Lithiated Azetidine and Azetine Chemistry

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Abstract

New Azetidine and Azetine Chemistry

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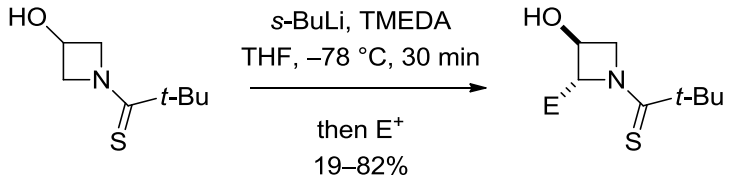
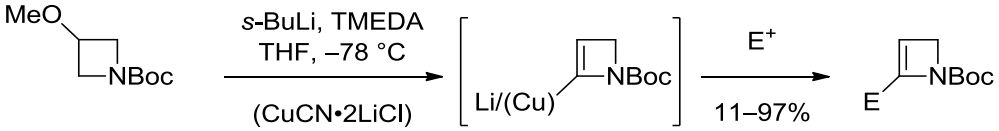
This work describes developments in new azetidine and azetine chemistry; specifically, methods developed for the introduction of functionality α- to nitrogen in both ring systems, with additionally *in situ* formation of the latter system, from azetidine substrates.

Chapter 1 discusses the growing importance of azetidines, and the current methods available for making substituted azetidines by ring formation. Further discussion comprises of current sp^3 C–H activation approaches α- to nitrogen in heterocyclic compounds as potential methods for sp^3 C–H activation on azetidines to give substituted azetidines. Previous work by the Hodgson group in this area is detailed.

Chapter 2 describes the advance made towards 2,3-disubstituted azetidines using the thiopivaloyl protecting/activating group, where the latter plays a key role. Optimisation, scope, selectivity and mechanistic insight into the α-deprotonation–electrophile trapping of a 3-hydroxy azetidine system is discussed, which successfully gives access to a range of 3-hydroxy-2-substituted azetidines. Preliminary investigations with 3-alkyl-2-substituted azetidines are also described.



Chapter 3 describes the development of a straightforward protocol to make 2-substituted-2-azetines, a rarely studied and difficult to access 4-membered azacycle subclass, from readily accessible azetidine starting materials using α-deprotonation–*in situ* elimination followed by further α-lithiation–electrophile trapping. Extension of this methodology by transmetallation from the intermediate organolithium to the organocuprate, resulting in greater electrophile scope, is also described.



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I think one of the key reasons why I ended up becoming a chemist is **Tom Lawless** whose passion for chemistry, excellent teaching ability, and willingness to attempt answering degree level questions to us A-level students made such an impact on me. Thank you.

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Abbreviations

2D – two dimensional

° C – degrees centigrade

[O] – oxidation

δ – chemical shift

μ – micro

Ac – acetyl

addn. – addition

AIBN – 2,2′-azobis(2-isobutyronitrile)

approx. – approximately

aq – aqueous

Ar – aryl

atm – atmosphere

B – base

BBH – bis(collidine)bromonium(I) hexafluorophosphate

Bn – benzyl

Boc – *tert*-butyloxycarbonyl

br – broad

brsm – based on recovered starting material

n-Bu – butyl

s-Bu – *sec*-butyl

t-Bu – *tert*-butyl

Bus – *tert*-butyl sulfonyl

Bz – benzoyl

C_2, C_3, C_4 – see Figure ii below

calcd – calculated

cat – catalytic

cm^{-1} – wavenumber

conc. – concentrated

m-CPBA – *meta*-chloroperbenzoic acid

d – day(s), doublet

DABCO – 1,4-diazabicyclo[2.2.2]octane

dba - dibenzylideneacetone

DEAD – diethyl azodicarboxylate

DIAD – diisopropyl azodicarboxylate

DIPEA - diisopropylethylamine

DKR – dynamic kinetic resolution

DMAP – 4-(*N*,*N*-dimethylamino)pyridine

DMF – dimethylformamide

DMP – Dess-Martin periodinane

DMPU - 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone

DMSO – dimethyl sulfoxide

DNA – deoxyribonucleic acid

dr – diastereoisomer ratio

DTR – dynamic thermodynamic resolution

E/E^+ – electrophile

e.g. – for example

epi – epimer

equiv – equivalent

er – enantiomer ratio

ESI – electrospray ionisation

Et – ethyl

FI – field ionisation

fod - 6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionate

g – gram(s)

h – hour(s)

HRMS – high resolution mass spectrometry

hv – photoirradiation

Hz – hertz

IR – infrared

J – coupling constant

K – kelvin

L/L* - generic ligand/ generic chiral ligand

LDA – lithium diisopropylamide

lit. – literature

LRMS – low resolution mass spectrometry

LTMP – lithium 2,2,6,6-tetramethylpiperidide

M – molar, parent mass

m – milli, multiplet, medium

Me – methyl

MHz – megahertz

min – minute(s)

mol – moles/molar

MOM – methoxymethyl

mp – melting point

Ms – methylsulfonyl

MS – molecular sieves

MTBE – methyl *tert*-butyl ether

m/z – mass to charge ratio

NMR – nuclear magnetic resonance

NOE – nuclear Overhauser effect

p. – page number

pp. – page numbers

Pd/C – palladium on carbon

PG – protecting group

Ph – phenyl

piv – pivaloyl

PMA - phosphomolybdic acid

PMB – *p*-methoxybenzyl

ppm – part(s) per million

Pr – propyl

i-Pr – isopropyl

py – pyridine

q – quartet

quant. – quantitative

quin – quintet

R – generic substituent

rac – racemic

Ref. – reference

R_f – retention factor

rt – room temperature

s – singlet, strong, second(s)

sat. – saturated

sept - septet

Si-gel – silica gel

sm – starting material

t – triplet

$t_{1/2}$ – half life

TBAF – tetrabutylammonium fluoride

TBS – *tert*-butyldimethylsilyl

Tf – trifluoromethanesulfonyl

TFA – trifluoroacetic acid

THF – tetrahydrofuran

TLC – thin layer chromatography

TMEDA – *N*,*N*,*N'*,*N'*-tetramethyl-1,2-ethylenediamine

TMS – trimethylsilyl

TOF – time of flight

Tol – toluene

Tr - triphenylmethyl

Ts – *p*-toluenesulfonyl

TSA – toluenesulfonic acid

v. – very

w – weak

w/v – weight per unit volume

Stereochemistry

Throughout this thesis relative stereochemistry will be represented by uniform lines, whereas absolute stereochemistry will be represented by tapered lines (Figure i).[1]

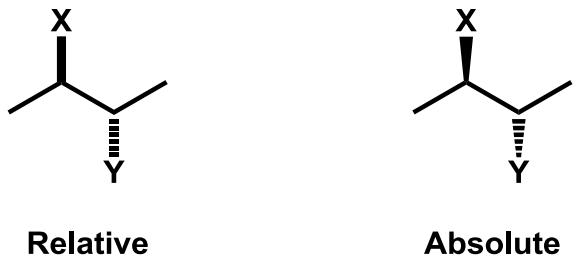

Figure i Stereochemical notation

Azetidine notation

C_2, C_3, C_4 refer to the carbon framework of the azetidine ring (Figure ii), where E represents an installed electrophile.

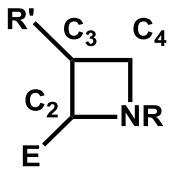

Figure ii Notation for carbon positions in azetidine ring

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1 Introduction

The work presented in this thesis describes the development of novel azetidine and azetine chemistry and, more specifically, methods for the introduction of functionality α- to nitrogen in these systems. The aim of the first half of the following introductory chapter is to provide a general overview of current methods available to synthesise substituted azetidines; the examples given will exemplify typical methods used for azetidine synthesis.

The latter half of the introductory chapter focuses on 'C–H activation' α- to nitrogen in azacycles, as a potential method for substituted azetidine synthesis. Currently, very few examples of successful C–H activation α- to nitrogen on an azetidine have been reported; these will be discussed. Furthermore, this section will provide a general overview of α-lithiation–electrophile trapping as a method for 'C–H activation' α- to nitrogen for substituted azacycle synthesis, and detail early promising results of this method which laid the foundations for the investigations in α-substituted azetidine and azetine synthesis.

1.1 Heterocycles

Not many years ago heterocyclic chemistry was considered a speciality field of natural product synthesis and medicinal chemistry. In recent years this has changed significantly, such that an estimated 85-90% of publications today are related in some way to heterocycles.[2]

1.1.1 Heterocycle use

Research concerning the use of heterocycles in natural product synthesis and in the pharmaceutical and agrochemical industries is considerable in areas such as alkaloids, DNA, vitamins, hormones, sugars, antibiotics, drugs, argochemicals and dyes. Heterocycles are now being utilised in more diverse areas, such as scaffolds for new materials, protecting groups, solvents and reagents, latent functionalities in organic synthesis, chemical building blocks that can be modified and substituted to

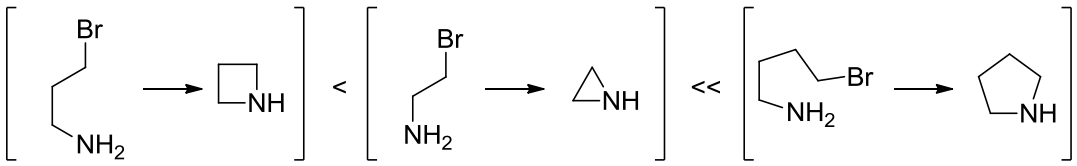
give new heterocyclic products, or if need be ring-opened to give new acyclic products, as well as furthering research towards continually needed new drug targets.[2]

The synthesis of functionalised heterocyclic compounds has become an integral part of synthetic organic chemistry, and as such, much research is devoted to developing new methods to synthesise, derivatise and utilise such compounds.

