cooling to −78 °C) had a detrimental effect on the yield of methylated product **288b**, indicating that the lithiated species is not chemically stable at this elevated temperature, but there was no significant change in the er (Table 28, entry 4). This result was somewhat surprising as the lithiated species was expected to be more configurationally labile at −40 °C. A possible explanation is that the diastereomeric organolithium/DIANANE **334a** complexes underwent chemical decomposition at differents rates during the warming stage. Removing the warming stage for the methylation step had no significant effect on the results for reactions with a total methylation time of 1 h (Table 28, entries 5 and 7). Methylation time was found to be a more important factor in this case: reducing the methylation time to 30 min resulted in a much lower yield of product **288b**, in slightly higher er, than observed for the corresponding reaction with a 4 h methylation time (Table 28, entries 8 and 9). A tentative explanation for these results is that the methylation step is relatively slow at −78 °C, and that the lithiated species is not entirely configurationally stable for 4 h at −78 °C.

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Pleasingly, a considerably higher level of enantioselectivity (91:9 er) could achieved by reducing the lithiation temperature from −78 °C to −98 °C and maintaining this

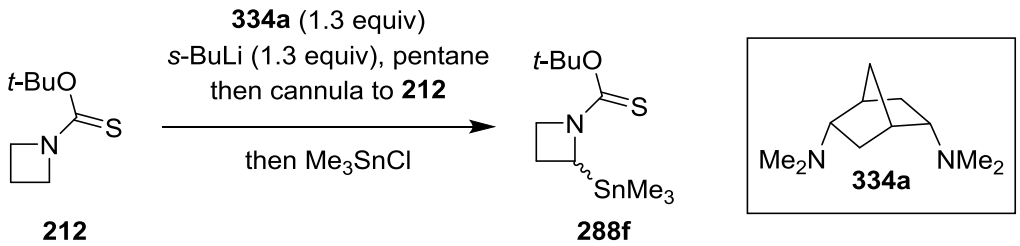
temperature throughout the methylation step, although methylated product **288b** was formed in lower yield (45%) under these conditions (Table 28, entry 11). This reaction was repeated several times to assess the reproducibility, and the results (yield and er) were consistent. However, by warming the reaction mixture to rt during the methylation step, a significantly lower er of methylated product **288b** was observed (Table 28, entry 10). A test deuteration reaction revealed that the lithiation step is incomplete after 1 h at −98 °C, with only 77% D (100% mass recovery) detected after this time. A higher level of D incorporation (95% D, 100% mass recovery) was achieved by repeating the deuteration reaction with an increased lithiation time of 3 h at −98 °C, indicating that lithiation is virtually complete after this time. Although the yield of methylated product **288b** could be improved by increasing the lithiation time to 3 h at −98 °C for the asymmetric methylation reaction (consistent with the deuteration results), this had a detrimental effect on the er (Table 28, entries, 12–14).

The above results could be tentatively rationalised by an enantioselective deprotonation mechanism (Scheme 43, p 36), and a lithiatied species which is configurationally unstable to some extent, resulting in lower levels of enantioselectivity with an increased reaction temperature or longer lithiation time. However, a number of our results for asymmetric stannylation (discussed below) were inconsistent with this explanation.

4.5. Asymmetric Stannylation

Many of the chiral ligands investigated for asymmetric methylation (see Table 27, p 152–153) were also tested for asymmetric stannylation of *N*-Botc-azetidine **212** using Me_3SnCl as the electrophile. Once again, tetramethyl-DIANANE **334a** gave the most encouraging results, providing a high yield (87%) of stannane **288f** with the highest enantioselectivity

($[\alpha]_D^{20}$ = +158.1, 66:34 er) in hexane. On the other hand, lower yields (<34%) and less promising specific rotation values (+38.6 to +0.2) were observed with DIANANE **334e** and tetramethyl-*trans*-cyclohexane-1,2-diamine **141**, while bispidine **332** and tetraethyl-DIANANE **334b** were found to completely inhibit the reaction (90% SM recovered). With tetramethyl-DIANANE **334a**, similar results were observed when the solvent was switched from hexane to pentane (Table 29, entry 1), but a lower yield (66%) of racemic stannane **288f** was formed in Et_2O. Initial attempts to determine the er of this substrate using chiral-SFC or chiral-HPLC were unsuccessful. The racemate was therefore screened across 137 permutations and combinations of chiral HPLC columns and solvents by 'Reach Separations', and suitable conditions were found (column: Lux Cellulose-3, eluent: isocratic at 5% *i*-PrOH in heptane) that provided adequate peak separation of the enantiomers (racemate showing a 51:49 ratio).



212 **288f**

Entry	Lithiation time (temp)	Stannylation time (temp)	% Yield	$[\alpha]_D^{20}$	er (*R*:*S*)[a]	% SM
1[b]	1 h (−78 °C)	30 min (−78 °C) then 30 min (rt)	90	+166.3	66:34	0
2		30 min (−78 °C)	80	+120.9	[c]	0
3	30 min (−78 °C)		86	+153.9	[c]	0
4[b]	5 min (−78 °C)	30 min (−78 °C) then 30 min (rt)	62	−42.3	46:54	38
5[b]		30 min (−78 °C)	77	+12.8	[c]	18
6	3 h (−98 °C)	1 h (−98 °C)	61	+105.8	[c]	38

7[b]	3 h (−98 °C)	30 min (−98 °C)	77	+145.1	[c]	21
8	1 h (−98 °C)	1 h (−98 °C)	70	−33.9	[c]	30
9		30 min (−98 °C) then 30 min (rt)	20	−96.8	38:62	75
10[b]		30 min (−98 °C)	70	−32.2	[c]	24
11	5 min (−98 °C)		36	−58.5	44:56	48

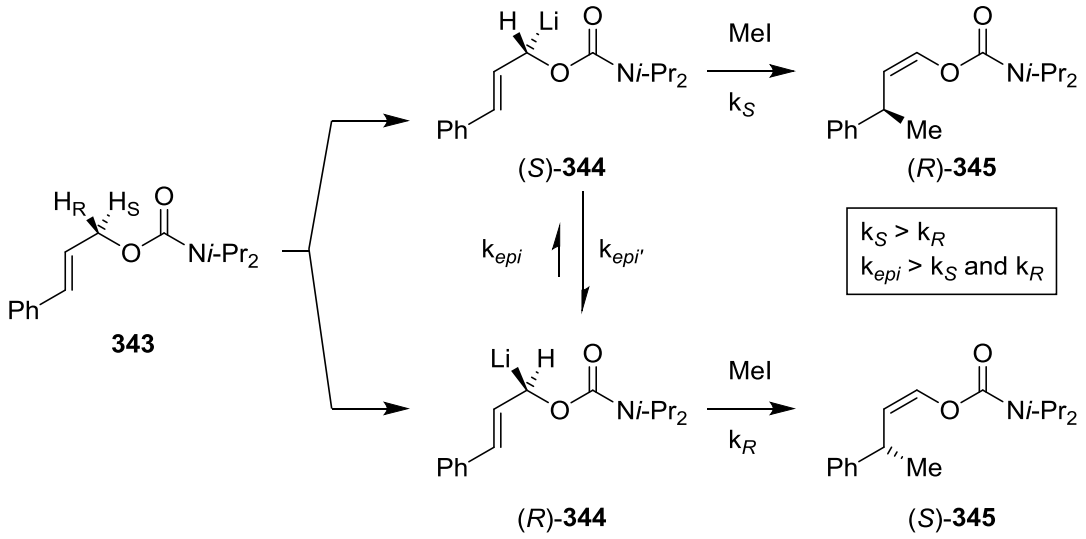
a) er determined by 'Reach Separations' using chiral-HPLC analysis, and sense of asymmetric induction tentatively assigned by analogy to methylated product (*R*)-**288b**. *b*) Reaction carried out at least twice and results were found to be reproducible. *c*) er was not determined.

Table 29. Conditions for asymmetric stannylation with tetramethyl-DIANANE **334a**.

Conditions for asymmetric stannylation of *N*-Botc-azetidine **212** with tetramethyl-DIANANE **334a** were further investigated in an attempt to improve the enantioselectivity (Table 29). To reduce costs, not all of the stannylated products **288f** were sent to 'Reach Separations' for er determination; instead, specific rotation values were used to compare enantioselectivities. Initially, removing the warming stage for the stannylation step or reducing the lithiation time (from 1 h to 30 min) appeared to have no significant effect on the results (Table 29, entries 2–3). Surprisingly, further reducing the lithiation time to just 5 min had a dramatic effect on the enantioselectivity, generating essentially racemic stannane **288f** in good yield (Table 29, entries 4–5). Entries 1, 4 and 5 were repeated several times to ensure reproducibility, and gave consistent results. In stark contrast to the above asymmetric methylation studies, reducing the lithiation temperature from −78 °C to −98 °C did not lead to an improvement in enantioselectivity for asymmetric stannylation. While no significant change in the results was observed for reactions with a lithiation time of 3 h at −98 °C (Table 29, entries 6–7), shorter lithiation times consistently resulted in a change in predominant sense of asymmetric induction at −98 °C (Table 29, entires 8–11). It was initially thought that this change may be due to different *s*-BuLi-ligand aggregates

dominating at a lower temperature, although this explanation is not consistent with the above results for asymmetric methylation.

In contrast to our previous results for asymmetric methylation, the above stannylation results are not consistent with enantioselective deprotonation being entirely responsible for asymmetric induction; the enantioselectivity may also be affected by a dynamic resolution (Scheme 43, p 36). A tentative explanation for these contrasting results is that the deprotonation step might provide only a low level of asymmetric induction, and the resulting diastereomeric α-lithio complexes might react with the electrophiles at different rates. A similar phenomenon was observed by Hoppe and co-workers during their studies on (−)-sp-mediated lithiation and substitution of carbamate **343** (Scheme 132).[131] Since higher yields of trapped products were generally achieved with stannylation compared to methylation after a lithiation time of 1 h at −98 °C, it is likely that Me_3SnCl is a more reactive electrophile than MeI in this case. It was speculated that the rate of interconversion of the two diastereomeric α-lithio complexes might be relatively slow, requiring a higher reaction temperature or longer reaction time for equilibrium to be reached for a DTR process (Scheme 43, p 36); this might explain why the highest ers for stannylation (although still modest) were achieved with longer lithiation times.

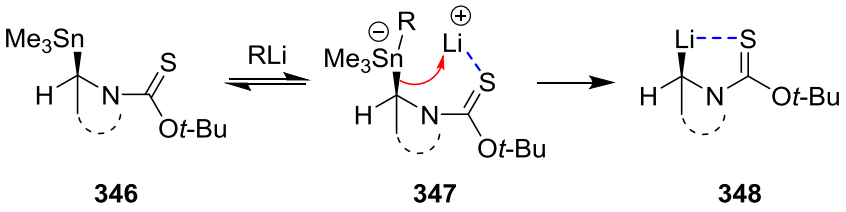


Scheme 132. Hoppe's studies on lithiation and substitution of carbamate **343**.[131]

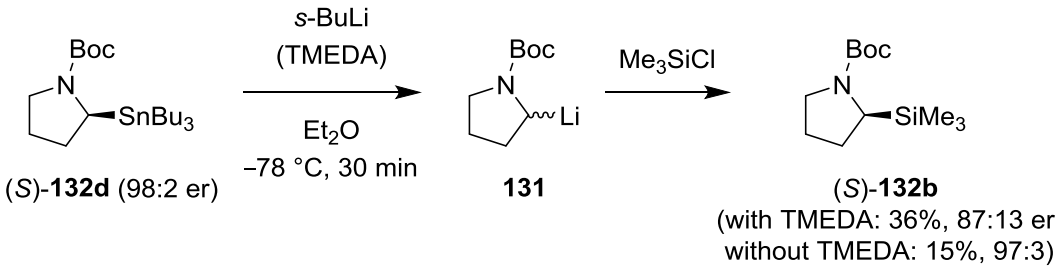
4.6. Investigating Configurational Stability

For the asymmetric α-lithiation–electrophile trapping reactions discussed above, configurational stability at the lithium-bearing stereogenic centre in the intermediate is clearly a very important factor. We envisaged that Sn-Li exchange of enantioenriched 2-stannylated azetidine (*R*)-**228f** could be used to probe the configurational stability of lithiated species **162b** (Table 30, p 166–167). Stannanes are known to rapidly react with organolithiums under thermodynamic control, allowing ligand exchange to produce the most stable organolithium.[113] In our case, ligand exchange is thermodynamically favourable to due to stabilisation of the resulting organolithium by chelation of the lithium to the heteroatom present in the *N*-protecting group. Stereospecific Sn-Li exchange reactions such as these are thought to involve formation of an intermediate 'ate' complex **347**, which virtually always collapses with retention of configuration to generate the organolithium;[244] the Li-coordinating heteroatom is believed to anchor the lithium cation, causing this retention of stereochemistry (Scheme 133).[113] Studies by Still estabilished that direct reaction of the intermediate 'ate' complex with electrophiles is unlikely, due to a

much lower reactivity of this species towards electrophiles compared to the organolithium.[245] Beak and co-workers previously used this technique to investigate the configurational stability of the related 2-lithio-*N*-Boc-pyrrolidine **131** (Scheme 134).[112] Highly enantioenriched 2-stannylated-pyrrolidine (*S*)-**132d** underwent Sn-Li exchange, with or without the addition of achiral ligand TMEDA, resulting in highly enantioenriched silylated product (*S*)-**132b**, albeit in low yield. These experiments proved that 2-lithio-*N*-Boc-pyrrolidine **131** is configurationally stable in Et_2O, but the presence of TMEDA slightly decreases the configurational stability of this lithiated species.



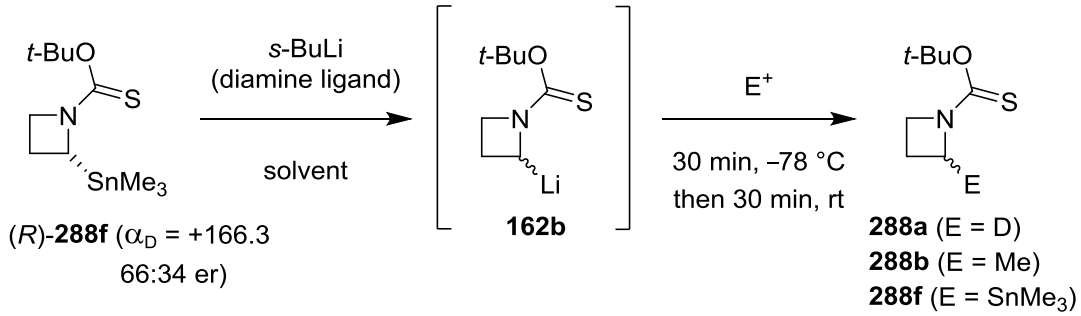
Scheme 133. Sn-Li exchange mechanism.



Scheme 134. Sn-Li exchange reactions of enantioenriched 2-stannylated-pyrrolidine (*S*)-**132d**.[112]

Enantioenriched 2-stannylated-azetidine (*R*)-**288f** was subjected to Sn-Li exchange conditions in Et_2O, and was then reacted with a number of electrophiles. In the absence of a diamine ligand, both stannylation and methylation resulted in good yields of essentially racemic products **288f** and **288b** (Table 30, entries 1–2). A test deuteration reaction under

the same conditions resulted in a high yield of fully deuterated product **288a**, with no SM recovered, indicating that Sn-Li exchange step had gone to completion (Table 30, entry 3). Essentially racemic products were also formed in the presence of either TMEDA or tetramethyl-DIANANE **334a** (Table 30, entries 4–5). These results indicate that lithiated species **162b** is not configurationally stable in Et_2O, and that in this solvent the presence of TMEDA or tetramethyl-DIANANE **334a** does not improve the configurational stability. Furthermore, TMEDA appears to decrease the chemical stability of lithiated species **162b** in Et_2O, resulting in a lower yield of methylated product **288b** (Table 30, entry 4).



Entry	Solvent	Ligand	Transmetallation conditions	E^+	% Yield	$[\alpha]_D^{20}$	er (*R*:*S*)
1	Et_2O	**334a**	30 min (−78 °C)	Me_3SnCl	64	+5.0	[a]
2				MeI	78	−0.7	51:49
3				CD_3OD	83	-	-
4		TMEDA		MeI	35	−1.2	51:49
5		**334a**		Me_3SnCl	69	+2.9	[a]
6	hexane	none		CD_3OD	0[b]	-	-
7		**334a**			78[c]	-	-
8				Me_3SnCl	91	+123.6	62:38[d]
9				MeI	44	−22.3	77:23
10			5 min (−78 °C)		48	−17.6	71:29
11[e]					57	−25.5	77:23

12[e]	hexane	**334a**	1 h (−78 °C)	MeI	69	−18.0	79:21
13[e]				Me_3SnCl	67	−23.7	[a]
14[e]			30 min (−78 °C)		83	−36.1	47:53[d]
15[e]			5 min (−78 °C)		61	+2.6	[a]
16[e]				CD_3OD	92[f]	-	-

a) er was not determined. *b*) 88% SM recovered. *c*) 9% SM recovered. *d*) Sense of asymmetric induction tentatively assigned by analogy to methylated product (*R*)-**288b** *e*) Not warmed to rt after E^+ addition. *f*) 7% SM recovered.

Table 30. Sn-Li exchange reactions of enantioenriched 2-stannylated-azetidine (*R*)-**288f**.

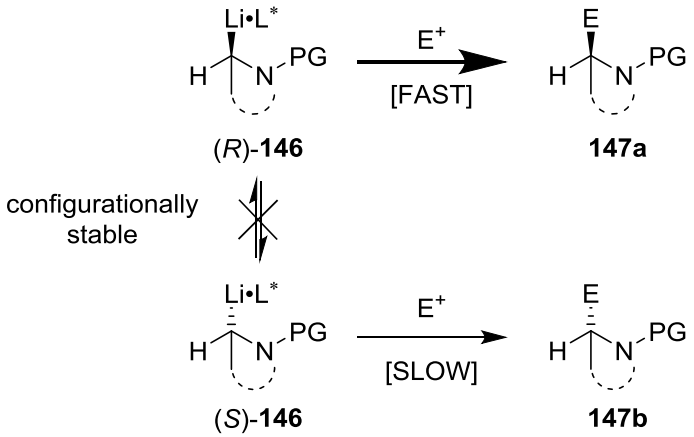
A test deuteration reaction revealed that Sn-Li exchange of enantioenriched stannane (*R*)-**288f** does not occur in hexane in the absence of a diamine ligand (Table 30, entry 6). However, this substrate readily underwent Sn-Li exchange in hexane in the presence of tetramethyl-DIANANE ligand **334a**, as shown by trapping with CD_3OD (Table 30, entry 7). Switching the electrophile to Me_3SnCl resulted in stannylated product with an er only slightly lower than starting material (Table 30, entry 8), indicating that lithiated species **162b** is substantially more configurationally stable in hexane than Et_2O in the presence of tetramethyl-DIANANE **334a**. This might explain why higher enantioselectivities were achieved in hexane than Et_2O in the above asymmetric α-lithiation-electrophile trapping reactions, assuming that asymmetric induction is (at least partially) caused by an enantioselective deprotonation mechanism (Scheme 43, p 36).

Sn-Li exchange of enantioenriched stannane (*R*)-**288f** in hexane followed by trapping with MeI resulted in methylated product **288b** with a slightly higher er than the starting material (Table 30, entry 9). This apparent difference in er might simply arise from the different techniques used for er determination of starting material and product (chiral-HPLC vs chiral-SFC). Alternatively, an improvement in the er might indicate that lithiated species

162b is somewhat configurationally labile, and the presence of chiral DIANANE ligand **334a** evokes a dynamic resolution process (Scheme 43, p 36). For reactions with MeI, no significant change in the results were observed by varying the transmetallation time or by preventing the reaction mixture from being warmed to rt during the methylation step (Table 30, entries 10–12). In stark contrast, Sn-Li exchange of enantioenriched stannane (*R*)-**288f** followed by trapping with Me_3SnCl resulted in essentially racemic product if the reaction mixture was not warmed to rt during the stannylation step, regardless of the transmetallation time (Table 30, entries 13–15). A test deuteration reaction showed that Sn-Li exchange, or direct deuteration of the 'ate' complex (less likely), is virtually complete within 5 min at −78 °C, even with no warming stage after CD_3OD addition (Table 30, entry 16).

No firm conclusions on the configurational stability of lithiated species **162b** could be made from the above Sn-Li exchange reactions. The inconsistencies in the results observed by switching the electrophile from MeI to Me_3SnCl are likely due to differences in the rate of reaction of these electrophiles with the two diastereomeric α-lithio complexes. We hoped to gain more information by employing Beak's "poor man's Hoffmann test",[122,246] which relies on a rate difference between the diastereomeric α-lithio complexes, and does not require the use of a chiral electrophile. Instead, this test involves comparison of the ers of products from reactions in which the lithitated species is complexed with a chiral ligand, and trapped with an excess or sub-stoichiometric amount of electrophile. With a configurationally stable lithiated species: both diastereomeric α-lithio complexes react to completion with an excess of electrophile, but a higher proportion of product is generated from the faster-reacting α-lithio complex with a sub-stoichiometric amount of electrophile (Scheme 135).[113] Configurational stability of the lithiated species is indicated if these two

experiments generate different ers. Therefore, asymmetric methylation of *N*-Botc-azetidine **212** with tetramethyl-DIANANE **334a** was repeated with 0.5 equiv MeI and compared to previous reactions with 3 equiv MeI. Although reducing the quantity of MeI appeared to result in a very minor change in er for reactions with a 1 h lithiation time (Table 28, entries 2–3, p 158), no change in er of methylated products **288b** was observed for reactions with a 5 min lithiation time (Table 28, entries 5–6, p 158). Unfortunately, a disadvantage of this test is that it cannot establish configurational lability, as highlighted by Beak and co-workers.[247]

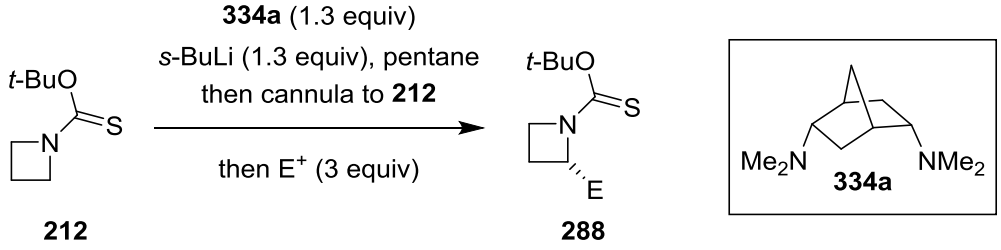


Scheme 135. Reaction rate difference between diastereomeric α-lithio complexes.

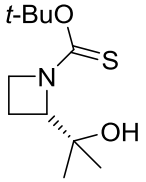
4.7. Electrophile Scope

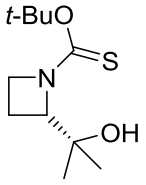
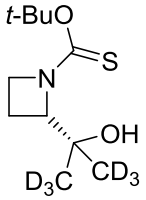
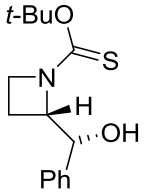
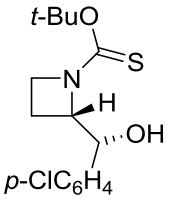
The above methylation and stannylation reactions with tetramethyl-DIANANE **334a** showed that enantioselectivity is electrophile-dependant; MeI is clearly a more 'suitable' electrophile than Me_3SnCl for this chemistry. Therefore, further investigation of the electrophile scope was deemed particularly important. Pleasingly, reaction with acetone at −78 °C resulted in a moderate yield (64%) of trapped product (*S*)-**288l** in 92:8 er (Table 31, entry 1). In this case, the yield and enantioselectivity were not significantly affected by

varying the reaction time for either the lithiation or electrophile trapping steps (Table 31, entries 2–7). Addition of CD_3OD (3 equiv) 20 min after acetone addition resulted in a low level of D incorporation (11% D) in the recovered starting material (Table 31, entry 4), indicating that the electrophile trapping step is almost complete after this time. In contrast to previous methylation reactions, lowering the lithiation temperature had a detrimental effect on the enantioselectivity for reactions with acetone (Table 31, entries 8–9). A tentatively explanation for these results is that the asymmetric induction is affected by a dynamic resolution process (Scheme 43, p 36), and that a higher lithiation temperature enables the 2 interconverting diastereomeric α-lithio complexes to reach equilibrium more rapidly. The yield of the above reactions with acetone was thought to be affected by a competing enolisation reaction; this was confirmed by trapping with acetone-D_6 which resulted in an improved yield of trapped product (*S*)-**288m** (kinetic isotope effect), along with highly deuterated recovered starting material (93% D) (Table 31, entries 10–11).



212 **288**

Entry	Product	Lithiation time (temp)	E^+ trapping time (temp)	% Yield (dr)	er (*S*:*R*)[a]	% SM
1	 (*S*)-**288l**	3 h (−78 °C)	1 h (−78 °C)	64	92:8	35
2		1 h (−78 °C)	3 h (−78 °C)	60		33
3			1 h (−78 °C)	47	91:9	51
4[b]			20 min (−78 °C)	49	89:11	40 (11% D)
5		10 min	3 h (−78 °C)	56	86:14	37

6	 (*S*)-**288l**	(−78 °C)	1 h (−78 °C)	63	84:16	37
7			20 min (−78 °C)	49	89:11	41
8		3 h (−98 °C)	1 h (−98 °C)	51	86:14	45
9		1 h (−98 °C)	1 h (−98 °C)	42	70:30	42
10	 (*S*)-**288m**	1 h (−78 °C)	1 h (−78 °C)	79	91:9	20 (93% D)
11		10 min (−78 °C)	20 min (−78 °C)	73	88:12	
12	 (*S*,*R*)-**288i**	1 h (−78 °C)	1 h (−78 °C)	88 (60:40)	86:14[c]	7
13		1 h (−98 °C)	1 h (−98 °C)	51 (71:29)	65:35[c]	49
14	 (*S*,*R*)-**288j**	1 h (−78 °C)	1 h (−78 °C)	64 (69:31)	80:20[c]	25
15		1 h (−98 °C)	1 h (−98 °C)	14 (64:36)	69:31[c]	86

a) er determined by chiral-HPLC analysis and sense of asymmetric induction assigned by analogy to methylated product (*R*)-**288b**. *b*) CD_3OD (3 equiv) added 20 min after addition of acetone. *c*) er of major diastereomer shown in table.

Table 31. Electrophile screen for reactions with tetramethyl-DIANANE **334a**.

Reactions with aromatic aldehydes (benzaldehyde and 4-chlorobenzaldehyde) in the presence of tetramethyl-DIANANE **334a** were also successful at −78 °C, generating trapped products (*S*,*R*)-**288i** and (*S*,*R*)-**288j** in good yields and ers, albeit as a mixture of diastereomers (Table 31, entries 12 and 14). As observed for the above reactions with acetone, reducing the lithiation temperature to −98 °C had a detrimental effect on the yields and ers of trapped products (*S*,*R*)-**288i** and (*S*,*R*)-**288j** produced with these aromatic aldehydes (Table 31, entries 13 and 15).

4.8. Summary

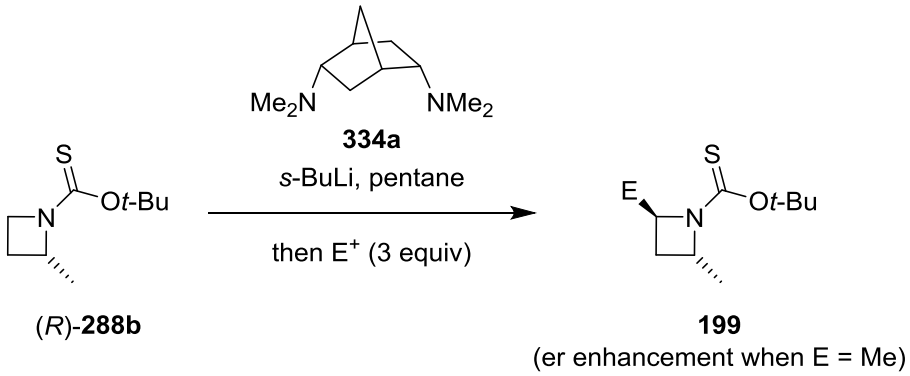
The synthesis and screening of a structurally diverse range of chiral diamine ligands for asymmetric α-lithiation–electrophile trapping of *N*-Botc-azetidine **212** has been carried out. Despite initial disappointments, with the vast majority of chiral ligands tested either inhibiting the reaction or resulting in poor enantioselectivity, reaction of Botc-protected azetidine **212** with *s*-BuLi/tetramethyl-DIANANE **334a** followed by electrophile trapping was found to provide the highest level of asymmetric induction in azetidine α-substitution to date (up to 92:8 er). This work also provides the best levels of enantioselectivity thus far for transformations involving a DIANANE-type ligand in combination with an organolithium. Furthermore, substituted azetidines could be generated in high yield and enantioselectivity with several electrophiles (MeI, acetone and aromatic aldehydes), demonstrating electrophile scope beyond the originally reported asymmetric methylation.[148]

4.9. Future Work

Potential future work on this topic includes:

- Examining this lithiation chemistry for formation of 2-halo or 2-boronate azetidines, for further functionalisation via cross-coupling. In addition, cross-coupling with previously synthesised 2-stannylated azetidines **288f**/**288g** and a range of coupling partners should be attempted.
- Further investigation of the electrophile scope for asymmetric α-lithiation–electrophile trapping of *N*-Botc-azetidine **212** with chiral DIANANE ligand **334a**.

- Seeking independent proof of stereochemistry for acetone/benzaldehyde/4-chlorobenzaldehdyde-trapped products from the above asymmetric reactions (previously assigned by analogy to the MeI-trapped product).
- Controlling 2,4-disubstituted azetidine stereochemistry by use of a chiral ligand for asymmetric α′-lithiation–electrophile trapping of enantioenriched 2-substituted *N*-Botc-azetidine substrates; er enhancement expected with 2-methyl substrate (as discussed in section 1.4.4.1., p 32).



- Application of this lithiation chemistry in a natural product synthesis (e.g. penaresidins A and B, Figure 3, p 3).

5. Experimental

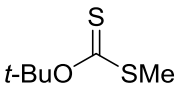
5.1. General Details

All reactions requiring anhydrous conditions were conducted in flame-dried apparatus under an atmosphere of nitrogen or argon. CH_2Cl_2, toluene, pentane, THF and Et_2O were degassed and dried over activated alumina under nitrogen.[248] TMEDA was distilled over CaH_2; MeI and BuI were passed through basic alumina immediately before use; Me_3SiCl was distilled and passed through basic alumina; benzaldehyde, *p*-anisaldehyde and allyl bromide were distilled; 4-chlorobenzaldehyde was recrystallised from Et_2O; acetone was refluxed over CaO and distilled; all other reagents were used as received. *s*-BuLi was titrated on arrival, and periodically thereafter, using 2-propanol solution in toluene with 0.2% 1,10-phenanthroline indicator titration solution for quantitative analysis of BuLi. Thin layer chromatography (TLC) was carried out on aluminium-backed plates pre-coated with silica (0.2 mm, 60 F254 nm), which were visualized UV light (λmax = 254 nm) and/or developed with basic potassium permanganate solution with heating. Flash column chromatography was carried out on Si-gel (43–63 μm) in the solvents systems indicated, applying head pressure by means of a low pressure nitrogen line (0.1–0.3 atm). Petroleum ether refers to the fraction boiling between 30 °C to 40 °C. Melting points are uncorrected. Infra-red spectra were recorded neat and the intensity of the peaks are reported as s, m, w, br, denoting strong, medium, weak and broad, respectively. ^1H, ^{13}C and ^{19}F NMR spectra were recorded at 25 °C in $CDCl_3$ or D_2O. ^{13}C DEPT, COSY and HSQC spectra were used to aid structure assignments. Data are expressed as chemical shifts (δ) in parts per million (ppm) relative to $CDCl_3$ (^1H δ 7.27 ppm, ^{13}C δ 77.0 ppm, respectively) or D_2O (^1H δ 4.75 ppm) as the internal standard on the δ scale. TMS (^{13}C δ 0.00 ppm) or $CFCl_3$ (^{19}F δ 0.00

ppm) were employed as external references. The multiplicity of each signal is reported as s, d, t, q, quin, br, m, denoting singlet, doublet, triplet, quartet, quintet, broad, and multiplet, respectively. Proton coupling constants *J* are reported to the nearest 0.1 Hz. Discernible NMR signals for minor rotamers or diastereomers are indicated in parentheses. High resolution mass spectra were obtained by field ionisation (FI), or by electrospray ionisation (ESI) using tetraoctylammonium bromide or sodium dodecyl sulfate as the lock mass; values are quotes as ratio of mass to charge (m/z) in Daltons, and relative intensities of assignable peaks observed are quoted as a percentage value of the base peak.

5.2. Experimental Conditions

***O-tert*-butyl *S*-methyl carbonodithioate (203)**

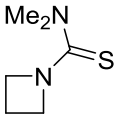


To a solution of dry KO*t*-Bu (from a new bottle or freshly sublimed) (2.53 g, 22.57 mmol) in toluene (52 mL) at 75 °C was added CS_2 (1.41 mL, 23.48 mmol), over 5 min. The reaction mixture was stirred at 75 °C for a further 10 min. The resulting pale yellow solid was collected by filtration, washed with benzene (20 mL), dried (high vacuum overnight) and suspended in Et_2O (32 mL). MeI (1.92 mL, 30.78 mmol) was added dropwise and the reaction mixture was stirred for at rt for 48 h. The reaction mixture was then filtered and concentrated under reduced pressure (water bath kept at 25 °C) to give a yellow liquid, xanthate **203** (2.6 g, 77%).

R_f 0.93 (20% EtOAc/petroleum ether); IR (neat/cm^{-1}) 2981 m, 2919 m, 1704 br, 1651 w, 1392 m, 1368 m, 1264 s, 1139 s, 1040 br, 961 w, 821 w; δ_H (400 MHz, $CDCl_3$) 2.47 (3H, s, SCH_3), 1.71 (9H, s, $C(CH_3)_3$); δ_C (125 MHz, $CDCl_3$) 213.3 (CS), 90.9 ($C(CH_3)_3$), 28.0

($C(CH_3)_3$), 19.2 (SCH_3). Compound ia too unstable at rt for analysis by mass spectrometry. Data is in good agreement with the literature.[171(a)]

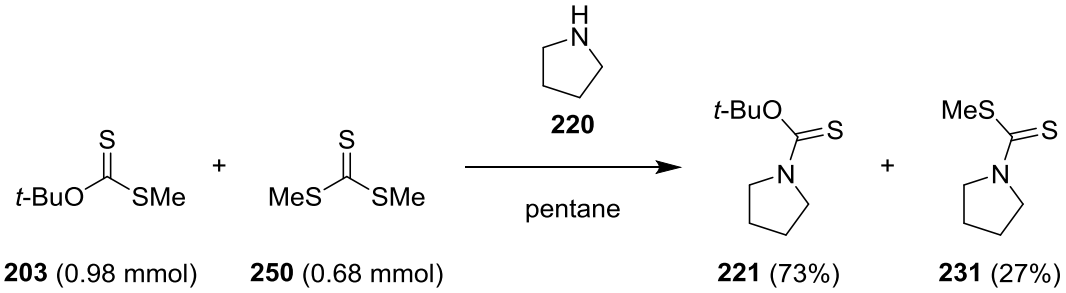
***N,N*-Dimethylazetidine-1-carbothioamide (216)**



To a pre-cooled solution of *t*-BuOH (80 mg, 1.08 mmol) in DMF (1.5 mL) was added NaH (60% w/w in mineral oil, 43 mg, 1.08 mmol) at 0 °C (ice-bath). The reaction mixture was stirred at rt for 30 min, warmed to 40 °C and stirred at this temperature for 1 min, then re-cooled to 0 °C before addition of azetidine-1-carbothioyl chloride (**214**)[151] (175 mg, 1.29 mmol) in DMF (0.5 mL). The reaction mixture was warmed to rt and stirred at rt for 12 h, then quenched with sat. aq NH_4Cl (10 mL), and extracted with Et_2O (3 × 10 mL). The combined organic extracts were washed with water (20 mL) and brine (20 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Purification of the resulting dark brown oil (SiO_2, 10–80% Et_2O/petroleum ether) gave a brown oil, thiourea **216** (33 mg, 18%).

R_f 0.1 (20% Et_2O/petroleum ether); IR (neat/cm^{-1}) 2951 , 2880 w, 1508 w, 1460 w, 1394 m, 1345 s, 1297 w, 1270 w, 1110 m, 1085 w, 1058 w, 947 w, 833 w; δ_H (400 MHz, $CDCl_3$) 4.21–4.17 (4H, m, NCH_2), 3.13 (6H, s, NCH_3), 2.22–2.14 (2H, m, CH_2); δ_C (100 MHz, $CDCl_3$) 187.2 (C=S), 55.1 (NCH_2), 42.0 (NCH_3), 14.8 (CH_2); HRMS (ESI^+) calcd for $C_6H_{13}N_2S$: 145.0794, found 145.0794.

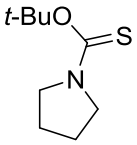
Synthesis of *O-tert*-butyl pyrrolidine-1-carbothioate (221) and side product methyl pyrrolidine-1-carbodithioate (231)



203 (0.98 mmol) **250** (0.68 mmol) **221** (73%) **231** (27%)

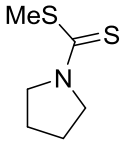
To a mixture of *O-tert*-butyl *S*-methyl carbonodithioate (**203**)[171(a),249] (161 mg, 0.98 mmol) and dimethyl carbonotrithioate (**250**) (94 mg, 0.68 mmol) in pentane (0.5 mL) was added pyrrolidine (66 µL, 0.78 mmol) at 0 °C (ice-bath). The reaction mixture was stirred at 0 °C for 1 h, then stirred at rt for 1 h, then concentrated under reduced pressure. Purification of the resulting yellow oil (SiO_2, 5–10% Et_2O/petroleum ether) gave first pyrrolidine thiocarbamate **221** as a colourless oil (106 mg, 73% based on pyrrolidine), followed by pyrrolidine dithiocarbamate **231** as a white solid (34 mg, 27% based on pyrrolidine).

***O-tert*-Butyl pyrrolidine-1-carbothioate (221)**



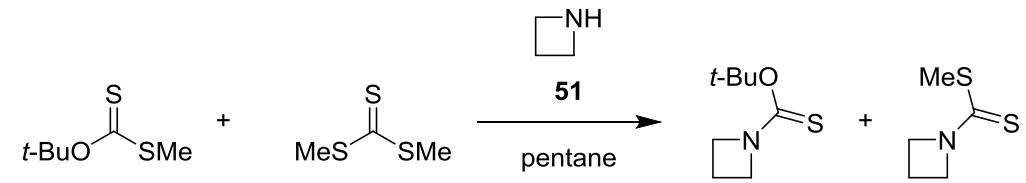
R_f 0.66 (5% EtOAc/petroleum ether); IR (neat/cm^{-1}) 2973 s, 2928 m, 2876 s, 1468 m, 1437 b, 1390 m, 1364 m, 1333 m, 1267 s, 1232 w, 1143 br, 997 w, 858 m; δ_H (400 MHz, $CDCl_3$) 3.70–3.66 (2H, m, NCH_2), 3.48–3.45 (2H, m, NCH_2), 1.94–1.88 (4H, m, NCH_2CH_2 × 2), 1.67 (9H, s, $C(CH_3)_3$); δ_C (100 MHz, $CDCl_3$) 183.2 (C=S), 84.7 ($C(CH_3)_3$), 51.1 (NCH_2), 48.3 (NCH_2), 28.5 ($C(CH_3)_3$), 25.6 (CH_2CH_2), 24.6 (CH_2CH_2); HRMS (FI^+) calcd for $C_9H_{17}NOS$: 187.1031, found 187.1025.

Methyl pyrrolidine-1-carbodithioate (231)



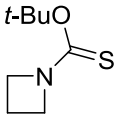
R_f 0.50 (5% EtOAc/petroleum ether); mp 78–80 °C; IR (neat/cm^{-1}) 2969 w, 2918 w, 2872 w, 1461 w, 1431 br, 1341 m,1330 m, 1252 w, 1184 w, 1163 s, 1007 s, 946 s 916 m; δ_H (400 MHz, $CDCl_3$) 3.96 (2H, t, J = 7.0 Hz, NCH_2), 3.66 (2H, t, J = 7.0 Hz, NCH_2), 2.67 (3H, s, CH_3S), 2.13–2.16 (2H, m, CH_2CH_2), 2.03–1.96 (2H, m, CH_2CH_2); δ_C (100 MHz, $CDCl_3$) 193.9 (CS), 54.9 (NCH_2), 50.5 (NCH_2), 26.0 (CH_2CH_2), 24.3 (CH_2CH_2), 19.4 (CH_3); HRMS (FI^+) calcd for $C_6H_{11}NS_2$: 161.0333, found 161.0331. All data is in good agreement with the literature.[250]

Synthesis of *O-tert*-butyl azetidine-1-carbothioate (212) and side-product methyl azetidine-1-carbodithioate (232)



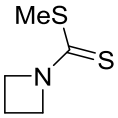
To a mixture of *O-tert*-butyl *S*-methyl carbonodithioate (**203**)[171(a),249] (2.23 g, 13.57 mmol) and dimethyl carbonotrithioate (**250**) (0.07 g, 0.51 mmol) in pentane (2 mL) was added azetidine (475 µL, 7.05 mmol) at 0 °C (ice-bath). The reaction mixture was stirred at 0 °C for 1.5 h, then stirred at rt for 1 h, then concentrated under reduced pressure. Purification of the resulting pale yellow oil (SiO_2, 5–20% Et_2O/petroleum ether) gave first azetidine thiocarbamate **212** as a colourless oil (1.17 g, 96% based on azetidine), followed by azetidine dithiocarbamate **232** as a white solid (0.05 g, 4% based on azetidine).

O-tert-Butyl azetidine-1-carbothioate (212)



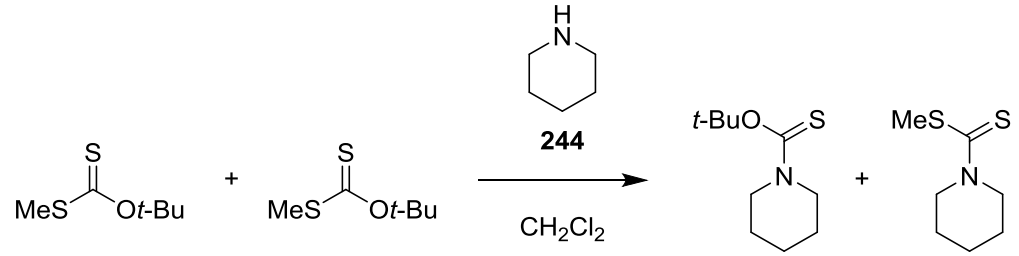
R_f 0.44 (5% EtOAc/petroleum ether); IR (neat/cm^{-1}) 2975 s, 2882 w, 1488 br, 1438 s, 1391 m, 1365 m, 1741 br, 1245 s, 1228 m, 1139 br, 1024 m, 944 w, 818 w; δ_H (400 MHz, $CDCl_3$) 4.13 (2H, t, J = 7.5 Hz, NCH_2), 4.01 (2H, t, J = 7.5 Hz, NCH_2), 2.21–2.14 (2H, m, NCH_2CH_2), 1.64 (9H, s, $C(CH_3)_3$); δ_C (100 MHz, $CDCl_3$) 184.9 (C=S), 84.6 ($C(CH_3)_3$), 51.7 (NCH_2), 50.6 (NCH_2), 28.4 ($C(CH_3)_3$), 13.9 (NCH_2CH_2); HRMS (FI$^+$) calcd for $C_8H_{15}NOS$: 173.0874, found 173.0869.

Methyl azetidine-1-carbodithioate (232)



R_f 0.34 (5% EtOAc/petroleum ether); mp 57–59 °C; IR (neat/cm^{-1}) 2975 w, 2917 br, 2860 w, 2361 w, 2342 w, 1736 w, 1479 s, 1451 s, 1429 s, 1288 m, 1257 w, 1245 w, 1148 m, 1429 s, 1288 m, 1257 w, 1245 w, 1148 m, 1009 w, 958 m, 883 w; δ_H (400 MHz, $CDCl_3$) 4.30 (2H, t, J = 7.7 Hz, NCH_2), 4.20 (2H, t, J = 7.7 Hz, NCH_2), 2.63 (3H, s, CH_3), 2.43–2.35 (2H, m, NCH_2CH_2); δ_C (100 MHz, DMSO) 193.2 (CS), 54.6 (NCH_2), 53.1 (NCH_2), 17.7 (CH_3), 14.9 (NCH_2CH_2); LRMS (ESI$^+$) 301.2 (41%), 347.2 (100%); HRMS (FI$^+$) calcd for $C_5H_9NS_2$: 147.0176, found 147.0176.

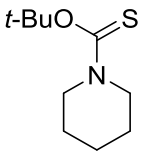
Synthesis of *O*-(*tert*-butyl) piperidine-1-carbothioate (245) and methyl piperidine-1-carbodithioate (246)



203 (1.69 mmol) **250** (0.70 mmol) **245** (36%) **246** (32%)

To a mixture of *O*-*tert*-butyl *S*-methyl carbonodithioate (**203**)[171(a),249] (278 mg, 1.69 mmol) and dimethyl carbonotrithioate (**250**) (97 mg, 0.70 mmol) in CH_2Cl_2 (630 µL) was added piperidine (188 µL, 1.90 mmol) at 0 °C (ice-bath). The reaction mixture was stirred at 0 °C for 30 min, and then stirred at rt for 30 min. The reaction mixture was concentrated under reduced pressure. Purification of the resulting pale yellow oil (SiO_2, 1% EtOAc/petroleum ether) gave first piperidine thiocarbamate **245** as a colourless oil (137 mg, 36% based on piperidine), followed by piperidine dithiocarbamate **246** as a colourless oil (105 mg, 32% based on piperidine).

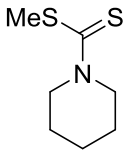
***O*-(*tert*-Butyl) piperidine-1-carbothioate (245):**



R_f 0.76 (5% EtOAc/petroleum ether); IR (neat/cm^{-1}) 2975 w, 2935 m, 2857 w, 1479 s, 1428 s, 1391 w, 1365 w, 1289 s, 1271 w, 1236 s, 1205 w, 1139 s, 1010 m, 954 w, 852 w; δ_H (400 MHz, $CDCl_3$) 4.02 (2H, br s, NCH_2), 3.64–3.61 (2H, m, NCH_2), 1.66 (9H, s, $C(CH_3)_3$), 1.63 (4H, br s, NCH_2CH_2 × 2), 1.53 (2H, br s, $N(CH_2)_2CH_2$); δ_C (100 MHz, $CDCl_3$) 184.8 (C=S), 85.2 ($C(CH_3)_3$), 49.7 (NCH_2), 46.9 (NCH_2), 28.6 ($C(CH_3)_3$), 26.0

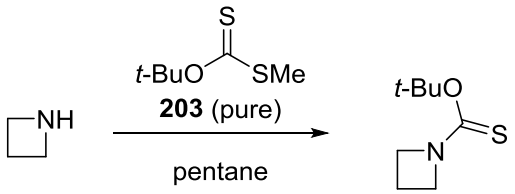
(NCH_2CH_2), 25.2 (NCH_2CH_2), 24.4 ($N(CH_2)_2CH_2$); HRMS (ESI^+) calcd for $C_{10}H_{19}NNaOS$: 224.1080, found 224.1078.

Methyl piperidine-1-carbodithioate (246):



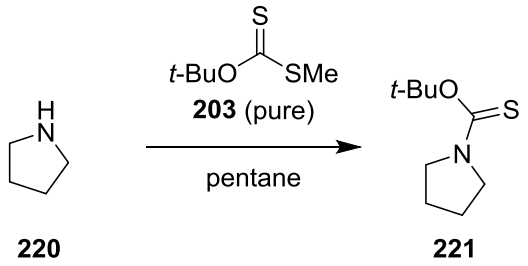
R_f 0.66 (5% EtOAc/petroleum ether); IR (neat/cm^{-1}) 2991 w, 2937 m, 2856 w, 1473 m, 1422 s, 1280 w, 1240 s, 1226 s, 1133 m, 1116 m, 1008 m, 983 m, 892 w, 853 w 805 w; δ_H (400 MHz, $CDCl_3$) 4.34-4.26 (2H, m, NCH_2), 3.93-3.85 (2H, m, NCH_2), 2.66 (3H, s, CH_3S), 1.75–1.65 (6H, m, $(CH_2)_3$); δ_C (100 MHz, $CDCl_3$) 196.8 (CS), 52.8 (NCH_2), 51.2 (NCH_2), 25.7 (NCH_2CH_2), 24.3 ($N(CH_2)_2CH_2$), 20.0 (CH_3); LRMS (ESI^+) 146.1 (55%), 176.1 ($[M+H]^+$, 26%), 224.1 (100%); HRMS (ESI^+) calcd for $C_7H_{13}NNaS_2$: 198.0382, found 198.0381. All data is in good agreement with the literature.[251]

Synthesis of *O*-*tert*-Butyl azetidine-1-carbothioate (212) using pure xanthate 203



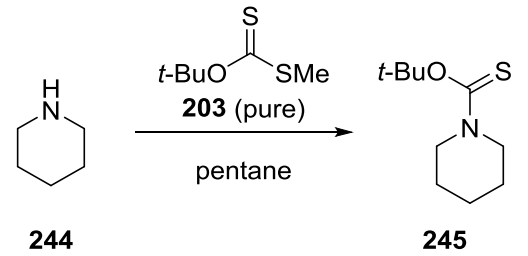
To a solution of *O*-*tert*-butyl *S*-methyl carbonodithioate (**203**)[171(a)] (300 mg, 1.83 mmol) in pentane (0.5 mL) at 0 °C (ice-bath) was added azetidine (112 µL, 1.66 mmol). The reaction mixture was stirred at 0 °C for 1.5 h, then stirred at rt for 1 h, then concentrated under reduced pressure. Purification of the resulting pale yellow oil (SiO_2, 5–20% Et_2O/petroleum ether) gave a colourless oil, azetidine thiocarbamate **212** (254 mg, 88%). Data as p 178.

Synthesis of *O*-*tert*-Butyl pyrrolidine-1-carbothioate (221) using pure xanthate 203



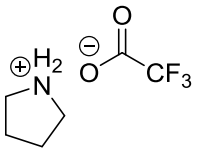
To a solution of *O*-*tert*-butyl *S*-methyl carbonodithioate (**203**)[171(a)] (300 mg, 1.83 mmol) in pentane (0.5 mL) at 0 °C (ice-bath) was added pyrrolidine (141 µL, 1.66 mmol). The reaction mixture was stirred at 0 °C for 1 h, then stirred at rt for 1 h, then concentrated under reduced pressure. Purification of the resulting yellow oil (SiO_2, 5–10% Et_2O/petroleum ether) gave a colourless oil, pyrrolidine thiocarbamate **221** (277 mg, 89%). Data as p 176.

***O*-(*tert*-Butyl) piperidine-1-carbothioate (245) using pure xanthate 203**



To a solution of *O*-*tert*-butyl *S*-methyl carbonodithioate (**203**)[171(a)] (300 mg, 1.83 mmol) in pentane (0.5 mL) at 0 °C (ice-bath) was added piperidine (164 µL, 1.66 mmol). The reaction mixture was stirred at 0 °C for 30 min, and then stirred at rt for 30 min. The reaction mixture was concentrated under reduced pressure. Purification of the resulting pale yellow oil (SiO_2, 1% EtOAc/petroleum ether) gave a colourless oil, piperidine thiocarbamate **245** (300 mg, 90%). Data as p 179.

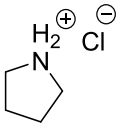
Pyrrolidinium trifluoroacetate (258a)



To a solution of *O*-*tert*-butyl pyrrolidine-1-carbothioate (**221**) (50 mg, 0.27 mmol) in CH_2Cl_2 (1 ml) at rt was added TFA (82 µl, 1.07 mmol). The reaction mixture was stirred for 1 h at rt, then concentrated under reduced pressure to give a colourless liquid, pyrrolidine salt **258a**[188] (49 mg, quant).

IR (neat/cm^{-1}) 2986 br, 2850 w, 2486 w, 1670 s, 1462 w, 1426 w, 1198 s, 1173 s, 1125 s, 833 m, 797 m; δ_H (300 MHz, $CDCl_3$) 9.43 (1H, br s, NH_2), 4.66 (1H, br s, NH_2), 3.27–3.23 (4H, m, NCH_2 × 2), 2.02–1.97 (4H, m, NCH_2CH_2 × 2); δ_C (125 MHz, $CDCl_3$) 162.1 (q, J = 36 Hz, C=O), 116 (Q, J = 292 Hz, CF_3), 45.1 (NCH_2 × 2), 24.2 ($(CH_2)_2$); δ_F (470 MHz, $CDCl_3$) −75.8.

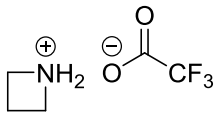
Pyrrolidinium chloride (258b)



A solution of HCl in Et_2O (2M, 534 µL, 1.07 mmol) was added to *O*-*tert*-butyl pyrrolidine-1-carbothioate (**221**) (50 mg, 0.27 mmol). The reaction mixture was stirred for 3 h at rt, then concentrated under reduced pressure to give a colourless solid, pyrrolidine salt **258b** (27 mg, 93%).

R_f 0.01 (5% EtOAc/petroleum ether); IR (neat/cm^{-1}); 2981 w, 2750 w, 2218 br, 2134 w, 1636 m, 1459 w 1089 w 1030 w, 912 w; δ_H (500 MHz, D_2O) 3.23–3.20 (4H, m, NCH_2 × 2), 1.95–1.91 (4H, m, $(CH_2)_2$); δ_C (125 MHz, D_2O) 45.5 (NCH_2 × 2), 23.6 ($(CH_2)_2$). ^1H NMR data is in good agreement with the literature.[252]

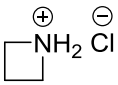
Azetidinium trifluoroacetate (259a)



To a solution of *O*-*tert*-butyl azetidine-1-carbothioate (**212**) (45 mg, 0.26 mmol) in CH_2Cl_2 (0.5 ml) at rt was added TFA (50 µl, 1.07 mmol). The reaction mixture was stirred for 30 min at rt, then concentrated under reduced pressure to give a grey liquid, azetidine salt **259a** (44 mg, quant).

IR (neat/cm^{-1}) 2993 br, 2682 w, 2361 w, 1672 s, 1178 s, 1127 s, 836 w, 799 w, 721 w; δ_H (500 MHz, $CDCl_3$) 9.49 (2H, br s, NH_2), 4.13–4.08 (4H, m, NCH_2 × 2), 2.56 (2H, quin, *J* = 8.4 Hz, NCH_2CH_2); δ_C (125 MHz, $CDCl_3$) 162.1 (q, *J* = 35 Hz, C=O), 116.5 (Q, *J* = 292 Hz, CF_3), 46.2 (NCH_2 × 2), 18.7 (NCH_2CH_2); δ_F (470 MHz, $CDCl_3$) −75.9.

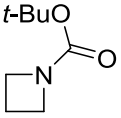
Azetidinium chloride (259b)



HCl (2 M in Et_2O, 577 µL, 1.15 mmol) was added to *O*-*tert*-butyl azetidine-1-carbothioate (**212**) (50 mg, 0.29 mmol) at rt. The reaction mixture was stirred for 1 h at rt, then concentrated under reduced pressure to give a white solid, azetidine salt **259b**[51] (27 mg, quant).

IR (neat/cm^{-1}) 3386 br, 2928 s, 2644 m, 2394 w, 1639 w, 1449 m, 1317 s, 1254 m, 952 w, 909 m; δ_H (400 MHz, D_2O) 4.08 (4H, t, *J* = 8.4 Hz, NCH_2), 2.50 (2H, quin, *J* = 8.3 Hz, NCH_2CH_2); δ_C (100 MHz, D_2O) 46.8 (NCH_2), 18.4 (NCH_2CH_2).

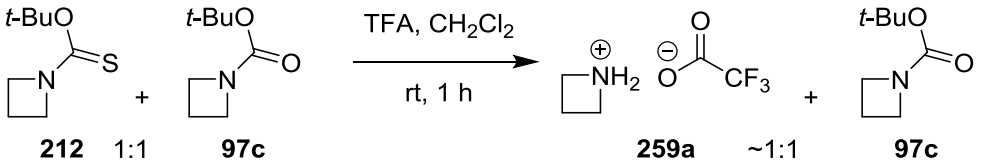
***tert*-Butyl azetidine-1-carboxylate (97c)**



Prepared by analogy to a literature[169] procedure for *N*-Boc-pyrrolidine. Boc_2O (0.57 mL, 2.5 mmol) was added dropwise to an ice-cold, stirred solution of azetidine (0.17 mL, 2.5 mmol) and Et_3N (0.70 mL, 5 mmol) in CH_2Cl_2 (10 mL) and the reaction mixture was stirred overnight, warming to rt. After quenching with aq HCl (1 M, 5 mL) and partitioning, the aq layer was extracted with CH_2Cl_2 (3 x 15 mL) and the combined organic layers washed with H_2O (30 mL) and brine (30 mL), dried (Na_2SO_4) and concentrated under reduced pressure. Purification of the pale yellow oil (SiO_2, 50% Et_2O/petroleum ether) gave a colourless oil, *N*-Boc-azetidine **97c**[253] (376 mg, 96%).

R_f 0.3 (20% Et_2O/petroleum ether); IR (neat/cm-1) 2975 m, 2888 w, 1698 br, 1479 w, 1455 w, 1390 s, 1365 s, 1304 w, 1180 m, 1132 s, 966 w; δ_H (400 MHz, $CDCl_3$) 3.94 (4H, t, J = 7.6 Hz, NCH_2), 2.17 (2H, quin, J = 7.6 Hz, NCH_2CH_2), 1.43 (9H, s, $C(CH_3)_3$); δ_C (100 MHz, $CDCl_3$) 156.3 (C=O), 79.1 $C(CH_3)_3$), 49.2 (br, NCH_2), 28.4 ($C(CH_3)_3$), 15.3 (CH_2); LRMS (ESI^+) 180.1 ($[M+Na]^+$, 100%).

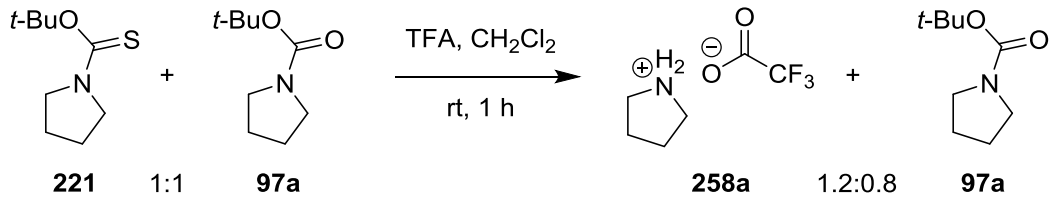
Selective deprotection of *N*-Botc-azetidine 212 in the presence of *N*-Boc-azetidine 97c



212 1:1 **97c** **259a** ~1:1 **97c**

To a solution of *O-tert*-butyl azetidine-1-carbothioate (**212**) (22 mg, 0.13 mmol) and *tert*-butyl azetidine-1-carboxylate (**97c**) (20 mg, 0.13 mmol) in CH_2Cl_2 (0.5 ml) at rt was added TFA (29 µl, 0.38 mmol). The reaction mixture was stirred for 1 h at rt, then concentrated under reduced pressure to give a colourless oil (43 mg). ^1H NMR analysis (400 MHz, $CDCl_3$, see Appendix, p A1) indicated a 1.02:0.98 ratio of azetidine salt **259a** and *N*-Boc-azetidine **97c**.

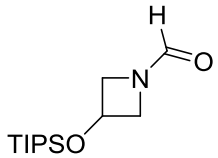
Selective deprotection of *N*-Botc-pyrrolidine 221 in the presence of *N*-Boc-pyrrolidine 97a



221 1:1 **97a** **258a** 1.2:0.8 **97a**

To a solution of *O-tert*-butyl pyrrolidine-1-carbothioate (**221**) (50 mg, 0.27 mmol) and *tert*-butyl pyrrolidine-1-carboxylate (**97a**)[169] (46 mg, 0.27 mmol) in CH_2Cl_2 (1 ml) at rt was added TFA (41 µl, 0.53 mmol). The reaction mixture was stirred for 1 h at rt, then concentrated under reduced pressure to give a colourless oil (93 mg). ^{1}H NMR analysis (400 MHz, $CDCl_3$, see Appendix, p A2) indicated a 1.2:0.8 ratio of pyrrolidine salt **258a** and *N*-Boc-pyrrolidine **97a**.

3-((Triisopropylsilyl)oxy)azetidine-1-carbaldehyde (E1)

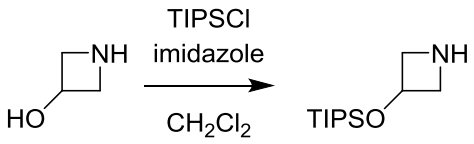


A suspension of 3-hydroxyazetidine hydrochloride (250 mg, 2.28 mmol) and imidazole (932 mg, 13.7 mmol) in DMF (3 mL) was stirred at rt for 10 min before the addition of TIPSCl (1.1 mL, 5.1 mmol). The reaction was stirred at rt for a further 3 d before addition of H_2O (60 mL), followed by Et_2O (60 mL). The mixture was partitioned and the aq layer was extracted with E_2O (60 mL) and brine (6 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Purification of the resulting pale brown oil (SiO_2, 10–100% EtOAc/petroleum ether) gave a brown oil, *N*-formylated azetidine **E1** (381 mg, 65%).

R_f 0.47 (EtOAc); IR (neat/cm^{-1}) 2943 w, 2867 w, 1672 s, 1464 m, 1419 m, 1366 m, 1250 w, 1184 m, 1137 s, 1069 m, 1014 w, 994 w, 882 m, 787 m; δ_H (400 MHz, $CDCl_3$) 8.01

(1H, br s, HC=O), 4.79–4.73 (1H, m, OCH), 4.35–4.31 (1H, m NC*H*H′), 4.26–4.22 (1H, m, NC*H*H′), 3.98 (1H, dd, *J* = 8.8, 4.6 Hz, NCH*H*′), 3.83 (1H, dd, *J* = 10.4, 4.8 Hz, NCH*H*′), 1.12–0.97 (21 H, m, SiCH × 3, CH_3 × 6); δ_C (100 MHz, $CDCl_3$) 162.0 (C=O), 63.0 (OCH), 58.5 (NCH_2), 57.5 (NCH_2), 17.7 (CH_3), 11.7 (SiCH); HRMS (ESI^+) calcd for $C_{13}H_{28}NO_2Si$: 258.1884, found 258.1879.

3-((Triisopropylsilyl)oxy)azetidine (266)



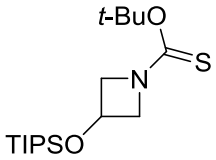
265 **266** (81%)

A suspension of 3-hydroxyazetidine hydrochloride (250 mg, 2.28 mmol) and imidazole (932 mg, 13.7 mmol) in CH_2Cl_2 (3 mL) was stirred at rt for 10 min before the addition of TIPSCl (1.1 mL, 5.1 mmol). The reaction was stirred at rt for a further 48 h before addition of H_2O (6 mL), followed by aq NaOH (6 M, 2 mL). The mixture was partitioned and the organic layer was washed with H_2O (2 × 6 mL) and brine (6 mL). The aq extracts were then re-extracted with CH_2Cl_2 (2 × 6 mL) and the combined organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure. HCl (2 M in Et_2O, 3 mL) was added to the resulting pale yellow liquid and the mixture was stirred at rt for 1 h before addition of H_2O (6 mL). The mixture was partitioned and the organic layer was extracted with H_2O (2 × 6 mL). The combined aq extracts were basified by addition of aq NaOH (6 M) until pH paper indicated ~pH 10, then extracted with Et_2O (3 × 10 mL), dried (Na_2SO_4) and concentrated under reduced pressure to give a colourless oil, TIPS-protected 3-hydroxyazetidine **266** (425 mg, 81%).

R_f 0.49 (1% Et_3N/20% MeOH/petroleum ether); IR (neat/cm^{-1}) 2943 m, 2866 m, 1739 w, 1542 w, 1463 m, 1383 s, 1169 s, 1126 m, 1013 w, 994 w, 863 s, 682 m; δ_H (400 MHz,

$CDCl_3$) 4.66 (1H, quin, *J* = 6.5 Hz, OCH), 3.66–3.56 (4H, m, NCH_2), 2.06 (1H, br s, NH), 1.05–1.00 (21 H, m, SiCH × 3, CH_3 × 6); δ_C (100 MHz, $CDCl_3$) 66.3 (OCH), 58.0 (NCH_2), 17.8 (CH_3), 11.8 (SiCH); HRMS (ESI^+) calcd for $C_{12}H_{28}NOSi$: 230.1935, found 230.1931.

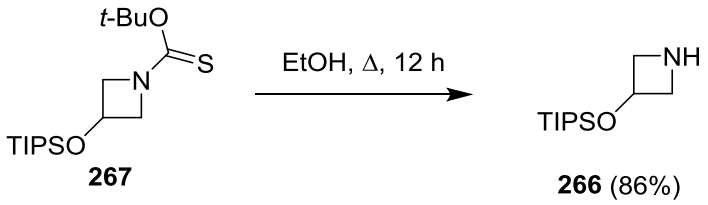
_O_-(_tert_-Butyl) 3-((triisopropylsilyl)oxy)azetidine-1-carbothioate (267)



To a mixture of *O-tert*-butyl *S*-methyl carbonodithioate (**203**)[171(a),249] (200 mg, 1.22 mmol) and dimethyl carbonotrithioate (**250**) (15 mg, 0.11 mmol) in pentane (1 mL) at 0 °C (ice-bath) was added 3-((triisopropylsilyl)oxy)azetidine (**266**) (200 mg, 0.87 mmol). The reaction mixture was stirred at 0 °C for 1 h, and then stirred at rt for 1 h. The reaction mixture was concentrated under reduced pressure. Purification of the resulting pale yellow oil (SiO_2, 1–1.5% Et_2O/petroleum ether) gave a colourless oil, azetidine thiocarbamate **267** (196 mg, 65%).

R_f 0.32 (2% Et_2O/petroleum ether); IR (neat/cm^{-1}) 2943 w, 2867 w, 1482 s, 1444 s, 1391 w, 1366 w, 1275 m, 1228 w, 1133 s, 1009 s, 882 s, 683 m; δ_H (400 MHz, $CDCl_3$) 4.58 (1H, tt, *J* = 6.5, 4.3 Hz, OCH), 4.31 (1H, ddd, *J* = 10.7, 6.6, 1.5 Hz, NC*H*H′), 4.19 (1H, ddd, *J* = 10.5, 6.6, 1.5 Hz, NC*H*H′), 3.99–3.95 (1H, m, NCH*H*′), 3.84–3.80 (1H, m, NCH*H*′), 1.63 (9H, s, $C(CH_3)_3$), 1.10–1.00 (21 H, m, SiCH × 3, CH_3 × 6); δ_C (100 MHz, $CDCl_3$) 185.2 (C=S), 84.9 ($C(CH_3)_3$), 62.1 (NCH_2), 60.7 (NCH_2), 60.3 (OCH), 28.3 ($C(CH_3)_3$), 17.7 ($CHCH_3$), 11.7 (SiCH); HRMS (ESI^+) calcd for $C_{17}H_{35}NNaO_2SSi$: 368.2050, found 368.2043.

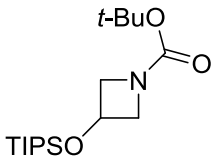
Thermal deprotection of *N*-Botc-azetidine 267



267 **266** (86%)

A solution of *O*-(*tert*-butyl) 3-((triisopropylsilyl)oxy)azetidine-1-carbothioate (**267**) (16 mg, 0.05 mmol) in EtOH (2 mL) was stirred under reflux for 12 h, then concentrated under reduced pressure to give a colourless oil, free amine **266** (86%). Data as p 186–187.

***tert*-Butyl 3-((triisopropylsilyl)oxy)azetidine-1-carboxylate (268)**

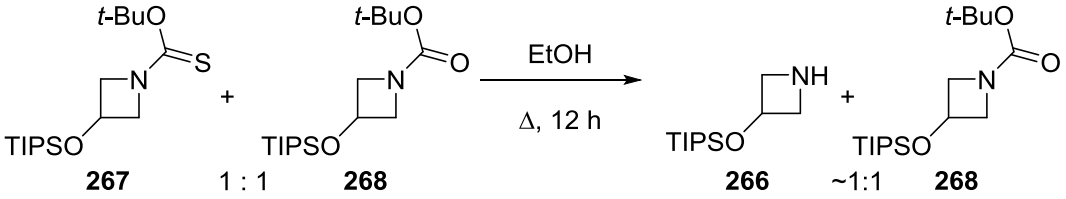


To a solution of di-*tert*-butyl dicarbonate (327 μL, 1.43 mmol) in EtOH (4 mL) at rt was added a solution of 3-((triisopropylsilyl)oxy)azetidine (**266**) (218 mg, 0.95 mmol) in EtOH (4 mL). After 10 min, imidazole (65 mg, 0.95 mmol) was added and after a further 5 min the reaction mixture was concentrated under reduced pressure. $CHCl_3$ (8 mL) was added and the mixture was washed with 1% aq HCl (2 × 8 mL, 0 °C) with cooling (ice-bath). The organic phase was dried ($MgSO_4$) and concentrated under reduced pressure. Purification of the resulting pale yellow oil (SiO_2, 5–10% Et_2O/petroleum ether) gave a colourless oil, Boc-protected-azetidine **268** (290 mg, 93%).

R_f 0.24 (5% Et_2O/petroleum ether); IR (neat/cm^{-1}) 2944 m, 2867 m, 1707 s, 1463 m, 1402 s, 1366 m, 1251 w, 1123 m, 1064 s, 1014 s, 948 w, 883 s, 773 w, 680 m; δ_H (400 MHz, $CDCl_3$) 4.60 (1H, tt, *J* = 6.6, 4.7 Hz, OCH), 4.11–4.07 (2H, m, NC*H*H′), 3.79 (2H, dd, *J* = 9.5, 4.6 Hz, NCH*H*′), 1.43 (9H, s, $C(CH_3)_3$), 1.07–1.00 (21 H, m, SiCH × 3, CH_3 × 6); δ_C (125 MHz, $CDCl_3$) 156.4 (C=O), 79.3 ($C(CH_3)_3$), 61.6 (OCH), 59.5 (NCH_2), 28.4

($C(CH_3)_3$), 17.7 ($CHCH_3$), 11.8 (SiCH); HRMS (ESI^+) calcd for $C_{17}H_{35}NNaO_3Si$: 352.2278, found 352.2268.

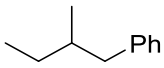
Selective thermal deprotection of *O*-(*tert*-Butyl) 3-((triisopropylsilyl)oxy)azetidine-1-carbothioate (267) in the presence of *tert*-Butyl 3-((triisopropylsilyl)oxy)azetidine-1-carboxylate (268)



267 1 : 1 **268** **266** ~1:1 **268**

A solution of *O*-(*tert*-butyl) 3-((triisopropylsilyl)oxy)azetidine-1-carbothioate (**267**) (30 mg, 0.087 mmol) and *tert*-butyl 3-((triisopropylsilyl)oxy)azetidine-1-carboxylate (**268**) (29 mg, 0.088 mmol) in EtOH (4 mL) was heated at reflux for 12 h. The reaction mixture was concentrated under reduced pressure to give a colourless oil (48 mg). ^{1}H NMR analysis (400 MHz, $CDCl_3$, see Appendix, p A2) indicated a ~1:1 mixture of free amine **266** and *N*-Boc-azetidine **268**.

(2-Methylbutyl)benzene (270)

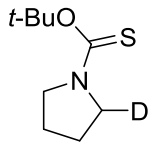


A solution of *O*-*tert*-butyl pyrrolidine-1-carbothioate **221** (179 mg, 0.96 mmol) in Et_2O (6 mL) was cooled to −78 °C (acetone/dry-ice) before the addition of TMEDA (343 µL, 2.29 mmol). *s*-BuLi (1.3 M in cyclohexane/ hexane, 2.61 mL, 1.43 mmol) was then added dropwise over 3 min. The reaction mixture was stirred for 30 min at −78 °C before the addition of BnBr (341 µL, 2.87 mmol). The reaction mixture was stirred for a further 10 min at −78 °C, warmed to rt, stirred at rt for 22 h, then quenched with sat. aq NH_4Cl (10 mL), and extracted with Et_2O (4 × 10 mL). The combined organic extracts were washed

with water (20 mL) and brine (20 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Purification of the resulting brown oil (SiO_2, 0–10% Et_2O/petroleum ether) gave a colourless oil, (2-methylbutyl)benzene (**270**)[200] (73 mg, 34% yield based on *s*-BuLi).

(5% Et_2O/petroleum ether); δ_H (400 MHz, $CDCl_3$) 7.31–7.09 (5H, m, Ar), 2.66 (1H, dd, *J* = 13.4, 6.1 Hz, C*H*H′Ph), 2.39 (1H, dd, *J* = 13.4, 8.1 Hz, CH*H*′Ph), 1.73–1.58 (1H, m, C*H*CH_3), 1.47–1.37 (1H, m, C*H*H′CH_3), 1.26–1.14 (1H, m, CH*H*′CH_3), 0.93 (3H, t, *J* = 7.4 Hz, CH_2CH_3), 0.87 (3H, t, *J* = 6.7 Hz, $CHCH_3$); δ_C (100 MHz, $CDCl_3$) 141.7 (Ar), 129.2 (Ar), 126.0 (Ar), 125.5 (Ar), 43.3 (CH_2Ph), 36.7 (C*H*CH_3), 29.2 (CH_2CH_3), 18.9 ($CHCH_3$), 11.5 (CH_2CH_3). All data is in good agreement with the literature.[200]

O-tert-Butyl (2-$^2H_1$)pyrrolidine-1-carbothioate (269c)



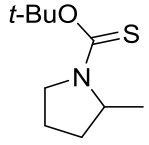
A solution of *O-tert*-butyl pyrrolidine-1-carbothioate (**221**) (50 mg, 0.27 mmol) in Et_2O (2 mL) was cooled to −78 °C (acetone/dry-ice) before the addition of TMEDA (96 µL, 0.64 mmol). *s*-BuLi (1.3 M in cyclohexane/hexane, 267 µL, 0.35 mmol) was then added dropwise over 3 min. The reaction mixture was stirred for 30 min at −78 °C before the addition of CD_3OD (0.78 mL, 19.23 mmol). The reaction mixture was stirred for a further 10 min at −78 °C, warmed to rt, stirred at rt for 10 min, then quenched with sat. aq NH_4Cl (10 mL), and extracted with Et_2O (4 × 5 mL). The combined organic extracts were washed with water (10 mL) and brine (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Purification of the resulting colourless oil (SiO_2, 0–10% Et_2O/petroleum ether) gave a colourless oil, deuterated pyrrolidine **269c** (50 mg, 100% mass recovery, 98% D by FI HRMS analysis).

R_f 0.5 (5% EtOAc/petroleum ether); IR (neat/cm^{-1}) 2973 m, 2877 w, 1436 br, 1390 m, 1364 m, 1331 m, 1265 s, 1227 w, 1140 s, 999 w, 935 w, 832 m; δ_H (400 MHz, $CDCl_3$) 3.69–3.43 (3H, m, NCH_2 and NCHD), 1.94–1.87 (4H, m, $(CH_2)_2$), 1.67 (9H, s, $C(CH_3)_3$); δ_C (100 MHz, $CDCl_3$) (rotamer mixture) 183.3 (C=S), 84.8 ($C(CH_3)_3$), 51.2 (48.3) (NCH_2), 50.9 (48.0) (T, J = 22.0 Hz, NCHD), 28.5 ($C(CH_3)_3$), 25.6 (25.5) (NCH_2CH_2), 24.6 (24.5) ($CHDCH_2$); HRMS (FI^+) calcd for $C_9DH_{16}NOS$: 188.1094, found 188.1092.

General Procedure A: α-deprotonation–electrophile trapping of *O-tert*-butyl pyrrolidine-1-carbothioate (221)

A solution of *O-tert*-butyl pyrrolidine-1-carbothioate (**221**) (1 equiv) in Et_2O (7.4 mL/mmol **221**) was cooled to −78 °C (acetone/dry-ice) before the addition of TMEDA (1.3 equiv). *s*-BuLi (1.3 M in cyclohexane/hexane, 1.3 equiv) was then added dropwise (~100 μL/min). The reaction mixture was stirred for 30 min at −78 °C before the addition of the electrophile (3 equiv). The reaction mixture was stirred for the time and at the temperature described below, then quenched with sat. aq NH_4Cl (10 mL), and extracted with Et_2O (4 × 10 mL). The combined organic extracts were washed with water (20 mL) and brine (20 mL), dried ($MgSO_4$) and concentrated under reduced pressure.

***O-tert*-Butyl 2-methylpyrrolidine-1-carbothioate (269b)**

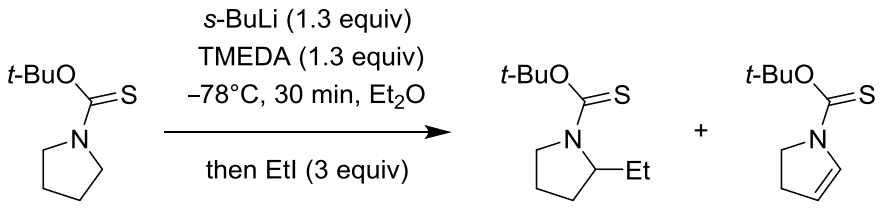


O-tert-Butyl pyrrolidine-1-carbothioate (**221**) (150 mg, 0.80 mmol) and MeI (156 μL, 1.04 mmol) were used following General Procedure A, with stirring following electrophile addition for 10 min at −78 °C, warming to rt over 10 min, then stirring at rt for a further 15

min. Purification of the resulting pale brown oil (SiO_2, 1–2% Et_2O/petroleum ether) gave a colourless oil, methylated pyrrolidine **269b** (109 mg, 68%).

R_f 0.57 (10% Et_2O/petroleum ether); IR (neat/cm^{-1}) 2971 s, 2928 m, 1429 b, 1390 m, 1365 m, 1324 m, 1260 s, 1146 b, 962 w, 840 w; δ_H (400 MHz, $CDCl_3$) (2.4:1 rotamer mixture by analysis of NCH signals in the 4.54–4.12 region) 4.18–4.12 (4.54–4.51) (1H, m, NC*H*), 3.77–3.60 (3.54–3.40) (2H, m, NCH_2), 2.08–1.83 (4H, m, CH_2), 1.65 (1.67) (9H, s, $C(CH_3)_3$), 1.17 (1.30) (3H, d, *J*= 6.3 Hz, NCHCH_3); δ_C (100 MHz, $CDCl_3$) (rotamer mixture) 183.2 (183.1) (C=S), 84.7 (84.6) (*C*$(CH_3)_3$), 57.1 (55.3) (NCH), 51.4 (48.3) (NCH_2), 32.8 (31.5) (NCH*C*H_2), 28.6 (28.5) (C(*C*$H_3)_3$), 23.2 (22.3) (NCH_2CH_2), 19.5 (18.1) (NCH*C*H_3); HRMS (FI^+) calcd for $C_{10}H_{19}NOS$: 201.1187, found 201.1192.

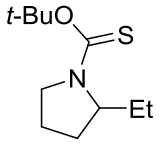
Synthesis of *O*-*tert*-butyl 2-ethylpyrrolidine-1-carbothioate (269d) and side-product *O*-(*tert*-butyl) 2,3-dihydro-1*H*-pyrrole-1-carbothioate (271)



221 **269d** (25%) **271** (25%)

O-*tert*-Butyl pyrrolidine-1-carbothioate (**221**) (100 mg, 0.53 mmol) and EtI (129 µL, 1.60 mmol) were used following General Procedure A, with stirring following electrophile addition for 10 min at −78 °C, warming to rt over 10 min, then stirring at rt for a further 15 min. Attempted purification of the resulting brown oil (SiO_2, 2–5% Et_2O/petroleum ether) gave a colourless oil, an inseparable mixture of ethylated pyrrolidine **269d** (29 mg, 25%) and enamine **271** (25 mg, 25%).

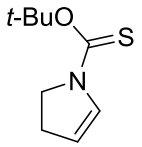
O-tert-Butyl 2-ethylpyrrolidine-1-carbothioate (269d)



Discernible characterisation data:

R_f 0.46 (5% EtOAc/petroleum ether); δ_H (400 MHz, $CDCl_3$) (3.7:1 rotamer mixture by analysis of NCH signals in the 4.27–3.88 region) 3.93–3.88 (4.27–4.22) (1H, m, NCH), (3.69–3.66) (3.47–3.43) (1H, m, NCH_2), 1.98–1.25 (6H, m, $NCH(CH_2)_2$ and CH_3CH_2), 1.66 (1.67) (9H, s, $C(CH_3)_3$), 0.87 (0.89) (3H, t, J = 7.5 Hz, CH_2CH_3); δ_C (100 MHz, $CDCl_3$) (rotamer mixture) 183.2 (C=S), 84.7 (84.6) ($C(CH_3)_3$), 61.2 (NCH), 51.4 (48.4) (NCH_2), 30.1 (29.5) ($NCHCH_2$), 28.5 ($C(CH_3)_3$), 27.9 (26.2) (CH_3CH_2), 24.3 (22.3) (NCH_2CH_2), 10.8 (10.7) (CH_2CH_3); HRMS (ESI^+) calcd for $C_{11}H_{21}NNaOS$: 238.1236, found 238.1232.

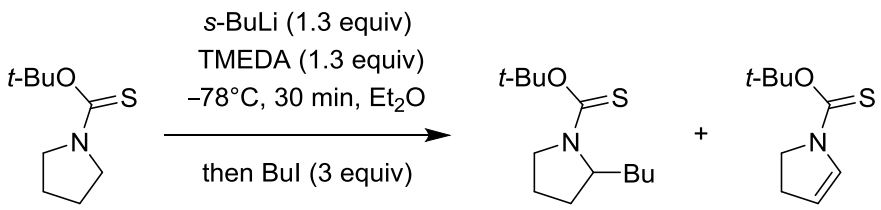
_O_-(_tert_-Butyl) 2,3-dihydro-1_H_-pyrrole-1-carbothioate (271)



Discernible characterisation data:

δ_H (400 MHz, $CDCl_3$) (2.2:1 rotamer mixture by analysis of NCH signals in the 7.26–6.77 region) 6.79–6.77 (7.26–7.24) (1H, m, NCH), 5.32–5.29 (5.38–5.36) (1H, m, NCH=C_H_), 4.04–3.99 (3.84–3.80) (2H, m, NCH_2), 2.67–2.62 (2.74–2.68) (2H, m, NCH_2CH_2), 1.66 (1.65) (9H, s, $C(CH_3)_3$).

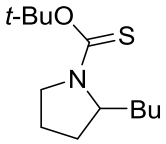
Synthesis of *O*-*tert*-butyl 2-butylpyrrolidine-1-carbothioate (269e) and side-product *O*-(*tert*-butyl) 2,3-dihydro-1*H*-pyrrole-1-carbothioate (271)



221 **269e** (21%) **271** (20%)

O-*tert*-Butyl pyrrolidine-1-carbothioate (**221**) (150 mg, 0.80 mmol) and BuI (273 µL, 2.40 mmol) were used following General Procedure A, with stirring following electrophile addition for 10 min at −78 °C, warming to rt over 10 min, then stirring at rt for a further 4 h. Attempted purification of the resulting dark brown oil (SiO_2, 2% Et_2O/petroleum ether) gave a pale yellow oil, an inseparable mixture of butylated pyrrolidine **269e** (40 mg, 21%) and enamine **271** (29 mg, 20%).

***O*-*tert*-Butyl 2-butylpyrrolidine-1-carbothioate (269e)**

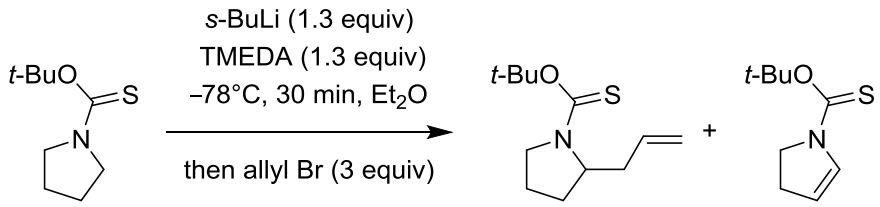


Discernible characterisation data:

R_f 0.67 (5% EtOAc/petroleum ether); δ_H (500 MHz, $CDCl_3$) (2.9:1 rotamer mixture by analysis of NCH_2 signals in the 3.69–3.39 region) 3.99–3.95 (4.33–4.30) (1H, m, NCH), 3.69–3.66 (3.49–3.39) (2H, m, NCH_2), 1.97–1.66 (6H, m, $NCH_2CH_2CH_2$ and $CH_3(CH_2)_2CH_2$), 1.67 (1.66) (9H, s, $C(CH_3)_3$), 1.39-1.20 (4H, m, $CH_3(CH_2)_2$), 0.90 (3H, t, J = 6.9 Hz, CH_3CH_2); δ_C (100 MHz, $CDCl_3$) (rotamer mixture) 183.1 (C=S), 84.7 (84.5) ($C(CH_3)_3$), 59.9 (61.7) (NCH), 51.3 (50.0) (NCH_2), 33.0 (31.1) ($NCH_2CH_2CH_2$), 30.0

(28.4) ($CH_3(CH_2)_2CH_2$), 30.0 (28.5) ($C(CH_3)_3$), 22.6 (NCH_2CH_2), 22.3 (CH_3CH_2), 14.1 (CH_3CH_2); HRMS (FI^+) calcd for $C_{13}H_{25}NOS$: 243.1657, found 243.1667.

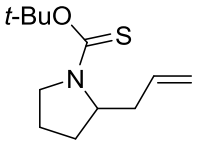
Synthesis of *O*-*tert*-butyl 2-allylpyrrolidine-1-carbothioate (269f) and side-product *O*-(*tert*-butyl) 2,3-dihydro-1*H*-pyrrole-1-carbothioate (271)



221 **269f** (34%) **271** (7%)

O-*tert*-Butyl pyrrolidine-1-carbothioate (**221**) (150 mg, 0.80 mmol) and allyl Br (208 µL, 2.40 mmol) were used following General Procedure A, with stirring following electrophile addition for 10 min at −78 °C, warming to rt over 10 min, then stirring at rt for a further 4 h. Attempted purification of the resulting brown oil (SiO_2, 2% Et_2O/petroleum ether) gave a pale yellow oil, an inseparable mixture of allylated pyrrolidine **269f** (61 mg, 34%) and enamine **271** (10 mg, 7%).

***O*-*tert*-Butyl 2-allylpyrrolidine-1-carbothioate (269f)**

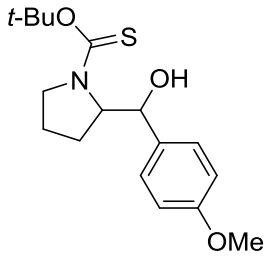


Discernible characterisation data:

R_f 0.63 (5% EtOAc/petroleum ether); δ_H (500 MHz, $CDCl_3$) (2.6:1 rotamer ratio by analysis of CH_2=CHC*H*H′ signals in the 2.91–2.43 region) 5.80–5.66 (1H, m, CH_2=C*H*) 5.10–5.03 (2H, m C*H*$_2$=CH), 4.08–4.04 (4.43–4.40) (1H, m, NCH), 3.72–3.63 (3.50–3.41) (2H, m, NCH_2), 2.48–2.43 (2.91–2.87) (1H, m, CH_2=CHC*H*H'), 2.16–2.07 (1H, m,

CH_2=CHCH*H*'), 1.94–1.81 (4H, m, $(CH_2)_2$), 1.67 (1.65) (9H, s, $C(CH_3)_3$); δ_C (100 MHz, $CDCl_3$) (rotamer mixture) 183.3 (C=S), 134.5 (135.1) (CH_2=*C*H), 117.5 (117.2) (*C*H_2=CH), 84.9 (84.7) (*C*$(CH_3)_3$), 59.1 (60.8) (NCH), 51.5 (48.6) (NCH_2), 37.6 (35.8) (CH_2=CH*C*H_2), 28.5 ($C(CH_3)_3$), 28.4 (28.0) ($N(CH_2)_2CH_2$), 22.2 (23.1) (NCH_2CH_2); HRMS (FI^+) calcd for $C_{12}H_{21}NOS$: 227.1344, found 227.1336.

***O-tert*-Butyl 2-(hydroxy(4-methoxyphenyl)methyl)pyrrolidine-1-carbothioate (269g)**



O-tert-Butyl pyrrolidine-1-carbothioate (**221**) (120 mg, 0.64 mmol) and *p*-anisaldehyde (234 µL, 1.92 mmol) were used following General Procedure A (but with only 1 equiv *s*-BuLi), with stirring following electrophile addition for 10 min at −78 °C, warming to rt over 10 min, then stirring at rt for a further 50 min. Purification of the resulting orange oil (SiO_2, 5–15% Et_2O/petroleum ether) gave first a pale yellow oil, minor diastereomer **269g-minor** (38 mg, 18%), followed by a yellow solid, major diastereomer **269-major** (98 mg, 47%).

Minor diastereomer 269g-minor

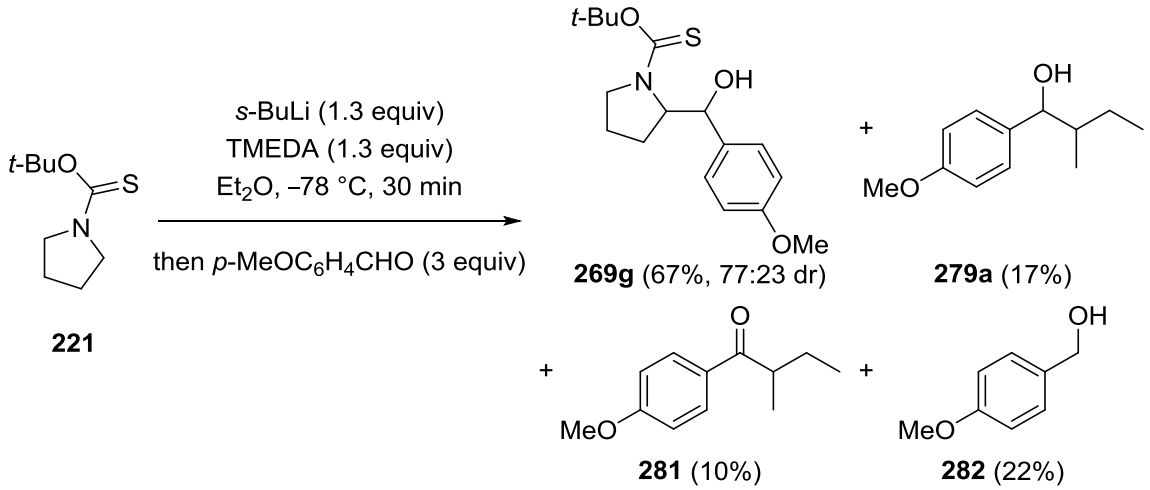
R_f 0.55 (20% EtOAc/petroleum ether); IR (neat/cm^{-1}) 3392 br, 2971 w, 2932 w, 2360 w, 1612 w, 1511 m, 1430 s, 1250 s, 1171 m, 1140 s, 1034 m, 907 w, 834 m, 733 w; δ_H (500 MHz, $CDCl_3$) (1:1 rotamer mixture by analysis of NCH signals in the 4.77–4.22 region) 7.40–6.75 (4H, m, Ar), 5.60–5.59 (5.27–5.26) (1H, m, C*H*OH), 4.77–4.74 (4.25–4.22) (1H, m, NCH), 3.97–3.68 (3.61-3.30) (2H, m, NCH_2), 3.80 (3.75) (3H, s, OCH_3), 2.20-

0.99 (4H, m, $(CH_2)_2$), 1.73 (1.70) (9H, s, $C(CH_3)_3$); δ_C (125 MHz, $CDCl_3$) (rotamer mixture) 185.0 (184.1) (C=S), 158.9 (Ar), 134.0 (133.2) (Ar), 127.2 (126.6) (Ar), 113.8 (113.6) (Ar), 85.7 (85.6) ($C(CH_3)_3$), 74.3 (73.1) (*C*HOH), 66.8 (65.3) (NCH), 55.3 (55.2) (CH_3O), 53.1 (50.1) (NCH_2), 28.7 (28.6) ($C(CH_3)_3$), 25.3 (25.2) ($NCHCH_2$), 23.7 (23.2) (NCH_2CH_2); HRMS (ESI^+) calcd for $C_{17}H_{25}NNaO_3S$: 346.1447, found 346.1440.

Major diastereomer 269g-major

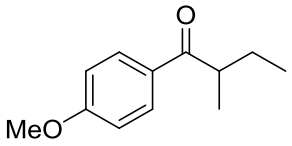
R_f 0.35 (20% EtOAc/petroleum ether); mp 98-100 °C; IR (neat/cm^{-1}) 3392 br, 2974 w, 2930 w, 1585 m, 1429 s, 1248 m, 1143 m, 1002 w, 867 w, 806 w; δ_H (500 MHz, $CDCl_3$) (3:1 rotamer mixture by analysis of NCH signals in the 4.95–4.41 region) 7.36–6.88 (4H, m, Ar), 4.95–4.92 (4.43–4.41) (1H, m, NCH), 4.75–4.73 (4.87–4.86) (1H, m, C*H*OH), 3.82 (3.81) (3H, s, OCH_3), 3.72–3.35 (2H, m, NCH_2), 1.91–1.81 (1.17–1.10) (2H, m, NCH_2CH_2), 1.78–1.62 (2H, m, $NCHCH_2$), 1.70 (1.77) (9H, s, $C(CH_3)_3$); δ_C (125 MHz, $CDCl_3$) (rotamer mixture) 186.4 (184.3) (C=S), 159.3 (159.4) (Ar), 135.0 (132.9) (Ar), 128.2 (127.5) (Ar), 113.8 (113.6) (Ar), 86.3 (86.0) ($C(CH_3)_3$), 77.2 (73.1) (*C*HOH), 66.7 (64.6) (NCH), 55.3 (CH_3O), 49.1 (52.0) (NCH_2), 28.6 ($C(CH_3)_3$), 27.1 (26.4) ($NCHCH_2$), 22.9 (22.1) (NCH_2CH_2); HRMS (FI^+) calcd for $C_{17}H_{25}NO_3S$: 323.1555, found 323.1564.

Synthesis of *O*-*tert*-butyl 2-(hydroxy(4-methoxyphenyl)methyl)pyrrolidine-1-carbothioate (269g) and side-products 279a, 281 and 282



O-*tert*-Butyl pyrrolidine-1-carbothioate (**221**) (150 mg, 0.80 mmol) and *p*-anisaldehyde (292 μL, 2.40 mmol) were used following General Procedure A, with stirring following electrophile addition for 10 min at −78 °C, warming to rt over 10 min, then stirring at rt for a further 50 min. Purification of the resulting orange oil (SiO_2, 5–15% Et_2O/petroleum ether) gave first a colourless oil, ketone side-product **281** (20 mg, 10% based on *s*-BuLi), followed by a thick yellow oil, an inseparable mixture of minor diastereomer **269g-minor** (42 mg, 16%) and side-product **279a** (35 mg, 17% based on *s*-BuLi), followed by a yellow solid, major diastereomer **269g-major** (136 mg, 53%), followed by a yellow oil, side-product **282** (72 mg, 22% based on *p*-anisaldehyde).

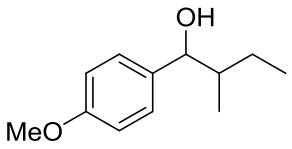
1-(4-Methoxyphenyl)-2-methylbutan-1-one (281)



R_f 0.59 (20% EtOAc/petroleum ether); IR (neat/cm^{-1}) 2966 m, 2934 w, 1672 s, 1600 s, 1510 m, 1461 m, 1308 w, 1256 s, 1222 s, 1176 s, 1155 m, 1032 w, 844 w, 760 w; δ_H (400 MHz, $CDCl_3$) 7.98–7.94 (2H, m, Ar), 6.97–6.93 (2H, m, Ar), 3.88 (3H, s, OCH_3), 3.41–

3.32 (1H, m C*H*CH_3), 1.88–1.77 (1H, m, C*H*H′CH_3), 1.54–1.44 (1H, m CH*H*′CH_3), 1.19–1.17 (3H, m CHC*H*$_3$), 0.92 (3H, td, *J* = 7.3 + 1.0 Hz, CH_2C*H*$_3$); δ_C (125 MHz, $CDCl_3$) 203.0 (C=O), 163.2 (Ar), 130.5 (Ar), 129.8 (Ar), 113.7 (Ar), 55.4 (OCH_3), 41.7 (*C*HCH_3), 28.8 (*C*H_2CH_3), 16.9 (CH*C*H_3), 11.8 (CH_2*C*H_3); LRMS (ESI^+) 193.1 ($[M+H]^+$ 10%), 215.1 ($[M+Na]^+$ 100). ^{1}H NMR data is in good agreement with the literature.[208]

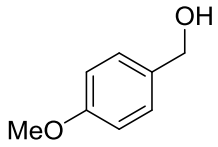
1-(4-Methoxyphenyl)-2-methylbutan-1-ol (279a)



Discernible characterisation data:

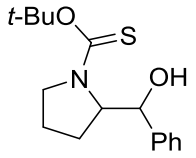
δ_H (500 MHz, $CDCl_3$) (1:1 diastereomer mixture by analysis of the C*H*OH signals at 4.44 and 4.37) 4.44 (4.37) (1H, d, *J* = 6.3 Hz (*J* = 7.3 Hz), C*H*OH), 0.95 (0.72) (3H, d, *J* = 6.9 Hz, CHC*H*$_3$) 0.93 (0.87) (3H, t, *J* = 7.6 Hz, CH_2C*H*$_3$); δ_C (125 MHz, $CDCl_3$) (diastereomer mixture) 136.0 (135.7) (Ar), 78.3 (77.9) (CHOH), 41.6 (41.9) (*C*HCH_3), 25.0 (25.7) (*C*H_2CH_3), 15.0 (14.2) (CH*C*H_3), 11.2 (11.6) (CH_2CH_3).