1.2 Azetidines

Of the classes of heterocycle, cyclic amines have become increasingly well used, due to conformation restriction, in drug targets, as well as in other areas. Much research has been conducted into the synthesis of piperidine and pyrrolidine systems. More recently, aziridines have also received significant interest from the synthetic community. However, compared to its higher and lower homologues, azetidines have received substantially less interest,[3] although substantial research has been carried out into azetidin-2-one (β-lactam) synthesis due to potent antibacterial activities.[4]

The relative paucity of research on azetidines may be in part due to the poor yields obtained from very early azetidine syntheses. Indeed, the rate of ring closure for 3-bromopropylamine (**1**) is 8 times lower than that for 2-bromoethylamine (**3**), and 62500 times lower than for 4-bromobutylamine (**5**); these rate differences indicate the higher energy requirement and difficulty in forming the azetidine core (Scheme 1.1).[5]



Scheme 1.1 Rates of cyclisation are lowest for azetidine formation in the halo-amine series.

Nevertheless, azetidines exhibit interesting biological activities.[6] They are being increasingly incorporated into drug molecules, for example as cholesterol level decreasing agents,[7] anti-obesity agents,[8] anti-thrombotics[9] and a number of other targets.[10] They are also utilised as ligands in metal-

catalysed transformations,[11] as chiral auxiliaries in enantioselective reactions,[12] and as amino acids to induce specific secondary structures in peptides,[13] as well as being present in a small number of natural products[14] (Figure 1.1).

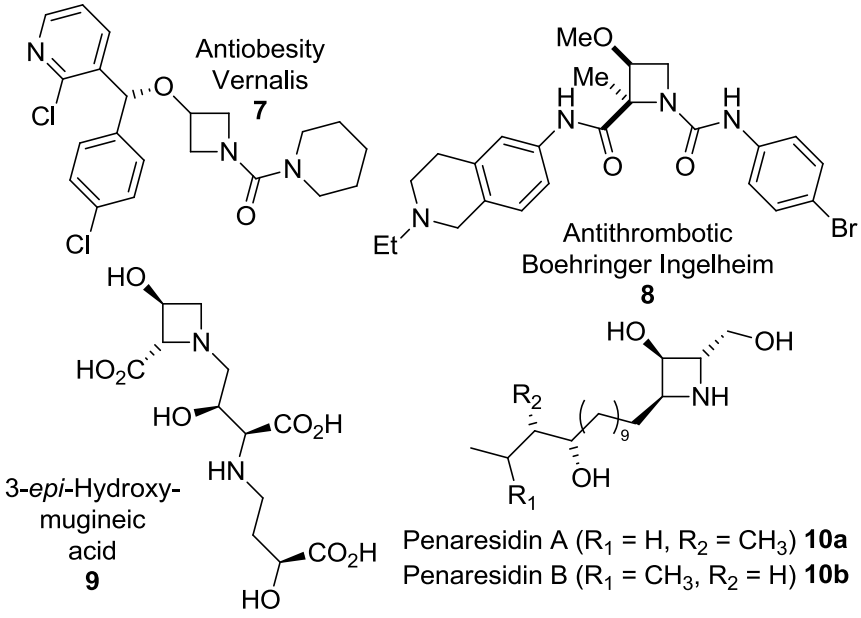


Figure 1.1 Examples of azetidine drug leads and natural products

As a result of this, efficient methods for azetidine synthesis are starting to appear in the literature[3,4,15] and presented below is a brief overview of some representative examples of azetidine synthesis and functionalisation.

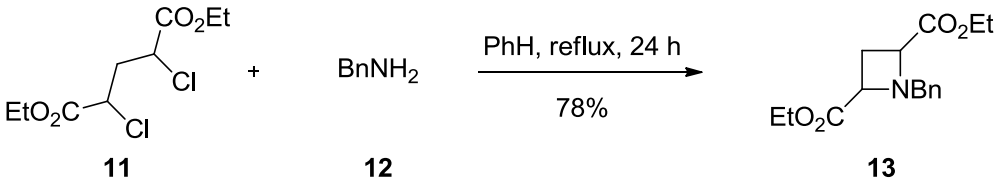
1.2.1 Ring formation

A number of methods for substituted azetidine synthesis use functionalised precursors in ring formation.

1.2.1.1 Addition to 1,3-dielectrophiles

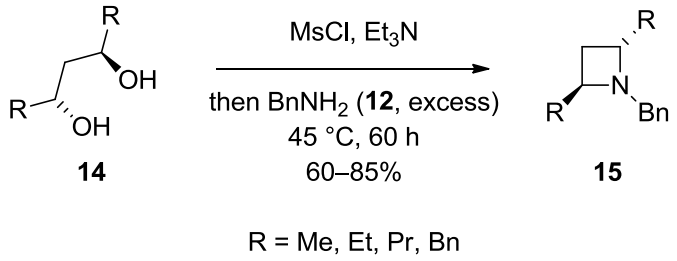
One of the most popular methods to access substituted azetidines is the direct addition of amines to 1,3-dihalo substrates. This strategy requires the ring substituents to be present on the 1,3-halo substrate before cyclisation, and can suffer from double intermolecular addition of the amine if the cyclisation step is not facile. Nevertheless, azetidines can be obtained in high yields in a number of cases, such as the cyclisation of 1,3-dichloride **11** with benzylamine (**12**) in refluxing benzene,

selectively giving amine addition and ring closure at the chlorine-bearing centres to give diester azetidine **13** in 78% yield (Scheme 1.2).[16]



Scheme 1.2 Benzyl amine addition to 1,3-dichloro substrate **11** to give azetidine **13**

A similar approach can be carried out with activated 1,3-diols; for example, activation of **14** to the corresponding bis-sulfonate by treatment with MsCl and subsequent cyclisation with $BnNH_2$ (**12**) to give **15** in 60-85% yield, depending on the size of the R group (Scheme 1.3).[17]

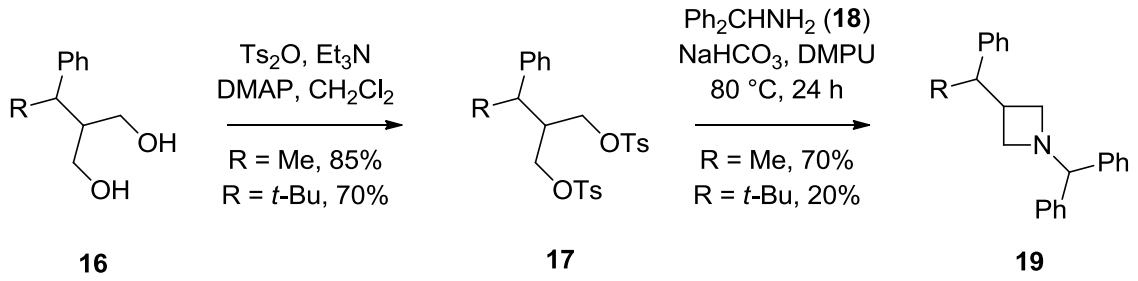


Scheme 1.3 Cyclisation of 1,3 diol **14**

It is important to note that while use of bis-sulfonates generally tolerates larger substituents for cyclisation when compared to groups allowed with cyclisation of 1,3-dihalo substrates, attempted cyclisation of **14** when the R groups are increased in size to isopropyl, does not lead to the corresponding azetidine.[17]

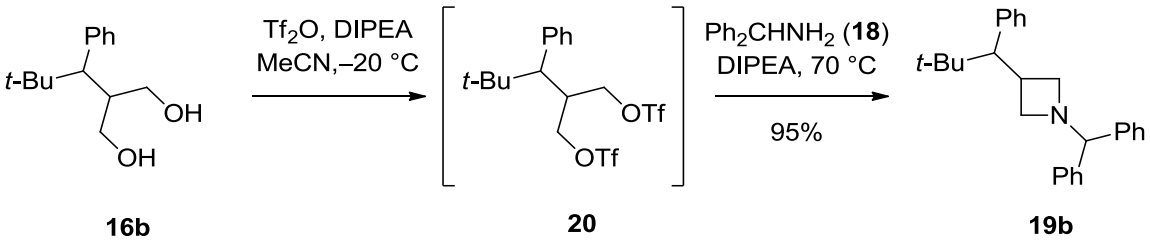
Activation of 1,3-diol **16** with Ts_2O followed by reaction with benzhydrylamine (**18**) gave azetidine **19** in 70% when R = Me; however, when R = *t*-Bu only 20% yield of **19** was obtained (Scheme 1.4). While increased steric bulk at the reaction centres slows down the rate of S_N2 reaction, increased steric bulk away from the reaction centres may disfavour the correct conformation for reaction and likewise result in lower rates of reaction. Bis-triflate activation of 1,3-diols provides a much better

leaving group, and has allowed these energetically more demanding cyclisations to proceed in good yields with bulky substituents.[18]



Scheme 1.4 Cyclisation of diol **16** with tosyl activation

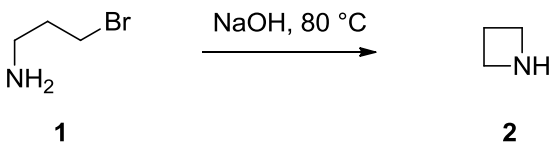
Treatment of diol **16b** with Tf_2O to form bis-triflate **20** *in situ*, followed by cyclisation using benzhydrylamine (**18**) gave azetidine **19b** in a significantly greater yield of 95% over 2 steps (Scheme 1.5).[18]



Scheme 1.5 Cyclisation of diol **16b** with triflate activation

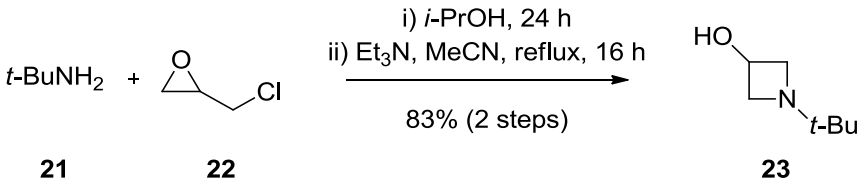
1.2.1.2 Cyclisation of amines

The other most common method, related to that above is cyclisation of γ-halo amines. One of the first azetidines published, in 1888 by Gabriel and Weiner, was azetidine (**2**) itself, synthesised by cyclisation of 3-bromopropan-1-amine (**1**) using NaOH under heating, followed by distillation, but no yield was reported (Scheme 1.6).[19]



Scheme 1.6 Early synthesis of azetidine (**2**) from 3-bromopropan-1-amine (**1**)

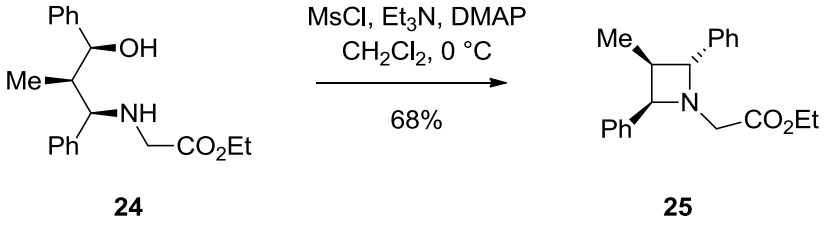
These cyclisations have been subsequently developed and it has been discovered that efficient cyclisation can be achieved when there is a sufficiently bulky group, often aromatic, on the nitrogen in order to help achieve the required conformation for cyclisation to occur.[20,21] Higher yields can be achieved using benzyl,[22] benzhydryl[23] and *tert*-butyl[21] type *N*-protecting groups (e.g. Scheme 1.7).