(4-Methoxyphenyl)methanol (282)



R_f 0.14 (20% EtOAc/petroleum ether); δ_H (400 MHz, $CDCl_3$) 7.27 (2H, d, *J* = 8.6 Hz, Ar), 6.88 (2H, d, *J* = 8.6 Hz, Ar), 4.57 (2H, s, CH_2), 3.79 (3H, s, CH_3), 2.28 (1H, br s, OH); δ_C (100 MHz, $CDCl_3$) 159.0 (Ar), 133.1 (Ar), 128.5 (Ar), 113.8 (Ar), 64.7 (CH_2), 55.2 (CH_3). NMR data is in good agreement with the literature.[209]

O-tert-Butyl 2-(hydroxy(phenyl)methyl)pyrrolidine-1-carbothioate (269h)



O-tert-Butyl pyrrolidine-1-carbothioate (**221**) (120 mg, 0.64 mmol) and benzaldehyde (195 µL, 1.92 mmol) were used following General Procedure A (but with only 1 equiv *s*-BuLi), with stirring following electrophile addition for 10 min at −78 °C, warming to rt over 10 min, then stirring at rt for a further 50 min. Purification of the resulting pale orange oil (SiO_2, 2–20% Et_2O/petroleum ether) gave first a colourless oil, minor diastereomer **269h-minor** (40 mg, 21%), followed by a pale yellow oil, major diastereomer **269h-major** (100 mg, 53%).

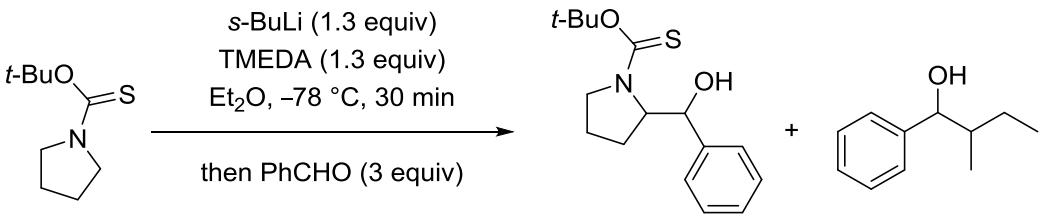
Minor diastereomer 269h-minor

R_f 0.66 (20% EtOAc/petroleum ether); IR (neat/cm^{-1}) 3409 br, 3028 w, 2974 w, 2928 w, 2361 w, 1430 s, 1391 w, 1365 w, 1265 m, 1140 s, 1037 m, 1006 w, 904 w, 702 s; δ_H (500 MHz, $CDCl_3$) (1:1 rotamer mixture by analysis of NCH signals in the 4.79–4.27 region) 7.50–7.25 (5H, m, Ar), 5.72–5.71 (5.35-5.34) (1H, m, C*H*OH), 4.79-4.77 (4.29-4.27) (1H, m, NCH), 3.98–3.71 (3.64-3.33) (2H, m, NCH_2), 2.12–1.24 (4H, m, $(CH_2)_2$), 1.75 (1.71) (9H, s, $C(CH_3)_3$); δ_C (125 MHz, $CDCl_3$) (rotamer mixture) 184.8 (184.1) (C=S), 141.9 (141.2) (Ar), 128.4 (Ar), 127.2 (Ar), 126.0 (Ar), 85.7 (85.5) (*C*$(CH_3)_3$), 74.1 (73.3) (*C*HOH), 66.8 (65.2) (NCH), 53.1 (50.1) (NCH_2), 28.7 (28.6) (C(*C*$H_3)_3$), 25.3 (25.0) (NCH*C*H_2), 23.8 (23.2) (NCH_2*C*H_2); HRMS (ESI^+) calcd for $C_{16}H_{23}NNaO_2S$: 316.1342, found 316.1336.

Major diastereomer 269h-major

R_f 0.46 (20% EtOAc/petroleum ether); IR (neat/cm^{-1}) 3384 br, 3029 w, 2928 w, 1423 s, 1390 m, 1365 w, 1332 w, 1263 s, 1140 s, 1002 m, 976 w, 912 w, 866 w, 702 s; δ_H (500 MHz, $CDCl_3$) (2.4:1 rotamer mixture by analysis of the C*H*OH signals at 4.98 and 4.80) 7.44–7.28 (5H, m, Ar), 4.97–4.94 (4.47–4.43) (1H, m, NCH), 4.98 (4.80) (1H, d, *J* = 8.6 Hz, C*H*OH), 3.71–3.35 (2H, m, NCH_2) 1.93–1.57 (2H, m, NCHC*H*$_2$), 1.88–1.80 (1.13–1.04) (2H, m, NCH_2CH_2), 1.77 (1.71) (9H, s, $C(CH_3)_3$); δ_C (125 MHz, $CDCl_3$) (rotamer mixture) 186.4 (184.3) (C=S), 142.7 (140.9) (Ar), 128.4 (Ar), 127.8 (Ar), 127.1 (Ar), 86.3 (86.0) (*C*$(CH_3)_3$), 77.5 (73.4) (*C*HOH), 66.6 (64.6) (NCH), 49.1 (52.0) (NCH_2), 28.5 (28.6) (C(*C*$H_3)_3$), 27.0 (26.4) (NCH*C*H_2), 22.9 (22.0) (NCH_2CH_2); HRMS (FI^+) calcd for $C_{16}H_{23}NO_2S$: 293.1450, found 293.1454.

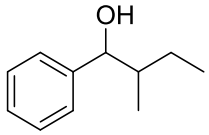
Synthesis of *O-tert*-butyl 2-(hydroxy(phenyl)methyl)pyrrolidine-1-carbothioate (269h) and side-product 2-methyl-1-phenylbutan-1-ol (279b)



221 **269h** (70%, 77:23 dr) **279b** (11%)

O-tert-Butyl pyrrolidine-1-carbothioate (**221**) (150 mg, 0.80 mmol) and benzaldehyde (244 µL, 2.40 mmol) were used following General Procedure A, with stirring following electrophile addition for 10 min at −78 °C, warming to rt over 10 min, then stirring at rt for a further 50 min. Purification of the resulting brown oil (SiO_2, 10–15% Et_2O/petroleum ether) gave first a yellow oil, an inseparable mixture of minor diastereomer **269h-minor** (37 mg, 16%) and side-product **279b** (19 mg, 11% based on *s*-BuLi), followed by a yellow oil, major diastereomer **269h-major** (128 mg, 54%).

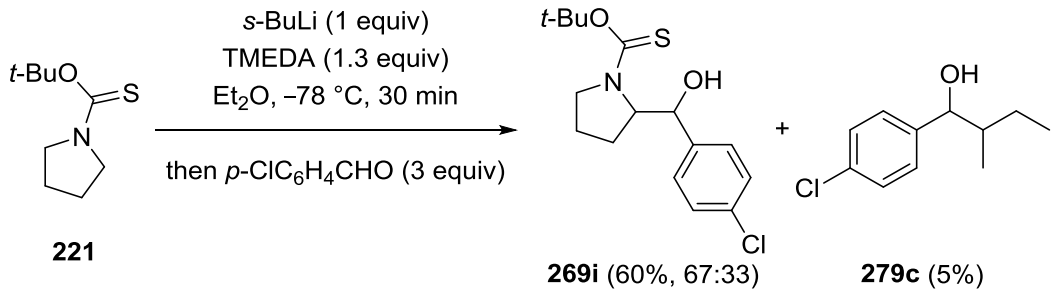
2-Methyl-1-phenylbutan-1-ol (279b)



Discernible characterisation data:

δ_H (500 MHz, $CDCl_3$) (1:1 diastereomer mixture by analysis of the C*H*OH signals at 4.53 and 4.44) 4.53 (4.44) (1H, d, *J* = 6.0 Hz (*J* = 7.3 Hz), C*H*OH), 0.94 (0.89) (3H, t, *J* = 7.3 Hz (*J* = 7.4 Hz), CH_2CH_3), 0.94 (0.75) (3H, d, *J* = 6.6 Hz, $CHCH_3$); δ_C (125 MHz, $CDCl_3$) (diastereomer mixture) 143.8 (143.5) (Ar), 78.7 (78.0) (CHOH), 41.6 (41.9) ($CHCH_3$), 25.8 (25.2) (CH_2CH_3), 15.0 (13.9) ($CHCH_3$), 11.6 (11.3) (CH_2CH_3). NMR data is in good agreement with the literature.[254]

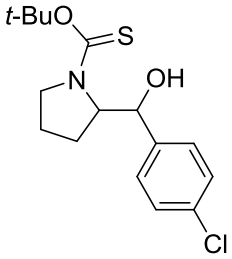
Synthesis of *O-tert*-butyl 2-((4-chlorophenyl)(hydroxy)methyl)pyrrolidine-1-carbothioate (269i) and side-product 1-(4-chlorophenyl)-2-methylbutan-1-ol (279c)



221 **269i** (60%, 67:33) **279c** (5%)

O-tert-Butyl pyrrolidine-1-carbothioate (**221**) (120 mg, 0.64 mmol) and 4-chlorobenzaldehyde (270 µL, 1.92 mmol) were used following General Procedure A (but with only 1 equiv *s*-BuLi), with stirring following electrophile addition for 10 min at −78 °C, warming to rt over 10 min, then stirring at rt for a further 50 min. Purification of the resulting orange oil (SiO_2, 5–20% Et_2O/petroleum ether) gave first a pale yellow oil, an inseparable mixture of minor diastereomer **269i-minor** (42 mg, 20%) and side-product **279c** (7 mg, 5% based on *s*-BuLi), followed by a yellow solid, major diastereomer **269i-major** (85 mg, 40%).

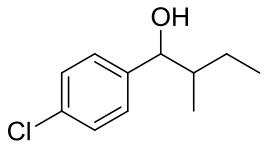
Minor diastereomer 269i-minor



Discernible characterisation data:

R_f 0.73 (20% EtOAc/petroleum ether); IR (neat/cm^{-1}) 1490 s; δ_H (500 MHz, $CDCl_3$) (1.3:1 rotamer mixture ratio by analysis of NCH signals in the 4.71–4.21 region) 7.43–7.22 (4H, m, Ar), 5.68–5.68 (5.29–5.28) (1H, m, C*H*OH), 4.71–4.69 (4.23–4.21) (1H, m, NCH), 3.63–3.58 (3.96–3.91) (1H, m, NC*H*H′), 3.38–3.33 (3.72–3.68) (1H, m, NCH*H*′), 2.08–1.04 (4H, m, NCH_2CH_2 and $NCHCH_2$), 1.70 (1.73) (9H, s, $C(CH_3)_3$); δ_C (125 MHz, $CDCl_3$) (rotamer mixture) 184.9 (184.0) (C=S), 140.4 (139.7) (Ar), 132.9 (Ar), 128.5 (128.3) (Ar), 127.3 (126.7) (Ar), 85.7 (85.9) ($C(CH_3)_3$), 72.4 (73.3) (*C*HOH), 66.7 (65.0) (NCH), 50.1 (53.0) (NCH_2), 28.6 (28.5) ($C(CH_3)_3$), 25.1 (24.8) ($NCHCH_2$), 23.8 (23.2) (NCH_2CH_2); HRMS (FI^+) calcd for $C_{16}H_{22}NO_2ClS$: 327.1060, found 327.1060.

1-(4-Chlorophenyl)-2-methylbutan-1-ol (279c)

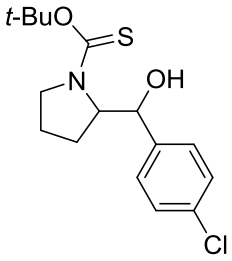


Discernible characterisation data:

δ_H (500 MHz, $CDCl_3$) (1.5:1 diastereomer mixture by analysis of the C*H*OH signals at 4.52 and 4.42) 4.42 (4.52) (1H, d, J = 6.9 Hz (J = 5.7 Hz), C*H*OH), 2.80 (1H, br s, OH), 0.92 (0.89) (3H, t, J = 7.6 Hz (J = 7.3 Hz), CH_2CH_3), 0.73 (0.89) (3H, d, J = 6.9 Hz (J = 6.6 Hz), $CHCH_3$); δ_C (125 MHz, $CDCl_3$) (diastereomer mixture) 141.9 (142.3) (Ar), 78.0

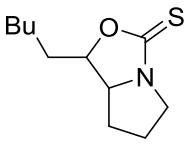
(77.2) (CHOH), 41.9 (41.6) (*C*HCH$_3$), 24.7 (25.7) (*C*H$_2$CH$_3$), 13.8 (14.9) (CH*C*H$_3$), 11.2 (11.6) (CH$_2$CH$_3$). NMR data is in good agreement with the literature.[207]

Major diastereomer 269i-major



R_f 0.51 (20% EtOAc/petroleum ether); mp 103–105 °C; IR (neat/cm^{-1}) 3389 br, 2972 w, 2924, w, 1424 s, 1390 m, 1266 m, 1141 s, 1090 w, 1013 w, 830 m; δ_H (500 MHz, $CDCl_3$) (2:1 rotamer mixture by analysis of C*H*OH signals at 4.98 and 4.81) 7.37–7.21 (4H, m, Ar), 4.81 (4.98) (1H, d, J = 9.1 Hz (J = 6.0 Hz), C*H*OH), 4.91-4.88 (4.42-4.39) (1H, m, NCH), 3.71–2.92 (2H, m, NCH$_2$), 1.88–1.84 (1.12-1.04) (2H, m, NCH$_2$C*H*$_2$), 1.80–1.55 (2H, m, NCHC*H*$_2$), 1.70 (1.76) (9H, s, C(CH$_3$)$_3$); δ_C (125 MHz, $CDCl_3$) (rotamer mixture) 186.5 (184.4) (C=S), 141.3 (139.4) (Ar), 133.6 (133.8) (Ar), 128.6 (Ar), 128.5 (128.4) (Ar), 86.5 (86.1) (*C*(CH$_3$)$_3$), 76.7 (72.7) (*C*HOH), 66.5 (64.5) (NCH), 52.1 (49.1) (NCH$_2$), 28.5 (28.6) (C(*C*H$_3$)$_3$), 26.9 (26.3) (NCH*C*H$_2$), 23.0 (22.1) (NCH$_2$*C*H$_2$); HRMS (ESI$^+$) calcd for $C_{16}H_{22}ClNNaO_2S$: 350.0952, found 350.0939.

1-Pentyltetrahydropyrrolo[1,2-c]oxazole-3(1H)-thione (286a)



O-tert-Butyl pyrrolidine-1-carbothioate (**221**) (150 mg, 0.80 mmol) and hexanal (295 µL, 2.40 mmol) were used following General Procedure A, with stirring following electrophile addition for 10 min at −78 °C, warming to rt over 10 min, then stirring at rt for a further 50

min. Purification of the resulting orange oil (SiO_2, 2–20% Et_2O/petroleum ether) gave first a pale yellow oil, the first diastereomer **286a-first** (65 mg, 38%), followed by a pale yellow oil, the second diastereomer **286a-second** (68 mg, 40%).

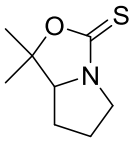
Diastereomer 286a-first

R_f 0.31 (20% EtOAc/petroleum ether); IR (neat/cm^{-1}) 2955 m, 2930 m, 2860 m, 2360 w, 1450 s, 1333 m, 1233 s, 1147 s, 1093 w, 1020 w, 800 w; δ_H (500 MHz, $CDCl_3$) 4.50–4.44 (1H, m, OCH), 3.85–3.74 (1H, m, NCH), 3.80–3.73 (1H, m, NC*H*H′), 3.45–3.38 (1H, m, NCH*H*′), 2.26–2.19 (1H, m, NCH_2CHH'), 2.11–2.03 (1H, m, NCH_2CHH'), 2.11–2.06 (1H, m, NCHC*H*H′), 1.61–1.59 (NCHCH*H*′), 1.92–1.83 (1H, m, OCHC*H*H′), 1.77–1.68 (1H, m, OCHCH*H*′), 1.48–1.26 (6H, m, $CH_3(CH_2)_3$), 0.89–0.85 (3H, m, CH_3); δ_C (125 MHz, $CDCl_3$) 188.9 (C=S), 87.1 (OCH), 68.1 (NCH), 47.1 (NCH_2), 34.1 ($OCHCH_2$), 31.3 ($CH_3CH_2CH_2$), 30.5 ($NCHCH_2$), 26.7 (NCH_2CH_2), 24.3 ($OCHCH_2CH_2$), 22.3 (CH_3CH_2), 13.8 (CH_3); HRMS (ESI^+) calcd for $C_{11}H_{19}NNaOS$: 236.1080, found 236.1079.

Diastereomer 286a-second

R_f 0.29 (20% EtOAc/petroleum ether); IR (neat/cm^{-1}) 2953 m, 2929 m, 2860 w, 1739 s, 1484 m, 1424 s, 1365 s, 1273 s, 1217 s, 1181 m, 1101 w, 906 w; δ_H (500 MHz, $CDCl_3$) 4.84–4.78 (1H, m, OCH), 4.17–4.11 (1H, m, NCH), 3.89–3.81 (1H, m, NC*H*H′), 3.43–3.37 (1H, m, NCH*H*′), 2.20–2.13 (1H, m, NCH_2CHH'), 2.09–1.93 (1H, m, NCH_2CHH'), 1.80–1.52 (4H, m, $NCHCH_2$ and $OCHCH_2$), 1.34–1.23 (6H, m, $CH_3(CH_2)_3$), 0.87–0.83 (3H, m, CH_3); δ_C (125 MHz, $CDCl_3$) 189.8 (C=S), 81.8 (OCH), 65.8 (NCH), 47.7 (NCH_2), 30.4 ($CH_3CH_2CH_2$), 25.6 ($OCHCH_2$), 25.3 ($NCHCH_2$), 24.8 (NCH_2CH_2), 22.2 ($OCHCH_2CH_2$ and CH_3CH_2), 13.8 (CH_3); HRMS (ESI^+) calcd for $C_{11}H_{19}NNaOS$: 236.1080, found 236.1072.

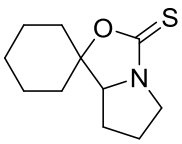
1,1-Dimethyltetrahydropyrrolo[1,2-c]oxazole-3(1H)-thione (286b)



O-tert-Butyl pyrrolidine-1-carbothioate (**221**) (150 mg, 0.80 mmol) and acetone (176 µL, 2.40 mmol) were used following General Procedure A, with stirring following electrophile addition for 10 min at −78 °C, warming to rt over 10 min, then stirring at rt for a further 45 min. Purification of the resulting pale brown oil (SiO_2, 5–20% Et_2O/petroleum ether) gave a pale yellow solid, cyclised product **286b** (70 mg, 51%).

R_f 0.19 (20% EtOAc/petroleum ether); mp 73–75 °C; IR (neat/cm^{-1}) 2975 m, 2957 m, 2886 w, 1495 s, 1460 s, 1448 s, 1370 m, 1326 s, 1292 m, 1264 s, 1230 w, 1134 s, 1096 m, 1045 m, 990 w, 839 m; δ_H (500 MHz, $CDCl_3$) 3.90–3.86 (1H, m, NCH), 3.85–3.81 (1H, m, NC*H*H′), 3.47–3.42 (1H, m, NCH*H*′), 2.27–2.21 (1H, m, NCHC*H*H′), 2.11–2.02 (1H, m, NCHCH*H*′), 1.88–1.82 (1H, m, NCH_2CHH'), 1.67–1.61 (1H, m, NCH_2CHH'), 1.58 (3H, s, CH_3), 1.39 (3H, m, CH_3); δ_C (125 MHz, $CDCl_3$) 188.2 (C=S), 86.8 ($C(CH_3)_3$), 71.8 (NCH), 47.4 (NCH_2), 28.2 (CH_3), 26.6 (NCH), 26.1 (NCH_2CH_2), 22.9 (CH_3); HRMS (ESI^+) calcd for $C_8H_{13}NNaOS$: 194.0610, found 194.0610.

Tetrahydro-3'H-spiro[cyclohexane-1,1'-pyrrolo[1,2-c]oxazole]-3'-thione (286c)

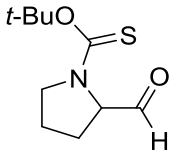


O-tert-Butyl pyrrolidine-1-carbothioate (**221**) (150 mg, 0.80 mmol) and cyclohexanone (249 µL, 2.40 mmol) were used following General Procedure A, with stirring following electrophile addition for 10 min at −78 °C, warming to rt over 10 min, then stirring at rt for

a further 4 h. Purification of the resulting pale brown oil (SiO_2, 5–20% Et_2O/petroleum ether) gave a thick yellow oil, cyclised product **286c** (42 mg, 25%).

R_f 0.13 (20% EtOAc/petroleum ether); IR (neat/cm^{-1}) 2934 m, 2860 w, 2360 w, 1739 w, 1487 m, 1444 s, 1368 w, 1322 m, 1266 s, 1226 s, 1183 s, 1124 m, 1006 w, 916 m, 895 s, 825 w; δ_H (500 MHz, $CDCl_3$) 3.84–3.80 (1H, m, NCH), 3.81–3.77 (1H, m, NC*H*H′), 3.45–3.39 (1H, m, NCH*H*′), 2.26–2.18 (1H, m, NCHC*H*H′), 2.08–2.01 (1H, m, NHCH*H*′), 1.86–1.35 (12H, m, NCH_2CH_2 and $(CH_2)_5$); δ_C (125 MHz, $CDCl_3$) 188.2 (C=S), 88.3 (C_q-CH_2), 71.4 (NCH), 47.1 (NCH_2), 37.6 (C_q-CH_2), 32.1 (C_q-CH_2), 26.2 (NCHCH_2), 25.7 (NCH_2CH_2), 24.6 (C_q-$(CH_2)_2CH_2$), 22.4 (C_q-CH_2CH_2), 22.29 (C_q-CH_2CH_2); HRMS (ESI^+) calcd for $C_{11}H_{17}NNaOS$: 234.0923, found 234.0919.

***O-tert*-Butyl 2-formylpyrrolidine-1-carbothioate (269j)**

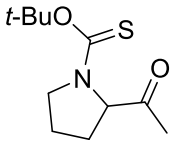


O-tert-Butyl pyrrolidine-1-carbothioate (**221**) (141 mg, 0.75 mmol) and DMF (175 µL, 2.26 mmol) were used following General Procedure A, with stirring following electrophile addition for 10 min at −78 °C, warming to rt over 10 min, then stirring at rt for a further 20 min, resulting in a brown oil, formylated pyrrolidine **269j** (142 mg, 88%).

R_f 0.28 (10% EtOAc/petroleum ether); IR (neat/cm^{-1}) 2976 w, 2881 w, 1728 m, 1424 s, 1391 w, 1366 w, 1337 w, 1277 s, 1142 s; δ_H (400 MHz, $CDCl_3$) (1.1:1 rotamer mixture by analysis of NCH signals in the 4.73–4.27 region) 9.61 (9.45) (1H, d, J = 2.3 Hz, CHO), 4.73–4.68 (4.32–4.27) (1H, m, NCH), 3.93–3.79 (3.69–3.58) (2H, m NCH_2), 2.34–1.89 (4H, m, $(CH_2)_2$), 1.68 (1.62) (9H, s, $C(CH_3)_3$); δ_C (100 MHz, $CDCl_3$) (rotamer mixture) 198.2 (198.7) (CHO), 184.0 (184.9) (C=S), 86.5 (85.9) ($C(CH_3)_3$), 68.2 (66.6) (NCH), 48.9

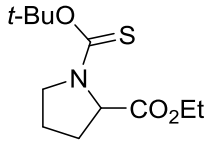
(51.8) (NCH_2), 28.0 (28.2) ($C(CH_3)_3$), 27.8 (27.4) ($NCHCH_2$), 24.4 (23.3) (NCH_2CH_2); HRMS (FI^+) calcd for $C_{10}H_{17}NO_2S$: 215.0980, found 215.0982.

***O-tert*-Butyl 2-acetylpyrrolidine-1-carbothioate (E2)**



O-tert-Butyl pyrrolidine-1-carbothioate (**221**) (120 mg, 0.64 mmol) and *N*,*N*-dimethylacetamide (179 µL, 1.92 mmol) were used following General Procedure A, with stirring following electrophile addition for 10 min at −78 °C, warming to rt over 10 min, then stirring at rt for a further 1 h. Purification of the resulting pale brown oil (SiO_2, 2–20% Et_2O/petroleum ether) gave a thick yellow oil, acetylated pyrrolidine **E2** (3 mg, 2%). R_f 0.15 (5% EtOAc/petroleum ether); IR (neat/cm^{-1}) 2976 w, 2929 w, 2880 w, 1726 m, 1430 s, 1392 w, 1365 w, 1232 m, 1145 s, 988 w, 895 w, 865 w, 807 w; δ_H (500 MHz, $CDCl_3$) (1:1 rotamer mixture by analysis of NCH signals at 4.90 and 4.42) 4.90 (4.42) (1H, dd, J = 9.14, 3.78 Hz (J = 8.83, 4.73 Hz), NCH), 3.94–3.89 (3.86–3.81) (2H, m, NC*H*H′), 3.71–3.67 (3.60–3.55) (2H, m, NCH*H′*), 2.30–2.14 (1.99–1.85) (4H, m, $NCH(CH_2)_2$), 2.26 (2.12) (3H, s, $NCHCOCH_3$) 1.66 (1.61) (9H, s, $C(CH_3)_3$); δ_C (125 MHz, $CDCl_3$) (rotamer mixture) 206.6 (206.0) (C=O), 184.7 (183.8) (C=S), 86.3 (85.6) ($C(CH_3)_3$), 68.8 (67.5) (NCH), 51.9 (49.0) (NCH_2), 29.7 (28.3) ($NCHCH_2$), 28.4 (28.2) ($C(CH_3)_3$), 27.5 (25.5) ($NCHCOCH_3$), 24.1 (23.2) (NCH_2CH_2); HRMS (ESI^+) calcd for $C_{11}H_{19}NNaO_2S$: 252.1029, found 252.1024.

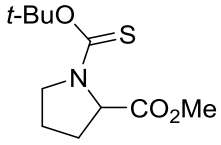
Ethyl 1-(tert-butoxycarbonothioyl)pyrrolidine-2-carboxylate (269k)



O-tert-Butyl pyrrolidine-1-carbothioate (**221**) (150 mg, 0.80 mmol) and ethyl chloroformate (230 µL, 2.40 mmol) were used following General Procedure A, with stirring following electrophile addition for 10 min at −78 °C, warming to rt over 10 min, then stirring at rt for a further 4 h. Purification of the resulting brown oil (SiO_2, 2–5% Et_2O/petroleum ether) gave a colourless oil, ethyl ester **269k** (78 mg, 38%).

R_f 0.55 (20% EtOAc/petroleum ether); IR (neat/cm^{-1}) 2977 w, 1742 m, 1425 s, 1391 w, 1366 w, 1337 w, 1283 br, 1142 s, 1094 w, 1030 w, 842 w, 730 w; δ_H (500 MHz, $CDCl_3$) (1.8:1 rotamer mixture by analysis of NCH signals at 4.76 and 4.40) 4.40 (4.76) (1H, dd, *J* = 8.8, 3.8 Hz (*J* = 9.1, 2.8 Hz), NCH), 4.22–2.14 (2H, m, C*H*$_2$CH$_3$), 3.88–3.84 (3.71–3.66) (1H, m, NC*H*H′), 3.79–3.73 (3.54–3.49) (1H, m, NCH*H*′), 2.31–1.86 (4H, m, $(CH_2)_2$), 1.59 (1.65) (9H, s, $C(CH_3)_3$), 1.27 (3H, t, *J* = 7.3 Hz, CH_2CH_3); δ_C (125 MHz, $CDCl_3$) (rotamer mixture) 183.8 (184.8) (C=S), 171.6 (CO_2), 85.4 (85.8) (*C*$(CH_3)_3$), 60.7 (63.2) (NCH), 61.1 (61.0) (*C*H_2CH_3), 48.7 (51.6) (NCH_2), 30.7 (29.5) (NCH*C*H_2), 28.2 (28.4) (C(*C*$H_3)_3$), 23.2 (24.1) (NCH_2CH_2), 14.2 (14.1) (CH_2CH_3); HRMS (ESI^+) calcd for $C_{12}H_{21}NNaO_3S$: 282.1134, found 282.1131.

Methyl 1-(tert-butoxycarbonothioyl)pyrrolidine-2-carboxylate (269l)

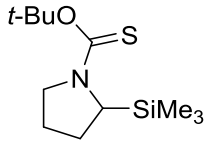


O-tert-Butyl pyrrolidine-1-carbothioate (**221**) (120 mg, 0.64 mmol) and methyl cyanoformate (153 µL, 1.92 mmol) were used following General Procedure A, with

stirring following electrophile addition for 10 min at −78 °C, warming to rt over 10 min, then stirring at rt for a further 4 h. Purification of the resulting orange oil (SiO_2, 5% EtOAc/petroleum ether) gave a colourless oil, methyl ester **269l** (23 mg, 15%).

R_f 0.59 (20% EtOAc/petroleum ether); IR (neat/cm^{-1}) 2977 br, 2261 w, 2342 w, 1748 m, 1428 w, 1392 s, 1366 w, 1338 w, 1285 br, 1206 w, 1145 m; δ_H (500 MHz, $CDCl_3$) (1.7:1 rotamer mixture by analysis of NCH signals at 4.80 and 4.43) 4.43 (4.80) (1H, dd, J = 8.51, 4.1 Hz (J = 9.14, 2.84 Hz), NCH), 3.90–3.51 (2H, m, NCH_2), 3.73 (3.75) (3H, s, OCH_3), 2.33–1.89 (4H, m, $(CH_2)_2$), 1.60 (1.66) (9H, s, $C(CH_3)_3$); δ_C (125 MHz, $CDCl_3$) (rotamer mixture) 183.9 (184.9) (C=S), 172.2 (172.1) (CO_2), 85.9 (85.6) ($C(CH_3)_3$), 60.7 (63.1) (NCH), 52.1 (52.2) (OCH_3), 51.6 (51.8) (NCH_2), 30.8 (29.6) ($NCHCH_2$), 28.2 (28.4) ($C(CH_3)_3$), 23.3 (24.1) (NCH_2CH_2); HRMS (ESI^+) calcd for $C_{11}H_{19}NNaO_3S$: 268.0978, found 268.0976.

***O-tert*-Butyl 2-(trimethylsilyl)pyrrolidine-1-carbothioate (269m)**

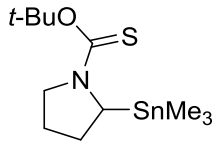


O-tert-Butyl pyrrolidine-1-carbothioate (**221**) (150 mg, 0.80 mmol) and Me_3SiCl (305 µL, 2.40 mmol) were used following General Procedure A, with stirring following electrophile addition for 10 min at −78 °C, warming to rt over 10 min, then stirring at rt for a further 45 min. Purification of the resulting pale brown oil (SiO_2, 2% Et_2O/petroleum ether) gave a colourless oil, silylated pyrrolidine **269m** (153 mg, 74%).

R_f 0.44 (2% EtOAc/petroleum ether); IR (neat/cm^{-1}) 2968 b, 2882 w, 1436 s, 1389 m, 1364 m, 1246 s, 1135 s, 992, w, 957 w, 836 s, 753 m; δ_H (500 MHz, $CDCl_3$) (2.7:1 rotamer mixture by analysis of $Si(CH_3)_3$ signals at −1.7 and −0.9) 3.80 (4.17) (1H, d, J = 9.1 Hz (J = 7.6 Hz), NCH), 3.88–3.82 (3.59–3.54) (1H, m, NC*H*H′), 3.53–3.48 (3.42–3.37) (1H, m,

NCH*H′*), 2.09–2.00 (1.85–1.76) (2H, m, NCHCH_2), 2.00–1.89 (2H, m, NCH_2CH_2), 1.69 (1.63) (9H, s, $C(CH_3)_3$), 0.06 (0.13) (9H, s, $^2J_{29Si-H}$ = 7 Hz, $Si(CH_3)_3$); δ_C (125 MHz, $CDCl_3$) (rotamer mixture) 181.5 (181.8) (C=S), 84.0 (85.0) ($C(CH_3)_3$), 52.1 (52.9) (J_{29Si-C} = 55 Hz (J_{29Si-C} = 59 Hz), NCH), 51.6 (48.4) (NCH_2), 28.7 (28.6) ($C(CH_3)_3$), 27.8 (27.2) (NCH_2CH_2), 24.0 (25.5) ($NCHCH_2$), −1.7 (−0.9) (J_{29Si-C} = 52 Hz, $Si(CH_3)_3$); HRMS (FI^+) calcd for $C_{12}H_{25}NOS^{28}Si$: 259.1426, found 259.1420.

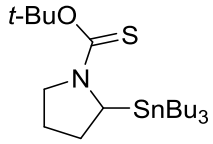
O-tert-Butyl 2-(trimethylstannyl)pyrrolidine-1-carbothioate (269n)



O-tert-Butyl pyrrolidine-1-carbothioate (**221**) (150 mg, 0.80 mmol) and Me_3SnCl (479 mg, 2.40 mmol) were used following General Procedure A, with stirring following electrophile addition for 10 min at −78 °C, warming to rt over 10 min, then stirring at rt for a further 4 h. Purification of the resulting pale brown oil (SiO_2, 1–2% Et_2O/petroleum ether) gave a colourless oil, stannylated pyrrolidine **269n** (193 mg, 69%).

R_f 0.71 (5% EtOAc/petroleum ether); IR (neat/cm^{-1}) 2972 w, 2913 w, 2359 w, 1441 s, 1390 w, 1365 w, 1277 m, 1256 w, 1142 s, 995 w, 765 m; δ_H (500 MHz, $CDCl_3$) (2.7:1 rotamer mixture by analysis of $Sn(CH_3)_3$ signals at 0.14 and 0.12) 4.03–4.00 (1H, m, NCH), 3.74–3.44 (2H, m, NCH_2), 2.33–1.74 (4H, m, $(CH_2)_2$), 1.63 (1.69) (9H, s, $C(CH_3)_3$), 0.12 (0.14) (9H, s, $^2J_{119Sn-H}$ = 52 Hz, $^2J_{117Sn-H}$ = 50 Hz, $Sn(CH_3)_3$); δ_C (125 MHz, $CDCl_3$) (rotamer mixture) 179. 6 (179.5) (C=S), 83.9 (84.9) ($C(CH_3)_3$), 54.4 (52.0) ($J_{119Sn-C}$ = 425 Hz, $J_{117Sn-C}$ = 406 Hz ($J_{119Sn-C}$ = 393 Hz, $J_{117Sn-C}$ = 375 Hz), NCH), 48.7 (51.5) (NCH_2), 29.0 (30.2) ($NCHCH_2$), 28.6 (28.8) ($C(CH_3)_3$), 26.3 (24.8) (NCH_2CH_2), −7.5 (−9.1) ($J_{119Sn-C}$ = 317 Hz, $J_{117Sn-C}$ = 309 Hz ($J_{119Sn-C}$ = 314 Hz, $J_{117Sn-C}$ = 299 Hz), $Sn(CH_3)_3$); HRMS (FI^+) calcd for $C_{12}H_{25}NOS^{120}Sn$: 351.0679, found 351.0674.

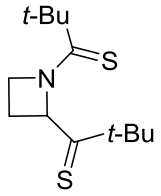
***O-tert*-Butyl 2-(tributylstannyl)pyrrolidine-1-carbothioate (269o)**



O-tert-Butyl pyrrolidine-1-carbothioate (**221**) (100 mg, 0.53 mmol) and Bu_3SnCl (290 µL, 1.07 mmol) were used following General Procedure A, with stirring following electrophile addition for 20 min at −78 °C, warming to rt over 10 min, then stirring at rt for a further 15 min. Purification of the resulting colourless oil (SiO_2, 1–3% Et_2O/petroleum ether) gave a colourless oil, stannylated pyrrolidine **269o** (179 mg, 70%).

R_f 0.71 (5% EtOAc/petroleum ether); IR (neat/cm^{-1}) 2956 m, 2924 m, 2871 w, 2854 w, 1464 m, 1443 s, 1390 w, 1376 w, 1299 m, 1278 w, 1256 w, 1144 s, 1071 w, 996 w, 958 w, 842 w; δ_H (400 MHz, $CDCl_3$) (2.6:1 rotamer mixture by analysis of NCH signals in the 4.11–4.03 region) 4.06–4.03 (4.11–4.08) (1H, m, NCH), 3.48–3.44 (3.67–3.63) (1H, m, NCH_2), 2.05–1.97 (2H, m, NCH_2CH_2), 1.86–1.72 (2.28–2.17) (2H, m, $NCHCH_2$), 1.64 (1.70) (9H, s, $C(CH_3)_3$), 1.58–1.42 (2H, m, $SnCH_2CH_2$), 1.37–1.42 (2H, m, CH_2CH_3), 0.97–0.86 (2H, m, $SnCH_2$), 0.89 (3H, t, J = 7.33, CH_2CH_3); δ_C (100 MHz, $CDCl_3$) (rotamer mixture) 178.9 (179.4) (C=S), 83.8 (84.7) ($C(CH_3)_3$), 54.1 (53.4) (NCH), 48.6 (51.5) (NCH_2), 29.2 (29.0) ($NCHCH_2$), 29.1 (28.8) ($SnCH_2CH_2$), 28.6 ($C(CH_3)_3$), 27.6 (27.5) (CH_2CH_3), 26.6 (25.0) (NCH_2CH_2), 13.7 (12.9) (CH_2CH_3), 11.4 (9.8) ($J_{119Sn-C}$ = 314 Hz, $J_{117Sn-C}$ = 299 Hz ($J_{119Sn-C}$ = 303 Hz, $J_{117Sn-C}$ = 290 Hz), $SnCH_2$); HRMS (FI^+) calcd for $C_{21}H_{43}NOS^{120}Sn$: 477.2087, found 477.2096.

1,1'-(Azetidine-1,2-diyl)bis(2,2-dimethylpropane-1-thione) (287)



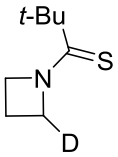
A solution of 1-(azetidin-1-yl)-2,2-dimethylpropane-1-thione (**164**)[148] (160 mg, 1.00 mmol) in Et_2O (6 mL) was cooled to −78 °C (acetone/dry-ice) before the addition of TMEDA (360 µL, 2.4 mmol). *s*-BuLi (1.3 M in cyclohexane/hexane, 920 µL, 1.20 mmol) was then added dropwise over 9 min. The reaction mixture was stirred for 30 min at −78 °C before the addition of CD_3OD (1.0 mL, 24.6 mmol). The reaction mixture was stirred for a further 10 min at −78 °C, warmed to rt, stirred at rt for 10 min, then quenched with aq HCl (1 M, 5 mL), and extracted with Et_2O (4 × 5 mL). The combined organic extracts were washed with water (10 mL) and brine (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Purification of the resulting dark pink oil (SiO_2, 15–20% Et_2O/petroleum ether) gave a pink solid, 2-thiopivaloyl azetidine **287** (51 mg, 39%).

R_f 0.35 (10% EtOAc/petroleum ether); mp 73–75 °C; IR (neat/cm^{-1}) 2965 w, 2923 w, 1464 s, 1450 m, 1428 s, 1362 w, 1330 s, 1231 w, 1194 w, 1115 w, 1005 w, 969 w; δ_H (400 MHz, $CDCl_3$) 6.10 (1H, ddd, J = 10.0, 5.0, 1.5 Hz, NCH), 4.60–4.45 (2H, m, NCH_2), 2.60–2.50 (1H, m, NCH_2CHH'), 1.68–1.81 (1H, m, NCH_2CHH'), 1.39 (9H, s, $NC=SC(CH_3)_3$) 1.36 (9H, s, $CHC=SC(CH_3)_3$); δ_C (125 MHz, $CDCl_3$) 259.1 (CHC=S), 209.1 (NC=S), 74.7 (NCH), 54.9 (NCH_2), 51.5 ($CHC=S\text{-}C_q$), 43.0 ($NC=S\text{-}C_q$), 30.0 ($CHC=SC(CH_3)_3$), 29.7 ($NC=SC(CH_3)_3$), 24.2 (NCH_2CH_2); HRMS (ESI^+) calcd for $C_{13}H_{24}NS_2$: 258.1345, found 258.1351.

General Procedure B: α-deprotonation–electrophile trapping of 1-(azetidin-1-yl)-2,2-dimethylpropane-1-thione (164)

A solution of 1-(azetidin-1-yl)-2,2-dimethylpropane-1-thione (**164**)[148] (1 equiv) in THF (6 mL/mmol **164**) was cooled to −78 °C (acetone/dry-ice) before the addition of TMEDA (2.4 equiv). *s*-BuLi (1.3 M in cyclohexane/hexane, 1.3 equiv) was then added rapidly in 1 portion (1 mL in <2 s). The reaction mixture was stirred for 30 min at −78 °C before the addition of the electrophile (3 equiv). The reaction mixture was stirred for the time and at the temperature described below, then quenched with sat. aq HCl (1 M, 10 mL), and extracted with Et_2O (4 × 10 mL). The combined organic extracts were washed with water (20 mL) and brine (20 mL), dried ($MgSO_4$) and concentrated under reduced pressure.

1-[(2-$^2H_1$)Azetidin-1-yl]-dimethylpropane-1-thione (165f)

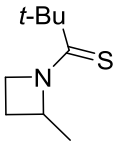


1-(Azetidin-1-yl)-2,2-dimethylpropane-1-thione (**164**)[148] (160 mg, 1.00 mmol) and CD_3OD (1.00 mL, 24.60 mmol) were used following General Procedure B, with stirring following electrophile addition for 10 min at −78 °C, warming to rt over 10 min, then stirring at rt for a further 10 min. Purification of the resulting colourless oil (SiO_2, 5–20% Et_2O/petroleum ether) gave a colourless oil, deuterated azetidine **165f** (119 mg, 74% mass recovery, 100% D by FI HRMS analysis).

R_f 0.18 (10% EtOAc/petroleum ether); δ_H (400 MHz, $CDCl_3$) 4.52–4.23 (3H, m, NCH_2 and NCHD), 2.27 (2H, q, J = 8.0 Hz, NCH_2CH_2), 1.33 (9H, s, $C(CH_3)_3$); δ_C (125 MHz, $CDCl_3$) (rotamer mixture) 209.5 (C=S), 56.9 (56.0) (NCH_2), 56.6 (55.7) (T, J = 23.0 Hz, NCHD), 43.0 ($C(CH_3)_3$), 26.6 ($C(CH_3)_3$), 14.6 (NCH_2CH_2); HRMS (FI^+) calcd for $C_8DH_{14}NS$:

158.0988, found 158.0988; all characterisation data is in good agreement with the literature.[148]

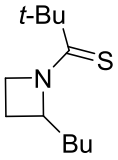
2,2-Dimethyl-1-(2-methylazetidin-1-yl)propane-1-thione (165a)



1-(Azetidin-1-yl)-2,2-dimethylpropane-1-thione (**164**)[148] (160 mg, 1.00 mmol) and MeI (180 μL, 3.0 mmol) were used following General Procedure B, with stirring following electrophile addition for 10 min at −78 °C, warming to rt over 10 min, then stirring at rt for a further 10 min. Purification of the resulting colourless oil (SiO_2, 30% Et_2O/petroleum ether) gave a pale yellow oil, methylated azetidine **165a** (125 mg, 73%).

R_f 0.38 (30% Et_2O/petroleum ether); IR (neat/ cm^{-1}) 2963 w, 2926 w, 1456 s, 1426 s, 1394 w, 1363 m, 1331 w, 1291 w, 1255 m, 1237 w, 1139 m, 994 w, 931 w; δ_H (400 MHz, $CDCl_3$) (6:1 rotamer mixture by analysis of NCHCH_3 signals at 1.64 and 1.60) 4.88–4.79 (1H, m, NC*H*), 4.59–4.51 (1H, m, NC*H*H′), 4.44–4.37 (1H, m, NCH*H*′), 2.56–2.47 (1H, m, C*H*H′), 1.87–1.79 (1H, m, CH*H*′), 1.60 (1.64) (3H, d, J = 6.5 Hz, NCHCH_3), 1.31 (9H, s, C$(CH_3)_3$); δ_C (100 MHz, $CDCl_3$) 209.6 (C=S), 64.7 (NCH), 55.6 (NCH_2), 43.2 ($C(CH_3)_3$), 29.6 (C$(CH_3)_3$), 23.1 (CH_2), 18.4 (CHCH_3); LRMS (ESI^+) 172.1 ($[M+H]^+$ 15%), 194.1 ($[M+Na]^+$ 10), 409.1 (100); all characterisation data is in good agreement with the literature.[148]

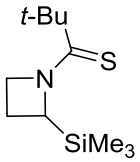
1-(2-Butylazetidin-1-yl)-2,2-dimethylpropane-1-thione (165d)



1-(Azetidin-1-yl)-2,2-dimethylpropane-1-thione (**164**)[148] (160 mg, 1.00 mmol) and BuI (347 µL, 3.0 mmol) were used following General Procedure B, with stirring following electrophile addition for 10 min at −78 °C, warming to rt over 10 min, then stirring at rt for a further 10 min. Purification of the resulting colourless oil (SiO_2, 2–4% Et_2O/petroleum ether) gave a pale yellow oil, butylated azetidine **165d** (238 mg, 71%).

R_f 0.25 (10% Et_2O/petroleum ether); IR (neat/cm^{-1}) 2958 m, 2925 m, 2871 w, 1457 m, 1426 s, 1394 w, 1362 m, 1256 m, 1140 m, 1000 m; δ_H (400 MHz, $CDCl_3$) (10:1 rotamer ratio by analysis of NCH signals in the 4.79–4.64 region) 4.79–4.72 (4.71–4.64) (1H, m, NCH), 4.53–4.46 (4.24–4.18) (1H, m, NC*H*H′), 4.42–4.36 (4.24–4.18) (1H, m, NCH*H*′), 2.51–2.34 (2H, m, C*H*$_2$(CH_2)$_2$$CH_3$), 1.96–1.88 (1H, m, NCH_2C*H*H′), 1.81–1.72 (1H, m, NCH_2CH*H*′), 1.39–1.23 (13H, m, C(CH_3)$_3$) and (C*H*$_2$)$_2$$CH_3$), 0.91 (3H, t, *J* = 7.0 Hz, CH_2C*H*$_3$); δ_C (100 MHz, $CDCl_3$) 209.5 (C=S), 68.7 (NCH), 55.8 (NCH_2), 43.3 (*C*(CH_3)$_3$), 30.2 (*C*H_2(CH_2)$_2$$CH_3$), 29.6 (C(*C*$H_3$)$_3$), 25.7 (*C*$H_2$$CH_3$), 22.5 (*C*$H_2$$CH_2$$CH_3$), 21.1 ($CH_2$), 14.0 ($CH_2$*C*$H_3$); LRMS ($ESI^+$) 214.2 ($[M+H]^+$, 100%); all characterisation data is in good agreement with the literature.[148]

2,2-Dimethyl-1-(2-(trimethylsilyl)azetidin-1-yl)propane-1-thione (165g)



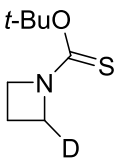
1-(Azetidin-1-yl)-2,2-dimethylpropane-1-thione (**164**)[148] (160 mg, 1.00 mmol) and Me_3SiCl (250 µL, 2.0 mmol) were used following General Procedure B, with stirring following electrophile addition for 20 min at −78 °C, warming to rt over 10 min, then stirring at rt for a further 20 min. Purification of the resulting yellow solid (SiO_2, 10% Et_2O/petroleum ether) gave a white solid, silylated azetidine **165g** (187 mg, 80%).