Scheme 1.7 High yielding approach to azetidine **23** utilising *tert*-butyl *N*-protecting group

Cyclisation without bulky *N*-substituents can be achieved, but typically such examples originate from early azetidine research and tend to suffer from poorer yields.[24,25,26]

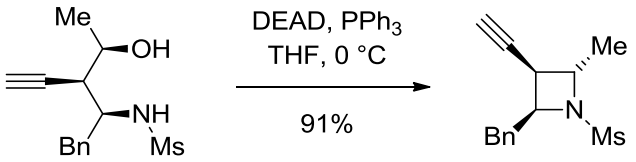
Further variation can be achieved by using non-halogen leaving groups. With a large array of sulfonates available, activated amino alcohols can similarly be used in azetidine syntheses, as demonstrated by the cyclisation of amino alcohol **24** with mesyl activation to give enantiopure azetidine **25** (Scheme 1.8).[27]



Scheme 1.8 Cyclisation of amino methylate to give azetidine **25**

This is the method of choice for the synthesis of enantiopure azetidines from single enantiomer amino alcohols, although the arrangement of substituents on the ring can have an adverse effect on the rate of cyclisation.[15a]

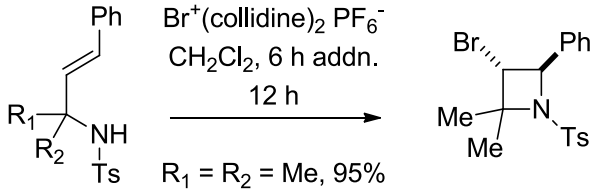
Other variations of ring closing syntheses include use of the Mitsunobu reaction, which can effect high yielding cyclisation of hydroxyl *N*-sulfonamides to give azetidines. Reaction of alcohol **26** with DEAD and PPh_3 in THF at 0 °C gave azetidine **27** in 91% yield (Scheme 1.9).[28]



26 **27**

Scheme 1.9 Mitsunobu cyclisation of alcohol **26** to give azetidine **27**

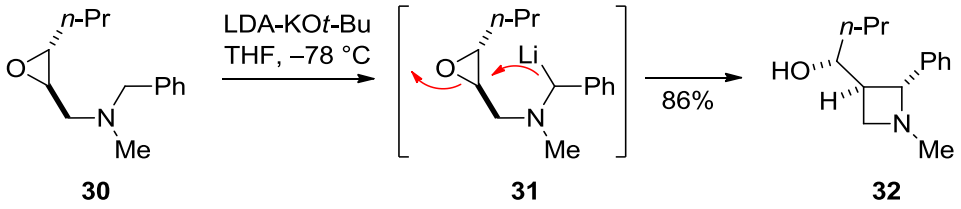
Use of bromine to form the corresponding bromonium ion/carbocation of allylic tosylamides **28** followed by ring closure gives azetidines **29** in 61–95% yields (Scheme 1.10).[29] However, reaction was limited to 3-aryl-substituted allylic tosylamides; use of 3,3-dimethyl allylic tosylamide did not result in azetidine formation. The second 3-Me group may block the required trajectory of approach for cyclisation.



28 **29**

Scheme 1.10 Cyclisation of allylic tosamide **28** with BBH to give azetidine **29**

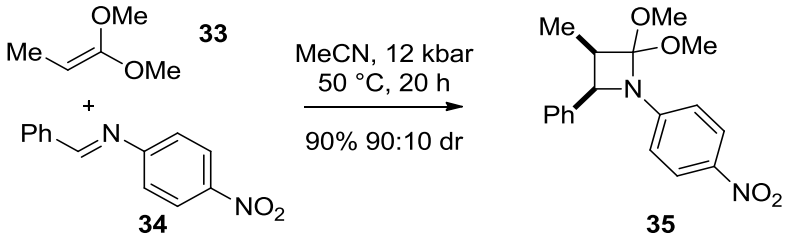
Use of *C*-cyclisation from an acyclic amine can be used as an alternative to *N*-cyclisation. In a recent paper by Faigl and co-workers,[30] metallation adjacent to nitrogen in *N*-benzyl and *N*-allyl epoxyamines **30** allowed carbo-cyclisation onto the epoxide, to give the corresponding 2,3-disubstituted azetidines **32** in a diastereoselective manner and in good yields (Scheme 1.11). Cyclisation of similar amino epoxides with the *N*-Me group changed for Et, Bn and Boc saw a progressive decrease in respective yields to 62%, 48% and 40%, possibly indicating, similar to above, a disfavouring of reactive conformers as *N*-R becomes larger.



Scheme 1.11 Cyclisation of α-metallated amino epoxide **31**

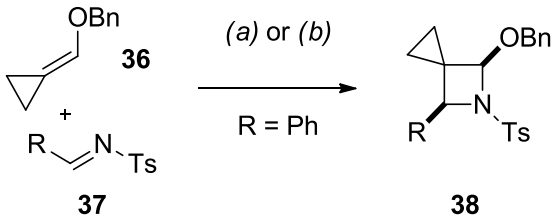
1.2.1.3 [2+2] cycloadditions

The first example of a [2+2] cycloaddition giving an azetidine was published in 1987 by Scheeren,[31] in which ketene acetal **33** was reacted with imine **34** at high pressure (12 kbar) to give azetidine **35** as a 90:10 mixture of diastereoisomers, in 90% yield (Scheme 1.12).



Scheme 1.12 [2+2] cycloaddition of ketene acetal **33** with imine **34** to give azetidine **35**

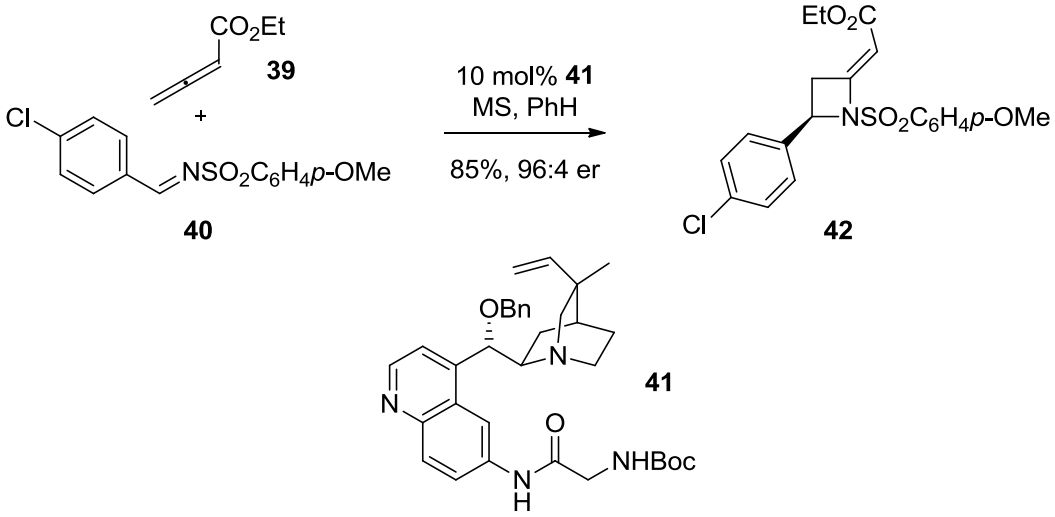
Limited examples exist of other [2+2] cycloadditions to give azetidines. Nakamura and co-workers[32] studied both thermally promoted and metal-catalysed [2+2] cycloadditions of strained cyclopropyl enol ethers **36** with similar imines **37**, providing azetidines **38** thermally in the range of 57-97% with diastereoselectivities up to 98:2, and 45-94% catalytically with diastereoselectivities up to >99:1 (Scheme 1.13). Poorer yields and selectivities were observed under both methods with R = CO_2Et (45% 97:3 catalytically, and 57% 55:45 thermally); a drop in selectivity was also observed in thermal cycloadditions when tosylimine is exchanged for a mesylimine with R = Ph or 4-$CF_3C_6H_4$ (83:17 and 80:20 respectively).



Reagents and conditions: (a) MeCN, 80 °C, 97%, 98:2 cis:trans.
(b) 10 mol% [Ag(fod)], 30 °C, EtOAc, 94%, >99:1 cis:trans.

Scheme 1.13 Thermal and catalytic [2+2] cycloaddition to give azetidine **38**

More recently, the enantioselective [2+2] cycloaddition of allenoates and imines has been shown to give access to 2,4-disubstituted azetidines in the presence of cinchona alkaloid amide catalysts. Reaction of allenoate **39** with imine **40** gave azetidine **42** in 85% yield and 96:4 er (Scheme 1.14).[33] This procedure tolerates both electron-withdrawing and weakly electron-donating substituents on the sulfonylimine phenyl ring, however strongly electron donating groups (*p*-OMe) gave diminished yields (46%), but enantioselectivities remained high (98:2 er).



Scheme 1.14 Enantioselective [2+2] cycloaddition of allenoate **39** and imine **40**

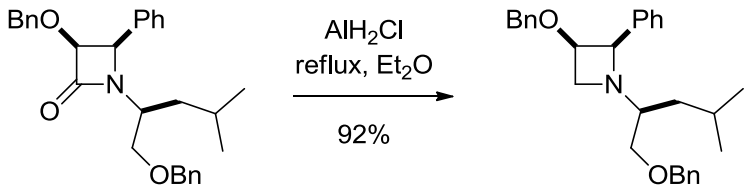
1.2.1.4 Other ring closure methods

Similar cyclisations can be carried out using homoallylic amines with phenylselenium halides[34], with palladium-catalysed intramolecular amination of β-amino allenes[35, 36] and cyclisation of γ-amino epoxides with a strong base,[37,38] among other methods.

1.2.1.5 Reduction of β-lactams

As noted earlier (Section 1.2, p. 2), while comparatively little research has been carried out towards azetidines, azetidin-2-ones (β-lactams) have been studied in detail due to their important biological activity as broad spectrum antibacterial agents.[4,39] Many methods[4] have been reported for azetidin-2-one synthesis, including Staudinger synthesis using ketenes and imines,[40] condensation of enolates and imines,[41] the copper-catalysed reaction of nitrones with terminal alkynes,[42] [2+2] cycloaddition of isocyanates to alkenes,[43]and cyclisation of various β-amino acids.[44]

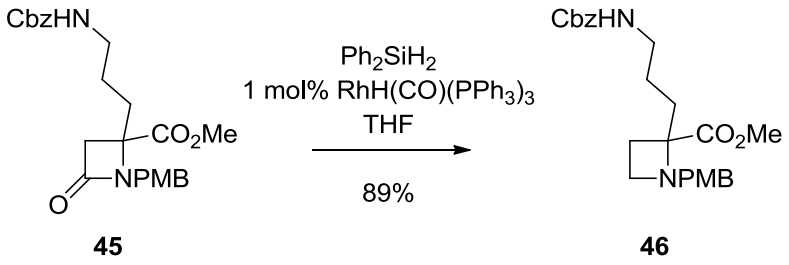
With methods towards the synthesis of azetidin-2-ones being relatively well described, many with high diastereoselectivities, the reduction of the β-lactam represents another important method towards substituted azetidine synthesis. An obvious problem associated with β-lactam reduction is the possibility of ring-opening, however, methods using specific reagents have been developed to only reduce the β-lactam. Monochloroalane (AlH_2Cl) and dichloroalane ($AlHCl_2$), prepared from $LiAlH_4$ and $AlCl_3$, have been found to be appropriate reducing agents for this purpose.[45] Use of these reagents, usually at reflux in ethereal solvents gives the corresponding azetidines from azetidin-2-ones, sometimes heavily functionalised, such as the reduction of azetidin-2-one **43** to give azetidine **44** in 92% yield (Scheme 1.15).[46]



43 **44**

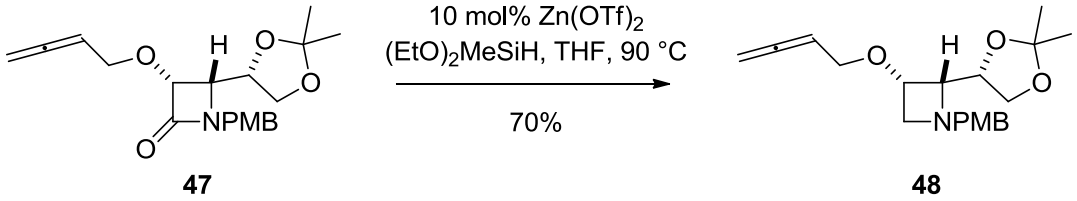
Scheme 1.15 β-lactam reduction using AlH_2Cl

Reduction of the β-lactam in the presence of other sensitive functional groups (methyl and *tert*-butyl esters) can also be achieved in a method developed by Gonzáles-Muniz, with diphenylsilane and a rhodium hydride catalyst, which has been used in the reduction of ester bearing azetidin-2-one **45** to give azetidine **46** in 89% yield (Scheme 1.16).[47]



Scheme 1.16 Chemoselective reduction of β-lactam **45**

More recently, extension of this approach to zinc-catalysed reduction was carried out using $Zn(OTf)_2$ with $(EtO)_2MeSiH$ at 90 °C in a sealed tube, which significantly reduced the overall cost of the transformation (Scheme 1.17).[48] This methodology, like previously, allowed reaction in the presence of other sensitive groups, such as reduction of azetidin-2-one **47** to give azetidine **48**, but did give slightly poorer yields when the group at C_3 was OAc (35%) and OCOPMB (49%).

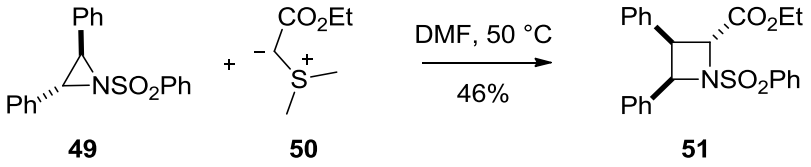


Scheme 1.17 Chemoselective silane reduction of β-lactam **47** catalysed by $Zn(OTf)_2$

1.2.1.6 Ring expansion, ring contraction

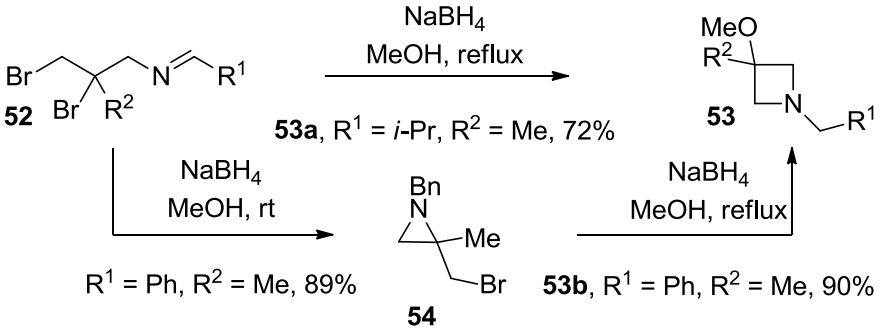
Accessing substituted azetidines can also be achieved by ring contraction, or by ring expansion of aziridines.

Ring expansion of aziridine **49** with dimethylsulfonium methylide **50** provides a method to give substituted azetidine **51** in moderate yield (Scheme 1.18),[49] although similar ring expansions fail with 2,3-dialkyl aziridines and only a poor yield was obtained with 2-methyl aziridine (5%).



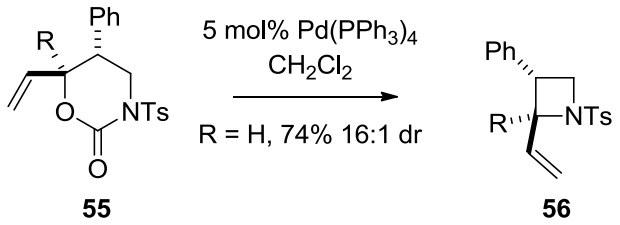
Scheme 1.18 Ring expansion of aziridine **49** to give azetidine **51**

More recently, ring expansion was also shown to be possible in the synthesis of azetidine **53**, in which starting imine **52** is cyclised, potentially via the corresponding aziridine, followed by further reaction to give desired substituted azetidine **53** (Scheme 1.19). The authors demonstrated that aziridine **54** could be formed and isolated under kinetic conditions, then further treated with $NaBH_4$ at reflux to give azetidine **53b**, indicating the aziridine was the kinetic product, and the azetidine was the thermodynamic product. They further suggest the azetidine is formed via a strained bicyclic aziridinium salt from the intermediate aziridine.[50]



Scheme 1.19 Ring expansion of aziridine **54** to give the corresponding azetidine **53**

Ring contractions to azetidines are rare, but have been carried out via photoirradiation of 2-cyano-1-pyrroline-1-oxides,[51] and treatment of perhydrooxathiazines with KOH,[52] to give the corresponding azetidines in moderate yields. In an interesting decarboxylative ring contraction, oxazinanone **55** undergoes reaction in the presence of a palladium catalyst to give the corresponding substituted azetidine **56** in 74% yield and 16:1 dr when R = H (Scheme 1.20) and 60–93% yields for other derivatives when R = H.[53] The authors note that substitution next to the vinyl group on the ring (R ≠ H), the azetidine is formed only in trace amounts.



55 **56**

Scheme 1.20 Palladium-catalysed decarboxylation to give azetidine **56**

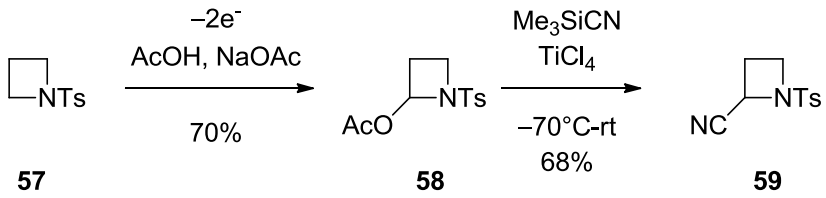
1.2.1.7 Limitations

The methods detailed above generally provide substituted azetidines in good yields, however the syntheses of many of the precursors are lengthy, particularly so for enantioenriched educts. These methods suffer from early stage divergence in order to provide a range of azetidine systems. Furthermore, in several cases, cyclisations fail or become increasingly inefficient as the functionalities on the acyclic precursors become sterically more demanding.

1.3 C–H activation α- to nitrogen

All the methods presented so far have required the substituents desired on the azetidine to be present on a precursor prior to ring formation. As noted above, there are limitations to this type of procedure. An alternative strategy towards functionalised azetidines is to pre-form the azetidine core and functionalise directly on the ring. This approach benefits from late stage divergence and avoids the synthesis of complex starting materials.