R_f 0.39 (20% Et_2O/petroleum ether); mp 47–49 °C; lit.[148] mp 48–49 °C; IR (neat/ cm^{-1}) 2966 w, 2946 w, 2896 w, 2870 w, 1485 s, 1472 s, 1442 s, 1392 w, 1362 w, 1243 s, 1194 w, 1135 m, 1110 w, 1019 w, 1001 w, 980 w, 867 m, 835 s, 754 m, 686 w; δ_H (400 MHz, $CDCl_3$) 4.61 (1H, ddd, J = 10.7, 6.3, 2.1 Hz, NCH), 4.52–4.40 (2H, m, NCH_2), 2.46–2.36 (1H, m, NCH_2CHH'), 2.09–2.01 (1H, m, NCH_2CHH'), 1.33 (9H, s, $C(CH_3)_3$), 0.17 (9H, s, $^2J_{29Si\text{-}H}$ = 7 Hz, $Si(CH_3)_3$); δ_C (100 MHz, $CDCl_3$) 206.0 (C=S), 62.1 (NCH), 57.0 (NCH_2), 42.7 ($C(CH_3)_3$), 29.8 ($C(CH_3)_3$), 17.0 (NCH_2CH_2), −1.4 ($Si(CH_3)_3$); LRMS (ESI^+) 230.2 ($[M+H]^+$, 100%); all characterisation data is in good agreement with the lit.[148]

General Procedure C: *α*-deprotonation-electrophile trapping of *O*-*tert*-butyl azetidine-1-carbothioate (212)

A solution of *O*-*tert*-butyl azetidine-1-carbothioate (**212**) (1 equiv) in THF (5 mL/mmol **212**) was cooled to −78 °C (acetone/dry-ice) before the addition of TMEDA (2.4 equiv). *s*-BuLi [1.3 M in cyclohexane/hexane, 1.3 equiv (1 equiv for reactions with aromatic aldehydes)] was then added dropwise (~100 µL/min). The reaction mixture was stirred for 30 min at −78 °C before the addition of the electrophile (3 equiv). The reaction mixture was stirred for the time and at the temperature described below, then quenched with sat. aq NH_4Cl (10 mL), and extracted with Et_2O (4 × 10 mL). The combined organic extracts were washed with water (20 mL) and brine (20 mL), dried ($MgSO_4$) and concentrated under reduced pressure.

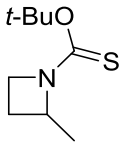
***O*-*tert*-Butyl (2-$^2H_1$)azetidine-1-carbothioate (288a)**



O-tert-Butyl azetidine-1-carbothioate (**212**) (40 mg, 0.23 mmol) and CD_3OD (28 μL, 0.69 mmol) were used following General Procedure C, with stirring following electrophile addition for 60 min at −78 °C, warming to rt over 10 min, then stirring at rt for a further 5 min. Purification of the resulting pale yellow oil (SiO_2, 10% Et_2O/petroleum ether) gave a colourless oil, deuterated azetidine **288a** (36 mg, 90% mass recovery, 95% D by HRMS analysis).

R_f 0.33 (5% EtOAc/petroleum ether); IR (neat/cm^{-1}) 2974 w, 2929 w, 1481 s, 1442 s, 1391 w, 1365 m, 1267 s, 1226 w, 1142 s, 1022 w, 898 w, 736 w; δ_H (500 MHz, $CDCl_3$) 4.12–3.96 (3H, m, NCHD and NCH_2), 2.17–2.13 (2H, m, NCHC*H*$_2$), 1.62 (9H, s, $C(CH_3)_3$); δ_C (125 MHz, $CDCl_3$) (rotamer mixture) 185.0 (C=S), 84.6 (*C*$(CH_3)_3$), 51.7 (50.6) (NCH_2), 51.4 (50.3) (T, J = 22.9 Hz, NCHD), 28.4 (C(*C*$H_3)_3$), 13.8 (13.9) (NCH*C*H_2); HRMS (FI^+) calcd for $C_8H_{14}DNOS$: 174.0937, found 174.0930.

O-tert-Butyl 2-methylazetidine-1-carbothioate (288b)

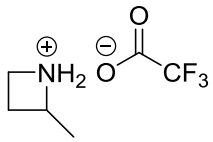


O-tert-Butyl azetidine-1-carbothioate (**212**) (50 mg, 0.29 mmol) and MeI (54 μL, 0.87 mmol) were used following General Procedure C, with stirring following electrophile addition for 10 min at −78 °C and then warmed to rt over 10 min. Purification of the resulting bright yellow oil (SiO_2, 0–5% EtOAc/*n*-hexane) gave a colourless oil, methylated azetidine **288b** (43 mg, 79%).

R_f 0.60 (5% EtOAc/petroleum ether); IR (neat/cm^{-1}) 2968 w, 1739 w, 1479 m, 1436 s, 1391 w, 1366 w, 1274 s, 1142 s; δ_H (500 MHz, $CDCl_3$) (2.5:1 rotamer mixture by analysis of NCH signals in the 4.56–4.34 region) 4.40–4.34 (4.56–4.50) (1H, m, NCH), 4.08–3.90 (2H, m, NCH_2), 2.39–2.28 (1H, m, NCHC*H*H′), 1.79–1.73 (1H, m, NCHCH*H*′), 1.64

(1.63) (9H, s, $C(CH_3)_3$), 1.42 (1.57) (3H, d, J = 6.3 Hz, NCHCH_3); δ_C (125 MHz, $CDCl_3$) (rotamer mixture) 185.3 (185.2) (C=S), 84.7 (84.5) ($C(CH_3)_3$), 59.9 (61.0) (NCH), 48.96 (49.04) (NCH_2), 28.48 (28.50) ($C(CH_3)_3$), 22.4 (22.8) (NCHCH_2), 20.6 (19.7) (NCHCH_3); HRMS (FI^+) calcd for $C_9H_{17}NOS$: 187.1031, found 187.1026.

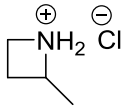
2-Methylazetidinium trifluoroacetate (292a)



To a solution of *O-tert*-butyl 2-methylazetidine-1-carbothioate (**288b**) (60 mg, 0.32 mmol) in CH_2Cl_2 (1 ml) at rt was added TFA (61 µl, 0.80 mmol). The reaction mixture was stirred for 1 h at rt, then concentrated under reduced pressure to give a colourless liquid, 2-methylazetidine salt **292a** (59 mg, quant).

IR (neat/cm^{-1}); 3434 br, 2987 br, 2680 br, 2494 br, 1671 s, 1452 w, 1428 w, 1395 w, 1339 w, 1173 s, 1129 s, 1045 w, 925 w, 835 m, 798 m, 721 m, 706 m; δ_H (400 MHz, $CDCl_3$) 9.26 (1H, br s, NHH′), 9.06 (1H, br s, NHH′), 4.60–4.58 (1H, m, NCH), 4.01–3.91 (2H, m, NCH_2), 2.63–2.55 (1H, m, CHH′), 2.35–2.26 (1H, m, CHH′), 1.54 (3H, d, J = 6.8 Hz, CH_3); δ_C (125 MHz, $CDCl_3$) 161.7 (q, J = 36 Hz, C=O), 116.2 (Q, J = 300 Hz, CF_3), 57.4 (NCH), 42.1 (NCH_2), 26.3 ($NCH_2C H_2$), 19.5 (CH_3); δ_F (377 MHz, $CDCl_3$) −75.9.

2-Methylazetidin-1-ium chloride (292b)

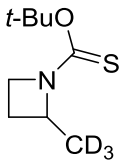


To a solution of *O-tert*-butyl 2-methylazetidine-1-carbothioate (**288b**) (234 mg, 1.25 mmol) in Et_2O (1 ml) was added a solution of HCl in Et_2O (2 M, 1.56 mL, 3.12 mmol).

The reaction mixture was stirred for 1 h at rt, then concentrated under reduced pressure to give salt **292b** as a colourless oil (134 mg, quant).

IR (neat/cm^{-1}) 3384 br, 2971 br, 2361 w, 2342 w, 1738 w, 1635 br, 1449 m, 1391 w, 1366 w, 1317 w, 1253 w, 1136 w, 1317 w, 1253 w, 1136 w, 1092 w, 1040 m, 921 m; δ_H (400 MHz, $CDCl_3$) 9.49 (1H, br s, NH), 4.61 (1H, br s, NC*H*H′), 3.98–3.94 (2H, m, NCH*H′* and C*H*CH_3), 3.06 (1H, br s, NH), 2.56 (1H, br s, NCH_2C*H*H′), 2.30 (1H, br s, NCH_2CH*H′*), 1.63 (3H, s, CH_3); δ_C (101 MHz, $CDCl_3$) 57.3 (*C*HCH_3), 42.1 (NCH_2), 26.2 (CH_2), 19.9 (CH_3).

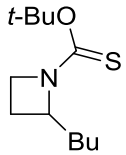
***O-tert*-Butyl 2-(CD_3)azetidine-1-carbothioate (288c)**



O-tert-Butyl azetidine-1-carbothioate (**212**) (70 mg, 0.40 mmol) and CD_3I (75 µL, 1.21 mmol) were used following General Procedure C, with stirring following electrophile addition for 10 min at −78 °C and then warmed to rt over 10 min. Purification of the resulting bright yellow oil (SiO_2, 2–5% EtOAc/*n*-hexane) gave a colourless oil, trapped product **288c** (56 mg, 73%).

R_f 0.28 (5% EtOAc/petroleum ether); IR (neat/cm^{-1}) 2974 br, 2926 w, 1477 m, 1464 m, 1437 s, 1390 w, 1365 w, 1272 s, 1239 w, 1227 w, 1137 s, 989 w, 929 w, 827 w; δ_H (400 MHz, $CDCl_3$) (3:1 rotamer mixture by analysis of NCH signals at 4.50 and 4.34) 4.34 (4.50) (1H, t, *J* = 7.0 Hz, NCH), 4.07–3.87 (2H, m, NCH_2), 2.39–2.26 (2H, m, NCHC*H*H′), 1.78–1.75 (2H, m, NCHCH*H′*), 1.63 (1.62) (9H, s, $C(CH_3)_3$); δ_C (125 MHz, $CDCl_3$) (rotamer mixture) 185.2 (185.1) (C=S), 84.6 (84.4) (*C*$(CH_3)_3$), 59.7 (60.8) (NCH), 48.9 (49.0) (NCH_2), 28.4 (C(*C*$H_3)_3$), 22.2 (22.7) (NCH*C*H_2), 19.7 (18.8) (SEP, *J* = 19.1 Hz, NCH*C*D_3); HRMS (FI^+) calcd for $C_9H_{14}{}^2H_3NOS$: 190.1219, found 190.1223.

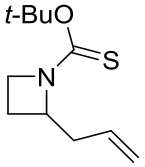
***O-tert*-Butyl 2-butylazetidine-1-carbothioate (288d)**



O-tert-Butyl azetidine-1-carbothioate (**212**) (117 mg, 0.68 mmol) and *n*-BuI (308 µL, 2.71 mmol) were used following General Procedure C, with stirring following electrophile addition for 30 min at −78 °C, warming to rt over 10 min, then stirring at rt for a further 20 min. Purification of the resulting yellow oil (SiO_2, 2–5% Et_2O/petroleum ether) gave a colourless oil, butylated azetidine **288d** (120 mg, 77%).

R_f 0.34 (5% EtOAc/petroleum ether); IR (neat/cm^{-1}) 2959 br, 2928 br, 1478 s, 1465 s, 1435 s, 1390 m, 1365 m, 1274 s, 1244 w, 1140 s, 1013 w, 993 w, 841 w, 735 w; δ_H (500 MHz, $CDCl_3$) (2.6:1 rotamer mixture by analysis of NCH signals in the region 4.45–4.26) 4.32–4.26 (4.45–4.40) (1H, m, NCH), 4.02–3.88 (2H, m, NCH_2), 2.38–2.22 (1H, m, NCH_2CHH'), 1.85–1.79 (1H, m, NCH_2CHH'), 1.72–1.64 (1.95–1.89) (2H, m, $CH_3(CH_2)_2CH_2$), 1.64 (1.63) (9H, s, $C(CH_3)_3$), 1.40–1.24 (4H, m, $CH_3CH_2CH_2$), 0.92 (3H, t, J = 7.0 Hz, CH_3CH_2); δ_C (125 MHz, $CDCl_3$) (rotamer mixture) 185.3 (185.2) (C=S), 84.7 (84.4) ($C(CH_3)_3$), 64.0 (65.1) (NCH), 49.4 (49.2) (NCH_2), 33.4 (32.2) ($NCHCH_2$), 28.5 ($C(CH_3)_3$), 26.3 (26.1) ($CH_3CH_2CH_2$), 22.5 (22.6) (CH_3CH_2), 20.4 (21.0) (NCH_2CH_2), 14.0 (14.1) (CH_3CH_2); HRMS (FI^+) calcd for $C_{12}H_{23}NOS$: 229.1500, found 229.1507.

***O-tert*-Butyl 2-allylazetidine-1-carbothioate (288e)**

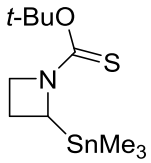


O-tert-Butyl azetidine-1-carbothioate (**212**) (151 mg, 0.87 mmol) and allyl bromide (226 µL, 2.61 mmol) were used following General Procedure C, with stirring following

electrophile addition for 30 min at −78 °C, warming to rt over 10 min, then stirring at rt for a further 20 min. Purification of the resulting yellow liquid (SiO_2, 5–50% Et_2O/petroleum ether) gave a colourless oil, allylated azetidine **288e** (99 mg, 53%).

R_f 0.59 (30% Et_2O/petroleum ether); IR (neat/cm^{-1}) 2975 m, 2926 w, 1641 w, 1477 s, 1435 s, 1390 m, 1365 m, 1348 w, 1138 s, 998 w, 917 m, 836 w, 733 w; δ_H (500 MHz, $CDCl_3$) (2.6:1 rotamer mixture by analysis of NCH signals in the 4.54–4.33 region) 5.82–5.70 (1H, m, CH_2=C*H*), 5.16–5.09 (2H, m, CH_2=CH), 4.38–4.33 (4.54–4.49) (1H, m NCH), 4.02–3.87 (2H, m, NCH_2), 2.60–2.55 (2.92–2.87) (1H, m, C*H*H′CH=CH_2), 2.53–2.47 (2.70–2.64) (1H, m, CH*H*′CH=CH_2), 2.30–2.16 (1H, m, NCH_2C*H*H′), 1.93–1.85 (1H, m, NCH_2CH*H*′), 1.64 (1.62) (9H, s, $C(CH_3)_3$); δ_C (125 MHz, $CDCl_3$) (rotamer mixture) 185.3 (185.2) (C=S), 132.4 (132.6) (CH_2=*C*H), 118.4 (118.2) (*C*H_2=CH), 84.9 (84.5) (*C*$(CH_3)_3$), 62.7 (63.6) (NCH), 49.22 (49.17) (NCH_2), 37.8 (36.3) (*C*H_2CH=CH_2), 28.5 (C(*C*$H_3)_3$), 19.4 (19.8) (NCH_2*C*H_2); HRMS (FI^+) calcd for $C_{11}H_{19}NOS$: 213.1187, found 213.1178.

O-tert-Butyl 2-(trimethylstannyl)azetidine-1-carbothioate (288f)

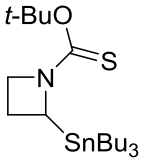


O-tert-Butyl azetidine-1-carbothioate (**212**) (160 mg, 0.92 mmol) and Me_3SnCl (368 mg, 1.85 mmol) were used following General Procedure C, with stirring following electrophile addition for 20 min at −78 °C, warming to rt over 10 min, then stirring at rt for a further 30 min. Purification of the resulting pale yellow oil (SiO_2, 10% Et_2O/petroleum ether) gave a colourless oil, stannane **288f** (224 mg, 72%).

R_f 0.55 (20% TBME/*n*-hexane); IR (neat/cm^{-1}) 2924 m, 2855 w, 1738 w, 1597 w, 1490 m, 1455 s, 1365 m, 1266 m, 1229 w, 1137 m, 1056 w, 890 w, 754 w; δ_H (400 MHz, $CDCl_3$) (2:1 rotamer mixture by analysis of $C(CH_3)_3$ signals at 1.66 and 1.61) 4.46–4.40 (1H, m,

NCH), 4.29–3.98 (2H, m, NCH_2), 2.56–2.39 (1H, m, NCH_2CHH'), 2.13–2.05 (1H, m, NCH_2CHH'), 1.61 (1.66) (9H, s, $C(CH_3)_3$), 0.20 (9H, s, $^2J_{119Sn-H}$ = 54 Hz, $^2J_{117Sn-H}$ = 52 Hz, $Si(CH_3)_3$); δ_C (100 MHz, $CDCl_3$) (rotamer mixture) 181.9 (C=S), 83.7 (84.7) ($C(CH_3)_3$), 55.1 (54.8) (NCH), 50.8 (52.4) (NCH_2), 28.5 (28.7) ($C(CH_3)_3$), 17.8 (18.3) (CH_2), −8.4 (−9.7) ($J_{119Sn-C}$ = 334 Hz, $J_{117Sn-C}$ = 319 Hz, $Si(CH_3)_3$); HRMS (FI^+) calcd for $C_{11}H_{23}NOS^{120}Sn$: 337.0522, found 337.0525.

***O-tert*-Butyl 2-(tributylstannyl)azetidine-1-carbothioate (288g)**

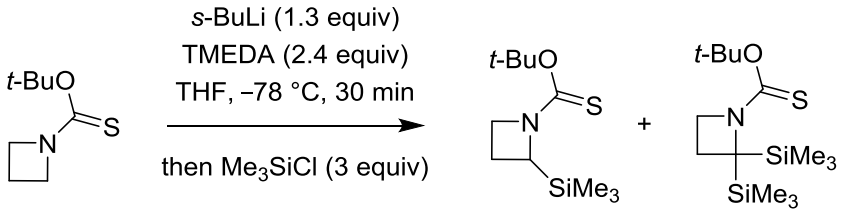


O-tert-Butyl azetidine-1-carbothioate (**212**) (150 mg, 0.87 mmol) and Bu_3SnCl (704 µL, 2.60 mmol) were used following General Procedure C, with stirring following electrophile addition for 30 min at −78 °C, warming to rt over 10 min, then stirring at rt for a further 20 min. Purification of the resulting colourless oil (SiO_2, 1–3% Et_2O/petroleum ether) gave a colourless oil, stannane **288g** (300 mg, 75%).

R_f 0.65 (10% Et_2O/petroleum ether); IR (neat/cm^{-1}) 2956 w, 2923 m, 1490 s, 1446 m, 1390 w, 1365 w, 1265 s, 1225 w, 1138 s, 1073 w, 1023 w, 875 w, 823 w; δ_H (400 MHz, $CDCl_3$) (2:1 rotamer mixture by analysis of $C(CH_3)_3$ signals at 1.66 and 1.60) 4.48–4.45 (1H, m NCH), 4.15–4.09 (4.28–4.21) (1H, td, J = 10.0, 5.0 Hz, $NCHH'$), 4.05–3.99 (4.15–4.09) (1H, m, $NCHH'$), 2.56–2.39 (1H, m, NCH_2CHH'), 2.17–2.06 (1H, m, NCH_2CHH'), 1.60 (1.66) (9H, s, $C(CH_3)_3$), 1.64–1.43 (6H, m, $Sn(CH_2CH_2CH_2CH_3)_3$), 1.36–1.26 (6H, m, $Sn(CH_2CH_2CH_2CH_3)_3$), 0.97 (1.03) (9H, t, J = 8.0 Hz, $Sn(CH_2CH_2CH_2CH_3)_3$), 0.92–0.88 (6H, m, $Sn(CH_2CH_2CH_2CH_3)_3$); δ_C (125 MHz, $CDCl_3$) (rotamer mixture) 181.2 (181.7) (C=S), 83.5 (84.6) ($C(CH_3)_3$), 55.1 (54.4) ($J_{119Sn-C}$ = 325 Hz, $J_{117Sn-C}$ = 302 Hz ($J_{119Sn-C}$ = 294 Hz, $J_{117Sn-C}$ = 280 Hz), NCH), 50.8 (52.7) (NCH_2), 29.1 (29.0) ($SnCH_2CH_2$),

28.5 (28.7) ($C(CH_3)_3$), 27.5 (27.4) (CH_3CH_2), 18.2 (18.7) ($NCHCH_2$), 13.69 (13.65) (CH_3CH_2), 11.0 (9.5) ($J_{119Sn-C}$ = 322 Hz, $J_{117Sn-C}$ = 308 Hz ($J_{119Sn-C}$ = 318 Hz, $J_{117Sn-C}$ = 302 Hz), $SnCH_2$); HRMS (FI^+) calcd for $C_{20}H_{41}NOS^{120}Sn$: 463.1931, found 463.1928.

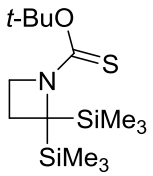
Synthesis of *O-tert*-Butyl 2-(trimethylsilyl)azetidine-1-carbothioate (288h) and side-product *O-tert*-butyl 2,2-bis(trimethylsilyl)azetidine-1-carbothioate (293a)



212 **288h** (76%) **293a** (5%)

O-tert-Butyl azetidine-1-carbothioate (**212**) (147 mg, 0.85 mmol) and Me_3SiCl (323 µL, 2.54 mmol) were used following General Procedure C, with stirring following electrophile addition for 30 min at −78 °C, warming to rt over 10 min, then stirring at rt for a further 20 min. Purification of the resulting pale yellow oil (SiO_2, 2–5% Et_2O/petroleum ether) gave first a colourless oil, disilylated azetidine **293** (13 mg, 5%), followed by a colourless oil, silylated azetidine **288h** (158 mg, 76%).

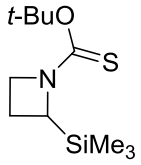
***O-tert*-Butyl 2,2-bis(trimethylsilyl)azetidine-1-carbothioate (293a)**



R_f 0.81 (5% EtOAc/petroleum ether); IR (neat/cm^{-1}) 2961 w, 2360 w, 2342 w, 1481 s, 1445 s, 1390 w, 1365 w, 1274 m, 1249 s, 1223 m, 1137 s, 1007 m, 937 m, 884 w, 838 s, 757 w, 735 w, 689 w; δ_H (400 MHz, $CDCl_3$) (10:1 mixture of rotamers by analysis of $Si(CH_3)_3$ signals at 0.24 and 0.15) 4.07–4.04 (2H, m, NCH_2), 2.17–2.14 (2H, m,

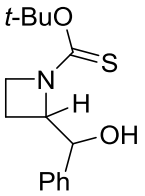
NCH_2CH_2), 1.73 (1.58) (9H, s, $C(CH_3)_3$), 0.15 (0.24) (18H, s, $^2J_{29Si\text{-}H}$ = 6 Hz, $Si(CH_3)_3$ × 2); δ_C (100 MHz, $CDCl_3$) (rotamer mixture) 182.1 (C=S), 85.5 ($C(CH_3)_3$), 61.7 (C_q-Si), 52.3 (50.6) (NCH_2), 29.0 (28.7) ($C(CH_3)_3$), 19.6 ($NCHCH_2$), −1.83 (−0.68) ($J_{29Si\text{-}C}$ = 52 Hz, $Si(CH_3)_3$ × 2); HRMS (ESI^+) calcd for $C_{14}H_{31}NNaOS^{28}Si_2$: 340.1557, found 340.1551.

***O-tert*-Butyl 2-(trimethylsilyl)azetidine-1-carbothioate (288h)**



R_f 0.59 (5% EtOAc/petroleum ether); IR (neat/cm^{-1}) 2961 w, 2882 w, 1483 s, 1445 s, 1390 m, 1365 m, 1267 s, 1248 s, 1227 m, 1022 w, 992 w, 937 w, 754 w, 737 w, 695 w; δ_H (400 MHz, $CDCl_3$) (3.5:1 rotamer mixture by analysis of $C(CH_3)_3$ signals at 1.66 and 1.61) 4.26–3.89 (3H, m, NCH and NCH_2), 2.43–2.25 (1H, m, $NCHCHH'$), 1.99–1.89 (1H, m, $NCHCHH'$), 1.66 (1.61) (9H, s, $C(CH_3)_3$), 0.11 (0.18) (9H, s, $^2J_{29Si\text{-}H}$ = 7 Hz, $Si(CH_3)_3$); δ_C (100 MHz, $CDCl_3$) (rotamer mixture) 183.8 (C=S), 85.0 ($C(CH_3)_3$), 57.3 (NCH), 52.7 (51.1) (NCH_2), 28.7 (28.5) ($C(CH_3)_3$), 16.6 ($NCHCH_2$), −3.2 (−2.2) ($Si(CH_3)_3$); HRMS (ESI^+) calcd for $C_{11}H_{23}NNaOS^{28}Si$: 268.1162, found 268.1158.

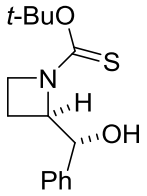
***O-tert*-Butyl 2-(hydroxy(phenyl)methyl)azetidine-1-carbothioate (288i)**



O-tert-Butyl azetidine-1-carbothioate (**212**) (150 mg, 0.87 mmol) and benzaldehyde (264 µL, 2.60 mmol) were used following General Procedure C for an aromatic aldehyde, with stirring following electrophile addition for 2 h at −78 °C. Purification of the resulting pale brown oil (SiO_2, 5–30% Et_2O/petroleum ether) gave first a colourless oil, the minor

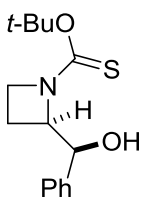
diastereomer (*R**,*R**)-**288i-minor** (53 mg, 22%), followed by a colourless oil, the major diastereomer (*R**,*S**)-**288i-major** (127 mg, 52%); stereochemistry was assigned by analogy to **288j**.

_O_-(_tert_-Butyl) (_R_*)-2-((_R_*)-hydroxy(phenyl)methyl)azetidine-1-carbothioate ((_R_*,_R_*)-288i-minor)



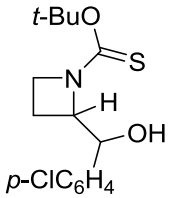
R_f 0.43 (20% EtOAc/petroleum ether); IR (neat/cm^{-1}) 3397 br, 2974 w, 2927 w, 2360 w, 1481 s, 1450 m, 1436 s, 1391 w, 1366 w, 1281 s, 1143 s, 1069 w, 1015 w, 977 w, 927 w, 701 w; δ_H (500 MHz, $CDCl_3$) (1.4:1 rotamer mixture by analysis of NCH signals in the region 4.92–4.50) 7.44–7.28 (5H, m, Ar), 5.33 (5.29) (1H, br s, C*H*OH), 4.92–4.89 (4.52–4.50) (1H, m, NCH), 4.32 (2.56) (1H, br s, OH), 4.00–3.39 (2H, m, NCH_2), 2.36–1.87 (2H, m, NCH_2CH_2), 1.65 (1.72) (9H, s, $C(CH_3)_3$); δ_C (125 MHz, $CDCl_3$) (rotamer mixture) 186.3 (186.4) (C=S), 139.5 (139.1) (Ar), 128.5 (Ar), 128.1 (Ar), 127.5 (127.8) (Ar), 126.9 (Ar) 125.8 (Ar), 85.6 (85.7) ($C(CH_3)_3$), 73.5 (71.8) (*C*HOH), 69.8 (68.9) (NCH), 49.1 (50.0) (NCH_2), 28.4 (28.5) ($C(CH_3)_3$), 16.1 (14.3) (NCH_2CH_2); HRMS (ESI^+) calcd for $C_{15}H_{21}NNaO_2S$: 302.1185, found 302.1183.

_O_-(_tert_-Butyl) (_R_*)-2-((_S_*)-hydroxy(phenyl)methyl)azetidine-1-carbothioate ((_R_*,_S_*)-288i-major)



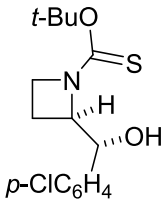
R_f 0.31 (20% EtOAc/petroleum ether); IR (neat/cm^{-1}) 3295 br, 2975 w, 2928 w, 1476 s, 1462 s, 1452 s, 1437 s, 1392 m, 1366 m, 1278 s, 1198 m, 1086 s, 1061 w, 1039 w, 1027 w, 865 w, 823 w; δ_H (400 MHz, $CDCl_3$) (3:1 rotamer mixture by analysis of C*H*OH signals in the region 4.98–4.89) 7.43–7.29 (5H, m, Ar), 5.90 (1H, br s, OH), 4.97 (4.90) (1H, d, *J* = 8.6 Hz (*J* = 7.8 Hz), C*H*OH), 4.78–4.72 (4.57–4.44) (1H, m, NCH), 4.03–3.81 (2H, m, NCH_2), 2.05–1.78 (2H, m, NCH_2CH_2), 1.67 (1.74) (9H, s, $C(CH_3)_3$); δ_C (100 MHz, $CDCl_3$) (rotamer mixture) 187.3 (C=S), 139.6 (Ar), 128.5 (Ar), 128.4 (Ar), 128.1 (Ar), 127.4 (Ar), 127.0 (Ar), 86.2 ($C(CH_3)_3$), 79.2 (*C*HOH), 70.8 (69.7) (NCH), 48.8 (49.6) (NCH_2), 28.4 (28.5) ($C(CH_3)_3$), 18.2 (17.3) (NCH_2CH_2); HRMS (ESI$^+$) calcd for $C_{15}H_{21}NNaO_2S$: 302.1185, found 302.1179.

O-tert-Butyl 2-((4-chlorophenyl)(hydroxy)methyl)azetidine-1-carbothioate (288j)



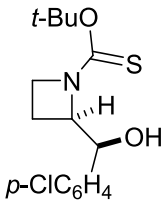
O-tert-Butyl azetidine-1-carbothioate (**212**) (150 mg, 0.87 mmol) and a solution of 4-chlorobenzaldehyde (365 mg, 2.60 mmol) in THF (0.5 mL) were used following General Procedure C for an aromatic aldehyde, with stirring following electrophile addition for 2 h at −78 °C. Purification of the resulting pale brown oil (SiO_2, 5–20% Et_2O/petroleum ether) gave first a colourless oil, the minor diastereomer (*R**,*R**)-**288j-minor** (57 mg, 21%), followed by a white solid, the major diastereomer (*R**,*S**)-**288j-major** (131 mg, 48%); stereochemistry was determined by conversion to the corresponding *N*-piv azetidines (*R**,*R**)-**294** and (*R**,*S**)-**294** and comparing characterization data to that of an authentic sample of (*R**,*R**)-**294**, see below.

O-tert-Butyl (_R_*)-2-((_R_*)-(4-chlorophenyl)(hydroxy)methyl)azetidine-1-carbothioate ((_R_*,_R_*)-288j-minor)



R_f 0.43 (20% EtOAc/petroleum ether); IR (neat/cm^{-1}) 3396 br, 2975 m, 2928 w, 1480 s, 1436 s, 1391 m, 1366 m, 1281 s, 1142 s, 1090 m, 1013 m, 977 w, 912 w, 837 w, 823 w, 781 w; δ_H (400 MHz, $CDCl_3$) (1.9:1 rotamer mixture by analysis of NCH signals at 4.88 and 4.46) 7.38–7.25 (4H, m, Ar), 5.25 (1H, d, J = 4.0 Hz, C*H*OH), 4.88 (4.46) (1H, t, J = 7.1 Hz (J = 6.3 Hz), NCH), 4.56 (2.74) (1H, d, J = 6.8 Hz (J = 3.0 Hz), OH), 3.76 (4.00–3.88) (1H, td (m), J = 9.6, 6.1 Hz, NC*H*H′), 3.40 (4.00–3.88) (1H, td (m), J = 9.3, 6.7 Hz, NCH*H*′), 2.14–2.05 (2.30–2.22) (1H, m, NCH_2CHH'), 2.00–1.84 (1H, m, NCH_2CHH'), 1.64 (1.71) (9H, s, $C(CH_3)_3$); δ_C (100 MHz, $CDCl_3$) (rotamer mixture) 186.5 (C=S), 138.1 (137.6) (Ar), 133.3 (133.5) (Ar), 128.3 (128.6) (Ar), 128.2 (127.2) (Ar), 85.8 ($C(CH_3)_3$), 73.2 (71.2) (*C*HOH), 69.6 (68.7) (NCH), 49.0 (50.0) (NCH_2), 28.3 (28.5) ($C(CH_3)_3$), 16.1 (14.2) (NCH_2CH_2); HRMS (FI^+) calcd for $C_{15}H_{20}NO_2SCl$: 313.0903, found 313.0905.

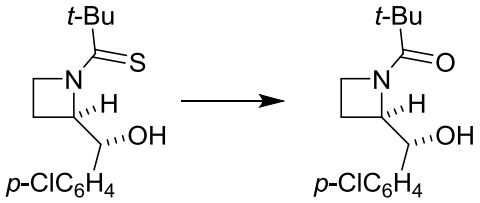
O-tert-Butyl (_R_*)-2-((_S_*)-(4-chlorophenyl)(hydroxy)methyl)azetidine-1-carbothioate ((_R_*,_S_*)-288j-major)



R_f 0.28 (20% EtOAc/petroleum ether); mp 100–102 °C (decomposes); IR (neat/cm^{-1}) 3276 br, 2976 w, 2927 w, 1477 s, 1462 s, 1436 s, 1392 m, 1366 m, 1276 s, 1142 s, 1090 w, 1069 w, 1039 w, 1014 m, 910 w, 822 m, 732 m; δ_H (400 MHz, $CDCl_3$) (3.4:1 rotamer mixture

by analysis of C*H*OH signals at 4.95 and 4.87) 7.37–2.28 (4H, m, Ar), 5.94 (1H, br s, OH), 4.95 (4.87) (1H, d, *J* = 8.6 (7.8) Hz, C*H*OH), 4.71–4.65 (4.51–4.45) (1H, m, NCH), 4.01–3.78 (2H, m, NCH_2), 2.02–1.91 (1.81–1.69) (2H, m, NCH_2CH_2), 1.65 (1.73) (9H, s, $C(CH_3)_3$); δ_C (100 MHz, $CDCl_3$) (rotamer mixture) 187.4 (C=S), 138.2 (137.2) (Ar), 133.8 (Ar), 128.7 (128.6) (Ar), 128.55 (128.3) (Ar), 86.3 (87.3) ($C(CH_3)_3$), 78.3 (76.2) (*C*HOH), 70.5 (69.3) (NCH), 48.8 (49.5) (NCH_2), 28.3 (28.4) ($C(CH_3)_3$), 18.0 (17.1) (NCH_2CH_2); HRMS (FI^+) calcd for $C_{15}H_{20}NO_2SCl$: 313.0903, found 313.0908.

Synthesis of an authentic sample of 1-((*R)-2-((*R**)-(4-chlorophenyl)(hydroxy)methyl)azetidin-1-yl)-2,2-dimethylpropan-1-one ((*R*,R**)-294)**

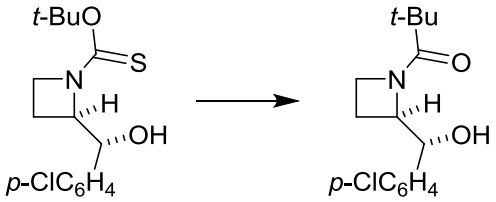


(*R**,*R**)-**165h** (*R**,*R**)-**294**

Aq H_2O_2 (35%, 1.7 mL) was added to an ice-cold, stirred solution of AcOH (1.3 mL). A solution of 1-((*R**)-2-((*R**)-(4-chlorophenyl)(hydroxy)methyl)azetidin-1-yl)-2,2-dimethylpropane-1-thione ((*R**,*R**)-**165h**)[148] (30 mg, 0.10 mmol) in CH_2Cl_2 (0.5 mL) was added slowly and the reaction mixture was stirred at 0 °C for 4 h, then poured onto sat. aq $NaHCO_3$ (15 mL) and extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed successively with sat. aq $NaHCO_3$ (10 mL), H_2O (10 mL) and brine (10 mL), then dried (Na_2SO_4) and concentrated under reduced pressure. Purification of the resulting pale yellow oil (SiO_2, 20–40% EtOAc/petroleum ether) gave a white solid, *N*-piv-azetidine (*R**,*R**)-**294** (18 mg, 64%).

R_f 0.24 (40% EtOAc/petroleum ether); mp 107–110 °C; IR (neat/cm^{-1}) 3364 br, 2968 m, 1593 s, 1484 s, 1426 s, 1365 m, 1238 w, 1149 w, 1090 m, 1013 m, 978 w, 836 w, 755w; δ_H (400 MHz, $CDCl_3$) 7.37–7.24 (4H, m, Ar), 6.21 (1H, br d, J = 7.2 Hz, OH), 4.96 (1H, ddd, J = 9.0, 6.5, 1.9 Hz, NCH), 4.72 (1H, br d, J = 3.2 Hz, C*H*OH), 4.12 (1H, td, J = 8.9, 6.0 Hz, NC*H*H′), 3.60–3.55 (1H, m, NCH*H*′), 2.34–2.25 (1H, m, NCH_2CHH'), 1.94–1.85 (1H, m, NCH_2CHH'), 1.18 (9H, s, $C(CH_3)_3$); δ_C (100 MHz, $CDCl_3$) 179.8 (C=O), 138.3 (Ar), 133.4 (Ar), 128.7 (Ar), 128.0 (Ar), 75.0 (CHOH), 67.7 (NCH), 50.7 (NCH_2), 38.4 ($C(CH_3)_3$), 26.9 ($C(CH_3)_3$), 18.0 (NCH_2CH_2); HRMS (ESI$^+$) calcd for $C_{15}H_{21}NO_2Cl$: 282.1255, found 282.1251.

Synthesis of 1-((*R)-2-((*R**)-(4-chlorophenyl)(hydroxy)methyl)azetidin-1-yl)-2,2-dimethylpropan-1-one ((*R**,*R**)-294) from 288j-minor**

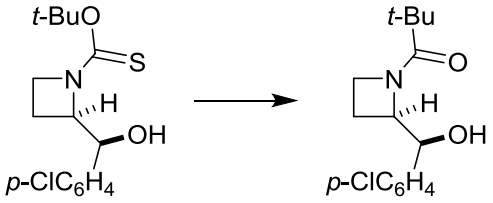


288j-minor (*R**,*R**)-**294**

HCl (2 M in Et_2O, 1 mL, 2.00 mmol) was added to *O*-*tert*-butyl 2-((4-chlorophenyl)(hydroxy)methyl)azetidine-1-carbothioate (**288j-minor**) (22 mg, 0.07 mmol). The reaction mixture was stirred at rt for 1 h, then concentrated under reduced pressure. Py (1 mL) and DMAP (2 mg, 0.016 mmol) were added to the resulting white solid and the reaction mixture was heated to 70 °C for 10 min, then cooled to 0 °C. pivCl (9 µL, 0.073 mmol) was added and the reaction mixture was stirred at rt for 12 h. HCl (2 M, aq, 10 mL) was added and the reaction mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were washed with H_2O (10 mL) and brine (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Purification of the resulting dark

brown oil (SiO_2, 20–40% EtOAc/petroleum ether) gave *N*-piv azetidine (*R**,*R**)-**294** as a white solid (11 mg, 56%). Data as above.

Synthesis of 1-((*R)-2-((*S**)-(4-chlorophenyl)(hydroxy)methyl)azetidin-1-yl)-2,2-dimethylpropan-1-one ((*R**,*S**)-294) from 288j-major**



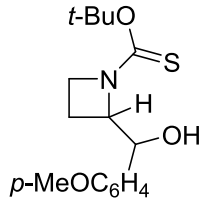
288j-major (*R**,*S**)-**294**

A solution of HCl (2 M in Et_2O, 2.5 mL, 5.00 mmol) was added to *O*-*tert*-butyl 2-((4-chlorophenyl)(hydroxy)methyl)azetidine-1-carbothioate (**288j-major**) (66 mg, 0.21 mmol) at rt. The reaction mixture was stirred at rt for 1 h, then concentrated under reduced pressure. py (1.5 mL) and DMAP (5 mg, 0.04 mmol) were added to the resulting white solid and the reaction mixture was heated to 70 °C for 10 min, then cooled to 0 °C. pivCl (28 µL, 0.23 mmol) was added and the reaction mixture was stirred at rt for 12 h. HCl (2 M, aq, 15 mL) was added and the reaction mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were washed with H_2O (10 mL) and brine (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Purification of the resulting pale brown oil (SiO_2, 20% EtOAc/petroleum ether) gave a white solid, *N*-piv-azetidine (*R**,*S**)-**294** (22 mg, 37%).

R_f 0.46 (40% EtOAc/petroleum ether); mp 140–142 °C; IR (neat/cm^{-1}) 3188 br, 2965 m, 1578 s, 1483 m, 1427 s, 1365 w, 1353 w, 1220 w, 1086 w, 1073 w, 835 m, 756 w; δ_H (400 MHz, $CDCl_3$) 7.36–7.30 (4H, m, Ar), 6.72 (1H, s, OH), 4.73 (1H, d, *J* = 8.7 Hz, C*H*OH), 4.56 (1H, q, *J* = 15.9, 8.5 Hz, NCH), 4.28 (2H, t, *J* = 7.8 Hz, NCH_2), 1.96–1.82 (2H, m, NCH_2CH_2), 1.24 (9H, s, $C(CH_3)_3$); δ_C (100 MHz, $CDCl_3$) 180.6 (C=O), 138.0 (Ar), 133.8

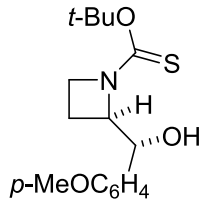
(Ar), 128.7 (Ar), 128.6 (Ar), 78.5 (CHOH), 69.6 (NCH), 50.6 (NCH_2), 38.6 ($C(CH_3)_3$), 26.9 ($C(CH_3)_3$), 19.2 (NCH_2CH_2); HRMS (ESI^+) calcd for $C_{15}H_{21}NO_2Cl$: 282.1255, found 282.1254. Data differs from that of an authentic sample of (*R**,*R**)-**294**, see above.

O-tert-Butyl 2-(hydroxy(4-methoxyphenyl)methyl)azetidine-1-carbothioate (288k)



O-tert-Butyl azetidine-1-carbothioate (**212**) (150 mg, 0.87 mmol) and *p*-anisaldehyde (316 µL, 2.60 mmol) were used following General Procedure C for an aromatic aldehyde, with stirring following electrophile addition for 2 h at −78 °C. Purification of the resulting pale brown oil (SiO_2, 5–30% Et_2O/petroleum ether) gave first a colourless oil, the minor diastereomer (*R**,*R**)-**288k-minor** (45 mg, 17%), followed by a white solid, the major diastereomer (*R**,*S**)-**288k-major** (108 mg, 40%); stereochemistry was assigned by analogy to **288j**.

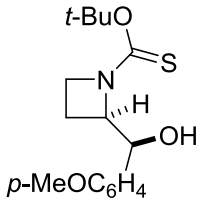
_O_-(_tert_-Butyl) (*R)-2-((*R**)-hydroxy(4-methoxyphenyl)methyl)azetidine-1-carbothioate ((*R**,*R**)-288k-minor)**



R_f 0.32 (20% EtOAc/petroleum ether); IR (neat/cm^{-1}) 3424 br, 2973 m, 2931 w, 2836 w, 1612 w, 1585 w, 1512 m, 1482 s, 1464 s, 1437 s, 1391 m, 1366 m, 1280 s, 1248 s, 1172 m, 1144 s, 1034 m, 976 w, 911 w, 847 w, 832 w, 734 w; δ_H (500 MHz, $CDCl_3$) (1.4:1 rotamer mixture by analysis of NCH signals at 4.89 and 4.48) 7.37–7.34 (7.26–7.24) (2H, m, Ar),

6.91–6.88 (2H, m, Ar), 5.22 (1H, br s, C*H*OH), 4.89 (4.48) (1H, t, *J* = 6.0 (7.0) Hz, NCH), 4.41 (2.48) (1H, d (br s), *J* = 6.5 Hz, OH), 4.00–3.90 (1H, m, NC*H*H′), 3.82 (3.81) (3H, s, OCH_3), 3.75 (3.40) (1H, td, *J* = 10.0, 6.0 (9.5, 7.0) Hz, NCH*H*′), 2.14–2.07 (2.35–2.27) (1H, m, NCH_2CHH'), 2.03–1.89 (1H, m, NCH_2CHH'), 1.65 (1.72) (9H, s, $C(CH_3)_3$); δ_C (125 MHz, $CDCl_3$) (rotamer mixture) 186.3 (186.4) (C=S), 159.0 (159.2) (Ar), 131.6 (131.2) (Ar), 128.1 (127.0) (Ar), 113.5 (113.9) (Ar), 85.6 (85.7) ($C(CH_3)_3$), 73.5 (71.6) (*C*HOH), 69.9 (69.0) (NCH), 55.2 (55.3) (OCH_3), 49.0 (50.0) (NCH_2), 28.4 (28.5) ($C(CH_3)_3$), 16.3 (14.4) (NCH_2CH_2); HRMS (FI^+) calcd for $C_{16}H_{23}NO_3S$: 309.1399, found 309.1400.

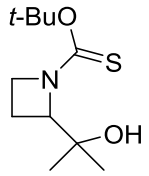
_O_-(_tert_-Butyl) (_R_*)-2-((_S_*)-hydroxy(4-methoxyphenyl)methyl)azetidine-1-carbothioate ((_R_*,_S_*)-288k-major)



R_f 0.28 (20% EtOAc/petroleum ether); mp 96–98 °C (dec); IR (neat/cm^{-1}) 3300 br, 2974 m, 2929 w, 2836 w, 1613 w, 1513 m, 1477 s, 1464 s, 1438 s, 1392 w, 1367 w, 1277 s, 1250 s, 1145 s, 1067 w, 1033 m, 912 w, 829 w, 733 w; δ_H (400 MHz, $CDCl_3$) (2.7:1 rotamer mixture by analysis of C*H*OH signals at 4.92 and 4.84) 7.35–7.27 (2H, m, Ar), 6.89–6.87 (2H, m, Ar), 5.86 (1H, br s, OH), 4.92 (4.84) (1H, d, *J* = 9.0 (8.0) Hz, C*H*OH), 4.74–68 (4.54–4.48) (1H, m, NCH), 3.88 (4.01–3.93) (2H, t (m), *J* = 7.8 Hz, NCH_2), 3.80 (3H, s, OCH_3), 2.03–1.91 (1.82–1.63) (2H, m, NCH_2CH_2), 1.66 (1.74) (9H, s, $C(CH_3)_3$); δ_C (100 MHz, $CDCl_3$) (rotamer mixture) 187.2 (C=S), 159.4 (Ar), 131.8 (Ar), 128.5 (128.2) (Ar), 113.8 (113.9) (Ar), 86.1 (87.2) ($C(CH_3)_3$), 78.7 (76.8) (*C*HOH), 70.9 (69.8) (NCH),

55.2 (OCH_3), 48.8 (49.5) (NCH_2), 28.4 (28.5) ($C(CH_3)_3$), 18.3 (17.3) (NCH_2CH_2); HRMS (FI^+) calcd for $C_{16}H_{23}NO_3S$: 309.1399, found 309.1404.

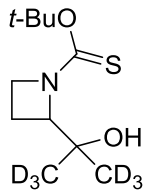
***O-tert*-Butyl 2-(2-hydroxypropan-2-yl)azetidine-1-carbothioate (288l)**



O-tert-Butyl azetidine-1-carbothioate (**212**) (70 mg, 0.40 mmol) and acetone (90 µL, 1.23 mmol) were used following General Procedure C, with stirring following electrophile addition for 3 h at −78 °C. Purification of the resulting pale yellow oil (SiO_2, 5–20% Et_2O/petroleum ether) gave a colourless oil, alcohol **288l** (60 mg, 65%).

R_f 0.22 (20% EtOAc/petroleum ether); IR (neat/cm^{-1}) 3335 br, 2975 w, 2930 w, 1474 w, 1437 s, 1391 m, 1366 m, 1271 s, 1248 m, 1225 m, 1142 s, 983 w, 911 w, 859 w; δ_H (400 MHz, $CDCl_3$) (1.7:1 rotamer mixture by analysis of NCH signals in the 4.57–4.31 region) 5.52 (1H, br s, OH), 4.57–4.53 (4.35–4.31) (1H, m, NCH), 4.10–3.82 (2H, m, NCH_2), 2.32–1.77 (2H, m, NCH_2CH_2), 1.63 (1.69) (9H, s, $C(CH_3)_3$), 1.30 (1.23) (3H, s, CH_3COH), 1.10 (1.15) (3H, s, CH_3COH); δ_C (100 MHz, $CDCl_3$) (rotamer mixture) 186.7 (C=S), 85.7 (87.0) ($C(CH_3)_3$), 74.6 (73.8) (NCH), 72.4 (72.3) (COH), 49.1 (50.4) (NCH_2), 28.3 ($C(CH_3)_3$), 24.8 (25.2) (CH_3COH), 22.9 (23.5) (CH_3COH), 18.6 (17.9) (NCH_2CH_2); HRMS (ESI^+) calcd for $C_{11}H_{21}NNaO_2S$: 254.1185, found 254.1189.

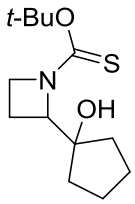
***O*-(*tert*-Butyl) 2-(2-hydroxypropan-2-yl-1,1,1,3,3,3-d_6)azetidine-1-carbothioate (288m)**



O-tert-Butyl azetidine-1-carbothioate (**212**) (60 mg, 0.35 mmol) and acetone-D_6 (76 µL, 1.04 mmol) were used following General Procedure C, with stirring following electrophile addition for 3 h at −78 °C. Purification of the resulting pale yellow oil (SiO_2, 10–40% Et_2O/petroleum ether) gave a colourless oil, alcohol **288m** (57 mg, 70%).

R_f 0.29 (20% EtOAc/petroleum ether); IR (neat/cm^{-1}) 3336 br, 2976 w, 2928 w, 1474 m, 1437 s, 1391 m, 1366 m, 1271 s, 1243 w, 1140 s, 1044 w, 1020 w, 946 w, 819 w; δ_H (500 MHz, $CDCl_3$) (1.6:1 rotamer mixture by analysis of NCH signals at 4.55 and 4.32) 5.49 (1H, br s, OH), 4.55 (4.32) (1H, dd, *J* = 8.4, 6.8 Hz (*J* = 8.2, 6.0 Hz), NCH), 4.09–3.82 (2H, m, NCH_2), 2.31–1.77 (2H, m, NCH_2CH_2), 1.63 (1.69) (9H, s, $C(CH_3)_3$); δ_C (125 MHz, $CDCl_3$) (rotamer mixture) 186.8 (186.1) (C=S), 85.8 (87.0) ($C(CH_3)_3$), 74.6 (73.8) (NCH), 72.2 (72.1) (COH), 49.2 (50.5) (NCH_2), 28.4 ($C(CH_3)_3$), 24.1 (SEP, *J* = 20.0 Hz, CD_3), 22.0 (SEP, *J* = 19.1 Hz, CD_3), 18.6 (17.9) (NCH_2CH_2); HRMS (ESI^+) calcd for $C_{11}H_{15}D_6O_2NNaS$: 260.1562, found 260.1557.

O-tert-butyl 2-(1-hydroxycyclopentyl)azetidine-1-carbothioate (288n)

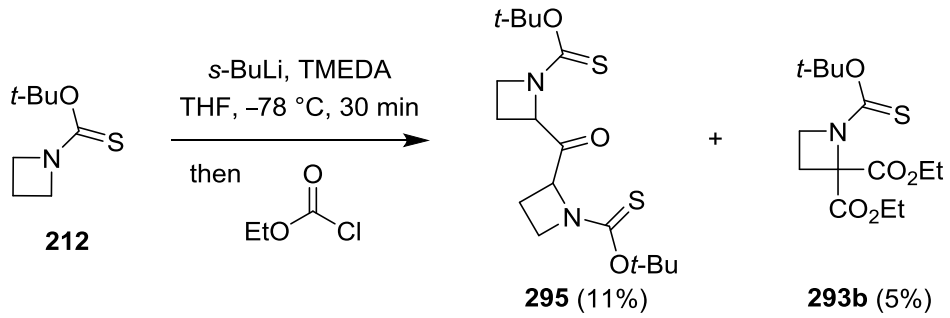


O-tert-Butyl azetidine-1-carbothioate (**212**) (150 mg, 0.87 mmol) and cyclopentanone (230 µL, 2.60 mmol) were used following General Procedure C, with stirring following electrophile addition for 2 h at −78 °C. Purification of the resulting pale yellow oil (SiO_2, 30% Et_2O/petroleum ether) gave a colourless oil, alcohol **288n** (98 mg, 44%).

R_f 0.34 (50% Et_2O/petroleum ether); IR (neat/cm^{-1}) 3333 br, 2964 m, 2873 w, 1475 m, 1432 s, 1391 m, 1366 m, 1271 s, 1138 s, 995 w, 938 w, 892 w, 821 w, 740 w; δ_H (400 MHz, $CDCl_3$) (1:1 rotamer mixture by analysis of NCH signals in the 4.79–4.42 region)

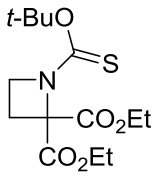
5.37 (2.67) (1H, br s, OH), 4.79–4.75 (4.45) (1H, m, (dd, *J* = 8.5, 6.0 Hz), NCH), 4.08–3.80 (2H, m, NCH_2), 2.30–1.51 (10H, m, NCH_2CH_2 and $(CH_2)_4$), 1.61 (1.68) (9H, s, $C(CH_3)_3$); δ_C (126 MHz, $CDCl_3$) (rotamer mixture) 186.3 (C=S), 86.6 (85.6) ($C(CH_3)_3$), 83.8 (83.7) (COH), 73.0 (72.1) (NCH), 50.8 (49.1) (NCH_2), 37.7 (36.2) (CH_2COH), 35.3 (35.3) (CH_2COH), 28.4 (28.4) ($C(CH_3)_3$), 25.3 (24.7) (CH_2CH_2COH), 24.0 (23.7) (CH_2CH_2COH), 18.0 (17.7) (NCH_2CH_2); HRMS (ESI^+) calcd for $C_{13}H_{23}NNaO_2S$: 280.1342, found 280.1333.

Synthesis of diethyl 1-(*tert*-butoxycarbonothioyl)azetidine-2,2-dicarboxylate (293b) and *O,O*'-di-*tert*-butyl 2,2'-carbonylbis(azetidine-1-carbothioate) (295)



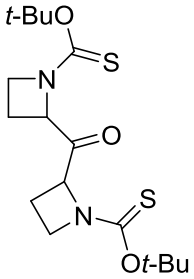
O-tert-Butyl azetidine-1-carbothioate (**212**) (71 mg, 0.41 mmol) and ethyl chloroformate (118 µL, 1.23 mmol) were used following General Procedure C, with stirring following electrophile addition for 10 min at −78 °C. Purification of the resulting pale yellow oil (SiO_2, 10–20% Et_2O/petroleum ether) gave first a colourless oil, 2,2-disubstituted azetidine **293b** (7 mg, 5%), followed by a colourless oil, dimer **295** (17mg, 11%) as a mixture of inseparable diastereomers.

Diethyl 1-(*tert*-butoxycarbonothioyl)azetidine-2,2-dicarboxylate (293b)



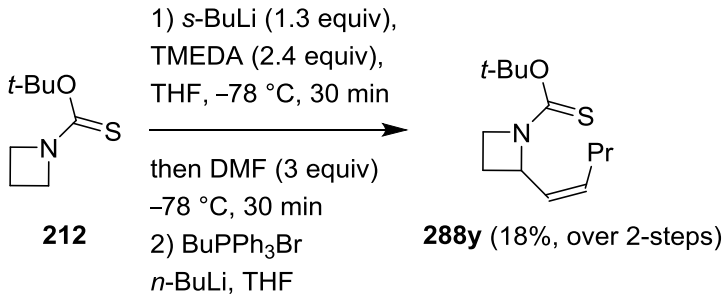
R_f 0.22 (30% Et_2O/petroleum ether); IR (neat/cm^{-1}) 2980 w, 2932 w, 1739 s, 1462 m, 1423 s, 1391 m, 1366 w, 1280 s, 1147 w, 1105 s, 1017 m, 952 w, 825 w; δ_H (500 MHz, $CDCl_3$) (5:1 rotamer mixture by analysis of $C(CH_3)_3$ signals at 1.64 and 1.60) 4.35-4.23 (4H, m, OCH_2), 4.11–4.08 (2H, m, NCH_2CH_2), 2.62–2.59 (2H, m, NCH_2), 1.60 (1.64) (9H, s, $C(CH_3)_3$), 1.33 (6H, t, J = 7.0 Hz, OCH_2CH_3); δ_C (125 MHz, $CDCl_3$) 186.3 (C=S), 167.1 (C=O), 86.4 ($C(CH_3)_3$), 72.4 (NC_q), 62.2 (OCH_2), 48.9 (NCH_2CH_2), 28.0 ($C(CH_3)_3$), 24.8 (NCH_2), 14.1 (CH_2CH_3); HRMS (ESI^+) calcd for $C_{14}H_{23}NNaO_5S$: 340.1189, found 340.1179.

_O,O'_-Di-_tert_-butyl 2,2'-carbonylbis(azetidine-1-carbothioate) (295)



R_f 0.15 (30% Et_2O/petroleum ether); IR (neat/cm^{-1}) 2975 w, 2928 w, 1738 br, 1474 m, 1435 s, 1391 w, 1366 w, 1285 s, 1145 s, 1066 s, 941 w, 862 w; δ_H (500 MHz, $CDCl_3$) (mixture of diastereomers and rotamers) 5.11–4.89 (2H, m, NCH), 4.12–3.90 (4H, m, NCH_2), 2.55–2.08 (4H, m, $NCHCH_2$), 1.64 (1.61) (18H, s, $C(CH_3)_3$); δ_C (125 MHz, $CDCl_3$) (mixture of diastereomers and rotamers) 202.5 (200.8) (C=O), 186.5 (186.0) (C=S), 185.7 (185.4) (C=S), 86.1 (85.9) ($C(CH_3)_3$), 85.7 (85.5) ($C(CH_3)_3$), 66.2 (NCH), 65.5 (65.1) (NCH), 49.7 (NCH_2), 49.2 (49.0) (NCH_2), 30.3 (28.3) ($C(CH_3)_3$), 28.2 ($C(CH_3)_3$), 19.2 (19.0) ($NCHCH_2$); HRMS (ESI^+) calcd for $C_{17}H_{28}N_2NaO_3S_2$: 395.1434, found 395.1419.

(*Z*)-*O*-*tert*-Butyl 2-(pent-1-en-1-yl)azetidine-1-carbothioate (288y)



212 **288y** (18%, over 2-steps)

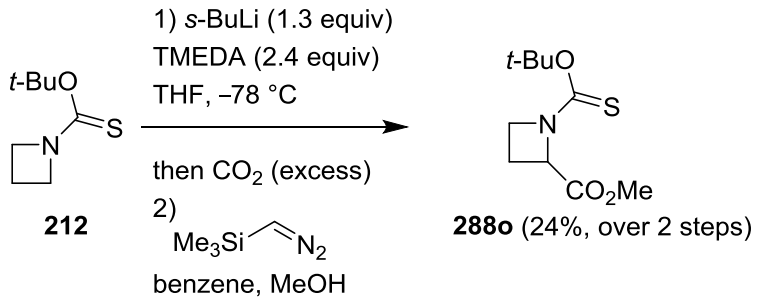
O-*tert*-Butyl azetidine-1-carbothioate (**212**) (150 mg, 0.87 mmol) and DMF (201 µL, 2.60 mmol) were used following General Procedure C, with stirring following electrophile addition for 30 min at −78 °C. The resulting pale yellow oil (crude aldehyde **288s**, 167mg) was used directly in the following Wittig reaction:

n-BuLi (2.54 M in , 327 µL, 0.83 mmol) was added dropwise to an ice-cold solution of $BuPPh_3Br$ in THF (14 mL). The reaction mixture was stirred at 0 °C for 10 min, warmed to rt over 10 min, stirred at rt for 10 min, then re-cooled to 0 °C. A solution of the crude aldehyde **288s** (167 mg, 0.83 mmol) in THF (1 mL) was added dropwise. The reaction mixture was stirred for 1 h at 0 °C, warmed to rt over 10 min, stirred at rt for 50 min, then quenched with sat. aq. NH_4Cl (10 mL), extracted with Et_2O (4 × 10 mL), dried ($MgSO_4$), passed through silica and concentrated under reduced pressure. Purification of the resulting pale brown oil (SiO_2, 5% Et_2O/petroleum ether) gave a colourless oil, alkene **288y** (38 mg, 18%).

R_f 0.47 (10% EtOAc/petroleum ether); IR (neat/cm^{-1}) 3004 w, 2961 m, 2929 w, 2873 w, 1476 s, 1464 s, 1435 s, 1390 m, 1365 m, 1277 s, 1227 w, 1142 s, 1045 w, 906 w, 852 w, 820 w, 738 w; δ_H (400 MHz, $CDCl_3$) (3.6:1 rotamer mixture by analysis of NCH signals in the 5.20–5.00 region) 5.66–5.46 (2H, m, CH=CH), 5.06–5.00 (5.20–5.15) (1H, m, NCH), 4.11–3.87 (2H, m, NCH_2), 2.48–2.35 (1H, m NCH_2CHH'), 2.22–1.96 (2H, m,

$CH_3CH_2CH_2$), 1.48–1.29 (1H, m, NCH_2CHH'), 1.58 (1.62) (9H, s, $C(CH_3)_3$), 1.50–1.29 (2H, m, CH_3CH_2), 0.89 (0.91) (3H, t, J = 7.3 Hz (J = 6.8 Hz), CH_3CH_2); δ_C (126 MHz, $CDCl_3$) (mixture of rotamers) 185.4 (CS), 132.6 (131.8) (NCHCH), 129.4 (128.9) ($N(CH)_2CH$), 84.8 (84..6) (C_q-$(CH_3)_3$), 61.1 (59.9) (NCH), 49.3 (49.1) (NCH_2), 30.0 (29.5) ($CH_3CH_2CH_2$), 28.4 (28.3) ($C(CH_3)_3$), 22.8 (22.6) (NCH_2CH_2), 22.5 (22.3) (CH_3CH_2), 13.8 (13.7) (CH_3CH_2); HRMS (FI^+) calcd for $C_{13}H_{23}NOS$: 241.1500, found 241.1494.

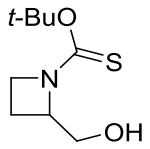
Methyl 1-(*tert*-butoxycarbonothioyl)azetidine-2-carboxylate (288o)



O-tert-Butyl azetidine-1-carbothioate (**212**) (170 mg, 0.99 mmol) and CO_2 gas (from dry ice, passed through $CaCl_2$ and then bubbled through the reaction mixture) were used following General Procedure C, with stirring following electrophile addition for 30 min at −78 °C, warming to rt over 10 min, then stirring at rt for a further 20 min. After quenching with sat. aq NH_4Cl (5 mL), Et_2O (5 mL) was added and the organic layer discarded after partitioning. The aq layer was adjusted to pH=2 with aq HCl (3 M) and extracted with EtOAc (4 x 10 mL), the combined organic layers dried (Na_2SO_4) and concentrated under reduced pressure. The resulting residue was dissolved in benzene (5 mL) and MeOH (3 mL) and cooled to 0 °C. TMS-diazomethane (2.0 M in Et_2O) was added dropwise until the yellow colour persisted (ca. 1.5 mL). Following stirring for 30 min at rt, the reaction mixture was concentrated under reduced pressure. Purification of the resulting pale brown oil (SiO_2, 10–40% Et_2O/petroleum ether) gave a colourless oil, ester **288o** (55 mg, 24%).

R_f 0.32 (10% Et_2O/petroleum ether); IR (neat/cm^{-1}) 2976 m, 1743 s, 1465 m, 1432 s, 1392 m, 1366 m, 1271 s, 1203 m, 1141 s, 1059 m, 1003 w, 903 w, 834 w, 788 w, 734 w; δ_H (500 MHz, $CDCl_3$) (1.9:1 rotamer mixture by analysis of NCH signals at 4.80 and 4.69) 4.69 (4.80) (1H, dd, *J* = 9.1, 5.7 Hz (*J* = 9.1, 5.4 Hz), NCH), 4.20–3.95 (2H, m, NCH_2), 3.77 (3.78) (3H, s, OCH_3), 2.50–2.10) (2H, m, NCH_2CH_2), 1.58 (1.63) (9H, s, $C(CH_3)_3$); δ_C (125 MHz, $CDCl_3$) (rotamer mixture) 185.5 (186.3) (C=S), 170.3 (170.6) (CO_2), 85.6 (85.5) ($C(CH_3)_3$), 61.4 (62.3) (NCH), 52.18 (52.24) (OCH_3), 50.0 (49.5) (NCH_2), 28.2 (28.1) ($C(CH_3)_3$), 19.0 (18.9) (NCH_2CH_2); HRMS (FI^+) calcd for $C_{10}H_{17}NO_3S$: 231.0929, found 231.0932.

_O_-(_tert_-Butyl) 2-(hydroxymethyl)azetidine-1-carbothioate (288v)

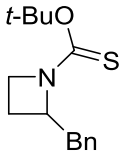


O-tert-Butyl azetidine-1-carbothioate (**212**) (160 mg, 0.92 mmol) and formaldehyde [from a mixture of paraformaldehyde (6 g, 200 mmol) and *p*-toluene sulfonic anhydride (979 mg, 3.00 mmol) heated at 85 °C][215] were used following General Procedure C, with stirring following electrophile addition for 15 min at −78 °C, warming to rt over 10 min, then stirring at rt for a further 30 min. Purification of the resulting thick orange oil (SiO_2, 20% EtOAc/petroleum ether) gave a colourless oil, alcohol **288v** (27 mg, 14%).

R_f 0.29 (30% EtOAc/petroleum ether); IR (neat/cm^{-1}) 3364 br, 2973 w, 2928 w, 1480 m, 1438 s, 1391 w, 1367 w, 1276 s, 1142 s, 1038 w, 976 w, 832 w; δ_H (400 MHz, $CDCl_3$) (1.8:1 rotamer mixture by analysis of NCH signals in the 4.75–4.41 region) 4.75–4.69 (4.44) (1H, m (dq, *J* = 8.8, 4.6 Hz), NCH), 4.06–3.70 (4H, m, NCH_2 and CH_2OH), 2.32–1.78 (3H, m, NCH_2CH_2 and OH), 1.62 (1.65) (9H, s, $C(CH_3)_3$); δ_C (100 MHz, $CDCl_3$) (rotamer mixture) 186.3 (C=S), 85.8 (85.7) ($C(CH_3)_3$), 67.3 (65.5) (NCH), 63.3 (63.9)

(CH_2OH), 48.8 (49.9) (NCH_2), 28.4 (28.3) ($C(CH_3)_3$), 17.5 (16.9) (NCH_2CH_2); HRMS (ESI^+) calcd for $C_9H_{17}NNaO_2S$: 226.0872, found 226.0868.

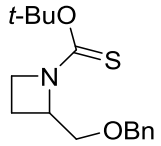
O-tert-Butyl 2-benzylazetidine-1-carbothioate (288w)



O-tert-Butyl azetidine-1-carbothioate (**212**) (150 mg, 0.87 mmol) and BnBr (0.31 mL, 2.60 mmol) were used following General Procedure C, with stirring following electrophile addition for 30 min at −78 °C, warming to rt over 10 min and then stirring at rt for a further 20 min. Purification of the resulting yellow residue (SiO_2, 5–50% Et_2O/petroleum ether) gave a colourless oil, benzylated azetidine **288w** (20 mg, 9%).

R_f 0.38 (10% Et_2O/petroleum ether); IR (neat/cm^{-1}) 3027 w, 2972 w, 2927 w, 1739 w, 1478 s, 1464 s, 1437 s, 1390 m, 1365 m, 1279 s, 1228 w, 1142 s, 1008 w, 928 w, 847 w, 725 w; δ_H (500 MHz, $CDCl_3$) (1.9:1 rotamer mixture by analysis of NCH signals in the 4.73–4.48 region) 7.34–7.15 (5H, m, Ar), 4.54–4.48 (4.73–4.68) (1H, m, NCH), 4.00–3.94 (3.63–3.58) (1H, td, J = 10.0, 6.0 (J = 9.0, 7.0 Hz), NC*H*H′), 3.87–3.79 (1H, m, NCH*H*′), 3.25 (3.45) (1H, dd, J = 13.7, 3.6 Hz (J = 13.6, 3.5 Hz), ArC*H*H′), 2.96 (3.24) (1H, dd, J = 13.6, 8.8 Hz, ArCH*H*′), 2.24–2.13 (1H, m, NCH_2C*H*H′), 1.92–1.83 (1H, m, NCH_2CH*H*′), 1.70 (1.66) (9H, s, $C(CH_3)_3$); δ_C (125 MHz, $CDCl_3$) (rotamer mixture) 185.5 (185.3) (C=S), 136.7 (137.0) (Ar), 129.3 (129.8) (Ar), 128.6 (128.3) (Ar), 126.7 (126.4) (Ar), 85.0 (84.6) ($C(CH_3)_3$), 64.1 (64.9) (NCH), 49.12 (49.05) (NCH_2), 39.8 (37.6) (PhCH_2), 28.5 ($C(CH_3)_3$), 19.8 (NCH_2CH_2); HRMS (FI^+) calcd for $C_{15}H_{21}NOS$: 263.1344, found 263.1341.

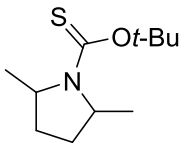
_O_-(_tert_-Butyl) 2-((benzyloxy)methyl)azetidine-1-carbothioate (288x)



O-tert-Butyl azetidine-1-carbothioate (**212**) (160 mg, 0.92 mmol) and benzyl chloromethyl ether (75% pure, 514 µL, 2.77 mmol) were used following General Procedure C, with stirring following electrophile addition for 1 h at −78 °C, warming to rt over 10 min, then stirring at rt for a further 10 min. Purification of the resulting pale yellow oil (SiO_2, 5–10% Et_2O/petroleum ether) gave a colourless oil, ether **288x** (85 mg, 31%).

R_f 0.15 (5% Et_2O/petroleum ether); IR (neat/cm^{-1}) 3029 w, 2972 w, 1477 m, 1464 m, 1452 m, 1391 w, 1365 w, 1276 s, 1064 s, 933 w, 840 w; δ_H (400 MHz, $CDCl_3$) (1.9:1 rotamer mixture by analysis of $C(CH_3)_3$ signals at 1.65 and 1.60) 7.39–7.28 (5H, m, Ar), 4.67–4.38 (3H, m, NC*H* and CH_2Ph), 4.08–3.87 (2H, m, NCH_2), 3.78 (4.23) (1H, dd, *J* = 10.0, 5.1 Hz (*J* = 10.4, 4.5 Hz), NCHC*H*H′O), 3.65 (3.78) (1H, dd, *J* = 10.0, 2.9 Hz (*J* = 10.3, 3.2 Hz), NCHCH*H*′O), 2.33–2.15 (2H, m, NCH_2CH_2), 1.60 (1.65) (9H, s, $C(CH_3)_3$); δ_C (100 MHz, $CDCl_3$) (rotamer mixture) 185.6 (C=S), 138.0 (138.5) (Ar), 128.4 (128.3) (Ar), 127.7 (127.8) (Ar), 127.6 (127.5) (Ar), 84.9 (84.7) (*C*$(CH_3)_3$), 73.5 (73.4) (*C*H_2Ph), 69.6 (68.4) (CH_2O), 62.9 (64.2) (NCH), 49.96 (50.04) (NCH_2), 28.5 (28.4) ($C(CH_3)_3$), 18.0 (18.3) (NCH_2CH_2); HRMS (ESI^+) calcd for $C_{16}H_{23}NNaO_2S$: 316.1342, found 316.1330.

O-tert-Butyl 2,5-dimethylpyrrolidine-1-carbothioate (302)

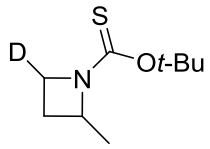


A solution of *O-tert*-butyl 2-methylpyrrolidine-1-carbothioate (**269b**) (73 mg, 0.36 mmol) in Et_2O (1.5 mL) was cooled to −78 °C (acetone/dry-ice) before the addition of TMEDA (130 µL, 0.87 mmol, 2.4 equiv.). *s*-BuLi (363 µL, 0.47 mmol, 1.3 M in

cyclohexane/hexane) was then added dropwise over 3 min. The reaction mixture was stirred for 1 h at −78 °C before the addition of MeI (68 μL, 1.09 mmol). The reaction mixture was stirred for a further 30 min at −78 °C, warmed to rt over 10 min, stirred at rt for 10 min, quenched with sat. aq. NH_4Cl (5 mL), and extracted with Et_2O (4 × 5 mL). The combined organic extracts were washed with water (10 mL) and brine (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Purification of the resulting colourless oil (SiO_2, 0–2% Et_2O/petroleum ether) gave a colourless oil, 2,5-dimethylated pyrrolidine **302** (44 mg, 56%), as a ~1:1 mixture of inseparable diastereomers.

R_f 0.45 (5% EtOAc/petroleum ether); IR (neat/cm^{-1}) 2968 m, 2929 w, 1455 w, 1414 s, 1390 m, 1365 w, 1340 w, 1286 w, 1256 m, 1235 m, 1137 m, 1099 s, 1035 w, 973 w, 820 w; δ_H (400 MHz, $CDCl_3$) (1:1 diastereomer mixture) 4.59–4.02 (2H, m, NCH), 2.27–1.49 (4H, m, $(CH_2)_2$), 1.67 (1.67) (9H, s, $C(CH_3)_3$), 1.35 (1.33) (3H, d, J = 7.0 Hz, NCHCH_3), 1.18 (1.27) (3H, d, J= 6.0 Hz, NCHCH_3); δ_C (100 MHz, $CDCl_3$) (diastereomer mixture) 183.1 (183.4) (C=S), 84.6 (84.7) ($C(CH_3)_3$), 57.5 (58.4) (NCH), 56.2 (55.6) (NCH), 30.54 (31.9) (NCHCH_2), 30.51 (29.1) (NCHCH_2), 28.6 ($C(CH_3)_3$), 21.9 (19.8) (CHCH_3), 17.9 (CHCH_3); HRMS (FI^+) calcd for $C_{11}H_{21}NOS$: 215.1344, found 215.1348.

O-tert-Butyl 2-methyl-4-($^2H_1$)azetidine-1-carbothioate (199a)

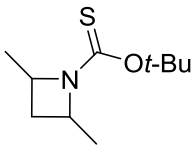


A solution of *O-tert*-butyl 2-methylazetidine-1-carbothioate (**288b**) (36 mg, 0.19 mmol) in THF (1 mL) was cooled to −78 °C (acetone/dry-ice) before the addition of TMEDA (69 μL, 0.46 mmol). *s*-BuLi (1.3 M in cyclohexane/hexane, 192 μL, 0.25 mmol) was then added dropwise over 2 min. The reaction mixture was stirred for 30 min at −78 °C, warmed to −40 °C over 15 min, and re-cooled to −78 °C before the addition of the CD_3OD

(23 μL, 0.57 mmol). The reaction mixture was stirred for a further 15 min at −78 °C, warmed to rt over 10 min, stirred at rt for 10 min, quenched with sat. aq NH_4Cl (10 mL), and extracted with Et_2O (4 × 10 mL). The combined organic extracts were washed with water (20 mL) and brine (20 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Purification of the resulting very pale yellow oil (SiO_2, 10% Et_2O/petroleum ether) gave a colourless oil, 2,4-disubstituted azetidine **199a** (18 mg, 50% mass recovery, 91% D by FI HRMS analysis), as a ~1:1 mixture of inseparable diastereomers.

R_f 0.29 (5% EtOAc/petroleum ether); IR (neat/cm^{-1}) 2967 w, 2928 w, 1469 s, 1436 s, 1391 w, 1365 w, 1342 w, 1274 s, 1140 s, 1005 w, 969 w, 955 w, 825 w; δ_H (500 MHz, $CDCl_3$) (2.1:1 rotamer mixture by analysis of NCH signals in the 4.57–4.34 region) 4.40–4.34 (4.57–4.50) (1H, m, NC*H*CH_3), 4.06–3.89 (1H, m, NCHD), 2.39–1.72 (2H, m, NCHC*H*$_2$), 1.65 (1.64) (9H, s, C(CH_3)$_3$), 1.43 (1.57) (3H, d, *J* = 6.0 Hz, NCHC*H*$_3$); δ_C (125 MHz, $CDCl_3$) (rotamer mixture) 185.3 (C=S), 84.7 (84.5) (*C*(CH_3)$_3$), 59.9 (61.0) (NCH), 48.7 (48.8) (T, *J* = 22.9 Hz, CHD), 28.5 (C(*C*H_3)$_3$), 22.2 (22.7) (NCH*C*H_2), 20.6 (19.8) (NCH*C*H_3); HRMS (FI^+) calcd for $C_9DH_{16}NOS$: 188.1094, found 188.1094.

O-tert-Butyl 2,4-dimethylazetidine-1-carbothioate (199c)

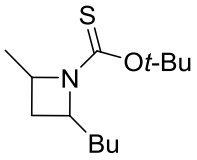


A solution of *O-tert*-butyl 2-methylazetidine-1-carbothioate (**288b**) (62 mg, 0.33 mmol) in THF (2 mL) was cooled to −78 °C (acetone/dry-ice) before the addition of TMEDA (119 μL, 0.79 mmol). *s*-BuLi (1.3 M in cyclohexane/hexane, 331 μL, 0.43 mmol) was then added dropwise over 3 min. The reaction mixture was stirred for 30 min at −78 °C before the addition of the MeI (62 μL, 1.00 mmol). The reaction mixture was stirred for a further 30 min at −78 °C, warmed to rt over 10 min, stirred at rt for 10 min, quenched with sat. aq

NH_4Cl (10 mL), and extracted with Et_2O (4 × 10 mL). The combined organic extracts were washed with water (20 mL) and brine (20 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Purification of the resulting very pale yellow oil (SiO_2, 0–2% Et_2O/petroleum ether) gave a colourless oil, *N*-Botc-2,4-dimethylazetidine **199c** (37 mg, 55%, 93% brsm), as a ~1:1 mixture of inseparable diastereomers.

R_f 0.38 (10% Et_2O/petroleum ether); IR (neat/cm^{-1}) 2965 w, 2927 w, 1465 m, 1430 s, 1390 w, 1365 w, 1347 w, 1268 s, 1225 w, 1138 s, 1003 m, 938 w, 835 m, 752 w; δ_H (400 MHz, $CDCl_3$) (1:1 diastereomer mixture) 4.54–4.19 (2H, m, NCH), 2.53 (1.98–1.87) (2H, dt (m), J = 11.1, 8.6 Hz, NCHCH_2), 1.64 (1.63) (9H, s, C(CH_3)$_3$), 1.56 (1.55) (3H, d, J = 6.0 Hz, NCHCH_3), 1.41 (1.39) (3H, d, J = 6.0 Hz, NCHCH_3); δ_C (100 MHz, $CDCl_3$) (diastereomer mixture) 186.4 (184.2) (C=S), 84.4 (*C*(CH_3)$_3$), 58.57 (58.54) (NCH), 58.1 (57.5) (NCH), 31.2 (31.1) (NCH*C*H_2), 28.6 (28.5) (C(*C*H_3)$_3$), 22.0 (21.3) (CH*C*H_3), 20.3 (19.0) (CH*C*H_3); HRMS (FI^+) calcd for $C_{10}H_{19}NOS$: 201.1187, found 201.1182.

O-tert-Butyl 2-butyl-4-methylazetidine-1-carbothioate (199d)

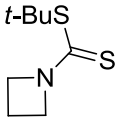


A solution of *O*-*tert*-butyl 2-butylazetidine-1-carbothioate (**288d**) (54 mg, 0.24 mmol) in Et_2O (1.5 mL) was cooled to −78 °C (acetone/dry-ice) before the addition of TMEDA (85 µL, 0.57 mmol). *s*-BuLi (235 µL, 0.31 mmol, 1.3 M in cyclohexane/hexane) was then added dropwise over 3 min. The reaction mixture was stirred for 30 min at −78 °C before the addition of MeI (44 µL, 0.71 mmol). The reaction mixture was stirred for a further 30 min at −78 °C, warmed to rt over 10 min, stirred at rt for 10 min, quenched with sat. aq. NH_4Cl (5 mL), and extracted with Et_2O (4 × 5 mL). The combined organic extracts were washed with water (10 mL) and brine (10 mL), dried ($MgSO_4$) and concentrated under

reduced pressure. Purification of the resulting very pale yellow oil (SiO_2, 0–2% Et_2O/petroleum ether) gave a colourless oil, *N*-Botc-2,4-disubstituted azetidine **199d** (26 mg, 46%, 68% brsm), as a ~1:1 mixture of inseparable diastereomers.

R_f 0.47 (10% Et_2O/petroleum ether); IR (neat/cm^{-1}) 2960 w, 2928 w, 1467 s, 1433 s, 1390 w, 1365 w, 1224 s, 1143 s, 1001 w, 959 w, 842 w; δ_H (500 MHz, $CDCl_3$) (rotamer mixture) 4.48–4.12 (2H, m, HCNCH), 2.50–1.58 (4H, m, NCHCH_2 and CH_2(CH_2)$_2$$CH_3$), 1.65 (1.64) (9H, s, C(CH_3)$_3$), 1.57 (1.55) (1.5H, d, *J* = 6.3 Hz, NCHCH_3), 1.48–1.20 (4H, m, CH_3(CH_2)$_2$), 1.40 (1.41) (1.5H, d, *J* = 6.3 Hz, NCHCH_3), 0.92 (0.90) (3H, t, *J* = 6.9 Hz (*J* = 7.3 Hz), CH_2CH_3); δ_C (125 MHz, $CDCl_3$) (rotamer mixture) 184.11 (186.8) (C=S), 184.07 (186.7) (C=S), 84.5 (84.6) (*C*(CH_3)$_3$), 84.4 (*C*(CH_3)$_3$), 62.2 (62.9) (NCH), 61.6 (62.8) (NCH), 58.2 (58.9) (NCH), 57.8 (58.5) (NCH), 32.5 (35.3) (NCH*C*H_2), 31.1 (33.9) (NCH*C*H_2), 29.3 (29.44) (NCH*C*H_2), 29.0 (29.39) (NCH*C*H_2), 28.62 (28.55) (C(*C*H_3)$_3$), 26.0 (27.0) (*C*$H_2$$CH_2$$CH_3$), 25.7 (26.5) (*C*$H_2$$CH_2$$CH_3$), 22.6 (22.5) (*C*$H_2$$CH_3$), 20.4 (21.7) (NCH*C*$H_3$), 19.1 (20.9) (NCH*C*$H_3$), 14.1 (14.0) ($CH_2$*C*$H_3$); HRMS ($FI^+$) calcd for $C_{13}H_{25}NOS$: 243.1657, found 243.1667.

tert-Butyl azetidine-1-carbodithioate (306)

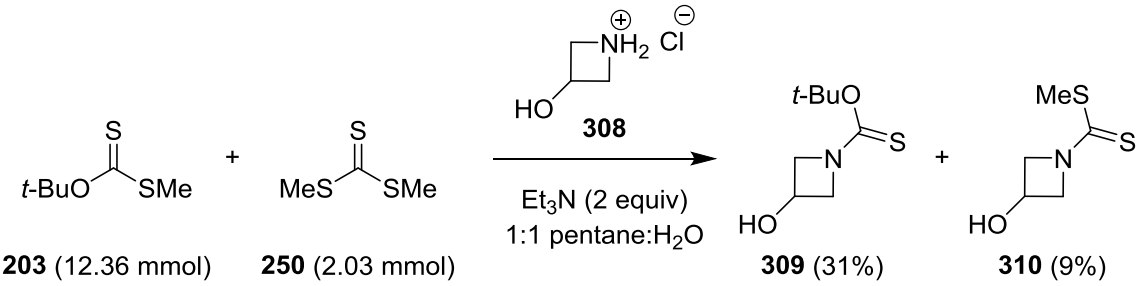


To a suspension of Cs_2CO_3 (1.25 g, 3.85 mmol) and tetrabutylammonium iodide (1.42 g, 3.85 mmol) in DMF (18 mL) was added azetidine (0.24 mL, 3.50 mmol) and CS_2 (0.23 mL, 3.85 mmol). After stirring at rt for 15 min, reaction mixture was then cooled to 0 °C, *t*-BuBr (0.43 mL, 3.85 mmol) was added and the reaction mixture was stirred for 24 h, warming to rt. The reaction mixture was then poured onto H_2O (60 mL), extracted with Et_2O (3 × 60 mL), washed with H_2O (2 × 60 mL) and brine (60 mL), dried ($MgSO_4$) and

concentrated under reduced pressure. Purification of the resulting brown oil (SiO_2, 5–20% Et_2O/ petroleum ether) gave a white solid, dithiocarbamate **306** (180 mg, 27%).

R_f 0.48 (30% Et_2O/petroleum ether); mp 64–65 °C; IR (neat/cm^{-1}) 2987 w, 2949 w, 2921 w, 2857 w, 2360 w, 2342 w, 1472 s, 1449 m, 1425 s, 1386 w, 1358 m, 1287 w, 1259 m, 1242 s, 1165 m, 1141 s, 1005 m, 962 s, 921 w; δ_H (400 MHz, $CDCl_3$) 4.25–4.11 (4H, m, NCH_2), 2.34–2.26 (2H, m, NCH_2CH_2), 1.64 (9H, s, $C(CH_3)_3$); δ_C (100 MHz, $CDCl_3$) 193.2 (C=S), 53.6 (NCH_2), 53.5 (NCH_2), 50.4 ($C(CH_3)_3$), 29.7 ($C(CH_3)_3$), 14.8 (NCH_2CH_2); HRMS (ESI+) calcd for $C_8H_{15}NNaS_2$: 212.0538, found 212.0537.

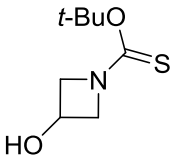
Synthesis of *O*-*tert*-Butyl 3-hydroxyazetidine-1-carbothioate (309) and side-product methyl 3-hydroxyazetidine-1-carbodithioate (310)



203 (12.36 mmol) **250** (2.03 mmol) **309** (31%) **310** (9%)

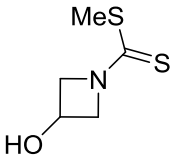
To a solution of impure *O*-*tert*-butyl *S*-methyl carbonodithioate (**203**)[171(a),249] (2.03 g, 12.36 mmol) and dimethyl carbonotrithioate (**250**) (0.28 g, 2.03 mmol) in pentane (2.5 mL) and H_2O (2.5 mL) was added 3-hydroxyazetidin-1-ium chloride (**308**) (1.10 g, 10.03 mmol) and Et_3N (1.68 mL, 12.04 mmol). The reaction mixture was stirred for 12 h at rt and then extracted with with Et_2O (3 × 10 mL) and concentrated under reduced pressure. Purification of the resulting pale yellow oil (SiO_2, 20–30% EtOAc/petroleum ether) first gave a colourless oil, azetidine thiocarbamate **309** (586 mg, 31%), followed by a white solid, azetidine dithiocarbamate **310** (151 mg, 9%).

O-tert-Butyl 3-hydroxyazetidine-1-carbothioate (309)



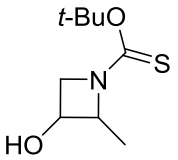
R_f 0.37 (50% EtOAc/petroleum ether); IR (neat/cm^{-1}) 3384 br, 2975 m, 2936 w, 2873 w, 1739 br, 1489 s, 1449 s, 1392 w, 1366 w, 1275 s, 1234 m, 1146 s, 1125 s, 990 m, 781 w; δ_H (400 MHz, $CDCl_3$) 4.58 (1H, br s, OCH), 4.34 (1H, dd, J = 11.0, 6.7 Hz, NC*H*H′), 4.22 (1H, dd, J = 10.9, 6.8 Hz, NC*H*H′), 3.97 (1H, dd, J = 11.1, 3.3 Hz, NCH*H*′), 3.85 (1H, dd, J = 11.1, 3.3 Hz, NCH*H*′), 2.57 (1H, br s, OH), 1.63 (9H, s, $C(CH_3)_3$); δ_C (100 MHz, $CDCl_3$) 185.4 (C=S), 85.3 ($C(CH_3)_3$), 61.5 (NCH_2), 60.2 (CHOH), 60.0 (NCH_2), 28.3 ($C(CH_3)_3$); HRMS (FI^+) calcd for $C_8H_{15}NO_2S$: 189.0824, found 189.0826.

Methyl 3-hydroxyazetidine-1-carbodithioate (310)



R_f 0.35 (50% EtOAc/petroleum ether); mp 66-68 °C; IR (neat/cm^{-1}) 3376 br, 2923 w, 2859 w, 1739 w, 1477 s, 1448 s, 1314 w, 1252 w, 1149 s, 1123 m, 1044 w, 992 m, 957 m, 835 w; δ_H (400 MHz, $CDCl_3$) 4.77–4.72 (1H, m, OCH), 4.51 (1H, ddd, J = 12.0, 7.0, 2.0 Hz, NC*H*H′), 4.4 (1H, ddd, J = 11.0, 7.0, 2.0 Hz, NC*H*H′), 4.14–4.09 (1H, m, NCH*H*′), 4.05–4.01 (1H, m, NCH*H*′), 2.92 (1H, br s, OH), 1.62 (9H, s, $C(CH_3)_3$); δ_C (100 MHz, $CDCl_3$) 196.0 (C=S), 64.1 (NCH_2), 62.2 (NCH_2), 61.1 (CHOH), 18.6 (CH_3); HRMS (FI+) calcd for $C_5H_9NOS_2$: 163.0126, found 163.0130.

_O_-(_tert_-Butyl) 3-hydroxy-2-methylazetidine-1-carbothioate (311b)



A solution of *O-tert*-butyl 2-methylazetidine-1-carbothioate (**309**) (150 mg, 0.79 mmol) in THF (3 mL) was cooled to −78 °C (acetone/dry-ice) before the addition of TMEDA (285 µL, 1.90 mmol). *s*-BuLi (1.3 M in cyclohexane/hexane, 1.83 mL, 2.38 mmol) was then added dropwise over 3 min. The reaction mixture was stirred for 30 min at −78 °C before the addition of the MeI (148 µL, 2.38 mmol). The reaction mixture was stirred for a further 30 min at −78 °C, warmed to rt over 10 min, stirred at rt for 20 min, quenched with sat. aq NH_4Cl (10 mL), and extracted with Et_2O (4 × 10 mL). The combined organic extracts were washed with water (20 mL) and brine (20 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Purification of the resulting very pale yellow oil (SiO_2, 10–30% EtOAc/petroleum ether) gave a colourless oil, methylated azetidine **311b** (29 mg, 18%), as a ~55:45 (*cis*:*trans*) mixture of inseparable diastereomers. Ratio of diastereomers was determined by integration of NCHCH_3 signals in the 1.57–1.38 ppm region of the ^{1}H NMR spectrum.

R_f 0.43 (50% EtOAc/petroleum ether); IR (neat/cm^{-1}) 3391 br, 2976 w, 2930 w, 1479 s, 1444 s, 1392 w, 1366 w, 1273 s, 1230 w, 1142 s, 943 w, 836 w; δ_C (125 MHz, $CDCl_3$) (rotamer mixture) 186.2 (186.3) (C=S), 185.4 (184.9) (C=S), 85.1 (85.2) (*C*$(CH_3)_3$), 85.0 (85.1) (*C*$(CH_3)_3$), 69.3 (70.6) (CHOH), 67.5 (68.1) (CHOH), 64.8 (66.5) (NCH), 61.9 (62.5) (NCH), 59.9 (59.1) (NCH_2), 58.8 (58.7) (NCH_2), 28.42 (28.40) (C(*C*$H_3)_3$), 18.0 (17.4) (NCH*C*H_3), 12.6 (11.6) (NCH*C*H_3); HRMS (FI$^+$) calcd for $C_9H_{17}NO_2S$: 203.0980, found 203.0980.

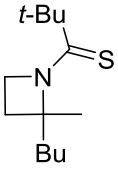
Discernible ^{1}H NMR data for *cis* product:

δ_H (500 MHz, $CDCl_3$) (2.2:1 rotamer mixture by analysis of NCHC*H*$_3$ signals at 1.52 and 1.38) 4.58–4.55 (4.69–4.62) (1H, m, C*H*OH), 4.45 (4.69–4.62) (1H, quind, *J* = 6.7, 1.9 Hz (m), NCH), 4.33 (4.22) (1H, dd, *J* = 11.4, 6.9 Hz (11.0, 7.3 Hz), NC*H*H′), 3.91 (1H, ddd, *J* = 11.5, 4.4, 1.7 Hz, NCH*H*′), 2.11 (2.32) (1H, br s, OH), 1.64 (1.63) (9H, s, C(CH_3)$_3$), 1.38 (1.52) (3H, d, *J* = 6.6 Hz (6.3 Hz), NCHC*H*$_3$).

Discernible ^{1}H NMR data for *trans* product:

δ_H (500 MHz, $CDCl_3$) (2.9:1 rotamer mixture by analysis of NCHC*H*$_3$ signals at 1.56 and 1.43) 4.09–4.07 (4.69–4.62) (1H, m, C*H*OH), 4.30 (1H, dd, *J* = 11.4, 1.6 Hz, NC*H*H′), 4.16–4.10 (4.69–4.62) (1H, m, NCH), 3.84 (3.75) (1H, dd, J = 11.3, 4.4 Hz, (11.0, 4.1 Hz), NCH*H*′), 2.11 (2.32) (1H, br s, OH), 1.64 (1.63) (9H, s, C(CH_3)$_3$), 1.43 (1.56) (3H, d, *J* = 6.3 Hz (6.6 Hz), NHC*H*$_3$).

1-(2-Butyl-2-methylazetidin-1-yl)-2,2-dimethylpropane-1-thione (312b)

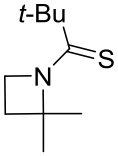


A solution of 1-(2-butylazetidin-1-yl)-2,2-dimethylpropane-1-thione (**165d**) (75 mg, 0.35 mmol) in THF (2 mL) was cooled to −78 °C (acetone/dry-ice) before the addition of TMEDA (126 µL, 0.84 mmol). *s*-BuLi (1.3 M in cyclohexane/hexane, 324 µL, 0.42 mmol) was then added quickly in one portion. The reaction mixture was stirred for 30 min at −78 °C before the addition of the MeI (66 µL, 1.1 mmol). The reaction mixture was stirred for a further 15 min at −78 °C, warmed to rt over 10 min, stirred at rt for 20 min, then quenched with sat. aq. NH_4Cl (5 mL), and extracted with Et_2O (4 × 5 mL). The combined organic extracts were washed with water (10 mL) and brine (10 mL), dried ($MgSO_4$) and

concentrated under reduced pressure. Purification of the pale yellow oil (SiO_2, 2–4% Et_2O/petroleum ether) gave a colourless oil, 2,2-disubstituted azetidine **312b** (33 mg, 41%, 69% brsm).

R_f 0.34 (10% Et_2O/petroleum ether); IR (neat/cm^{-1}) 2958 m, 2927 m, 2872 w, 1739 w, 1461 s, 1418 s, 1363 m, 1262 w, 1119 s, 995 m; δ_H (400 MHz, $CDCl_3$) 4.49–4.44 (1H, m, NC*H*H′), 4.40–4.35 (1H, m, NCH*H*′), 2.53–2.47 (1H, m, C*H*H′$CH_2CH_2CH_3$), 2.23–2.17 (1H, m, C*H*H′CH_2N), 1.96–1.90 (1H, m, CH*H*′CH_2N), 1.83–1.77 (1H, m, CH*H*′$CH_2CH_2CH_3$), 1.77 (3H, s, CH_3), 1.40–1.23 (4H, m, $CH_2CH_2CH_3$), 1.29 (9H, s, $(CH_3)_3$), 0.91 (3H, t, J = 7.0 Hz, CH_2CH_3); δ_C (100 MHz, $CDCl_3$) 208.7 (C=S), 77.3 (N*C*CH_3), 54.6 (NCH_2), 43.6 ($C(CH_3)_3$), 35.9 ($CH_2CH_2CH_2CH_3$), 29.3 ($C(CH_3)_3$), 27.8 (CH_2), 25.8 ($CH_2CH_2CH_3$), 23.8 (NCCH_3), 22.8 (CH_2CH_3), 14.1 (CH_2CH_3); HRMS (ESI^+) calcd for $C_{13}H_{25}NNaS$: 250.1600, found 250.1597.

1-(2,2-Dimethylazetidin-1-yl)-2,2-dimethylpropane-1-thione (312c)

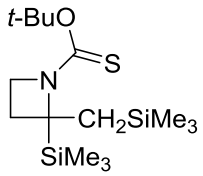


A solution of 2,2-dimethyl-1-(2-methylazetidin-1-yl)propane-1-thione (**165a**)[148] (59 mg, 0.34 mmol) in THF (2 mL) was cooled to −78 °C (acetone/dry-ice) before the addition of TMEDA (124 µL, 0.83 mmol). *s*-BuLi (1.3 M in cyclohexane/hexane, 317 µL, 0.41 mmol) was then added rapidly in 1 portion (1 mL in <2 s). The reaction mixture was stirred for 30 min at −78 °C before addition of MeI (64 µL, 1.0 mmol). The reaction mixture was stirred for a further 15 min at −78 °C, warmed to rt over 10 min, stirred at rt for 20 min, then quenched with sat. aq NH_4Cl (5 mL), and extracted with Et_2O (4 × 5 mL). The combined organic extracts were washed with water (10 mL) and brine (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Purification of the pale yellow solid (SiO_2, 3–5%

Et_2O/petroleum ether) gave a white solid, 2,2-disubstituted azetidine **312c** (32 mg, 50%, 59% brsm).

R_f 0.52 (30% Et_2O/petroleum ether); mp 65–67 °C; IR (neat/cm^{-1}) 2992 w, 2960 m, 2923 w, 1468 m, 1458 m, 1429 s, 1362 s, 1270 w, 1252 w, 1231 w, 1154 w, 1113 s; δ_H (400 MHz, $CDCl_3$) 4.51–4.46 (2H, m, NCH_2), 2.10–2.06 (2H, m, NCH_2CH_2), 1.79 (6H, s, $C(CH_3)_2$), 1.30 (9H, s, $(CH_3)_3$); δ_C (100 MHz, $CDCl_3$) 208.7 (C=S), 74.4 (NC_qCH_3), 54.3 (NCH_2), 43.6 ($C(CH_3)_3$), 31.1 (CH_2), 29.3 (($CH_3)_3$), 24.7 ($C_q(CH_3)_2$); HRMS (ESI^+) calcd for $C_{10}H_{19}NNaS$: 208.1130, found 208.1124.