Few methods have been studied in depth for the α-functionalisation of azetidines; however, the addition of nucleophiles to the C_2 position was demonstrated by Shono and co-workers in a two-step procedure.[54] Anodic oxidation of *N*-tosyl azetidine (**57**) in acetic acid with sodium acetate gave 2-acetylated azetidine **58** in 70% yield. Subsequent nucleophilic displacement using a Lewis acid gave 2-substituted azetidines **59** in 34-68% yield (Scheme 1.21).



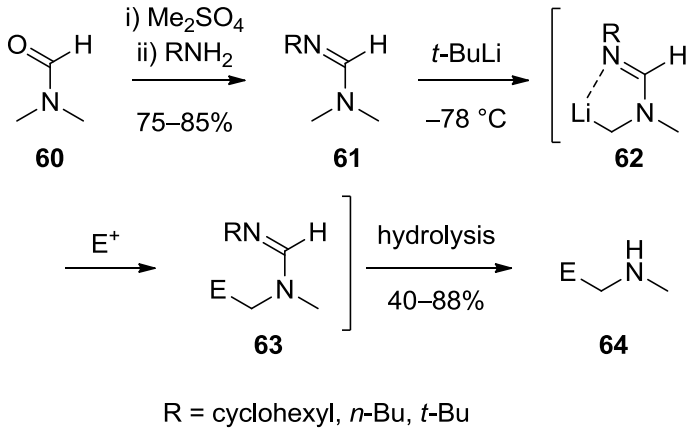
Scheme 1.21 Anodic oxidation of azetidine **57** to give substituted azetidines **59**

Davis and co-workers demonstrated that α-C–H insertion of Boc-protected azacycles with aryldiazoacetates can be achieved under rhodium catalysts, however, when attempted with *N*-Boc azetidine only a complex mixture of products was obtained.[55]

1.3.1 α-Lithiation with alkyllithium/diamine

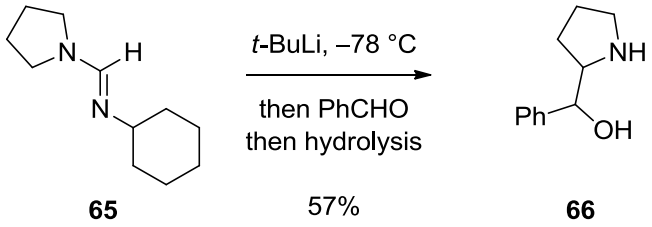
Several methods exist for the functionalisation of other azacycles, particularly direct sp^3 C–H 'bond activation' α- to nitrogen[56] to give substituted azacycles. One of the oldest methods for direct α-substitution of cyclic amines is by the use of a lithiating agent. Widely used are butyllithiums, typically with a deaggregation ligand, to achieve α-deprotonation,[56,57] followed by trapping of the resulting carbanion with suitable electrophiles, but use of bulky amide bases such as LDA or LTMP have also been applied,[57,58]

Meyers and co-workers demonstrated that α-lithiation of acyclic amines could be achieved from *N*,*N*-dimethyl amidines **61**, [59] synthesised from the corresponding *N*-formamide **60**. α-Lithiated formamidines **62** were trapped with alkyl halide, or carbonyl electrophiles in moderate to excellent yield followed by hydrolysis to the corresponding amine **64** or *N*-formamide (Scheme 1.22).



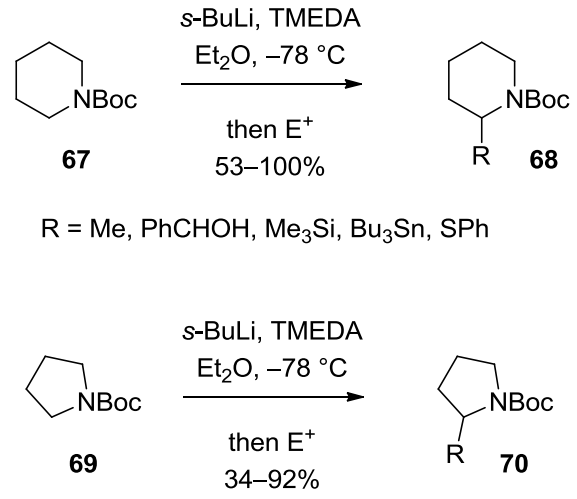
Scheme 1.22 α-Deprotonation–electrophile trapping of *N*-formamidines **61**

Meyers also demonstrated in the same report[59] that deprotonation could be achieved on a pyrrolidine derivative and trapped with PhCHO to give, after hydrolysis, α-substituted pyrrolidine **66** in 57% yield (Scheme 1.23).



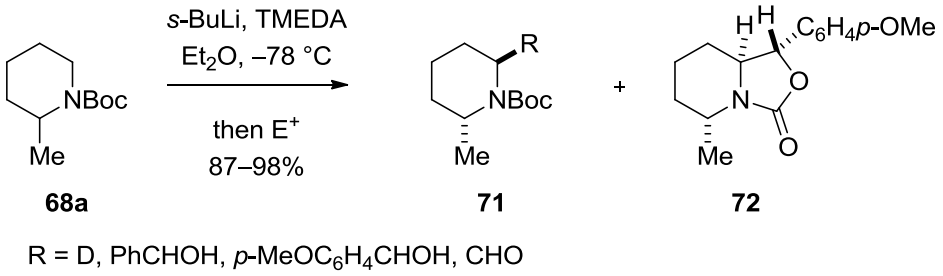
Scheme 1.23 α-Deprotonation–electrophile trapping of pyrrolidine **65**

Extensive investigation of metallation α- to nitrogen in cyclic amines was carried out by Beak and co-workers in which Boc-protected piperidines **67** and pyrrolidines **69** were α-lithiated adjacent to nitrogen and the resulting carbanion trapped with a wide range of electrophiles in good yields, to give the corresponding 2-substituted amines **68** and **70** (Scheme 1.24).[60]



Scheme 1.24 α-Lithiation and electrophile trapping of *N*-Boc piperidine **67** and pyrrolidine **69**

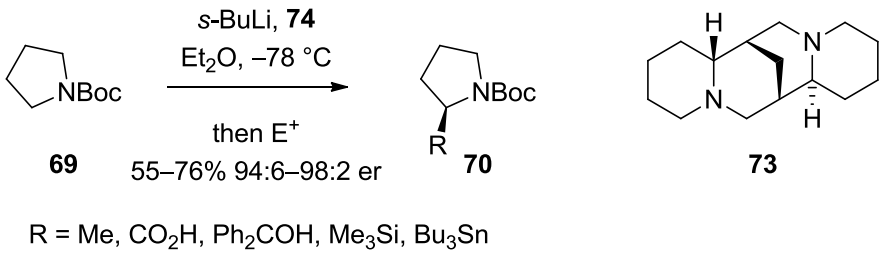
Further reaction could be achieved by re-subjecting mono-substituted products (e.g. **68a**) to lithiation and a second equivalent of electrophile, to give trans doubly-substituted products **71** in good to excellent yields; however, longer lithiation times were required to obtain good yields (Scheme 1.25).[60b] In the case of Boc piperidine with benzaldehyde trapping, quenching the reaction mixture at –78 °C gave the corresponding alcohol **71** (R = PhCHOH). In the case of *p*-anisaldehyde trapping, if the reaction mixture is warmed and held at –20 °C the intermediate *syn*-alkoxide isomer selectively cyclises onto the Boc group, to give the corresponding bicyclic carbamate **72**; the uncyclised *anti*-isomer alcohol **71** (R = *p*-MeOC$_6$H$_4$CHOH) is also isolated.



Scheme 1.25 Di-substitution of *N*-Boc piperidine **68a**

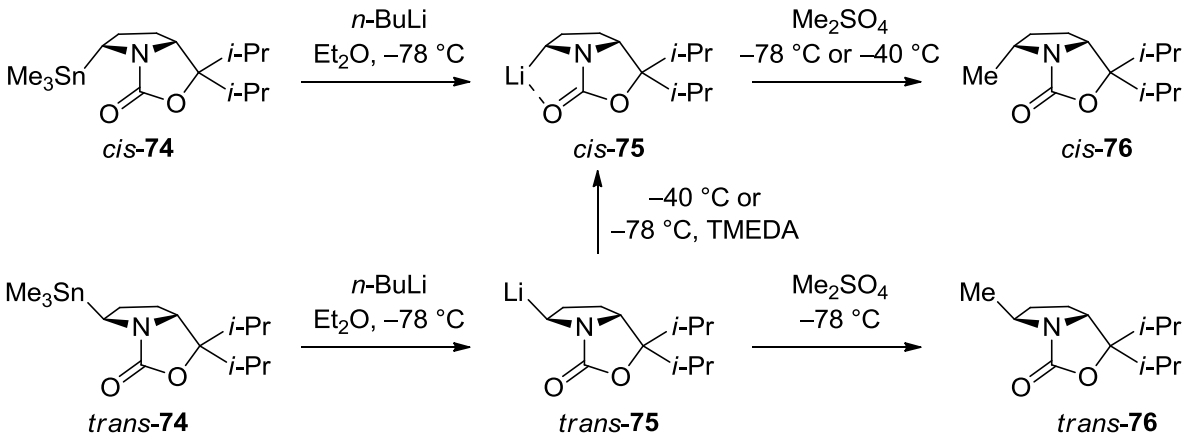
The lithiation methodology was extended to give enantioenriched substituted pyrrolidines **70** by exchanging TMEDA for the chiral ligand (–)-sparteine **73**, resulting in α-substituted products in up to

98:2 er (Scheme 1.26).[61] Other chiral ligands were also tested.[62] However, similar protocols aiming to give enantioenriched piperidines with (–)-sparteine (**73**) and other chiral ligands suffered from slow reaction times, low yields and poor selectivities.[63] In a more recent report, O'Brien and co-workers[64] utilised sparteine surrogate **78** (see Scheme 1.28, p. 19) to give the first examples of high yielding asymmetric deprotonation–electrophile trapping of *N*-Boc piperidine **67**.