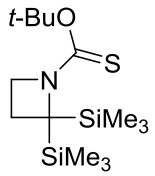
O-tert-Butyl 2-(trimethylsilyl)-2-((trimethylsilyl)methyl)azetidine-1-carbothioate (293c)



A solution of *O-tert*-butyl 2-(trimethylsilyl)azetidine-1-carbothioate (**288h**) (44 mg, 0.18 mmol) in THF (2 mL) was cooled to −78 °C (acetone/dry-ice) before the addition of TMEDA (64 µL, 0.43 mmol). *s*-BuLi (1.3 M in cyclohexane/hexane, 0.18 mL, 0.23 mmol) was added dropwise. The reaction mixture was stirred for 30 min at −78 °C before the addition of Me_3SiCH_2Cl (68 µL, 0.49 mmol). The reaction mixture was stirred for a further 15 min at −78 °C, warmed to rt over 10 min, stirred at rt for 20 min, then quenched with sat. aq. NH_4Cl (10 mL), and extracted with Et_2O (4 × 10 mL). The combined organic extracts were washed with water (20 mL) and brine (20 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Purification of the resulting colourless oil (SiO_2, 2% Et_2O/petroleum ether) gave a colourless oil, 2,2-disubstituted azetidine **293c** (13 mg, 22%, 31% brsm).

R_f 0.45 (10% Et_2O/petroleum ether); IR (neat/cm^{-1}) 2953 w, 2897 w, 1479 s, 1444 s, 1391 w, 1365 w, 1278 m, 1248 s, 1198 s, 1144 w, 963 w, 836 s, 736 w, 736 w, 691 w; δ_H (400 MHz, $CDCl_3$) 4.02–3.95 (1H, m, NC*H*H′), 3.90–3.83 (1H, m, NCH*H*′), 2.07 (2H, t, *J* = 7.8 Hz, CH_2), 1.69 (9H, s, $C(CH_3)_3$), 1.58 (1H, d, *J* = 15.1 Hz, C*H*H′$Si(CH_3)_3$), 0.93 (1H, d, *J* = 15.1 Hz, CH*H*′$Si(CH_3)_3$), 0.12 (9H, s, $^2J_{29Si-H}$ = 6 Hz, $Si(CH_3)_3$), 0.11 (9H, s, $^2J_{29Si-H}$ = 6 Hz, $Si(CH_3)_3$); δ_C (125 MHz, $CDCl_3$) 183.4 (C=S), 85.0 ($C(CH_3)_3$), 66.9 (NC_q), 49.1 (NCH_2), 28.9 ($C(CH_3)_3$), 23.4 (CH_2), 22.8 ($CH_2Si(CH_3)_3$), 0.42 (J_{29Si-C} = 51 Hz, $Si(CH_3)_3$), −3.25 (J_{29Si-C} = 52 Hz, $Si(CH_3)_3$); HRMS (ESI^+) calcd for $C_{15}H_{33}NNaOS^{28}Si_2$: 354.1717, found 354.1711.

O-tert-Butyl 2,2-bis(trimethylsilyl)azetidine-1-carbothioate (293a)

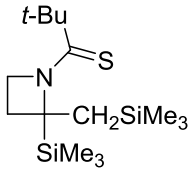


A solution of *O-tert*-butyl 2-(trimethylsilyl)azetidine-1-carbothioate (**288h**) (80 mg, 0.33 mmol) in THF (3 mL) was cooled to −78 °C (acetone/dry-ice) before the addition of TMEDA (166 µL, 1.11 mmol). *s*-BuLi (1.3 M in cyclohexane/hexane, 326 mL, 0.60 mmol) was added dropwise. The reaction mixture was stirred for 30 min at −78 °C before the addition of Me_3SiCl (124 µL, 0.98 mmol). The reaction mixture was stirred for a further 30 min at −78 °C, warmed to rt over 10 min, stirred at rt for 20 min, then quenched with sat. aq. NH_4Cl (10 mL), and extracted with Et_2O (4 × 10 mL). The combined organic extracts were washed with water (20 mL) and brine (20 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Purification of the resulting colourless oil (SiO_2, 2–50% Et_2O/petroleum ether) gave a colourless oil, 2,2-disubstituted azetidine **293a** (16 mg, 16%, 19% brsm). Data as p 224–225.

General Procedure D: α-deprotonation–electrophile trapping of 2,2-dimethyl-1-(2-(trimethylsilyl)azetidin-1-yl)propane-1-thione (165g)

A solution of 2,2-dimethyl-1-(2-(trimethylsilyl)azetidin-1-yl)propane-1-thione (**165g**) (1 equiv) in THF (8 mL/mmol **165g**) was cooled to −78 °C (acetone/dry-ice) before the addition of TMEDA (2.4 equiv). *s*-BuLi (1.3 M in cyclohexane/hexane, 1.3 equiv) was then added rapidly in 1 portion (1 mL in <2 s). The reaction mixture was stirred for 30 min at −78 °C before the addition of the electrophile (2–3 equiv). The reaction mixture was stirred for 20 min at −78 °C, warmed to rt over 10 min, and then stirred at rt for a further 20 min, then quenched with sat. aq HCl (1 M, 10 mL), and extracted with Et_2O (4 × 10 mL). The combined organic extracts were washed with water (20 mL) and brine (20 mL), dried ($MgSO_4$) and concentrated under reduced pressure.

2,2-Dimethyl-1-(2-(trimethylsilyl)-2-((trimethylsilyl)methyl)azetidin-1-yl)propane-1-thione (312d)

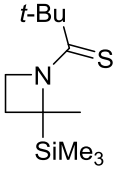


2,2-Dimethyl-1-(2-(trimethylsilyl)azetidin-1-yl)propane-1-thione (**165g**) (61 mg, 0.27 mmol) and Me_3SiCH_2Cl (113 µL, 0.81 mmol) were used following General Procedure D. Purification of the resulting yellow solid (SiO_2, 2–4% Et_2O/petroleum ether) gave a white solid, 2,2-disubstituted azetidine **312d** (63 mg, 75%).

R_f 0.58 (10% Et_2O/petroleum ether); mp 87–88 °C; IR (neat/cm^{-1}) 2967 w, 2949 w, 2890 w, 1464 m, 1444 s, 1315 w, 1126 m, 1098 w, 995 m, 927 w, 831 s, 757 m, 699 w, 681 w, 670 w; δ_H (400 MHz, $CDCl_3$) 4.58–4.51 (1H, m, NC*H*H′), 4.40–4.34 (1H, m, NCH*H*′), 2.29 (1H, ddd, *J* = 11.6, 10.2, 6.3 Hz, C*H*H′), 2.20 (1H, d, *J* = 14.7 Hz, C*H*H′Si$(CH_3)_3$),

2.05 (1H, ddd, J = 11.6, 10.2, 6.3 Hz, CH*H*′), 1.31 (9H, s, $C(CH_3)_3$), 1.19 (1H, d, J = 14.7 Hz, CH*H*′$Si(CH_3)_3$), 0.17 (9H, s, $^2J_{29Si\text{-}H}$ = 7 Hz, $Si(CH_3)_3$), 0.11 (9H, s, $^2J_{29Si\text{-}H}$ = 6 Hz, $Si(CH_3)_3$); δ_C (100 MHz, $CDCl_3$) 206.3 (C=S), 72.6 (NC_q), 55.4 (NCH_2), 43.0 ($C(CH_3)_3$), 29.7 ($C(CH_3)_3$), 24.4 (NCH_2CH_2), 22.1 ($CH_2Si(CH_3)_3$), 0.8 ($J_{29Si\text{-}C}$ = 51 Hz, $Si(CH_3)_3$), −0.9 ($J_{29Si\text{-}C}$ = 52 Hz, $Si(CH_3)_3$); HRMS (ESI^+) calcd for $C_{15}H_{33}NNaS^{28}Si_2$: 338.1764, found 338.1750.

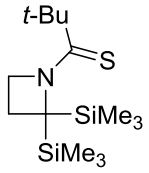
2,2-Dimethyl-1-(2-methyl-2-(trimethylsilyl)azetidin-1-yl)propane-1-thione (312e)



2,2-Dimethyl-1-(2-(trimethylsilyl)azetidin-1-yl)propane-1-thione (**165g**) (80 mg, 0.35 mmol) and MeI (65 µL, 1.05 mmol) were used following General Procedure D, resulting in a white solid, 2,2-disubstituted azetidine **312e** (85 mg, quant).

R_f 0.59 (10% Et_2O/petroleum ether); mp 88–89 °C; IR (neat/cm^{-1}) 2964 m, 2945 m, 2901 w, 1480 s, 1459 s, 1432 s, 1393 w, 1360 m, 1244 s, 1143 w, 1125 w, 1104 w, 1079 w, 959 m, 861 s, 829 s; δ_H (400 MHz, $CDCl_3$) 4.63–4.56 (1H, m, NC*H*H′), 4.40–4.34 (1H, m, NCH*H*′), 2.40–2.33 (1H, m, NCH_2CHH′), 1.83–1.77 (1H, m, NCH_2CH*H*′), 1.74 (3H, s, NC_qCH_3), 1.31 (9H, s, $C(CH_3)_3$), 0.17 (9H, s, $^2J_{29Si\text{-}H}$ = 7 Hz, $Si(CH_3)_3$); δ_C (100 MHz, $CDCl_3$) 206.2 (C=S), 69.6 (NC_q), 54.8 (NCH_2), 42.7 ($C(CH_3)_3$), 29.5 ($C(CH_3)_3$), 25.8 (NCH_2CH_2), 20.6 (NC_qCH_3), −1.6 ($Si(CH_3)_3$); HRMS (ESI^+) calcd for $C_{12}H_{25}NNaS^{28}Si$: 266.1369, found 266.1368.

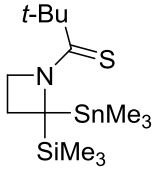
1-(2,2-bis(trimethylsilyl)azetidin-1-yl)-2,2-dimethylpropane-1-thione (312f)



2,2-Dimethyl-1-(2-(trimethylsilyl)azetidin-1-yl)propane-1-thione (**165g**) (80 mg, 0.35 mmol) and Me_3SiCl (133 µL, 1.05 mmol) were used following General Procedure D, resulting in a white solid, 2,2-disubstituted azetidine **312f** (105 mg, quant).

R_f 0.72 (10% EtOAc/*n*-hexane); mp 97–99 °C; IR (neat/cm^{-1}) 2965 w, 2160 w, 1978 w, 1463 s, 1396 w, 1364 w, 1259 m, 1246 s, 1126 m, 1067 w, 1012 w, 1003 w, 951 w, 902 w, 832 s, 754 m, 862 m; δ_H (400 MHz, $CDCl_3$) 4.41–4.37 (2H, m, NCH_2), 2.25–2.21 (2H, m, NCH_2CH_2), 1.31 (9H, s, $C(CH_3)_3$), 0.22 (18H, s, $Si(CH_3)_3$); δ_C (100 MHz, $CDCl_3$) 203.0 (C=S), 66.7 (NC_q), 55.9 (NCH_2), 42.3 ($C(CH_3)_3$), 29.8 ($C(CH_3)_3$), 20.1 (NCH_2CH_2), 0.14 ($J_{^{29}Si\text{-}C}$ = 52 Hz, $Si(CH_3)_3$); HRMS (ESI^+) calcd for $C_{14}H_{31}NNaS^{28}Si_2$: 324.1608, found 324.1598.

2,2-dimethyl-1-(2-(trimethylsilyl)-2-(trimethylstannyl)azetidin-1-yl)propane-1-thione (312g)

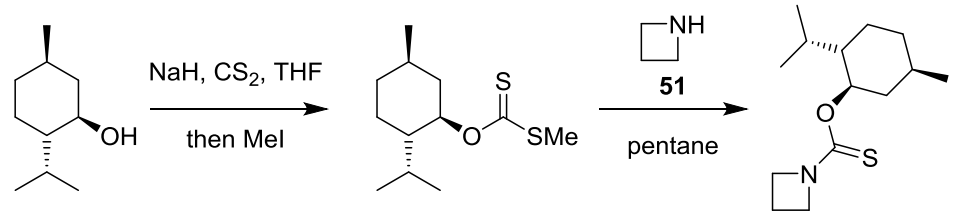


2,2-Dimethyl-1-(2-(trimethylsilyl)azetidin-1-yl)propane-1-thione (**165g**) (80 mg, 0.35 mmol) and Me_3SnCl (139 mg, 0.70 mmol) were used following General Procedure D. Purification of the resulting white solid (SiO_2, 2% Et_2O/petroleum ether) gave a white solid, 2,2-disubstituted azetidine **312g** (107 mg, 78%).

R_f 0.72 (10% Et_2O/petroleum ether); mp 100–101 °C; IR (neat/cm^{-1}) 2969 s, 2889 m, 1480 s, 1466 s, 1442 m, 1363 w, 1244 s, 1179 w, 1125 m, 1062 w, 866 m, 834 s, 754 s, 724 w,

675 w; δ_H (400 MHz, $CDCl_3$) 4.59–4.42 (2H, m, NCH_2), 2.44–2.30 (2H, m, NCH_2CH_2), 1.33 (9H, s, $C(CH_3)_3$), 0.17 (9H, s, $^2J_{119Sn-H}$ = 52 Hz, $^2J_{117Sn-H}$ = 50 Hz, $Sn(CH_3)_3$), 0.15 (9H, s, $Si(CH_3)_3$); δ_C (100 MHz, $CDCl_3$) 199.8 (C=S), 68.0 ($J_{119Sn-C}$ = 302 Hz, $J_{117Sn-C}$ = 289 Hz, J_{29Si-C} = 51 Hz, NC_q), 56.5 (NCH_2), 42.1 ($C(CH_3)_3$), 29.9 ($C(CH_3)_3$), 21.5 (NCH_2CH_2), −0.7 (J_{29Si-C} = 52 Hz, $Si(CH_3)_3$), −5.7 ($J_{119Sn-C}$ = 327 Hz, $J_{117Sn-C}$ = 312 Hz, $Sn(CH_3)_3$); HRMS (ESI^+) calcd for $C_{14}H_{31}NNaS^{28}Si^{120}Sn$: 416.0861, found 416.0850.

***O*-((1*R*,2*R*,5*R*)-2-Isopropyl-5-methylcyclohexyl) azetidine-1-carbothioate (319)**



317 **318** (crude) **319** (93%)

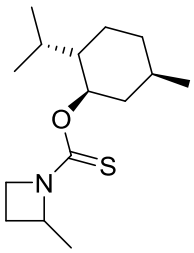
NaH (60 % w/w in mineral oil, 384 mg, 9.60 mmol) was added to a solution of (L)-menthol (0.56 mL, 3.20 mmol) in dry THF (7 mL) at rt. The reaction mixture was stirred at rt for 1.5 h and then CS_2 (0.193 mL, 3.20 mmol) was added, followed by dropwise addition of MeI (0.26 mL, 4.16 mmol). The reaction mixture was stirred at rt for 12 h before addition of sat. aq NH_4Cl (10 mL). The reaction mixture was extracted with Et_2O (3 × 10 mL), washed with water (20 mL) and brine (20 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure to give an orange oil, crude xanthate **318** (940 mg, ~95%), used without further purification.

δ_H (400 MHz, $CDCl_3$) 5.53 (1H, td, *J* = 10.9, 4.4 Hz, OCH), 2.56 (3H, s, SCH_3), 2.25–2.17 (1H, m, OCHC*H*H′), 1.92–1.85 (1H, m, C*H*$(CH_3)_2$), 1.75–1.46 (4H, m, CH_2 and C*H*CH_3 and OCH*H*′), 1.18–0.87 (9H, m, CH_3 and OCHCH*H*′ and CH_2), 0.81 (3H, d, *J* = 6.8 Hz, CH_3); all characterisation data is in good agreement with the literature.[229]

The crude xanthate **318** (787 mg, 3.19 mmol) was dissolved in pentane (6 mL) and cooled to 0 °C (ice-bath). Azetidine (0.179 mL, 2.66 mmol) was added and the reaction mixture was stirred for 60 min at 0 °C, followed by stirring for 90 min at rt, then concentrated under reduced pressure. Purification of the resulting orange solid (SiO_2, 0–5% EtOAc/*n*-hexane) gave a white solid, azetidine **319** (629 mg, 93% yield based on azetidine **51**)

R_f 0.50 (20% EtOAc/*n*-hexane); mp 83–85 °C; IR (neat/cm^{-1}) 2952 w, 2939 w, 2862 w, 2161 w, 2026 w, 1512 s, 1448 m, 1294 s, 1273 m, 1207 s, 1144 m, 1007, 902 w; δ_H (400 MHz, $CDCl_3$) 5.14 (1H, td, *J* = 10.8, 4.3 Hz, OCH), 4.18 (2H, br s, NCH_2), 4.05 (2H, t, *J* = 7.3 Hz, NCH_2), 2.28–2.17 (3H, m, NCH_2CH_2 and OCHC*H*H′), 1.89–1.85 (1H, m, C*H*$(CH_3)_2$), 1.70–1.67 (2H, m, $CHCH_2$), 1.51–1.45 (2H, m, CH ×2), 1.15–1.06 (1H, m, CHC*H*H′), 0.95–0.81 (8H, m, $CHCH_2$ and CH_3), 0.82 (3H, d, *J* = 6.8 Hz, CH_3); δ_C (100 MHz, $CDCl_3$) 186.5 (C=S), 80.7 (OCH), 52.2 (NCH_2), 50.3 (NCH_2), 47.4 (OCH*C*H), 40.9 ($OCHCH_2$), 34.3 (CH_2), 31.2 ($CHCH_3$), 26.4 ($CH(CH_3)_2$), 23.7 ($CHCH_2$), 22.0 ($CHCH_3$), 20.7 ($CH(CH_3)_2$), 17.0 ($CH(CH_3)_2$), 14.8 (NCH_2CH_2); HRMS (ESI^+) calcd for $C_{14}H_{25}NNaOS$: 278.1549, found 278.1546.

_O_-((1_R_,2_R_,5_R_)-2-Isopropyl-5-methylcyclohexyl) 2-methylazetidine-1-carbothioate (320)

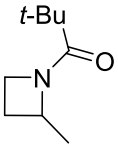


A solution of *O*-((1*R*,2*R*,5*R*)-2-isopropyl-5-methylcyclohexyl) azetidine-1-carbothioate (**319**) (80 mg, 0.31 mmol) in THF (2 mL) was cooled to −78 °C (acetone/dry-ice) before addition of TMEDA (113 µL, 0.75 mmol). *s*-BuLi (482 µL, 0.63 mmol) was added dropwise over 3 min. The reaction mixture was stirred at −78 °C for 30 min before

addition of MeI (59 μL, 0.94 mmol). The reaction mixture was stirred for a further 15 min at −78 °C, warmed to rt over 10 min, stirred at rt for 15 min, then quenched with a sat. aq NH_4Cl (3 mL) and extracted with Et_2O (3 × 5 mL). The combined organic extracts were washed with H_2O (10 mL) and brine (10 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. Purification of the resulting pale yellow oil (SiO_2, 0–5% TBME/*n*-hexane) gave a colourless oil, methylated azetidine **320** (80 mg, 95%), as a ~1:1 mixture of inseparable diastereomers; The diastereomeric ratio was determined by variable temperature NMR analysis: rotamer signals were no longer present in the ^{13}C NMR spectrum run at 120 °C, and integration of the 2 remaining signals for each C atom indicated a 1:1 mixture of diastereomers.

R_f 0.42 (10% TBME/*n*-hexane); IR (neat/cm^{-1}) 2955 m, 2925 m, 2869 w, 1485 s, 1466 s, 1440 s, 1338 w, 1242 s, 1212 w, 1193 m, 1142 s, 1038 w, 1024 w, 989 m, 891 w; δ_H (400 MHz, $CDCl_3$) (2:1 rotamer mixture by analysis of NCH signals in the 4.61–4.38 region) 5.25–5.14 (1H, m, OCH), 4.48–4.38 (4.61–4.50) (1H, m, NCH), 4.13–3.93 (2H, m, NCH_2), 2.47–2.32 (1H, m, CH_2CHH'), 2.18 (1H, m, CH_2CHH'), 1.92–1.76 (2H, m, $CH(CH_3)_2$ and CH_2CHH'), 1.69–1.66 (2H, m, $CHCHH'$ and CH_2CHH'), 1.50–1.42 (4H, m, $NCHCH_3$ and $OCHCH$), 1.18–1.05 (1H, m, $CHCHH'$), 0.96–0.81 (11H, m, CH_3 × 3, $CHCH_2$); δ_C (100 MHz, $CDCl_3$) (rotamer mixture) 187 (186.65) (C=S), 186.7 (186.3) (C=S), 80.37 (79.8) (OCH), 80.35 (79.7) (OCH), 59.8 (61.5) (NCH), 59.7 (61.4) (NCH), 49.3 (48.7) (NCH_2), 49.2 (48.6) (NCH_2), 47.52 (47.4) ($OCHCH$), 47.45 (47.2) ($OCHCH$), 41.05 (41.1), ($OCHCH_2$), 40.65 (40.7) ($OCHCH_2$), 34.3 (34.2) ($CHCH_2$), 31.2 (31.16) ($CHCH_2$), 26.4 (26.5) ($CH(CH_3)_2$), 26.0 (26.2) ($CH(CH_3)_2$), 23.7 (23.9) (CH_2), 23.1 (23.5) (CH_2), 22.9 (23.4) (CH_2), 22.85 (23.45) (CH_2), 22.1 (20.9) (CH_3), 22.0 (21.0) (CH_3), 21.2 (20.0) (CH_3), 20.8 (19.6) (CH_3), 17.0 (17.1) (CH_3), 16.5 (16.8) (CH_3); HRMS (ESI^+) calcd for $C_{15}H_{27}NNaOS$: 292.1706, found 292.1709.

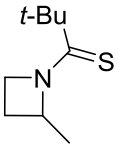
2,2-Dimethyl-1-(2-methylazetidin-1-yl)propan-1-one (328)



A solution of HCl in Et_2O (2 M, 3mL) was added to *O*-*tert*-butyl 2-methylazetidine-1-carbothioate (**288b**) (80 mg, 0.43 mmol). The reaction mixture was stirred at rt for 1 h, and was then concentrated under reduced pressure. The resulting colourless oil (46 mg) was dissolved in py (2 mL), DMAP (10 mg, 0.09 mmol) was added, and the reaction mixture was heated to 70 °C for 10 min and then cooled to 0 °C. pivCl (79 µL, 0.64 mmol) was added and the reaction mixture was stirred at rt for 12 h. aq HCl (2 M, 5 mL) was added and the reaction mixture was then extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with H_2O (15 mL) and brine (15 mL) dried ($MgSO_4$) and concentrated under reduced pressure. Purification of the resulting pale yellow oil (SiO_2, 10–30% EtOAc/petroleum ether) gave a colourless oil, *N*-pivaloyl-2-methyl-azetidine **328** (47 mg, 71%).

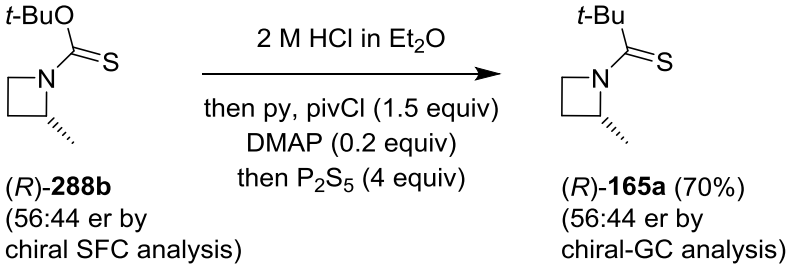
R_f 0.31 (60% EtOAc/petroleum ether); IR (neat/cm^{-1}) 2961 m, 2928 w, 2906 w, 1619 s, 1481 w, 1461 w, 1407 s, 1382 w, 1364 m, 1341 w, 1294 w, 1257 w, 1235 w, 1140 w, 1087 w, 1028 w, 959 w, 754 w; δ_H (400 MHz, $CDCl_3$) 4.45–4.37 (1H, m, NC*H*), 4.23–4.12 (1H, m, NCH_2), 2.37–2.28 (1H, m, CH*H*′), 1.76–1.88 (1H, m, C*H*H′), 1.37 (3H, d, J = 6.4 Hz, CH_3), 1.11 (9H, s, $C(CH_3)_3$); δ_C (100 MHz, $CDCl_3$) 178.0 (C=S), 58.2 (NCH), 50.5 (NCH_2), 38.4 ($C(CH_3)_3$), 27.0 ($C(CH_3)_3$), 24.1 (CH_2), 21.1 ($CHCH_3$); HRMS (ESI^+) calcd for $C_9H_{17}NNaO$: 178.1202, found 178.1210.

2,2-Dimethyl-1-(2-methylazetidin-1-yl)propane-1-thione (165a)



P_2S_5 (258 mg, 1.16 mmol) was added to a soultion of 2,2-dimethyl-1-(2-methylazetidin-1-yl)propan-1-one (**328**) (45 mg, 0.29 mmol) in py (2 mL) at 75 °C. The reaction mixture was stirred at 75 °C for 6 h, then cooled to rt and poured onto aq. HCl (3 M, 10 mL) and extracted with Et_2O (3 × 10 mL). The combined organic extracts were washed with aq. HCl (2 M, 10 mL), water (20 mL) and brine (20 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Purification of the resulting colourless oil (SiO_2, 5–10% Et_2O/petroleum ether) gave a colourless oil, *N*-thiopivaloyl-azetidine **165a** (40 mg, 81%); data as p 215.

(*R*)-2,2-Dimethyl-1-(2-methylazetidin-1-yl)propane-1-thione ((*R*)-165a)



(*R*)-**288b**
(56:44 er by
chiral SFC analysis)

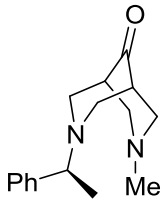
(*R*)-**165a** (70%)
(56:44 er by
chiral-GC analysis)

A solution of HCl in Et_2O (2 M, 3 mL, 6.0 mmol) was added to a sample of *O*-(*tert*-butyl) (*R*)-2-methylazetidine-1-carbothioate ((*R*)-**288b**) (44 mg, 0.24 mmol, 56:44 er)**.** The reaction mixture was stirred at rt for 5 h, then concentrated under reduced pressure. py (1 mL) and DMAP (6 mg, 0.05 mmol) were added to the resulting white solid and the reaction mixture heated to 70 °C for 10 min, then cooled to 0 °C. pivCl (43 µL, 0.35 mmol) was added and the reaction mixture stirred at rt for 12 h. P_2S_5 (209 mg, 0.94 mmol) and py (0.5 mL) was added and the reaction mixture stirred at 75 °C for 6 h, then aq HCl (3 M, 20 mL) was added and the reaction mixture extracted with CH_2Cl_2 (3 × 10 mL). The

combined organic extracts were washed with aq HCl (1 M, 10 mL), H_2O (10 mL) and brine (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Purification of the resulting dark red oil (SiO_2, 10% Et_2O/petroleum ether) gave a colourless oil, *N*-thiopivaloyl azetidine (*R*)-**165a**[148] (28 mg, 70% yield based on (*R*)-**288b**), in 56:44 (*R*:*S*) er (by chiral GC analysis, see Appendix, p A18, τ_R (major) = 36.1 min, τ_R (minor) = 36.5 min; lit.[148] τ_R (*R*) = 29.6 min, τ_R (*S*) = 30.0 min).

$[\alpha]_D^{25}$ −0.1 (*c* 1.27, $CHCl_3$); lit.[148] enantiomerically pure (*R*)-**165a** $[\alpha]_D^{25}$ −21.3 (*c* 1.15, $CHCl_3$); all other data as described for racemic **165a** (p 215).

3-Methyl-7-((*S*)-1-phenylethyl)-3,7-diazabicyclo[3.3.1]nonan-9-one (338)

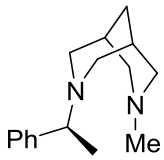


Prepared by a literature[128] procedure: A mixture of 1-methylpiperidin-4-one (**336**) (1.55 mL, 12.60 mmol), (*S*)-1-phenylethanamine (**337**) (1.63 mL, 12.60 mmol), paraformaldehyde (1.14 g, 37.80 mmol) and acetic acid (721 µL, 12.60 mmol) in EtOH (20 mL) was heated under reflux for 14 h. The mixture was allowed to cool, concentrated under reduced pressure and aq KOH (50% w/v, 20 mL), was added. The mixture was then extracted with Et_2O (3 × 50 mL), dried (Na_2SO_4) and concentrated under reduced pressure. Purification of the resulting pale orange oil by bulb-to-bulb distillation (190 °C, 0.1 mbar) gave a pale yellow oil, ketobispidine **338** (1.61 g, 49%).

$[\alpha]_D^{20}$ −2.9 (*c* 1.90, $CHCl_3$); IR (neat/cm^{-1}) 2975 w, 2938 w, 2808 w, 2787 w, 1736 s, 1709 m, 1493 w, 1450 w, 1389 m, 1327 w, 1287 m, 1152 w, 1134 w, 771 m, 702 s; δ_H (400 MHz, $CDCl_3$) 7.39–7.25 (5H, m, Ar), 3.61 (1H, q, *J* = 6.6 Hz, C*H*CH_3), 3.11–2.92 (6H, m, NCH_2), 2.70 (2H, ddd, *J* = 15.9, 11.1 4.5 Hz, NCH_2), 2.61–2.54 (2H, m, C*H*CO), 2.32

(3H, s, NCH_3), 1.39 (3H, d, *J* = 6.6 Hz, CHC*H*$_3$); δ_C (100 MHz, $CDCl_3$) 215.1 (C=O), 143.8 (Ar), 128.3 (Ar), 127.3 (Ar), 127.0 (Ar), 62.7 (NCH), 60.2 (NCH_2), 60.1 (NCH_2), 56.0 (NCH_2), 55.3 (NCH_2), 46.7 (*C*HCO), 46.6 (*C*HCO), 45.0 (NCH_3), 18.7 (CH*C*H$_3$); HRMS (FI^+) calcd for $C_{16}H_{22}N_2O$: 258.1732, found 258.1737.

3-Methyl-7-((*S*)-1-phenylethyl)-3,7-diazabicyclo[3.3.1]nonane (332)

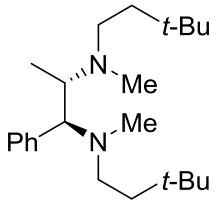


A stirred solution of 3-methyl-7-((*S*)-1-phenylethyl)-3,7-diazabicyclo[3.3.1]nonan-9-one (**338**) (1.57 g, 6.08 mmol), KOH (2.69 g, 48.01 mmol) and hydrazine monohydrate (1.53 mL, 31.6 mmol) in diethylene glycol (9.5 mL) was heated under reflux for 12 h. The volatile components were removed by distillation at 190 °C for 2 h. After this time, the distillate was recombined with the reaction mixture. The resultant mixture was diluted with H_2O (10 mL) then extracted with Et_2O (5 × 15 mL). The combined organic layers were washed with aq. NaOH (20% w/v, 5 × 20 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The resulting pale yellow oil was purified by bulb-to-bulb distillation (160 °C, 0.5 mbar) to give a colourless oil, bispidine **332** (875 mg, 59%).

$[\alpha]_D^{20}$ −7.0 (*c* 0.93, $CHCl_3$); IR (neat/cm^{-1}) 2876 w, 2774 w, 1466 w, 1451 s, 1373 w, 1316 w, 1276 w, 1224 m, 1145 w, 1129 w, 1113 w, 1085 w, 1002 w, 976 w, 922 w, 838 w, 812 w, 764 m, 701 s; δ_H (400 MHz, $CDCl_3$) 7.42–7.20 (5H, m, Ar), 3.42–3.41 (1H, m, NCH), 2.77–2.47 (6H, m, NCH_2), 2.29–2.24 (2H, m, NCH_2), 2.25 (3H, s, NCH_3), 1.97–1.91 (2H, m, C*H*CH_2), 1.64–1.60 (1H, m, CHC*H*H′), 1.41–1.27 (1H, m, CHCH*H*′), 1.33 (3H, d, *J* = 6.7 Hz, CHC*H*$_3$); δ_C (100 MHz, $CDCl_3$) 128.0 (Ar), 127.7 (Ar), 126.4 (Ar), 64.3 (NCH), 58.93 (NCH_2), 58.85 (NCH_2), 55.6 (NCH_2), 54.5 (NCH_2), 46.1 (NCH_3), 28.91 (*C*HCH_2), 28.88 (*C*HCH2), 28.7 (CH*C*H$_2$), 18.9 (CH*C*H$_3$); HRMS (ESI^+) calcd for $C_{16}H_{25}N_2$:

245.2012, found 245.2014; all characterisation data is in good agreement with the literature.[128]

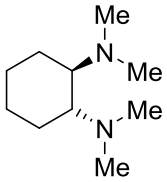
(1*S*,2*S*)-*N*1,*N*2-Bis(3,3-dimethylbutyl)-*N*1,*N*2-dimethyl-1-phenylpropane-1,2-diamine (333)



Prepared by a modified literature[242] procedure: To a solution of crude (1*S*,2*S*)-*N*2-(3,3-dimethylbutyl)-*N*1,*N*2-dimethyl-1-phenylpropane-1,2-diamine (**340**)[242] (0.96 g, 3.7 mmol) in dichloroethane (20 mL) was added 3,3-dimethylbutyraldehyde (1.15 mL, 9.15 mmol), $NaBH(OAc)_3$ (3.10 g, 14.6 mmol) and acetic acid (0.21 mL, 3.7 mmol), and the reaction mixture was stirred at rt for 24 h. A solution of aq NaOH (1 M, 100 mL) was added and the reaction mixture was stirred at room temperature for 5 min. The reaction mixture was extracted with CH_2Cl_2 (3 x 50 mL) and the combined organic extracts were washed with brine (50 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Attempted purification of the resulting pale yellow oil by bulb-to-bulb distillation (180 °C, 0.85 mbar) gave colourless oil, slightly impure pseudo-ephedrine-derived ligand **333** (1.25 g, ~87%, ~90% pure by NMR analysis). Further purification by preparative HPLC-MS was attempted and the resulting colourless oil was dissolved in CH_2Cl_2 (100 mL), washed with aq NaOH (1 M, 100 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a colourless oil, slightly impure pseudo-ephedrine-derived ligand **333**. This was passed through an isolute SCX-2 column (10 g, pre-wet with MeOH, loaded and washed with MeOH, removed from column with 2 M ammonia in MeOH) to give a colourless oil, pseudo-ephedrine-derived ligand **333** (558 mg, 44%).

$[\alpha]_D^{23}$ +33.6 (*c* 1.50, $CHCl_3$); lit.[242] $[\alpha]_D^{20}$ +36.2 (*c* 0.97, $CHCl_3$); IR (neat/cm^{-1}) 2953 s, 2866 w, 2361 w, 1646 w, 1466 s, 1391 w, 1364 m, 1249 w, 1230 w, 1123 w, 1028 w, 1002 w, 955 w, 864 w, 759 w, 703 s; δ_H (400 MHz, $CDCl_3$) 7.34–7.15 (5H, m, Ph), 3.60 (1H, d, *J* = 10.0 Hz, NCH), 3.41–3.33 (1H, m, C*H*CH_3), 2.59–2.42 (2H, m, NCH_2), 2.37–2.11 (2H, m, NCH_2), 2.29 (3H, s, NCH_3), 2.17 (3H, s, NCH_3), 1.57–1.37 (4H, m, C_qCH_2), 0.93 (9H, s, $C(CH_3)_3$), 0.86 (9H, s, $C(CH_3)_3$), 0.66 (3H, d, *J* = 6.1 Hz, CH_3); δ_C (100 MHz, $CDCl_3$) 129.4 (Ar), 127.7 (Ar), 126.8 (Ar), 70.0 (NCH), 56.1 (*C*HCH_3), 50.2 (NCH_2), 50.0 (NCH_2), 42.0 (CH_2), 41.2 (CH_2), 37.9 (CH_3), 36.6 (CH_3), 29.9 (*C*$(CH_3)_3$), 29.7 (C(*C*$H_3)_3$), 10.3 (CH*C*H_3); HRMS (ESI^+) calcd for $C_{23}H_{43}N_2$: 347.3421, found 347.3407; all characterisation data is in good agreement with the literature.[242]

(1*R*,2*R*)-*N*^{1},*N*^{1},*N*^{2},*N*^{2}-tetramethylcyclohexane-1,2-diamine (141)



Prepared by a slightly modified literature[243] procedure: (1*R*,2*R*)-Cyclohexane-1,2-diamine (**342**) (1.00 g, 8.76 mmol), was dissolved in aq formic acid (85%, 3.5 mL), and aq formaldehyde (40%, 4.2 mL) was added dropwise. The mixture was heated under reflux for 2.5 h, then allowed to cool to rt, and then cooled to 0 °C. The mixture was adjusted to pH 12 by addition of NaOH, extracted with Et_2O (3 × 10 mL), dried (Na_2SO_4) and concentrated under reduced pressure. Purification of the resulting orange oil by bulb-to-bulb distillation (100 °C, 10 mmbar) gave a colourless oil, tetramethyl-diamine **141** (1.06 g, 71%).

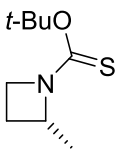
$[\alpha]_D^{20}$ −63.1 (*c* 1.12, $CHCl_3$); lit.[243] $[\alpha]_D^{20}$ −62.9 (*c* 1.05, $CHCl_3$); IR (neat/cm^{-1}) 2925 s, 2856 s, 2820 w, 2774 w, 1451 m, 1379 w, 1361 w, 1273 m, 1172 w, 1152 w, 1066 s, 1046 s,

1025 s, 951 w, 877 w, 851 w; δ_H (400 MHz, $CDCl_3$) 2.38–2.35 (2H, m, NCH), 2.26 (12H, s, CH_3), 1.84-1.81 (2H, m, CH_2), 1.73–1.71 (2H, m, CH_2), 1.17–1.05 (4H, m, CH_2); δ_C (100 MHz, $CDCl_3$) 63.8 (NCH), 40.1 (CH_3), 25.6 (CH*C*H_2), 22.7 (CH_2); HRMS (ESI^+) calcd for $C_{10}H_{23}N_2$: 171.1856, found 171.1863; all characterisation data is in good agreement with the literature.[214,255]

General Procedure E: Asymmetric α-deprotonation–electrophile trapping of *O*-*tert*-butyl azetidine-1-carbothioate (212) with chiral tetramethyl-DIANANE ligand 334a

A solution of (1*S*,2*S*,4*S*,5*S*)-N^2,N^2,N^5,N^5-tetramethylbicyclo[2.2.1]heptane-2,5-diamine (**334a**)[241] (1.3 equiv) in pentane (3.3 mL/mmol **334a**) was cooled to −78 °C and *s*-BuLi (1.3 M in cyclohexane/hexane, 1.3 equiv) was added dropwise (~100 μL/min). The reaction mixture was stirred for 10 min, and then transferred dropwise via cannula to a precooled solution of *O*-*tert*-butyl azetidine-1-carbothioate (**212**) (1 equiv) in pentane (4.3 mL/mmol **212**) at the appropriate lithiation temperature (−78 °C or −98 °C). The reaction mixture was stirred at this temperature for the appropriate lithiation time (1 h or 3 h) before the addition of the electrophile (2–3 equiv). The reaction mixture was stirred at the same temperature for a further 1 h, quenched with sat. aq HCl (1 M, 10 mL), and extracted with Et_2O (4 × 10 mL). The combined organic extracts were washed with water (30 mL) and brine (30 mL), dried ($MgSO_4$) and concentrated under reduced pressure.

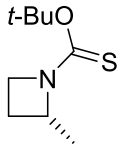
***O*-(*tert*-Butyl) (*R*)-2-methylazetidine-1-carbothioate ((*R*)-288b) (from reaction in Et_2O)**



O-tert-Butyl azetidine-1-carbothioate (**212**) (80 mg, 0.46 mmol) and MeI (87 µL, 1.39 mmol) were used following a modified General Procedure E (using Et_2O as solvent instead of pentane), with a lithiation temperature of −78 °C and lithiation time of 1 h. Purification of the resulting colourless oil (SiO_2, 0–5% EtOAc/hexane) gave a colourless oil, methylated azetidine (*R*)-**288b** (55 mg, 64%) in 56:44 er (chiral SFC analysis, see Appendix, p A20, τ_R (major) = 4.50 min, τ_R (minor) = 3.75 min). Absolute configuration of the major enantiomer was assigned by conversion to the corresponding *N*-thiopivaloyl azetidine (*R*)-**165a**, see p 261–262, and comparing chiral GC data with those for enantiomerically pure (*R*)-**165a**.[148]

$[\alpha]_D^{25}$ −4.1 (*c* 1.18, $CHCl_3$); all other data as described for racemic **288b** (p 218).

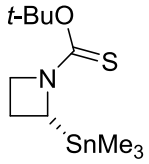
_O_-(*tert*-Butyl) (*R*)-2-methylazetidine-1-carbothioate ((*R*)-288b) (from reaction in pentane)



O-tert-Butyl azetidine-1-carbothioate (**212**) (160 mg, 0.92 mmol) and MeI (172 µL, 2.77 mmol) were used following General Procedure E, with a lithiation temperature of −98 °C and lithiation time of 1 h. Purification of the resulting colourless oil (SiO_2, 3–5% Et_2O/petroleum ether) gave a colourless oil, methylated azetidine (*R*)-**288b** (78 mg, 45%) in 91:9 er (chiral SFC analysis, see Appendix, p A21, τ_R (*R*) = 8.39 min, τ_R (*S*) = 7.15 min).

$[\alpha]_D^{25}$ −32.6 (*c* 1.12, $CHCl_3$); all other data as described for racemic **288b** (p 218).

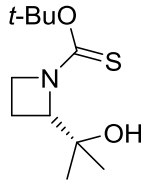
_O_-(_tert_-Butyl) (_S_)-2-(trimethylstannyl)azetidine-1-carbothioate ((_R_)-288f)



O-tert-Butyl azetidine-1-carbothioate (**212**) (80 mg, 0.46 mmol) and Me_3SnCl (184 mg, 0.92 mmol) were used following a modified General Procedure E, with a lithiation temperature of −78 °C and lithiation time of 1 h. After electrophile addition, the reaction mixture was stirred at −78 °C for 30 min, warmed to rt over 10 min, then stirred at rt for 20 min before the standard work-up for General Procedure E was carried out. Purification of the resulting colourless oil (SiO_2, 2% Et_2O/petroleum ether) gave a colourless oil, stannylated azetidine (*R*)-**288f** (139 mg, 90%) in 66:34 er (chiral-HPLC analysis by 'Reach Separations', see Appendix, p A22–A23, τ_R (major) = 7.28 min, τ_R (minor) = 8.14 min). Absolute configuration of the major enantiomer was assigned by analogy to (*R*)-**288b**.

$[\alpha]_D^{25}$ +166.3 (*c* 0.93, $CHCl_3$); all other data as described for racemic **288f** (p 222–223).

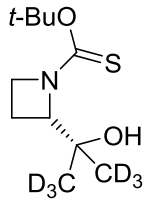
_O_-(_tert_-Butyl) (_S_)-2-(2-hydroxypropan-2-yl)azetidine-1-carbothioate ((_S_)-288l)



O-tert-Butyl azetidine-1-carbothioate (**212**) (60 mg, 0.35 mmol) and acetone (76 µL, 1.04 mmol) were used following General Procedure E, with a lithiation temperature of −78 °C and lithiation time of 3 h. Purification of the resulting yellow oil (SiO_2, 10–40% Et_2O/petroleum ether) gave a colourless oil, alcohol (*S*)-**288l** (51 mg, 64%) in 92:8 er (chiral HPLC analysis, see Appendix, p A24–A25, τ_R (major) = 12.18 min, τ_R (minor) = 14.17 min); Absolute configuration of the major enantiomer was assigned by analogy to (*R*)-**288b**.

$[\alpha]_D^{25}$ +87.8 (*c* 1.02, $CHCl_3$); all other data as described for racemic **288l** (p 234).

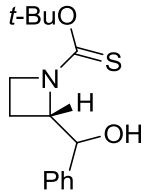
***O*-(*tert*-Butyl) (*S*)-2-(2-hydroxypropan-2-yl-1,1,1,3,3,3-d_6)azetidine-1-carbothioate ((S)-288m)**



O-tert-Butyl azetidine-1-carbothioate (**212**) (60 mg, 0.35 mmol) and acetone-D_6 (76 µL, 1.04 mmol) were used following General Procedure E, with a lithiation temperature of −78 °C and lithiation time of 1 h. Purification of the resulting yellow oil (SiO_2, 10–40% Et_2O/petroleum ether) gave a colourless oil, alcohol (*S*)-**288m** (65 mg, 79%) in 91:9 er (chiral HPLC analysis, see Appendix, p A26–A27, τ_R (major) = 12.30 min, τ_R (minor) = 14.20 min); Absolute configuration of the major enantiomer was assigned by analogy to (*R*)-**288b**.

$[\alpha]_D^{25}$ +78.6 (*c* 0.98, $CHCl_3$); all other data as described for racemic **288m** (p 235).

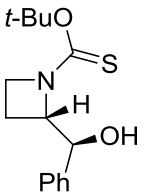
***O*-(*tert*-Butyl) (2*S*)-2-(hydroxy(phenyl)methyl)azetidine-1-carbothioate ((2*S*)-288i)**



O-tert-Butyl azetidine-1-carbothioate (**212**) (60 mg, 0.35 mmol) and benzaldehyde (106 µL, 1.04 mmol) were used following General Procedure E, with a lithiation temperature of −78 °C and lithiation time of 1 h. Purification of the resulting pale yellow oil (SiO_2, 5–30% Et_2O/petroleum ether) gave first a colourless oil, the minor diastereomer (*S,S*)-**288i-minor** (34 mg, 35%) in 85:15 er (chiral HPLC analysis, see Appendix, p A28–A28, τ_R

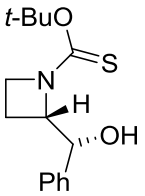
(major) = 11.57 min, τ_R (minor) = 12.66 min), followed by a colourless oil, the major diastereomer (*S*,*R*)-**288i-major** (51 mg, 53%) in 86:14 er (chiral HPLC analysis, see Appendix, p A30–A31, τ_R (major) = 26.02 min, τ_R (minor) = 36.09 min); Absolute configuration of the major enantiomer was assigned by analogy to (*R*)-**288b**.

_O_-(_tert_-Butyl) (_S_)-2-((_S_)-hydroxy(phenyl)methyl)azetidine-1-carbothioate ((_S_,_S_)-288i-minor)



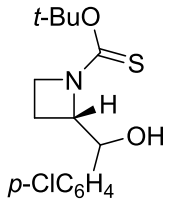
$[\alpha]_D^{25}$ +91.6 (*c* 0.98, $CHCl_3$); all other data as described for (*R**,*R**)-**288i-minor** (p 226).

_O_-(_tert_-Butyl) (_S_)-2-((_R_)-hydroxy(phenyl)methyl)azetidine-1-carbothioate ((_S_,_R_)-288i-major)



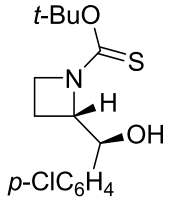
$[\alpha]_D^{25}$ +22.7 (*c* 1.03, $CHCl_3$); all other data as described for (*R**,*S**)-**288i-major** (p 226–227).

_O_-(_tert_-Butyl) (2_S_)-2-((4-chlorophenyl)(hydroxy)methyl)azetidine-1-carbothioate ((2_S_)-288j)



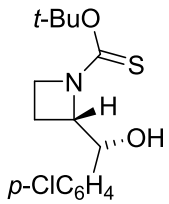
O-*tert*-Butyl azetidine-1-carbothioate (**212**) (60 mg, 0.35 mmol) and 4-chlorobenzaldehyde (146 μL, 1.04 mmol) were used following General Procedure E, with a lithiation temperature of −78 °C and lithiation time of 1 h. Purification of the resulting pale orange oil (SiO_2, 5–20% Et_2O/petroleum ether) gave first a colourless oil, the minor diastereomer (*S*,*S*)-**288j-minor** (22 mg, 20%) in 80:20 er (chiral HPLC analysis, see Appendix, p A32–A33, τ_R (major) = 13.05 min, τ_R (minor) = 11.74 min), followed by a white solid, the major diastereomer (*S*,*R*)-**288j-major** (48 mg, 44%) in 80:20 er (chiral HPLC analysis, see Appendix, p A34–A35, τ_R (major) = 19.70 min, τ_R (minor) = 8.34 min); Absolute configuration of the major enantiomer was assigned by analogy to (*R*)-**288b**.

_O_-(_tert_-Butyl) (_S_)-2-((_S_)-(4-chlorophenyl)(hydroxy)methyl)azetidine-1-carbothioate ((_S_,_S_)-288j-minor)



$[\alpha]_D^{25}$ +79.0 (*c* 0.90, $CHCl_3$); all other data as described for (*R**,*R**)-**288j-minor** (p 228).

_O_-(_tert_-Butyl) (_S_)-2-((_R_)-(4-chlorophenyl)(hydroxy)methyl)azetidine-1-carbothioate ((_S_,_R_)-288j-major)



$[\alpha]_D^{25}$ +23.2 (*c* 0.98, $CHCl_3$); all other data as described for (*R**,*S**)-**288j-major** (p 228–229).

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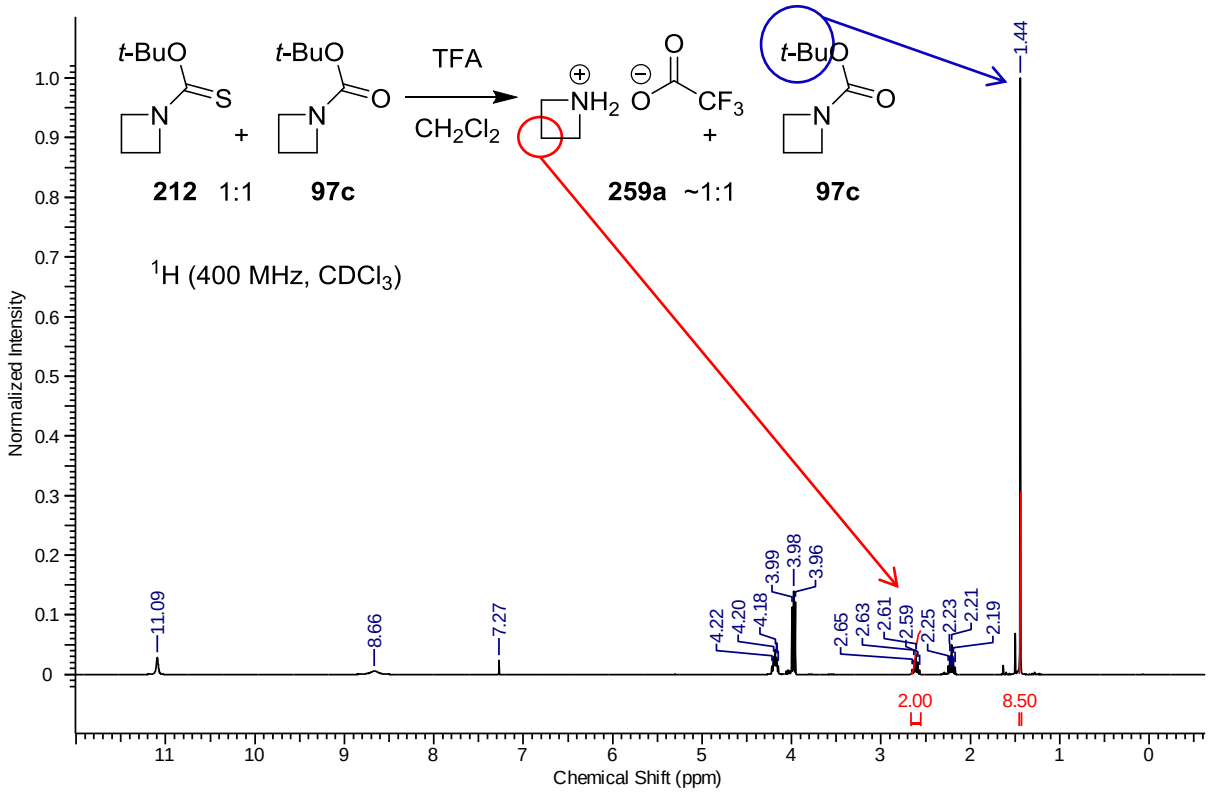
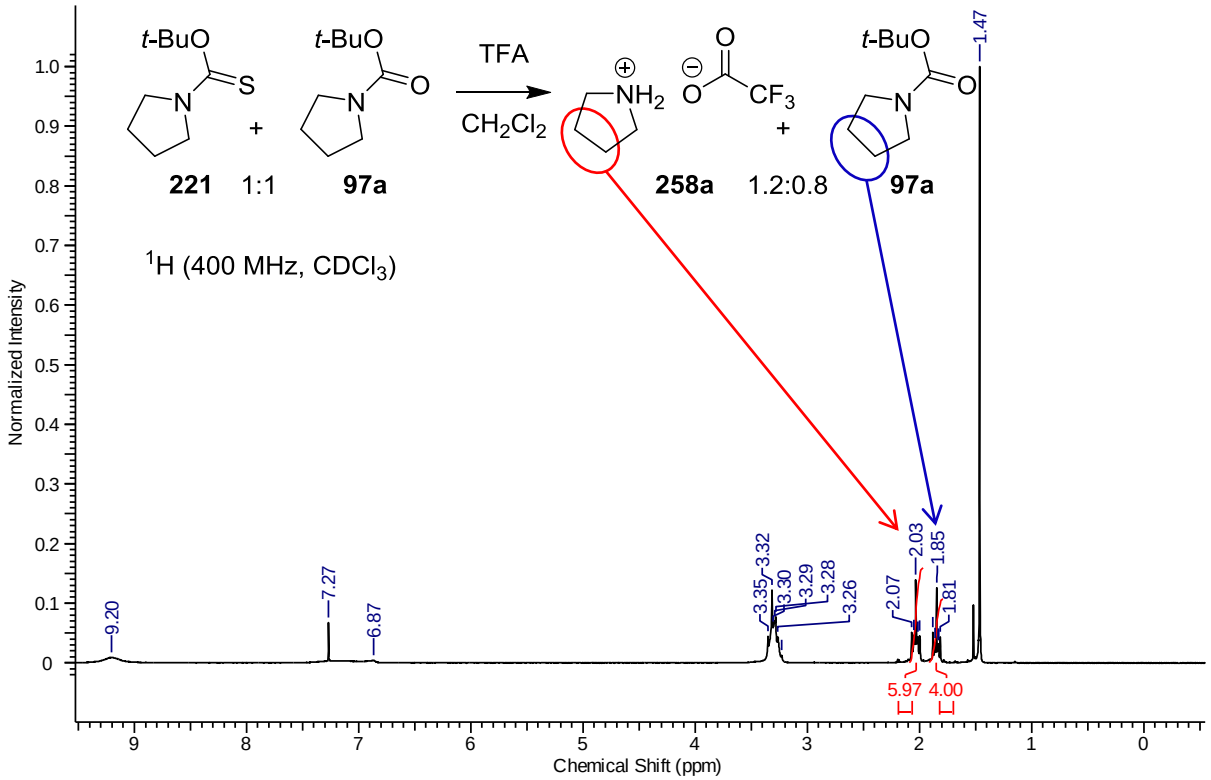
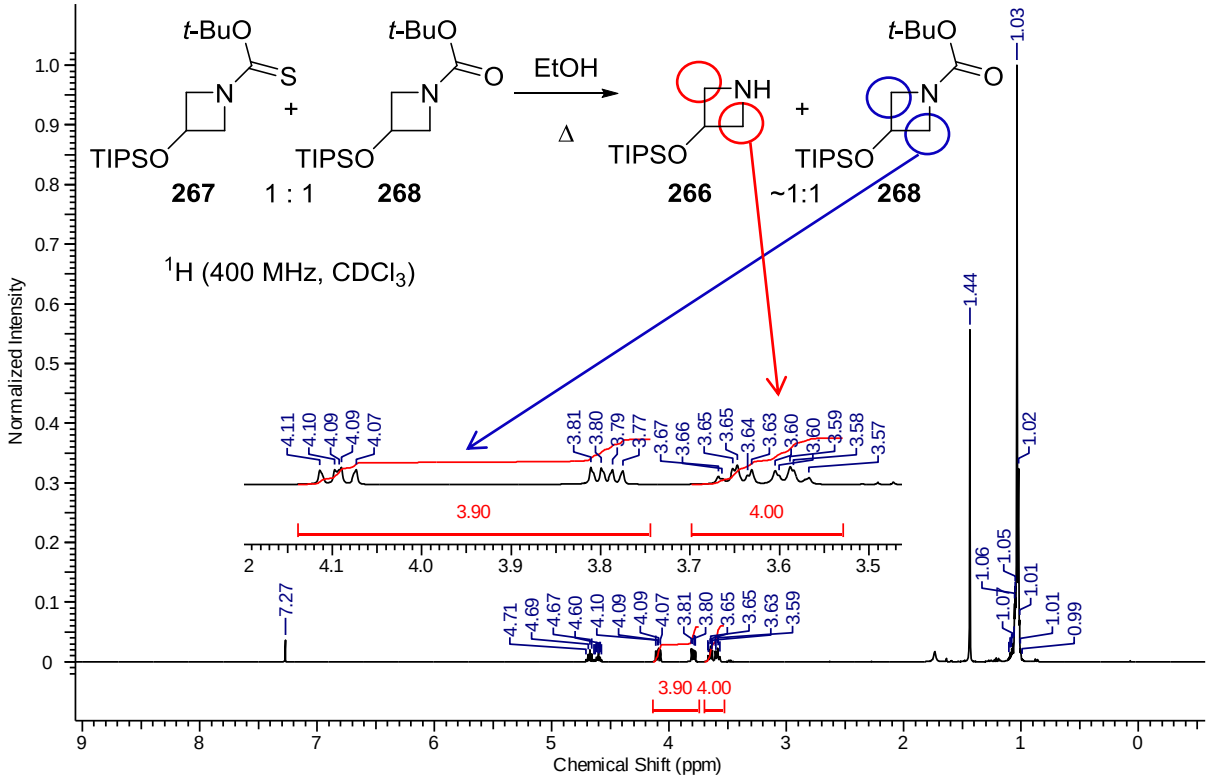
7. Appendix

7.1. ^{1}H NMR for selective deprotection reactions

The ratio of products obtained from reactions comparing the ease of deprotection of *N*-Botc compared to *N*-Boc, under acidic or thermal conditions, were calculated by integration of appropriate signals in the crude ^{1}H NMR. The signals used in these calculations are indicated in the following ^{1}H NMR spectra:




t-BuO
S
N
+
t-BuO
O
N
TFA
CH2Cl2
NH2
O
O
CF3
+
t-BuO
O
N
221
1:1
97a
258a
1.2:0.8
97a
1H (400 MHz, CDCl3)
Normalized Intensity
Chemical Shift (ppm)
9.20
7.27
6.87
3.35
3.32
3.30
3.29
3.28
3.26
2.07
2.03
1.85
1.81
1.47
5.97
4.00


t-BuO
S
N
+
TIPSO
t-BuO
O
N
TIPSO
EtOH
Δ
NH
TIPSO
+
t-BuO
O
N
TIPSO
267
1 : 1
268
266
~1:1
268
1H (400 MHz, CDCl3)
Normalized Intensity
Chemical Shift (ppm)
7.27
4.11
4.10
4.09
4.09
4.07
3.81
3.80
3.79
3.77
3.67
3.66
3.65
3.65
3.64
3.63
3.60
3.60
3.59
3.58
3.57
3.90
4.00
4.71
4.69
4.67
4.60
4.10
4.09
4.09
4.07
3.81
3.80
3.65
3.65
3.63
3.59
3.90 4.00
1.44
1.03
1.02
1.06
1.05
1.07
1.01
1.01
0.99

7.2. Calculation of rotational energy barriers

All experiments concerned with rotational energy barriers of *N*-thiopivaloyl-azetidine **164** were previously carried out in-house.[1] For a better comparison with the other systems tested, rotational energy barriers were re-calculated, by Prof Tim Claridge, from slightly modified rate constant (*k*) values to the literature.[2] All experiments and associated calculations concerned with rotation barriers of *N*-Botc-azetidine **212**, *N*-Boc-azetidine **97c**, 2-methyl-*N*-thiopivaloyl-azetidine **165a** and 2-methyl-*N*-Botc-azetidine **288b** are previously unpublished and were carried out in-house.[3]

7.2.1. *N*-thiopivaloyl-azetidine 164

A sample of *N*-thiopivaloyl-azetidine **164** was previously subjected to variable temperature ^{1}H NMR analysis (500 MHz, toluene-D_8), from 300 K to 370 K, allowing coalescence of the NCH_2 signals.[2] Experimental chemical shifts (blue values) and simulated chemical shifts (red values) are shown in Table 32; as fast exchange was approached, predictions for chemical shifts were required due to an unusual temperature dependence of the peak positions. gNMR was used to calculate rate constants (*k*) from chemical shifts obtained from line-shape simulations.

[1] Results obtained by B. Odell and T. D. W. Claridge, University of Oxford, **2010**.
[2] Pearson, C. *D. Phil Thesis*, University of Oxford, **2014**.
[3] Results obtained by B. Odell and T. D. W. Claridge, University of Oxford, **2014**.

Temp (K)	1/T	δA	δB	*k*	ln(*k*/T)
300	0.003333	3.931	3.6424		
310	0.003226	3.9358	3.6696		
320	0.003125	3.9403	3.6954		
330	0.00303	3.945	3.7201	6	−4.00733
340	0.002941	3.94927	3.74656	17	−2.99573
345	0.002899	3.951925	3.759505	28	−2.51134
350	0.002857	3.95425	3.77245	41	−2.14436
355	0.002817	3.956575	3.785395	70	−1.62362
360	0.002778	3.9589	3.79834	100	−1.28093
365	0.00274	3.961225	3.811285	144	−0.93008
370	0.002703	3.96355	3.82423	180	−0.72055

Table 32. Chemical shifts and rate constants for *N*-thiopivaloyl-azetidine **164**.

This data was used to generate the Eyring plot (Figure 18).

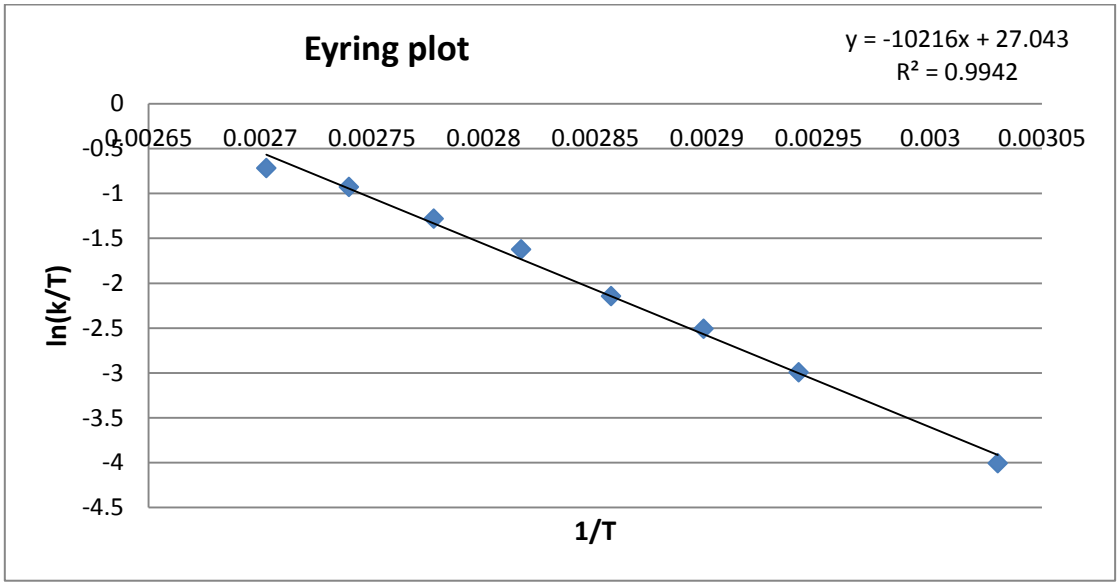


Figure 18. Eyring plot for *N*-thiopivaloyl-azetidine **164**.

From the Eyring plot it was determined:

$\Delta H^{\ddagger} \approx 84.9$ kJmol^{-1}

$\Delta S^{\ddagger} \approx 27.3$ JK^{-1}mol^{-1}

From these values it was calculated:

$\Delta G^{\ddagger} \approx 76.8$ kJmol^{-1} at 25 °C, $k \approx 2.141 \times 10^{-1}$ s^{-1}, $t_{1/2} \approx 3.2$ s.

$\Delta G^{\ddagger} \approx 79.6$ kJmol^{-1} at −78 °C, $k \approx 1.930 \times 10^{-9}$ s^{-1}, $t_{1/2} \approx 11.4$ years.

7.2.2. *N*-Botc-azetidine 212

A sample of *N*-Botc-azetidine **212** was subjected to variable temperature ^{1}H NMR analysis (500 MHz, toluene-D_8), from 298 K to 373 K, allowing coalescence of the NCH_2 signals (Figure 19).

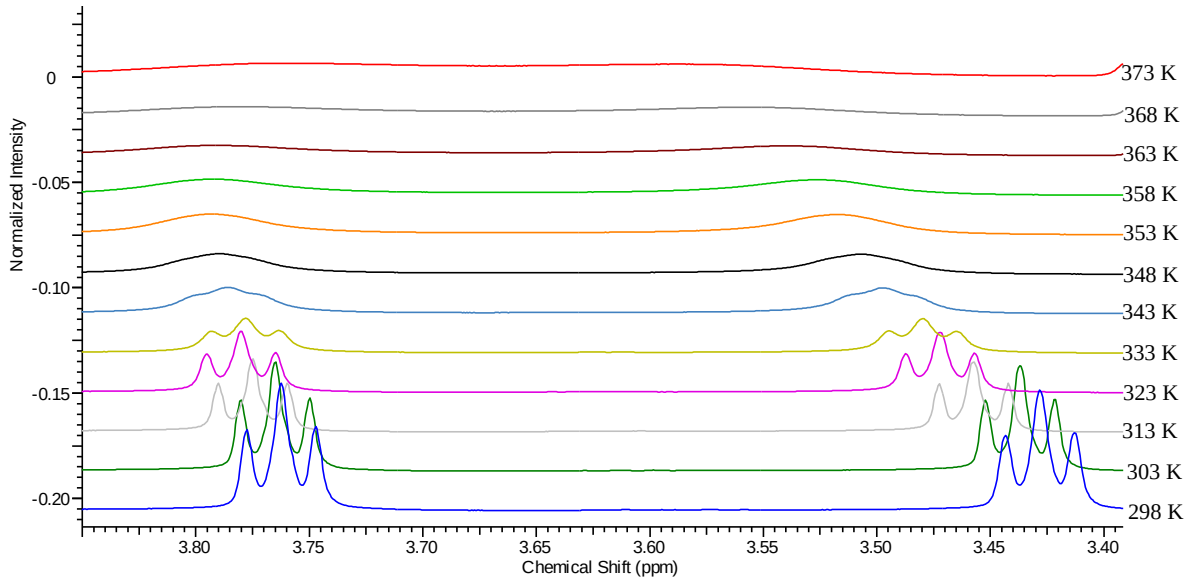


Figure 19. Variable temperature ^{1}H NMR for *N*-Botc-azetidine **212** (CH_2NCH_2 region).

Experimental chemical shifts (blue values) and simulated chemical shifts (red values) are shown in Table 33; as fast exchange was approached, predictions for chemical shifts were required due to an unusual temperature dependence of the peak positions. gNMR was used to calculate rate constants (*k*) from chemical shifts obtained from line-shape simulations.

T (K)	1/T	δA	δB	*k*	ln(*k*/T)
298	0.003356	3.7667	3.4321		
303	0.0033	3.7694	3.4411		
313	0.003195	3.7746	3.4572		
323	0.003096	3.7801	3.4722		
333	0.003003	3.7859	3.4871	10.500	−3.4567672
343	0.002915	3.7905	3.5016	26.400	−2.5643664
348	0.002874	3.7935	3.5100	39.300	−2.180978
353	0.002833	3.7962	3.5177	54.400	−1.8701039
358	0.002793	3.7988	3.5254	78.600	−1.5161613
363	0.002755	3.8015	3.5331	111.000	−1.1848726
368	0.002717	3.8042	3.5408	154.000	−0.8711303
373	0.002681	3.8069	3.5484	210.000	−0.5744709

Table 33. Chemical shifts and rate constants for *N*-Botc-azetidine **212**.

This data was used to generate the Eyring plot (Figure 20).

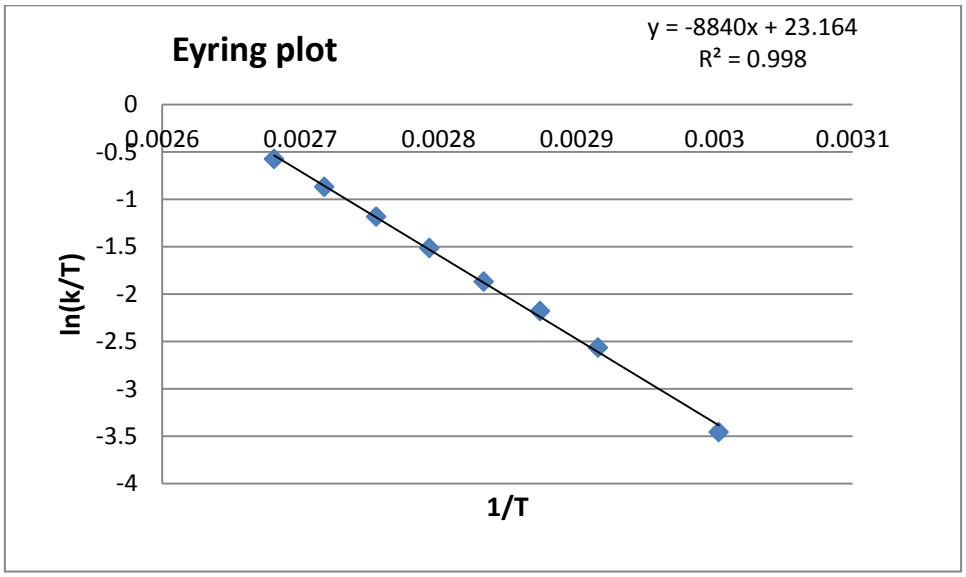


Figure 20. Eyring plot for *N*-Botc-azetidine **212**.

From the Eyring plot it was determined:

$\Delta H^{\ddagger} \approx$ 73.5 kJmol^{-1}

$\Delta S^{\ddagger} \approx$ −4.9 JK^{-1}mol^{-1}

From these values it was calculated:

$\Delta G^{\ddagger} \approx$ 75.0 kJmol^{-1} at 25 °C, $k \approx 4.427 \times 10^{-1}$ s^{-1}, $t_{1/2} \approx$ 1.6 s.

$\Delta G^{\ddagger} \approx$ 74.5 kJmol^{-1} at −78 °C, $k \approx 4.484 \times 10^{-8}$ s^{-1}, $t_{1/2} \approx$ 178.9 d.

7.2.3. *N*-Boc-azetidine 97c

A sample of *N*-Boc-azetidine **97c** was subjected to variable temperature ^{1}H NMR analysis (500 MHz, toluene-D_8), from 213 K to 298 K, allowing coalescence of the NCH_2 signals (Figure 21).

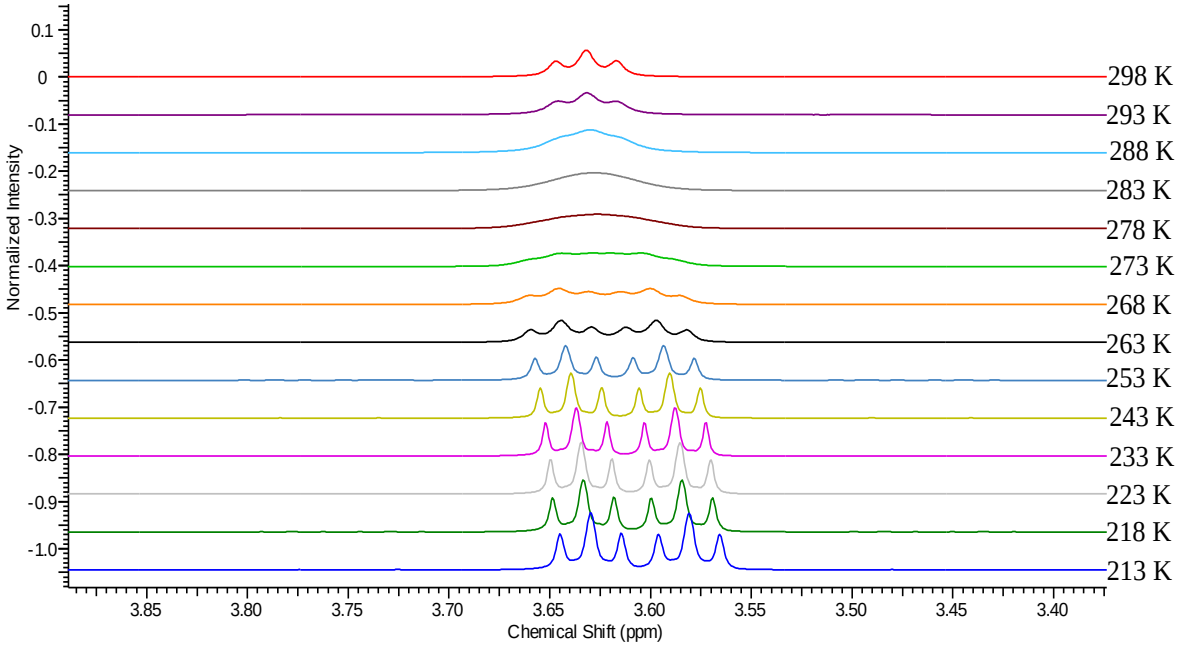


Figure 21. Variable temperature ^{1}H NMR for *N*-Boc-azetidine **97c** (CH_2NCH_2 region).

Experimental chemical shifts (blue values) and simulated chemical shifts (red values) are shown in Table 34; as fast exchange was approached, predictions for chemical shifts were required due to an unusual temperature dependence of the peak positions. gNMR was used to calculate rate constants (*k*) from chemical shifts obtained from line-shape simulations.

T (K)	1/T	δA	δB	*k*	ln(*k*/T)
213	0.004695	3.5836	3.6325		
218	0.004587	3.5847	3.6336		
223	0.004484	3.5858	3.6349		

233	0.004292	3.5884	3.6375		
243	0.004115	3.591	3.6399		
253	0.003953	3.5941	3.6427		
263	0.003802	3.596307	3.64515	6	−3.78039
268	0.003731	3.597612	3.646425	12	−3.10608
273	0.003663	3.598917	3.6477	22	−2.51843
278	0.003597	3.600222	3.648975	38	−1.99003
283	0.003534	3.601527	3.65025	70	−1.39695
288	0.003472	3.602832	3.651525	115	−0.91803
293	0.003413	3.604137	3.6528	221	−0.28201
298	0.003356	3.605442	3.654075	350	0.16084

Table 34. Chemical shifts and rate constants for *N*-Boc-azetidine **97c**.

This data was used to generate the Eyring plot (Figure 22).

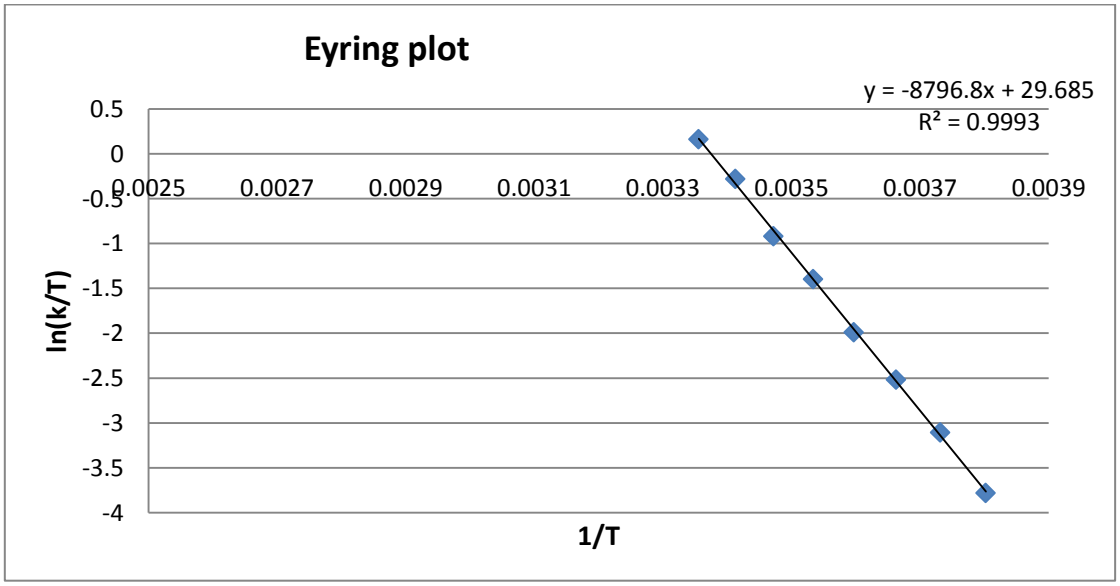


Figure 22. Eyring plot for *N*-Boc-azetidine **97c**.

From the Eyring plot it was determined:

$\Delta H^{\ddagger} \approx 73.1$ kJmol^{-1}

$\Delta S^{\ddagger} \approx 49.3$ JK^{-1}mol^{-1}

From these values it was calculated:

$\Delta G^{\ddagger} \approx 58.5$ kJmol^{-1} at 25 °C, $k \approx 3.454 \times 10^{2}$ s^{-1}, $t_{1/2} \approx 0.002$ s.

$\Delta G^{\ddagger} \approx 63.5$ kJmol^{-1} at −78 °C, $k \approx 3.966 \times 10^{-5}$ s^{-1}, $t_{1/2} \approx 4.9$ h.

7.2.4. 2-Methyl-*N*-thiopivaloyl-azetidine 165a

A sample of 2-methyl-*N*-thiopivaloyl-azetidine **165a** was subjected to variable temperature ^{1}H NMR analysis (500 MHz, toluene-D_8), from 298 K to 373 K, allowing coalescence of the NCHC*H*$_3$ and C(C*H*$_3$)$_3$ signals (Figure 23).

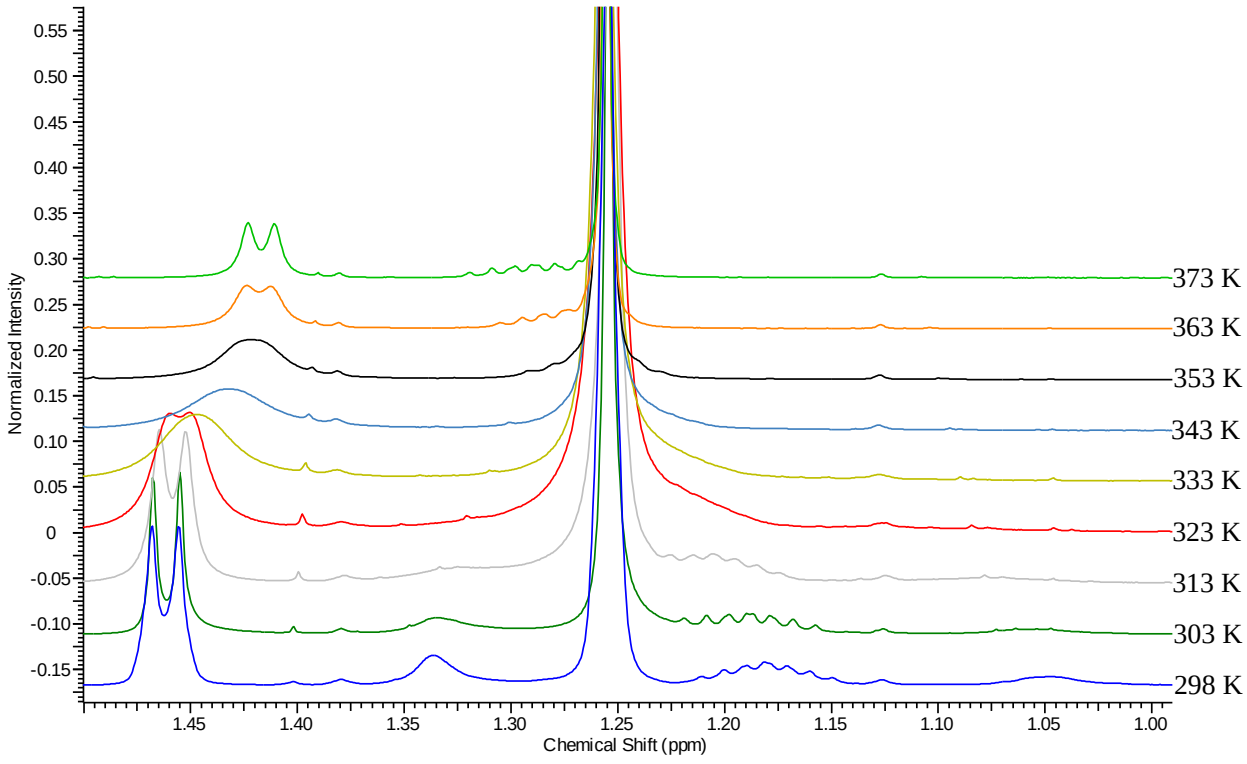


Figure 23. Variable temperature ^{1}H NMR for 2-methyl-*N*-thiopivaloyl-azetidine **165a** (NCHC*H*$_3$ and C(C*H*$_3$)$_3$ region).

Experimental chemical shifts (blue values) and simulated chemical shifts (red values) are shown in Table 35; as fast exchange was approached, predictions for chemical shifts were required due to an unusual temperature dependence of the peak positions. gNMR was used to calculate rate constants (*k*) from chemical shifts obtained from line-shape simulations (Table 36).

T (K)	1/T	major		minor	
		δMe	δ*t*-Bu	δMe	δ*t*-Bu
298	0.003356	1.423	1.216	1.006	1.298
303	0.0033	1.42008	1.2186	1.0175	1.296
313	0.003195	1.41768	1.2166	1.0395	1.294
323	0.003096	1.41528	1.2146	1.0615	1.292
333	0.003003	1.41288	1.2126	1.0835	1.29
343	0.002915	1.41048	1.2106	1.1055	1.288
353	0.002833	1.40808	1.2086	1.1275	1.286
363	0.002755	1.40568	1.2066	1.1495	1.284
373	0.002681	1.40328	1.2046	1.1715	1.282

Table 35. Chemical shifts for 2-methyl-*N*-thiopivaloyl-azetidine **165a**.

T (K)	major		minor	
	k	ln(*k*/T)	*k*	ln(*k*/T)
298	2	−5.00395	25	−2.4782
303	4	−4.32744	50	−1.8017
313	8	−3.66676	100	−1.14103
323	21	−2.73313	263	−0.2074
333	42	−2.07047	525	0.455256

343	72	−1.56106	900	0.964664
353	130	−0.99893	1625	1.526795
363	235	−0.43482	2938	2.090911
373	387	0.036846	4838	2.562575

Table 36. Rate constants for 2-methyl-*N*-thiopivaloyl-azetidine **165a**.

This data was used to generate the Eyring plots for rotation of the major rotamer (Figure 24) and the minor rotamer (Figure 25).

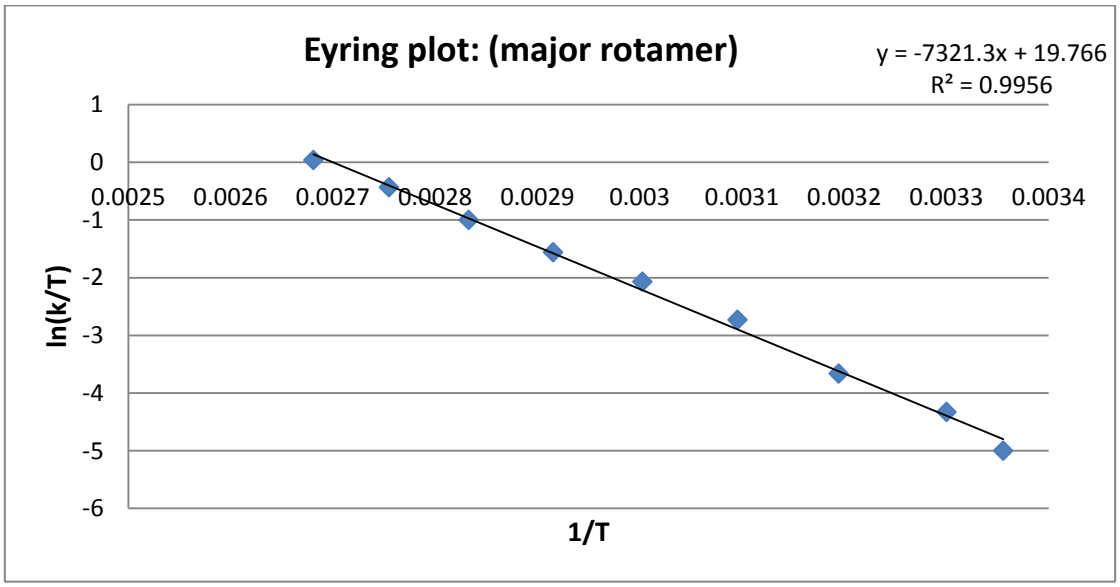


Figure 24. Eyring plot for major rotamer of 2-methyl-*N*-thiopivaloyl-azetidine **165a**.

From the Eyring plot for rotation of major rotamer it was determined:

$\Delta H^{\ddagger} \approx 60.9$ kJmol^{-1}

$\Delta S^{\ddagger} \approx -32.9$ JK^{-1}mol^{-1}

From these values it was calculated:

$\Delta G^{\ddagger} \approx 70.7$ kJmol^{-1} at 25 °C, $k \approx 2.511$ s^{-1}, $t_{1/2} \approx 0.3$ s.

$\Delta G^{\ddagger} \approx 67.3$ kJmol^{-1} at −78 °C, $k \approx 3.805 \times 10^{-6}$ s^{-1}, $t_{1/2} \approx 2.1$ d.

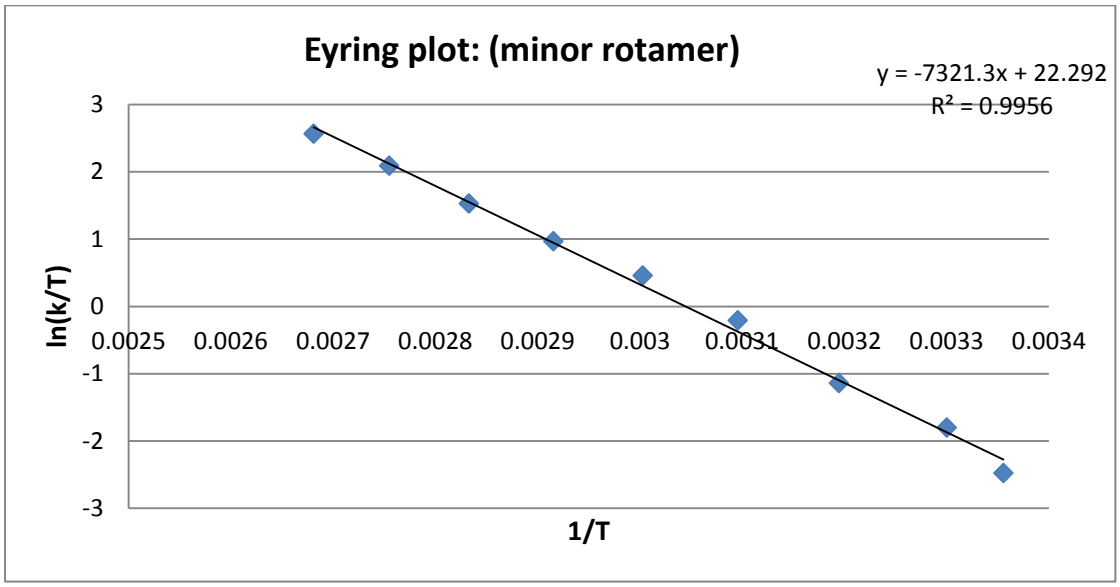


Figure 25. Eyring plot for minor rotamer of 2-methyl-*N*-thiopivaloyl-azetidine **165a**.

From the Eyring plot for rotation of the minor rotamer it was determined:

$\Delta H^{\ddagger} \approx 60.9$ kJmol^{-1}

$\Delta S^{\ddagger} \approx -12.2$ JK^{-1}mol^{-1}

From these values it was calculated:

$\Delta G^{\ddagger} \approx 64.5$ kJmol^{-1} at 25 °C, $k \approx 3.066 \times 10^{1}$ s^{-1}, $t_{1/2} \approx 0.02$ s.

$\Delta G^{\ddagger} \approx 63.2$ kJmol^{-1} at −78 °C, $k \approx 4.772 \times 10^{-5}$ s^{-1}, $t_{1/2} \approx 4.0$ h.

7.2.5. 2-Methyl-*N*-Botc-azetidine 288b

A sample of 2-methyl-*N*-Botc-azetidine **288b** was subjected to variable temperature ^{1}H NMR analysis (500 MHz, toluene-D_8), from 298 K to 373 K, allowing coalescence of the NCHC*H*$_3$ and C(CH_3)$_3$ signals (Figure 26).

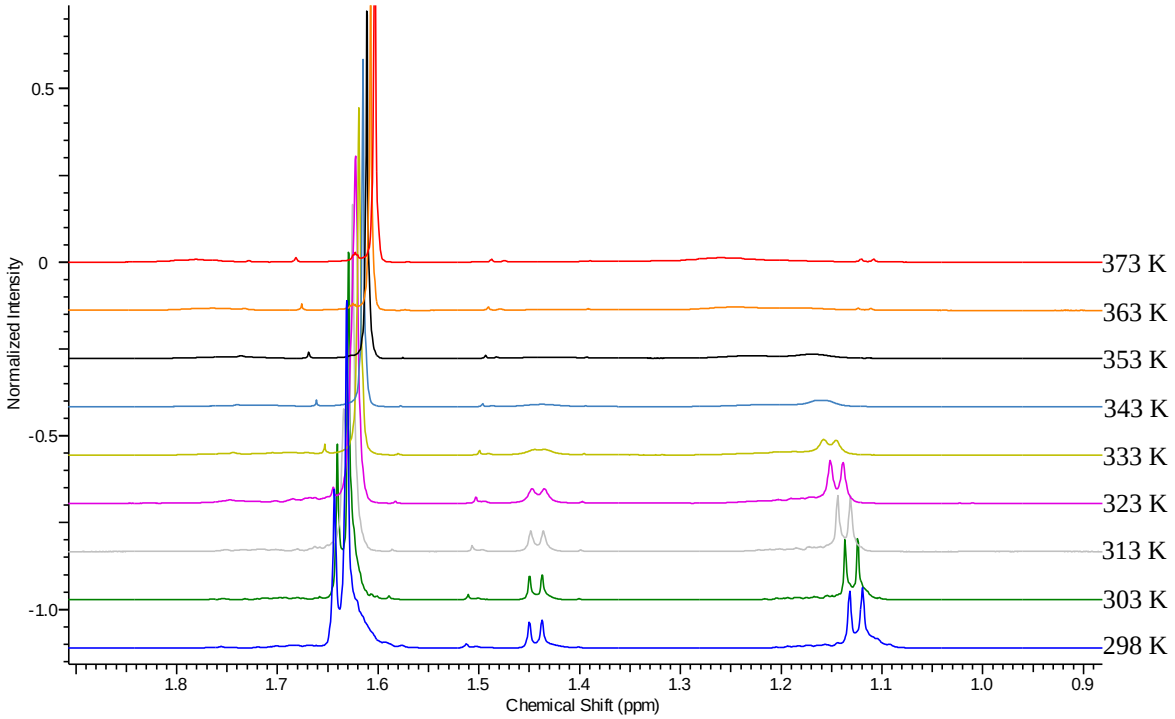


Figure 26. Variable temperature ^{1}H NMR for 2-methyl-*N*-Botc-azetidine **288b** (NCHC*H*$_3$ and C(CH_3)$_3$ region).

Experimental chemical shifts (blue values) and simulated chemical shifts (red values) are shown in Table 37; as fast exchange was approached, predictions for chemical shifts were required due to an unusual temperature dependence of the peak positions. gNMR was used to calculate rate constants (*k*) from chemical shifts obtained from line-shape simulations (Table 38).

T (K)	1/T	major		minor	
		δMe	δtBu	δMe	δtBu
298	0.003356	1.087	1.591	1.405	1.604
303	0.0033	1.093	1.59	1.405	1.601
313	0.003195	1.099	1.587	1.405	1.596
323	0.003096	1.109	1.582	1.405	1.589
333	0.003003	1.118	1.579	1.405	1.583
343	0.002915	1.127	1.575	1.405	1.577
353	0.002833	1.136	1.571	1.405	1.571
363	0.002755	1.145	1.568	1.405	1.565
373	0.002681	1.154	1.564	1.405	1.559

Table 37. Chemical shifts for 2-methyl-*N*-Botc-azetidine **288b**.

T (K)	major		minor	
	k	ln(*k*/T)	*k*	ln(*k*/T)
298				
303	0.5	−6.40688	1.4	−5.37726
313	0.8	−5.96935	2.24	−4.93973
323	3.3	−4.58373	9.24	−3.55411
333	7	−3.86223	19.6	−2.83261
343	18	−2.94736	50.4	−1.91774
353	30	−2.46527	84	−1.43565
363	70	−1.64591	196	−0.61629
373	150	−0.91094	420	0.118676

Table 38. Rate constants for 2-methyl-*N*-Botc-azetidine **288b**.

This data was used to generate the Eyring plots for rotation of the major rotamer (Figure 27) and the minor rotamer (Figure 28).

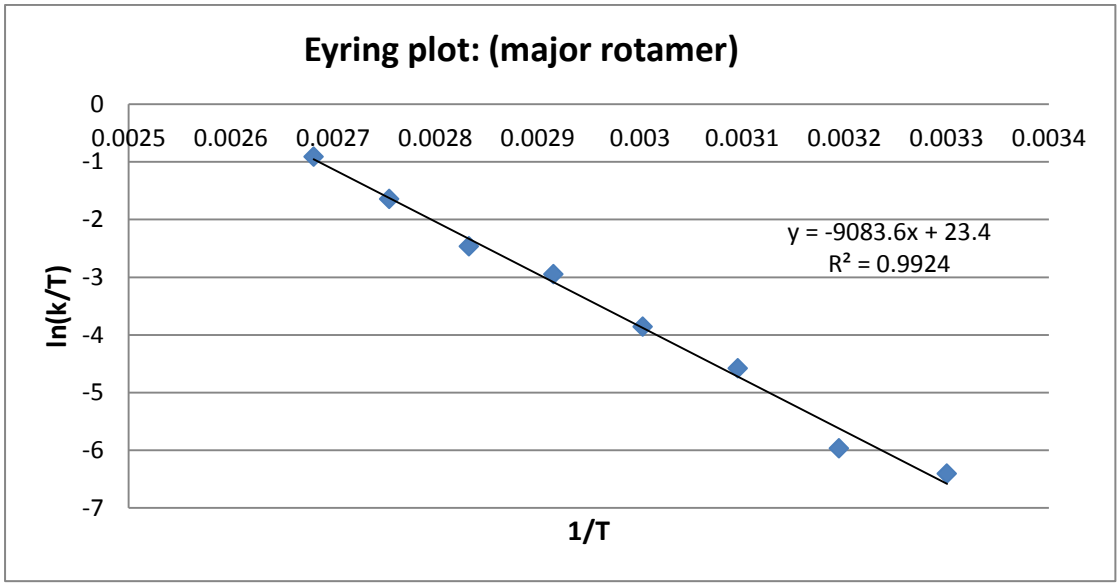


Figure 27. Eyring plot for major rotamer of 2-methyl-*N*-Botc-azetidine **288b**.

From the Eyring plot for rotation of the major rotamer it was determined:

$\Delta H^{\ddagger} \approx 75.5$ kJmol^{-1}

$\Delta S^{\ddagger} \approx -3.0$ JK^{-1}mol^{-1}

From these values it was calculated:

$\Delta G^{\ddagger} \approx 76.4$ kJmol^{-1} at 25 °C, $k \approx 2.516 \times 10^{-1}$ s^{-1}, $t_{1/2} \approx 2.8$ s.

$\Delta G^{\ddagger} \approx 76.1$ kJmol^{-1} at −78 °C, $k \approx 1.671 \times 10^{-8}$ s^{-1}, $t_{1/2} \approx 1.3$ years.

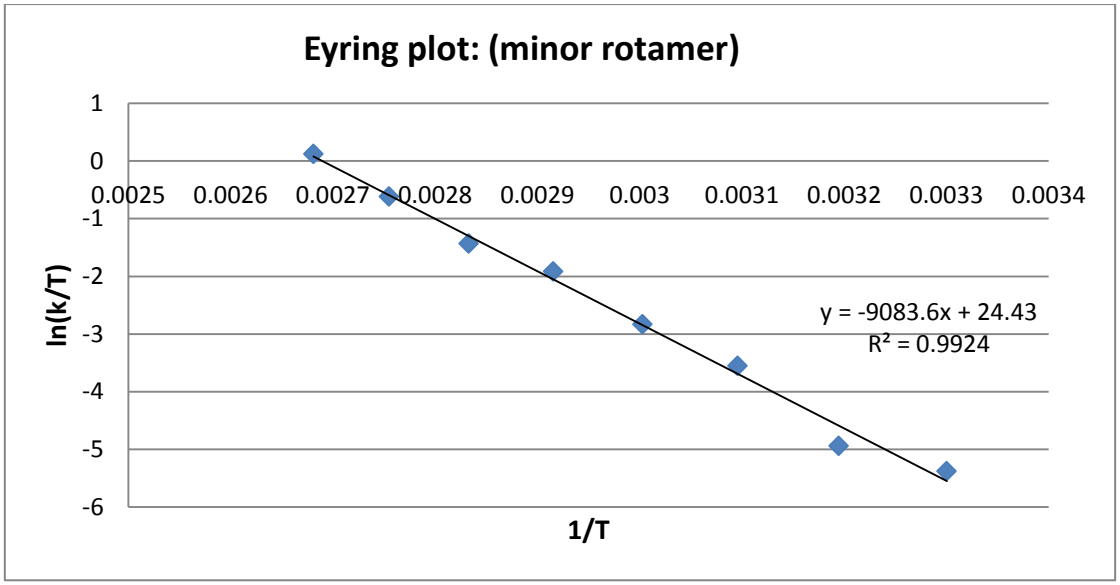


Figure 28. Eyring plot for major rotamer of 2-methyl-*N*-Botc-azetidine **288b**.