Scheme 1.26 Asymmetric lithiation–substitution using (–)-sparteine **73**

Cyclised products (Scheme 1.25) were utilised to determine configurational stability of the lithiated intermediate, using tin–lithium exchange experiments followed by electrophile trapping and dr determination of the resulting products.[65] In the case of Boc pyrrolidines *cis*-**74** and *trans*-**74**, *cis*-lithiated intermediate *cis*-**75** was found to be more stable than *trans*-lithiated intermediate *trans*-**75**, possibly due to enhanced complexation from the carbonyl oxygen. High cis and trans stereochemical retention can be achieved from the corresponding tin substrates by tin–lithium exchange at –78 °C. However, warming to –40 °C without TMEDA gave some epimerisation of *trans*-**75**; with TMEDA present epimerisation occurred at –78 °C (Scheme 1.27).

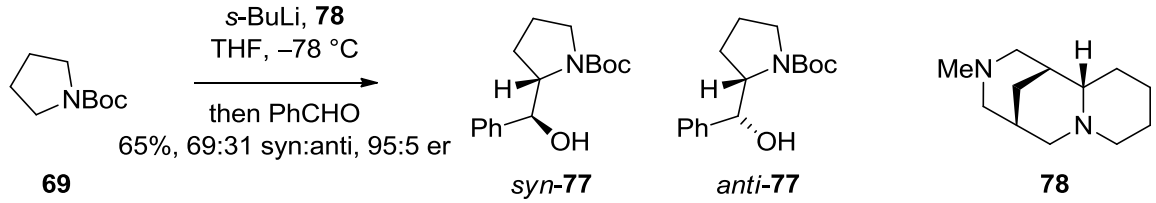


cis-**76** from *cis*-**74** at –78 °C, 69%, 99:1 dr
cis-**76** from *trans*-**74** at –40 °C, 24%, 66:34 dr
cis-**76** from *trans*-**74** at –78 °C, TMEDA, 21%, 99:1 dr
trans-**76** from *trans*-**74** at –78 °C, 56%, 1:99 dr

Scheme 1.27 Configurational stability study of Boc-pyrrolidine lithiated species

The asymmetric deprotonation of similar cyclic amines continues to be of interest, resulting in the screening of new ligands.[63b] Of specific note is the work of O'Brien and co-workers who reported chiral ligand **78**, known as the 'sparteine surrogate' which often operates as well as (–)-sparteine (**73**), but gives the opposite sense of asymmetric induction.[66] Furthermore, after demonstrating that α-lithiation of several examples of *N*-Boc azacycles can be achieved without the use of TMEDA in THF to give racemic α-substituted products,[67] they further demonstrated that asymmetric α-lithiation and trapping to give enantioenriched α-substituted products could also be achieved in THF with the correct choice of chiral ligand. It was found that the *s*-BuLi/THF complex may have a faster rate of α-deprotonation than the *s*-BuLi/(–)-sparteine (**73**) complex, which could explain lack of enantioenriched products from use of (–)-sparteine (**73**) in THF.[67] In an impressive report,[68] O'Brien and co-workers examined the complexing of organolithiums to chiral ligands in solution at –80 °C by ^{13}C NMR. They determined that in THF, (–)-sparteine (**73**) only complexes to the organolithium when greater than 3.0 equivalents of (–)-sparteine (**73**) is present, and a monomeric complex is only observed when greater than 6.0 equivalents of (–)-sparteine (**73**) is present. In contrast, use of sparteine surrogate **78** showed monomeric complex formation with only 1.0 equivalent sparteine

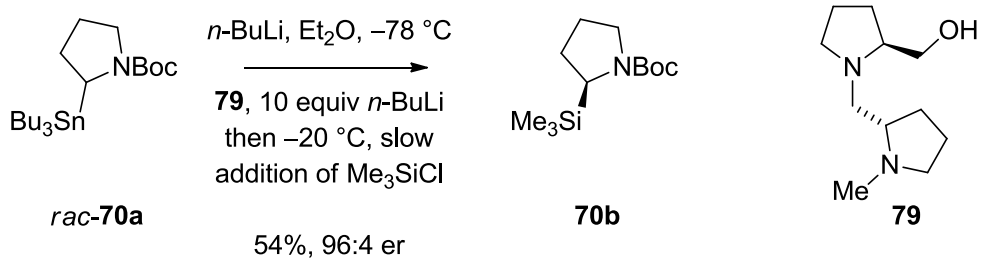
surrogate **78**. This information was demonstrated in the enantioselective α-deprotonation and trapping of *N*-Boc pyrrolidine (**69**) in THF to give highly enantioenriched products **77** (Scheme 1.28).[68]



Scheme 1.28 Asymmetric α-lithiation with sparteine surrogate **78** in THF

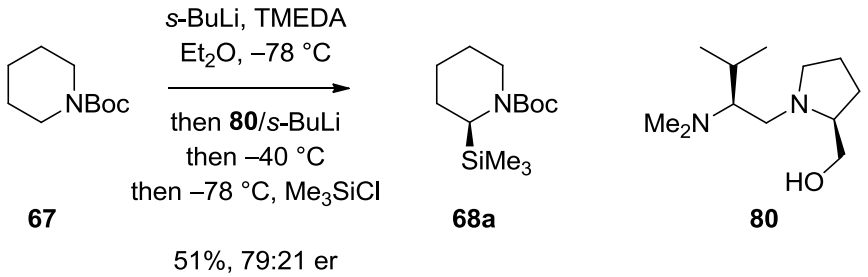
Enantioenriched 2-substituted cyclic amines can arise from enantioselective α-deprotonation in which the resulting α-lithiated intermediate is configurationally stable at low temperatures and traps with retention (or inversion) on addition of the electrophile. However, even if the α-lithiated intermediate is configurationally labile, enantioenriched products can still be achieved, by dynamic thermodynamic or dynamic kinetic resolution. Selection of an appropriate chiral ligand with the right reaction conditions, to favour formation of one organolithium-chiral ligand diastereomeric complex over the other, followed (typically after cooling) by a stereoselective electrophile trapping (DTR) where the trapping is quicker than interconversion of the organolithium-chiral ligand complex, gives an er which is a result of the ratio of the diastereomeric complexes. If interconversion between the two diastereomeric complexes is fast but electrophile trapping is slow, one of the organolithium-chiral ligand complexes may react faster with the electrophile than the other, therefore the er arises as a result of the differing reaction rates of the two complexes (DKR).[69]

Coldham and co-workers have shown that high levels of enantioselectivity in 2-substituted *N*-Boc pyrrolidines **70b** can be achieved by dynamic kinetic resolution. This chemistry uses chiral ligand **79** at –20 °C to allow equilibration between organolithium-chiral ligand complexes, with 10 equiv of *n*-BuLi, before slow addition of the electrophile Me_3SiCl (Scheme 1.29).[70]



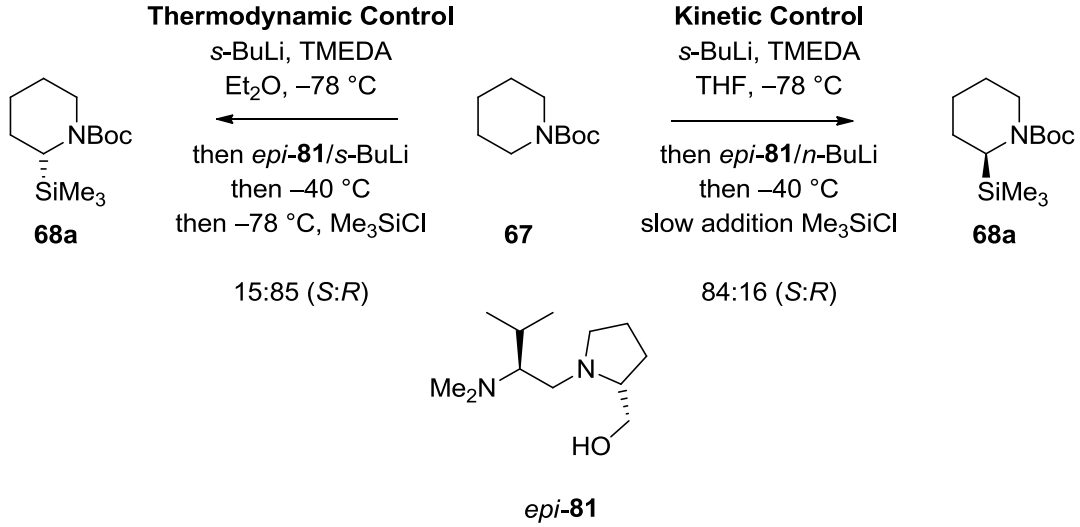
Scheme 1.29 Dynamic kinetic resolution approach to α-silyl *N*-Boc pyrrolidine **70b**

As indicated previously, α-deprotonation of piperidine substrates suffer from much poorer selectivities than its pyrrolidine congenes.[63] To provide an alternative method to enantioenriched 2-substituted piperidines, Coldham and co-workers successfully extended this work to piperidines; similar to the work with pyrrolidine, the experiments were limited to trapping with Me_3SiCl.[71] However, as Me_3SiCl was found to be highly selective, it could be used in lower amounts (2 equiv) as a sacrificial electrophile at –78 °C instead of at –20 °C, followed by addition of the desired electrophile (Bu_3SnCl and Me_2SO_4) to give low yields (12% and 19%, respectively) of highly enantioenriched substituted pyrrolidines with the opposite sense of enantioinduction (99:1 and 95:5 er respectively). Further research led to a dynamic resolution under thermodynamic control.[72] Reaction of the organolithium with TMEDA followed by addition of an appropriate chiral ligand (**80**) and warming to –40 °C set up the resolution in which the formation of one organolithium-chiral ligand complex was favoured over the other. Trapping with Me_3SiCl at –78 °C gave enantioenriched silylated pyrrolidine **68a** in 51% yield and 79:21 er (Scheme 1.30).