From the Eyring plot for rotation of the minor rotamer it was calculated:

$\Delta H^{\ddagger} \approx 75.5\ \text{kJmol}^{-1}$

$\Delta S^{\ddagger} \approx 5.6\ \text{JK}^{-1}\text{mol}^{-1}$

From these values it was calculated:

$\Delta G^{\ddagger} \approx 73.8\ \text{kJmol}^{-1}$ at 25 °C, $k \approx 7.185 \times 10^{-1}\ \text{s}^{-1}$, $t_{1/2} \approx 1.0$ s.

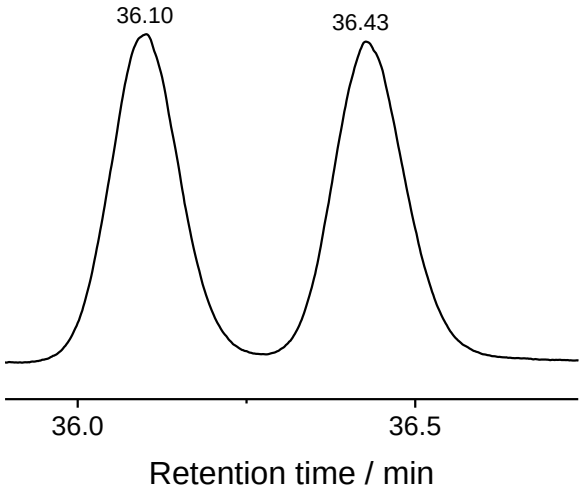
$\Delta G^{\ddagger} \approx 74.4\ \text{kJmol}^{-1}$ at −78 °C, $k \approx 4.769 \times 10^{-8}\ \text{s}^{-1}$, $t_{1/2} \approx 168.2$ d.

7.3. Chiral-GC Traces

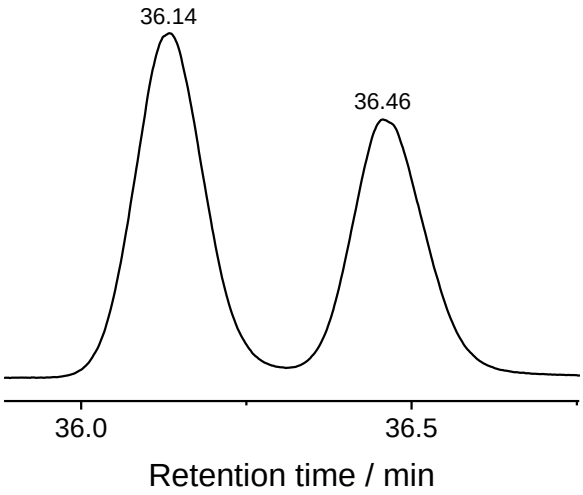
7.3.1. Chiral GC traces for 165a

Column: β-cyclodextrin, 0.22 mm × 30 m, thickness 0.25 µm, flow rate = 1 mL/min, carrier gas = He, T injector 220 °C, T detector (FID) 250 °C, T initial 40 °C, 5 min then 5 °C/min to 140 °C.

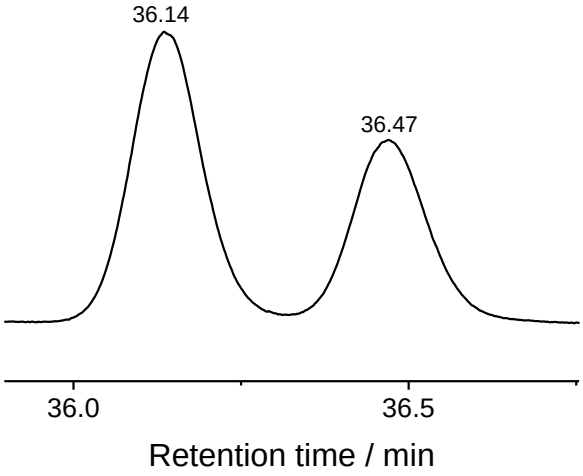
Racemic **165a**; 50:50 er



(*R*)-**165a**; from reaction in Et_2O; 56:44 (*R*:*S*) er



Spiking experiment: enantiomerically pure (*R*)-**165a**[148] added to racemic **165a**

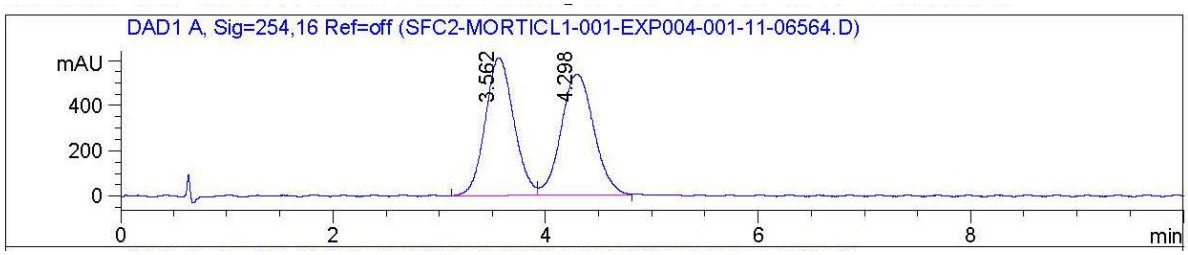


7.4. Chiral SFC Traces

7.4.1. Chiral SFC traces for 288b (initial conditions)

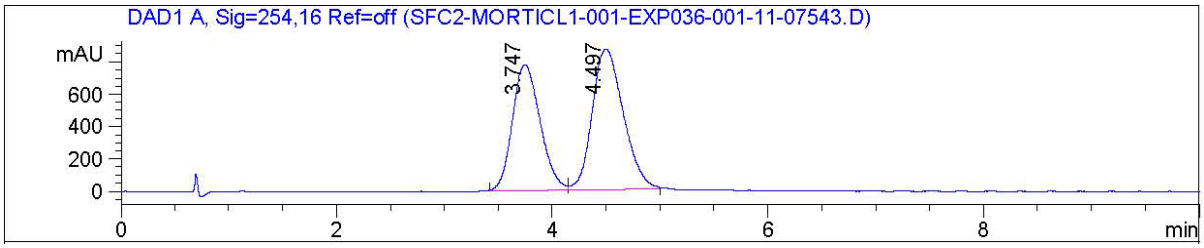
Column: CHIRALPAK IC, 150 × 2.1 mm, 3 µm, 40 °C, 0.7 mL/min, UV-vis (λ = 220 nm and 254 nm), eluent = isocratic at 5% *i*-PrOH in CO_2.

Racemic **288b**; 50:50 er



Peak #	RT [min]	Type	Width [min]	Area	Area %	Symmetry
1	3.562	MF	0.31211394.0430	49.94		0.896
2	4.298	FM	0.35611421.5410	50.06		0.935

(*R*)-**288b**; from reaction in Et_2O; 56:44 (*R*:*S*) er

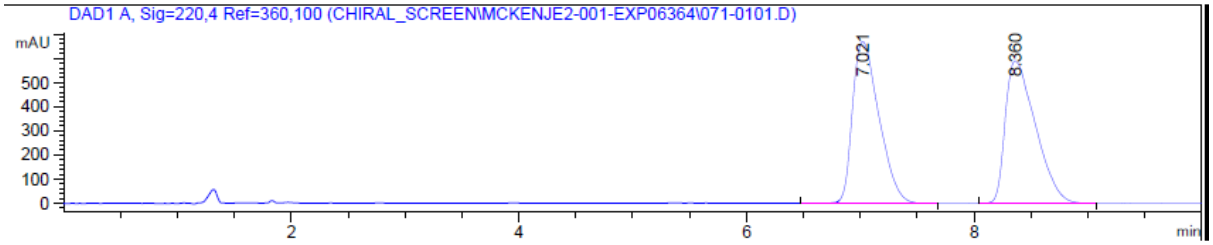


Peak #	RT [min]	Type	Width [min]	Area	Area %	Symmetry
1	3.747	BV	0.27713849.4268	44.23		0.781
2	4.497	VB	0.30617459.4141	55.77		0.736

7.4.2. Chiral SFC traces for 288b (alternative conditions)

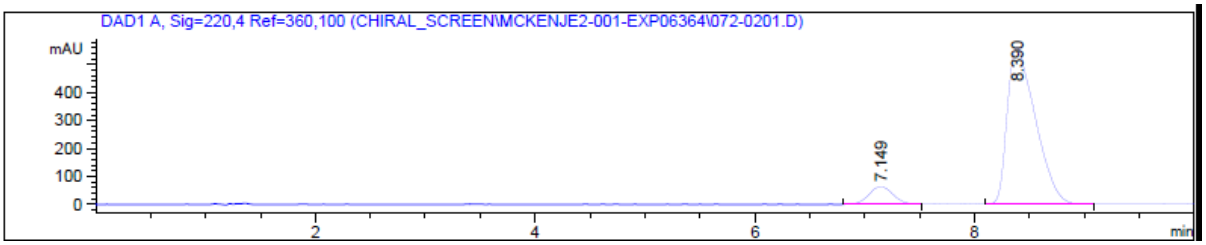
Column: CHIRALPAK IC, 250 × 4.6 mm, 5 µm, 40 °C, 3 mL/min, UV-vis (λ = 220 nm and 254 nm), eluent = isocratic at 5% *i*-PrOH in CO_2.

Racemic **288b**; 50:50 er



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.021	VB	0.2445	1.08327e4	670.59546	49.9184
2	8.360	VB	0.2687	1.08682e4	590.68292	50.0816

(*R*)-**288b**; from reaction in pentane; 91:9 (*R*:*S*) er



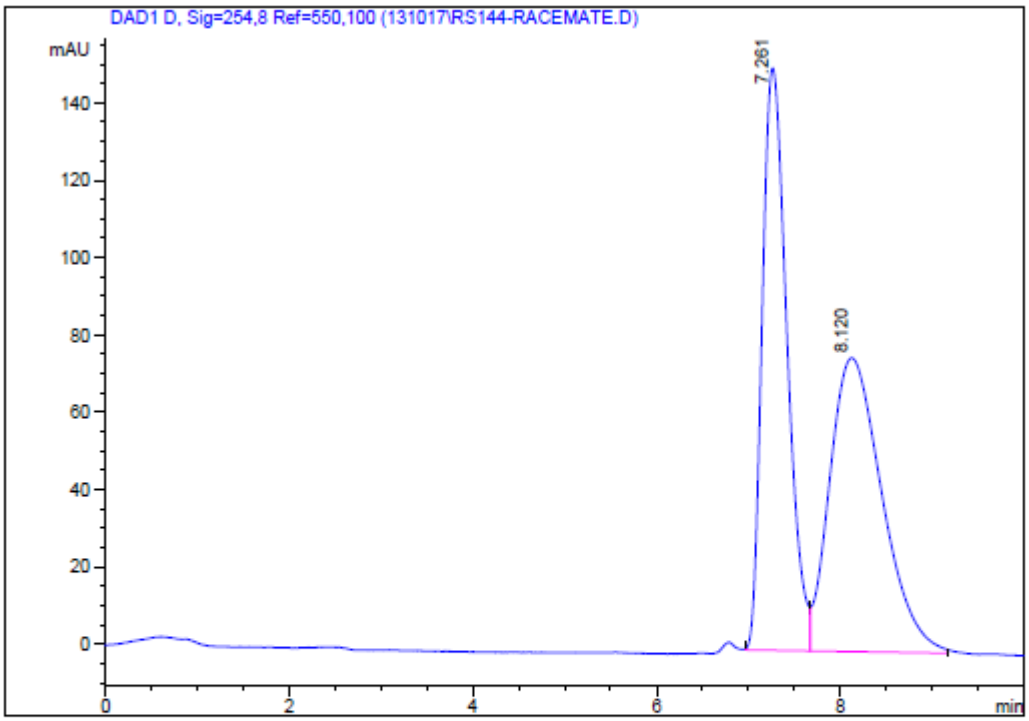
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.149	BV	0.2404	975.52692	63.09827	8.8898
2	8.390	VB	0.2538	9998.04297	561.40704	91.1102

7.5. Chiral-HPLC Traces

7.5.1. Chiral HPLC traces for 288f

Column: Lux Cellulose-3, 250 × 4.6 mm, 4.6 x 250mm, 5µm, 0.5 mL/min, vis (λ = 254 nm), eluent = isocratic at 5% *i*-PrOH in heptane.

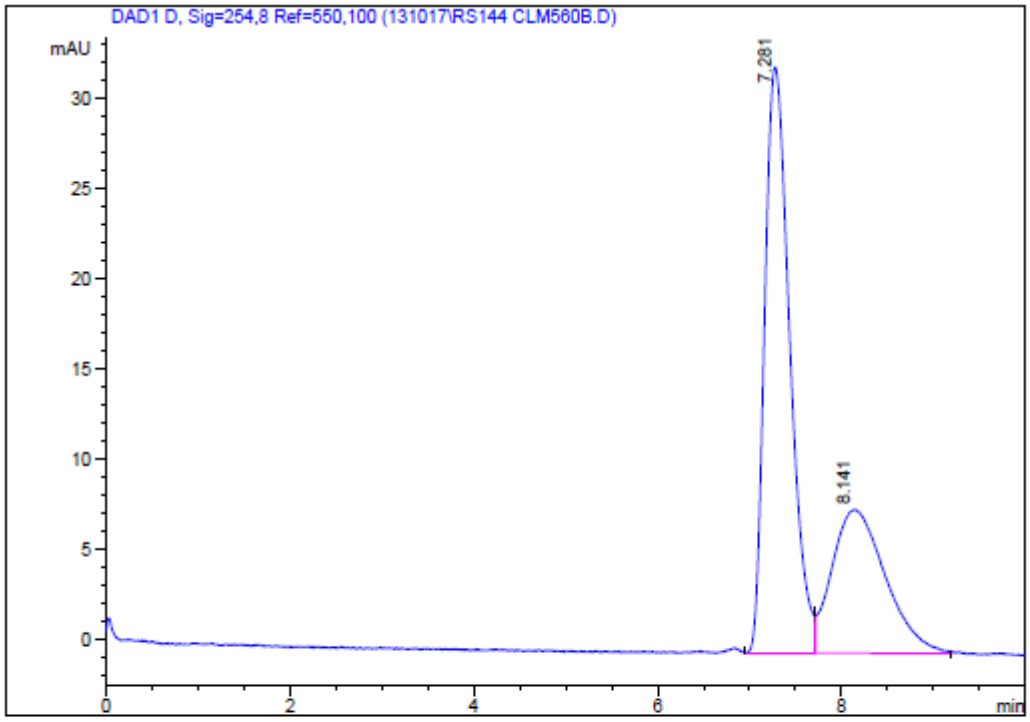
Racemic **288f**; 51:49 er



Signals

#	Meas. R	Height	Width	Symmetr	Area	Area %
1	7.261	150.538	0.313	0.706	2.831e3	48.544
2	8.120	76.011	0.658	0.701	3.001e3	51.456

(*R*)-**288f**; 66:34 (*R*:*S*) er



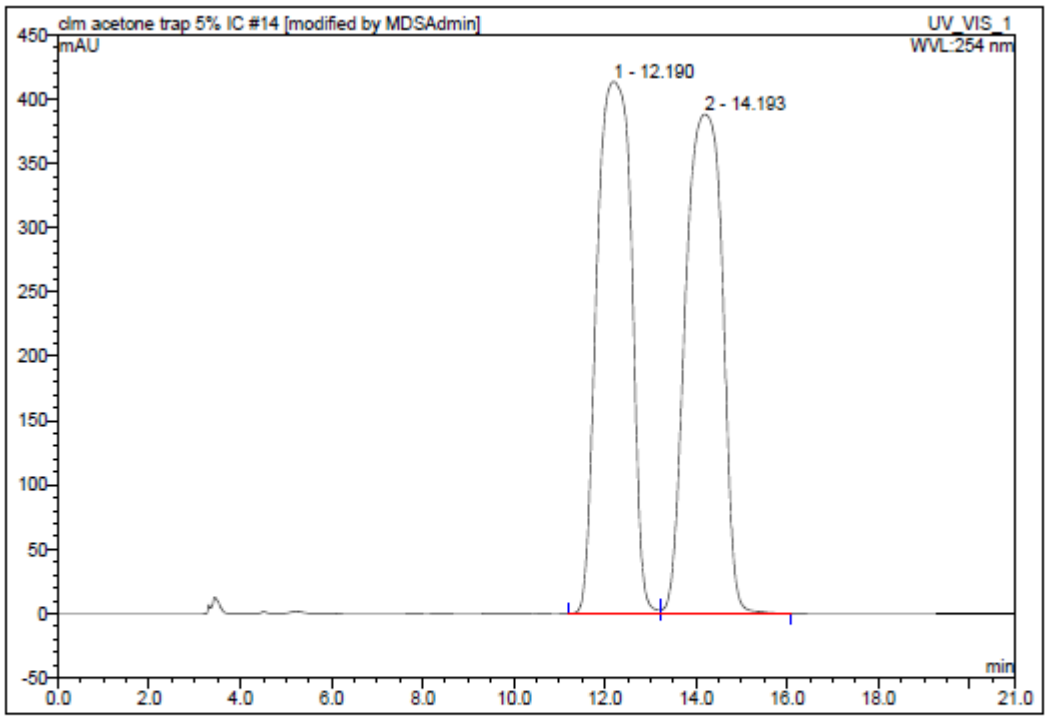
Signals

#	Meas. R	Height	Width	Symmetr	Area	Area %
1	7.281	32.472	0.294	0.699	619.140	65.766
2	8.141	7.960	0.624	0.684	322.290	34.234

7.5.2. Chiral HPLC traces for 288l

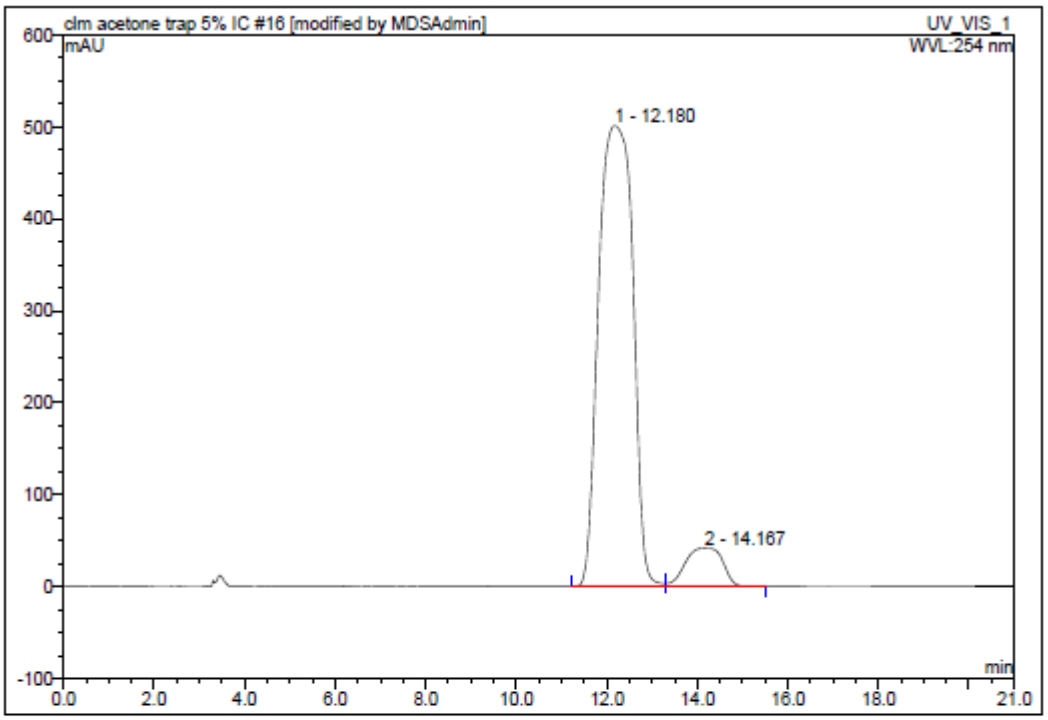
Column: CHIRALPAK AD-H, 250 × 4.6 mm, 5µm, 25 °C, 1 mL/ min, UV-vis (λ = 254 nm), eluent = isocratic at 2% *i*-PrOH in hexane.

Racemic **288l**; 50:50 er



No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	12.19	n.a.	413.181	361.894	49.88	n.a.	BM
2	14.19	n.a.	387.866	363.671	50.12	n.a.	MB
Total:			801.047	725.565	100.00	0.000	

(*S*)-**288l**; 92:8 (*S*:*R*) er

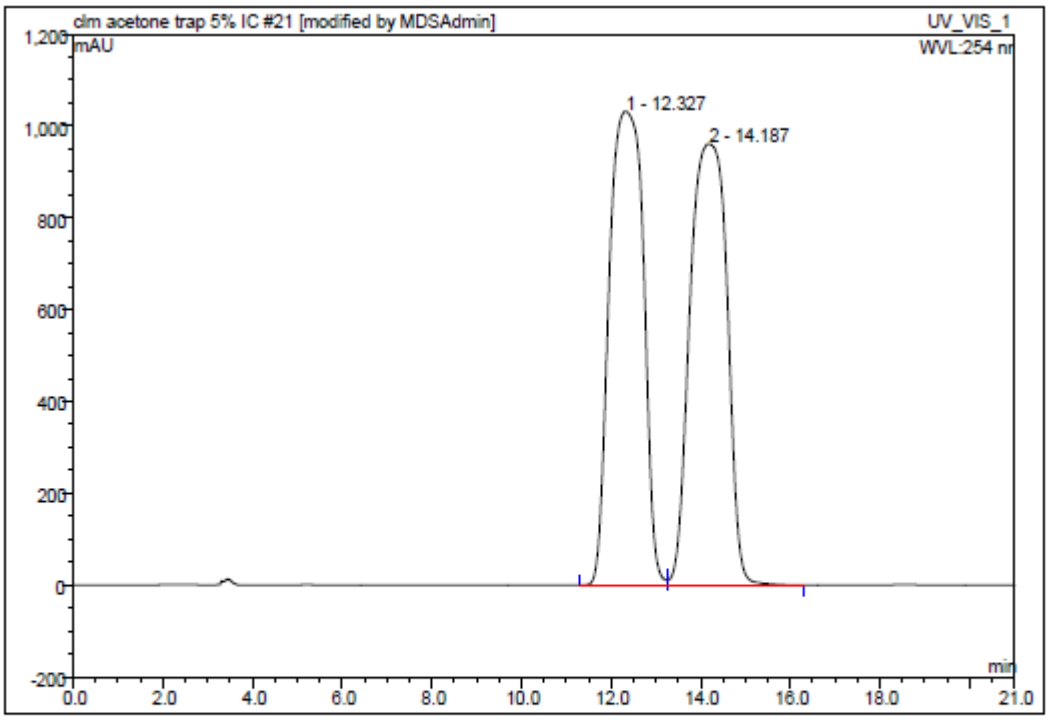


No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	12.18	n.a.	500.984	438.346	91.64	n.a.	BM
2	14.17	n.a.	41.863	40.007	8.36	n.a.	MB
Total:			542.847	478.353	100.00	0.000	

7.5.3. Chiral HPLC traces for 288m

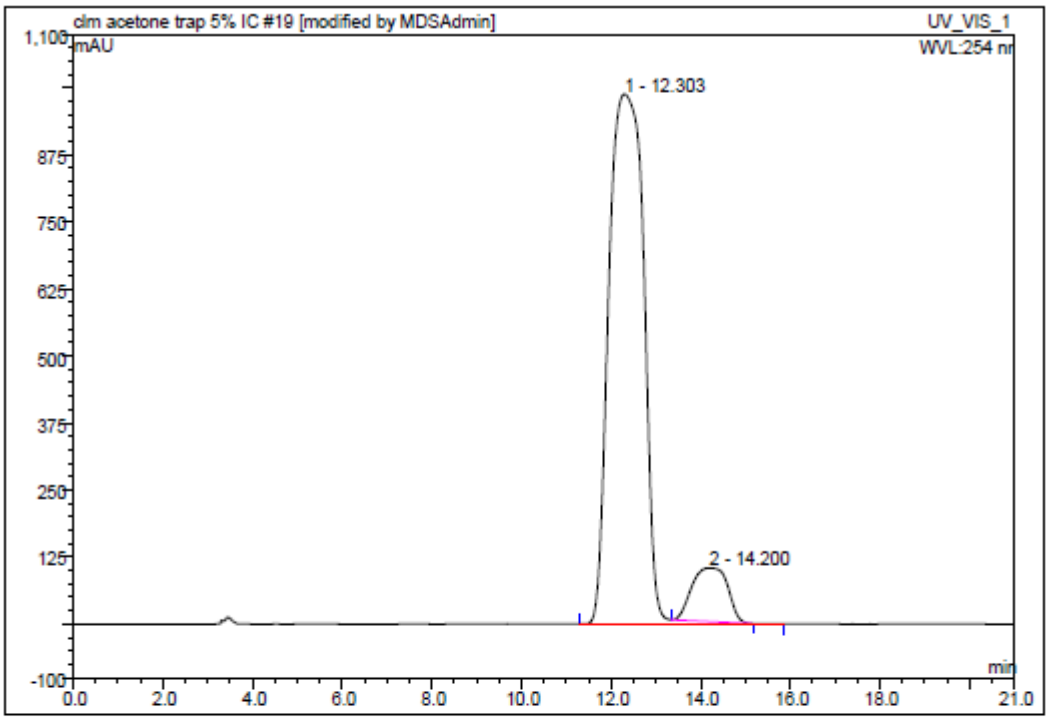
Column: CHIRALPAK AD-H, 250 × 4.6 mm, 5µm, 25 °C, 1 mL/ min, UV-vis (λ = 254 nm), eluent = isocratic at 2% *i*-PrOH in hexane.

Racemic **288m**; 50:50 er



No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	12.33	n.a.	1031.416	910.179	49.71	n.a.	BM
2	14.19	n.a.	960.232	920.936	50.29	n.a.	MB
Total:			1991.649	1831.114	100.00	0.000	

(*S*)-**288m**; 91:9 (*S*:*R*) er

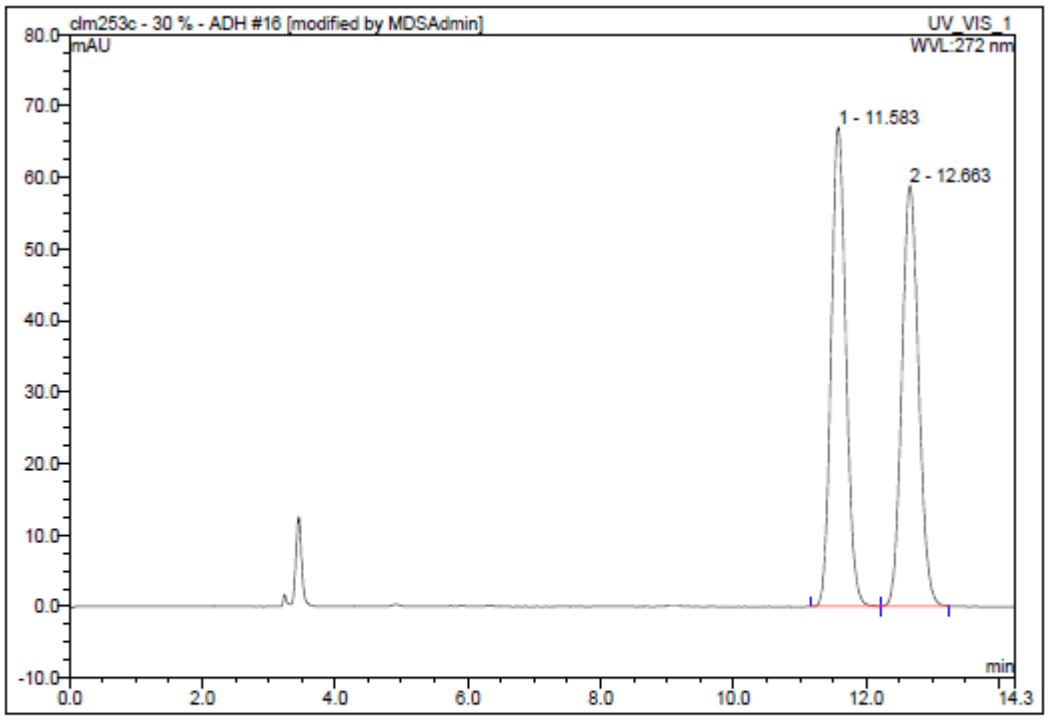


No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	12.30	n.a.	987.621	889.347	90.58	n.a.	BMB
2	14.20	n.a.	99.973	92.487	9.42	n.a.	Rd
Total:			1087.594	981.834	100.00	0.000	

7.5.4. Chiral HPLC traces for 288i-minor

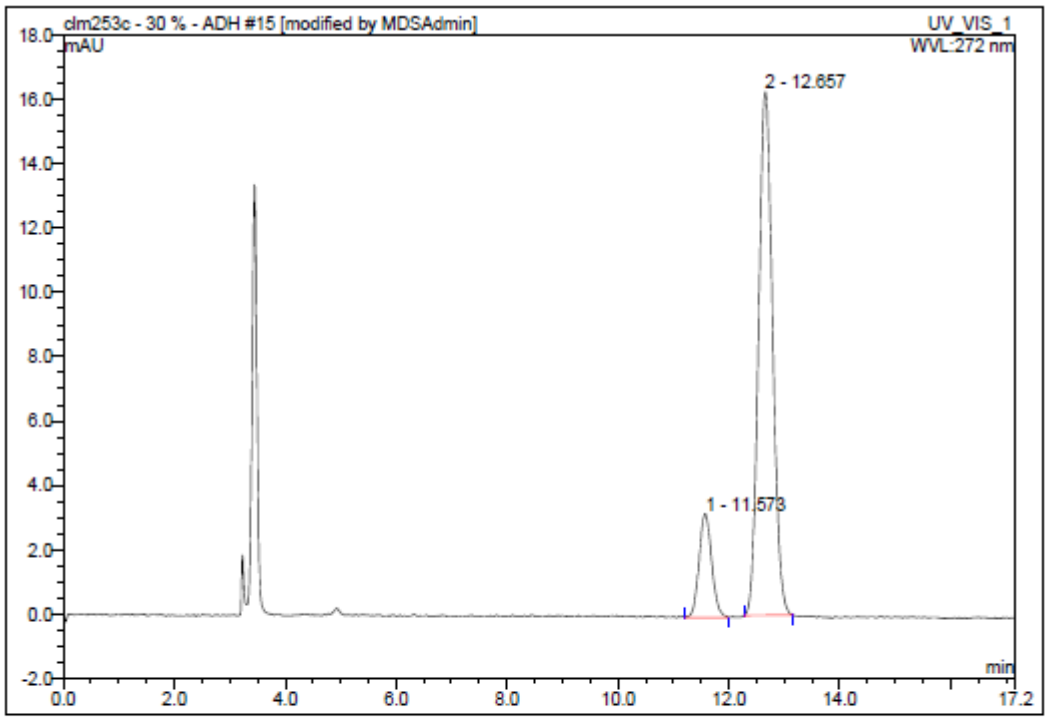
Column: CHIRALPAK AD-H, 250 × 4.6 mm, 5µm, 25 °C, 1 mL/min, UV-vis (λ = 272 nm), eluent = isocratic at 4% *i*-PrOH in hexane.

Racemic (*R**,*R**)-**288i-minor**; 50:50 er



No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	11.58	n.a.	67.093	17.305	50.06	n.a.	BM
2	12.66	n.a.	58.827	17.265	49.94	n.a.	MB
Total:			125.920	34.569	100.00	0.000	

(*S*,*S*)-**288i-minor**; 85:15 (*S*,*S*:*R*,*R*) er

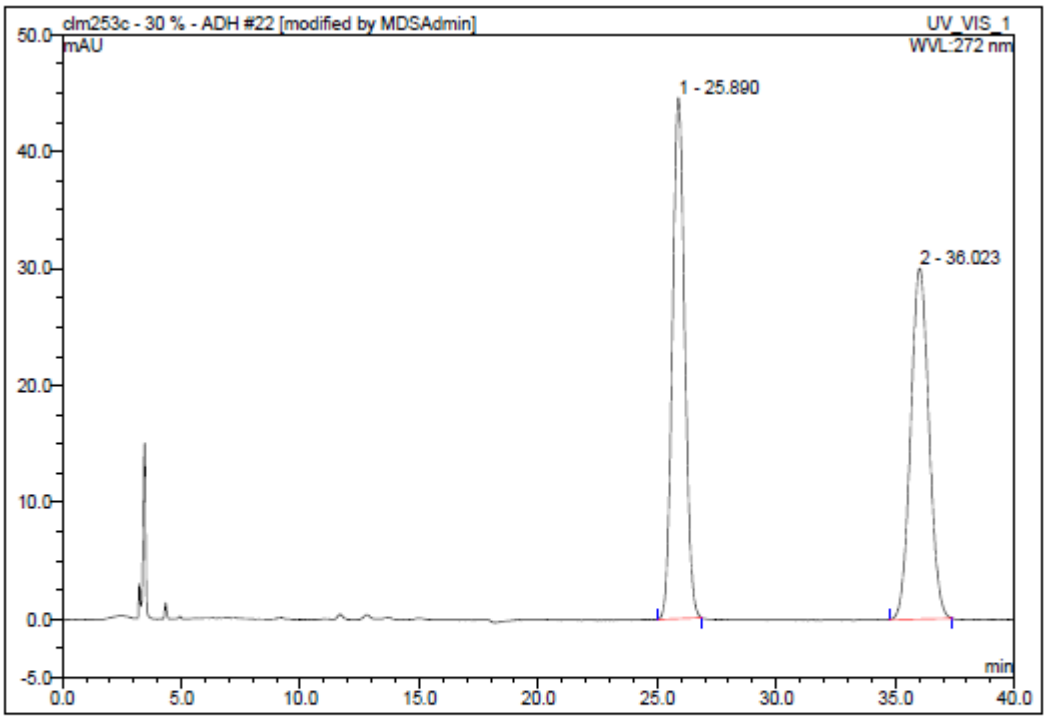


No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	11.57	n.a.	3.214	0.848	15.12	n.a.	BMB
2	12.66	n.a.	16.251	4.758	84.88	n.a.	BMB
Total:			19.465	5.605	100.00	0.000	

7.5.5. Chiral HPLC traces for 288i-major

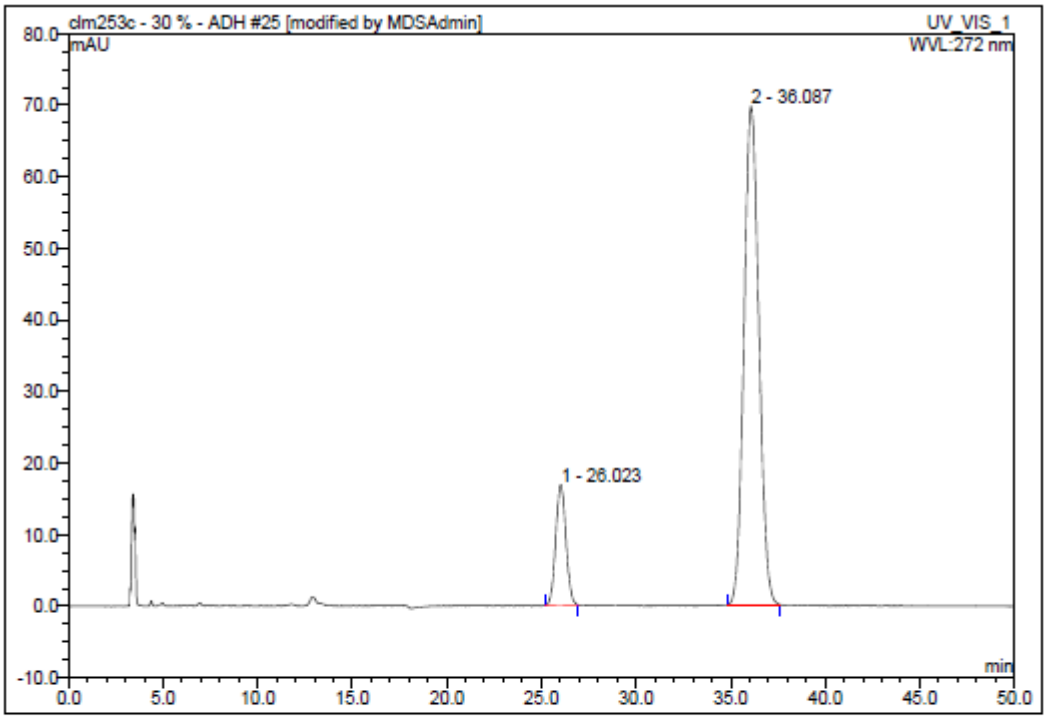
Column: CHIRALPAK AD-H, 250 × 4.6 mm, 5µm, 25 °C, 1 mL/min, UV-vis (λ = 272 nm), eluent = isocratic at 4% *i*-PrOH in hexane.

Racemic (*R**,*S**)-**288i-major**; 50:50 er



No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	25.89	n.a.	44.569	26.750	50.08	n.a.	BMB
2	36.02	n.a.	29.998	26.667	49.92	n.a.	BMB
Total:			74.567	53.417	100.00	0.000	

(*S*,*R*)-**288i-major**; 86:14 (*S*,*R*:*R*,*S*) er

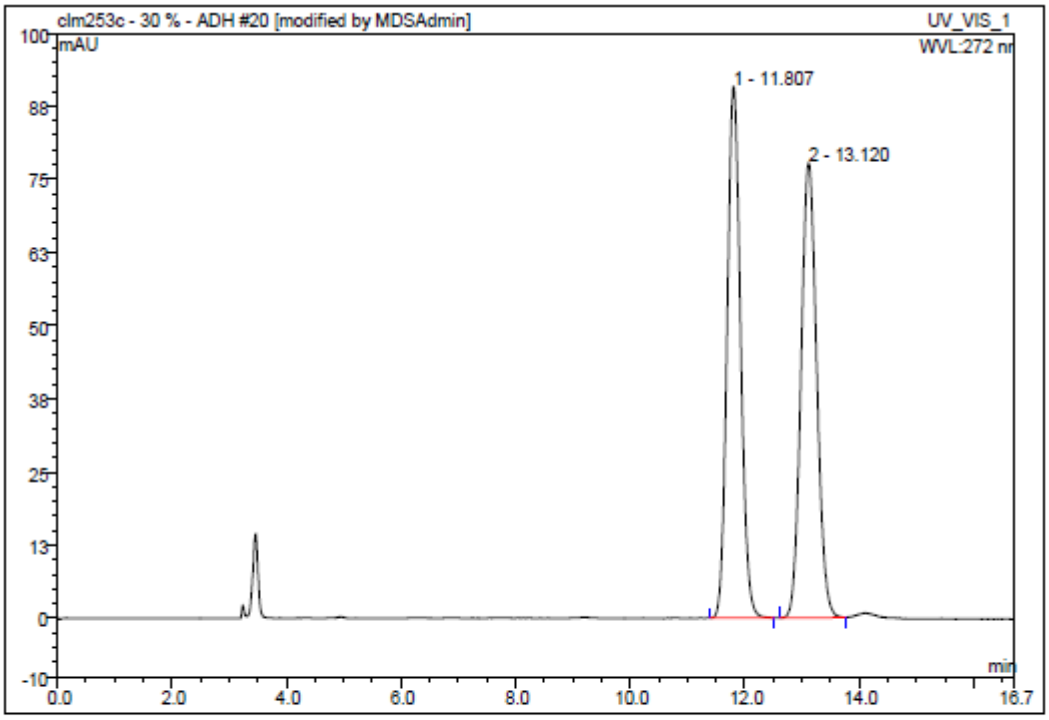


No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	26.02	n.a.	16.829	10.550	14.20	n.a.	BMB
2	36.09	n.a.	69.655	63.726	85.80	n.a.	BMB
Total:			86.484	74.276	100.00	0.000	

7.5.6. Chiral HPLC traces for 288j-minor

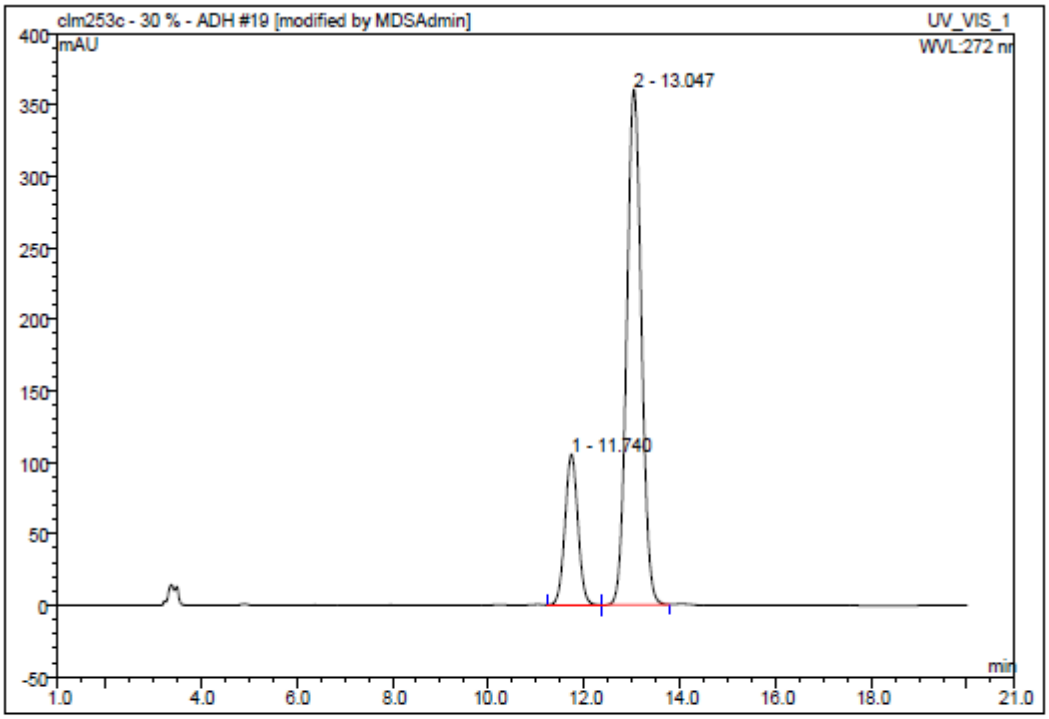
Column: CHIRALPAK AD-H, 250 × 4.6 mm, 5µm, 25 °C, 1 mL/min, UV-vis (λ = 272 nm), eluent = isocratic at 4% *i*-PrOH in hexane.

Racemic (*R**,*R**)-**288j-minor**; 50:50 er



No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	11.81	n.a.	90.787	24.676	50.02	n.a.	BMB
2	13.12	n.a.	77.713	24.660	49.98	n.a.	BMB*
Total:			168.500	49.336	100.00	0.000	

(*S*,*S*)-**288j-minor**; 80:20 (*S*,*S*:*R*,*R*) er

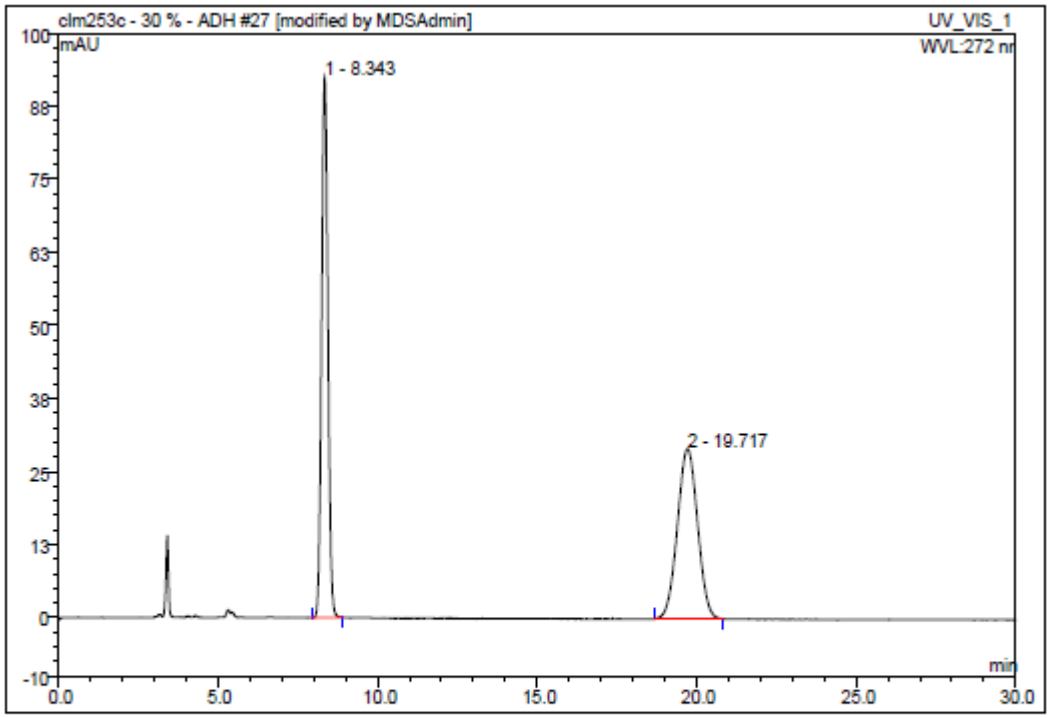


No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	11.74	n.a.	105.172	32.985	20.49	n.a.	BMB
2	13.05	n.a.	360.125	127.982	79.51	n.a.	BMB*
Total:			465.297	160.966	100.00	0.000	

7.5.7. Chiral HPLC traces for 288j-major

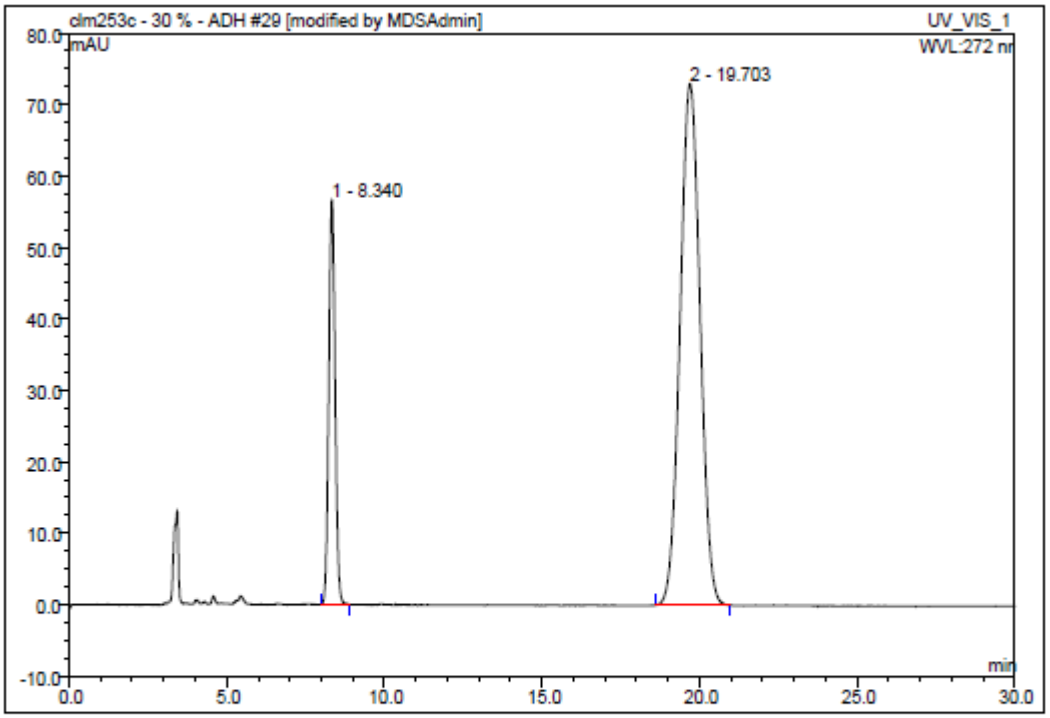
Column: CHIRALPAK AD-H, 250 × 4.6 mm, 5µm, 25 °C, 1 mL/min, UV-vis (λ = 272 nm), eluent = isocratic at 15% *i*-PrOH in hexane.

Racemic (*R**,*S**)-**288j-major**; 50:50 er



No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	8.34	n.a.	92.532	21.306	49.99	n.a.	BMB
2	19.72	n.a.	29.092	21.310	50.01	n.a.	BMB
Total:			121.624	42.616	100.00	0.000	

(*S*,*R*)-**288j-major**; 80:20 (*S*,*R*:*R*,*S*) er



No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	8.34	n.a.	56.623	13.213	19.73	n.a.	BMB
2	19.70	n.a.	72.967	53.755	80.27	n.a.	BMB
Total:			129.591	66.968	100.00	0.000	

7.6. Published report