Scheme 1.30 Dynamic thermodynamic resolution approach to 2-substituted piperidines **68a**

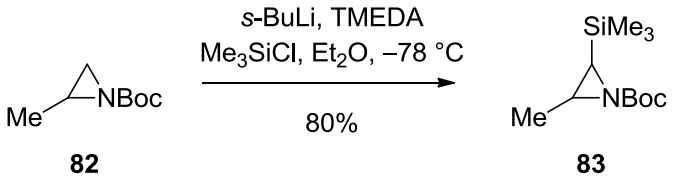
With *N*-Boc piperidine (**67**) and chiral ligand *epi*-**81**, DKR and DTR conditions gave opposite senses of enantioinduction.[72] Under kinetic control with slow Me_3SiCl trapping at –40 °C, an er of 84:16 *S*:*R* was obtained of silyl piperidine **68a** with ligand *epi*-**81**. Under thermodynamic control with fast Me_3SiCl trapping at –40 °C with the same ligand an er of 15:85 *S*:*R* was obtained. In this case, the minor complex formed under thermodynamic control reacts faster with Me_3SiCl such that the opposite sense of enantioenrichment is observed under kinetic control (Scheme 1.31).



Scheme 1.31 Example of, in this case, opposite selectivities under DTR and DKR conditions

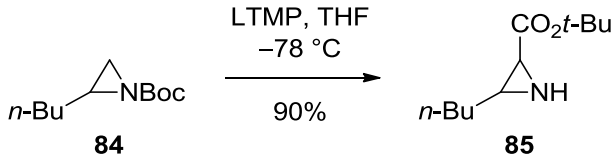
1.4 Previous work

With very little research carried out on the α-deprotonation of smaller azacycles, the Hodgson group has sought to extend functionalisation work in this area. This built on Beak's pioneering work of α-lithiation–electrophile trapping methodology on pyrrolidines and piperidines to terminal aziridines, of which Beak only gave one example: silylation of *N*-Boc aziridine **82** in which the silyl chloride had to be present during lithiation, to give silyl aziridine **83** in 80% yield (Scheme 1.32).[73]



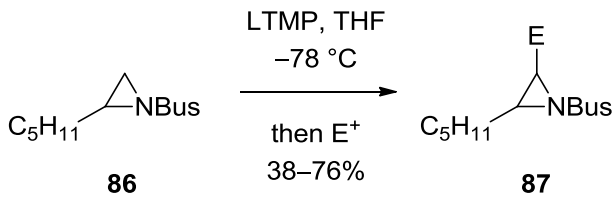
Scheme 1.32 Terminal aziridine silylation via α-deprotonation

Research in the Hodgson group indicated a rather unusual nitrogen to carbon migration of the *N*-Boc group in terminal aziridines **84**, once α-lithiated with LTMP, to give the corresponding free aziridine **85** (Scheme 1.33);[74] this presumably occurs on a slower timescale than *in situ* silylation, thus allowing Beak and co-workers to successfully form silyl aziridine **83**.



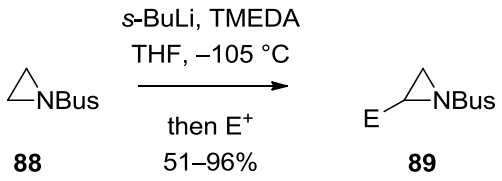
Scheme 1.33 *N*- to *C*- migration of Boc group under lithiation conditions

Earlier research in the Hodgson group demonstrated that α-deprotonation–electrophile trapping was possible on an aziridine substrate when an alternative *N*-protecting/activating group is used. Use of the Bus (*tert*-butylsulfonyl) group allowed *in situ* silylation of a range of terminal aziridines in good to excellent yields, and furthermore was compatible with external electrophile trapping, thereby opening up trapping possibilities with a range of incompatible *in situ* electrophiles to give substituted aziridines **87** in 38–76% yields (Scheme 1.34).[75]



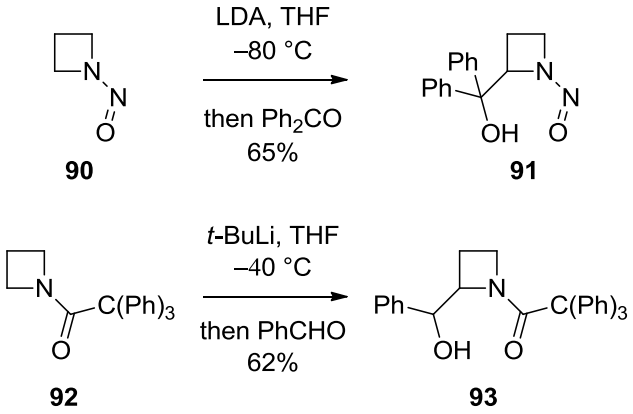
Scheme 1.34 α-Deprotonation–electrophile trapping of *N*-Bus terminal aziridine **86**

Extension of this work to aziridine **88** itself was carried out, again using the Bus activating group, to provide the first examples of α-deprotonation–electrophile trapping on *C*-unsubstituted aziridines to give 2-substituted aziridines **89** in good to excellent yield.[76] Efficient trapping with Me_3SiCl, Bu_3SnCl, $PhSO_2F$, enolisable and non-enolisable aldehydes and ketones, methyl cyanoformate and benzoyl cyanide was observed (Scheme 1.35).



Scheme 1.35 α-Deprotonation–electrophile trapping of *N*-Bus aziridine **88**

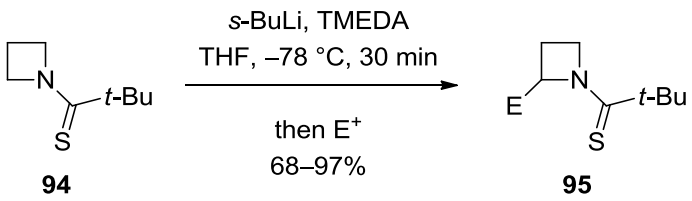
Having shown that derivatisation of aziridines is possible by α-deprotonation–electrophile trapping methodology, the Hodgson group sought to carry out the same type of transformation on the azetidine system. In contrast to other azacycles, only two examples of α-deprotonation–electrophile trapping on azetidine substrates were previously known, both of which were carried out by Seebach and co-workers[77] and only as isolated examples in papers concerned with functionalisation α- to nitrogen in a range of azacycles. In these examples, they used (carcinogenic) nitrosyl as well as triphenylacetyl protecting/activating groups to effect α-deprotonation; reaction of nitrosyl azetidine **90** with benzophenone gave alcohol **91** in 65% in the former and reaction of triphenylacetyl azetidine **92** with benzaldehyde gave alcohol **93** in 62% yield in the latter (Scheme 1.36).



Scheme 1.36 Early α-deprotonation–electrophile trapping methodologies on azetidines

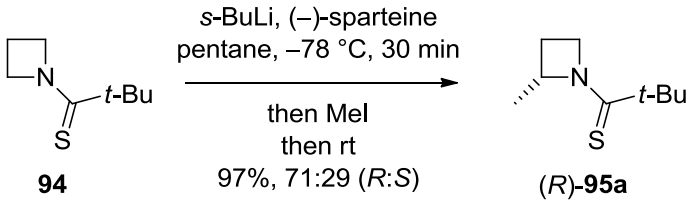
Surprisingly, no advance had been made in this area since the above reports by Seebach in around 1980. Given the difficulty in cyclisation of heavily functionalised azetidine precursors (which require early stage divergence if a range of substituted azetidines are required), the concept of α-deprotonation–electrophile trapping methodology to access 2-substituted and possibly 2,4-di-substituted azetidines remained an attractive idea for functionalised azetidine synthesis. This strategy towards substituted azetidine synthesis would benefit from late stage divergence to access a range of substituted azetidines, and the commercial availability of simple azetidine substrates, specifically azetidine (**2**) itself, would result in a short and comparatively cheap synthesis of α-substituted azetidines.

The Hodgson group studied the possibility of α-deprotonation–electrophile trapping methodology on azetidines. After evaluating a range of protecting/activating groups (TrCO,[79b] *t*-BuSO,[76] *t*-$BuSO_2$,[78] Boc,[60,61] $(EtO)_2PO$[74]) without seeing efficient α-deprotonation on azetidine, it was found that the rarely studied *N*-thiopivaloyl group **94**[79] gave efficient α-lithiation with *s*-BuLi and TMEDA in THF at –78 °C, and the resulting organolithium could be successfully trapped with a range of electrophiles (methyl iodide, butyl bromide, allyl bromide, benzyl bromide, benzaldehyde, acetone, carbon dioxide, trimethylsilyl chloride and trimethylstannyl chloride) to give access to 2-substituted azetidines **95** in high to excellent yields (Scheme 1.37).[80]



Scheme 1.37 Synthesis of 2-substituted azetidines

Furthermore, asymmetric induction could be carried out by replacing the deaggregation ligand TMEDA, with chiral diamine (–)-sparteine (**73**).[61] Asymmetric deprotonation and subsequent methylation with MeI gave methyl azetidine **95a** in 97% yield and 71:29 er (Scheme 1.38).[80]

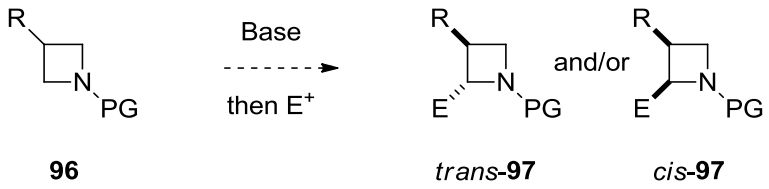


Scheme 1.38 Asymmetric induction using a chiral ligand

1.5 Proposed work

Encouraged by previous work, and the observed difficulty and often long syntheses required in accessing substituted azetidine systems, particularly enantioenriched substituted azetidines, my studies sought to extend these early results to develop methods towards azetidines with a greater degree of substitution.

The first aims of this project were to establish if 2,3-disubstituted azetidines **97** could be synthesised from 3-substituted azetine substrates **96** (Scheme 1.39). Also, if efficient α-deprotonation is possible on these systems, then to further evaluate a range of electrophile trappings and conditions with the aim of achieving high diastereoselectivities, potentially with functional group interconversions on the 3-position to alter/improve trapping diastereoselectivities, if required.



96 *trans*-**97** *cis*-**97**

Scheme 1.39 Proposed synthesis of 2,3-disubstituted azetidines

Alongside the above aim, we also wished to see if 2,4-disubstituted and ultimately 2,3,4-trisubstituted azetidines could be synthesised via this methodology, while maximising the diastereoselectivity on electrophile introduction.

Once proof of principle had been established, the project was envisaged to move onto the development of asymmetric substitution. Methods similar to those discussed earlier in Section 1.3.1 (p. 14) and carried out in Scheme 1.38 (p. 25) could be utilised further.

Finally, if these aims could be achieved, a longer term demonstration of this methodology would be sought in the synthesis of a natural product, potentially from the mugineic acid or penaresidin family (see Figure 1.1, p. 3).

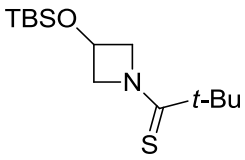
2 Results & Discussion: Azetidines

It was decided that 3-hydroxyazetidine would provide an interesting starting substrate for derivatisation, especially as it is used in a range of drug targets and is also present in a small number of natural products (see Figure 1.1, p. 3). Furthermore, the alcohol provides a further handle for functionalisation.

3-Hydroxyazetidine is commercially available (Sigma-Aldrich and Apollo Scientific) and can be efficiently synthesised on multi-kilo scale from epichlorohydrin using a simple protocol[23] and cheap starting materials.

2.1 Protected azetidinol substrates

It was considered that protecting the azetidinol hydroxyl with a bulky group could potentially block one face of the azetidine ring from α-deprotonation and therefore induce, or enhance, diastereoselectivity in the trapping. As a result TBS-protected 3-hydroxyazetidine **98** was targeted (Figure 2.1), given the silyl groups bulky nature, base stability and ease of deprotection.

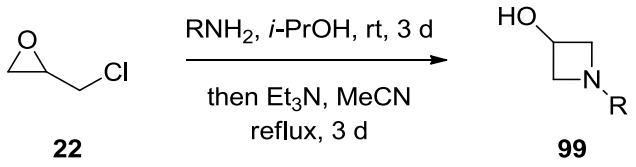


98

Figure 2.1 TBS-protected azetidinol **98**

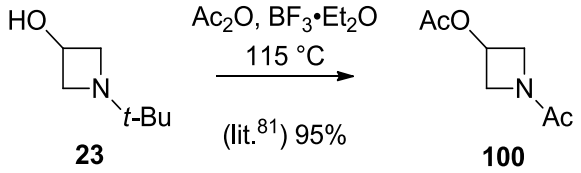
2.1.1 Substrate synthesis

3-Hydroxyazetidine **99** is easily accessed via cyclisation of an appropriate γ-halo amine, as discussed in Section 1.2.1.2 (p. 5). Reaction of epichlorohydrin (**22**) and a suitably bulky primary amine[20,21] under relatively forcing conditions (reflux for several days after initial γ-halo amine formation) is known in the literature[21,22,23] (Scheme 2.1).



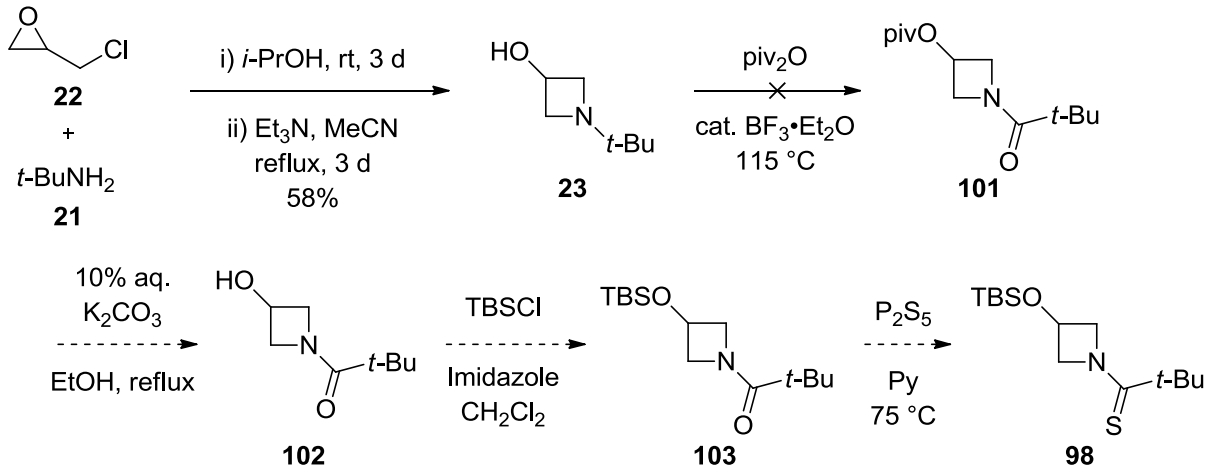
Scheme 2.1 Azetidinol formation from epichlorohydrin and a bulky amine

Using *t*-BuNH$_2$ (**21**) under these conditions gave 1-*tert*-butylazetidin-3-ol (**23**) in 58% yield after 6 days (lit.[21] 83%). A literature report indicated that acetylated azetidinol **100** can be readily synthesised from azetidinol **23** in neat Ac$_2$O with catalytic BF$_3$•Et$_2$O in 95% yield (Scheme 2.2).[81]



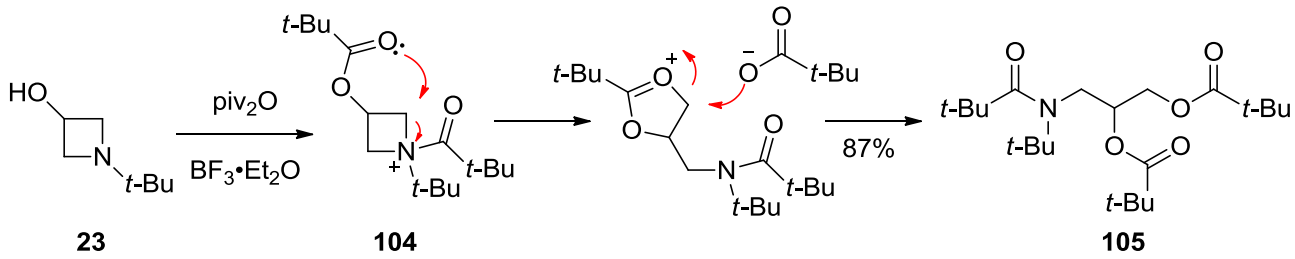
Scheme 2.2 Synthesis of diacylated azetidine **100** from *tert*-butyl azetidinol (**23**)

An analogous reaction was attempted of 1-*tert*-butylazetidin-3-ol (**23**) to dipivaloylated azetidine **101** with piv$_2$O (Scheme 2.3). It was anticipated that dipivaloylated azetidine **101** could subsequently be de-esterified, silylated and converted to target thioamide **98** with P$_2$S$_5$.



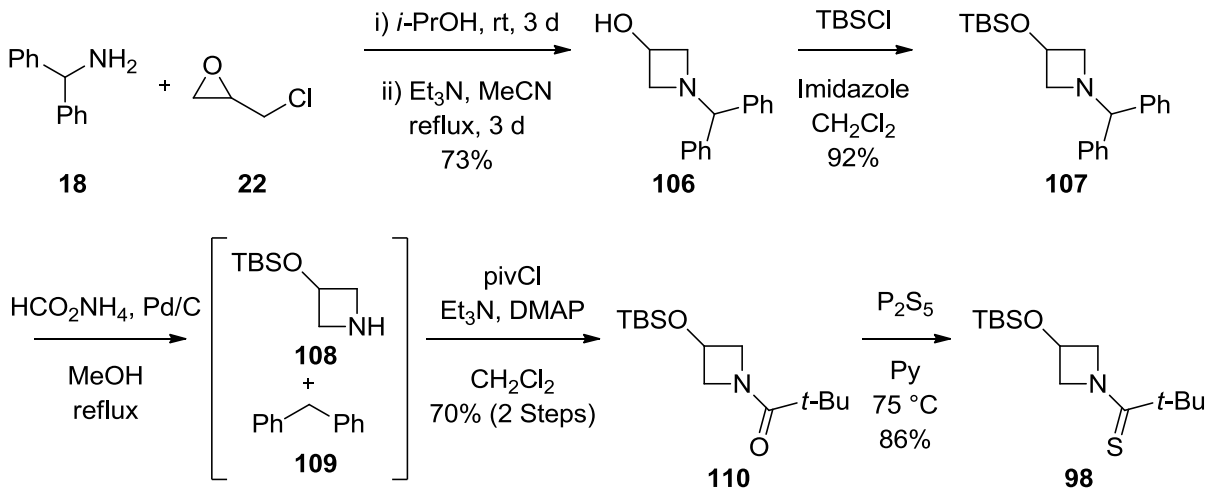
Scheme 2.3 Attempted synthesis of thioamide **98**

However, desired dipivaloylated azetidine **101** was not observed; but high mass recovery, approximately double the expected mass, of an unknown product was obtained. Given the production of an unknown product and lack of desired dipivaloylated azetidine **101**, the procedure was repeated in order to verify this observation; which resulted in the isolation of the same unknown product. Analysis indicated it to be ring-opened product **105**, supported by the presence of four *t*-Bu peaks in the ^{1}H NMR spectrum and three carbonyl carbons in the ^{13}C NMR spectrum (although mass spectrometry shows a parent ion of m/z 316.24 corresponding to ring-opened product **105** minus a piv group, which could potentially weaken the above assignment). Given the presence of two extra *tert*-butyl and carbonyl peaks compared with what was expected, it was suspected that further addition of piv_2O had occurred. Product **105** could be obtained by pivaloylation of the alcohol and, without loss of *N*-*t*-Bu, amine pivaloylation to give the strained ammonium species, followed by pivalate attack on the ring to relieve ring strain in 87% yield; alternatively, after ammonium formation, ester carbonyl-assisted ring-opening and finally pivalate addition to the oxonium to give **105**, might be envisaged (Scheme 2.4).



Scheme 2.4 Product from diacylation reaction

Without access to dipivaloylated **101** via this approach, access to target substrate thioamide **98** was sought from silyl-protected *N*-benzhydrylazetidin-3-ol (**106**) followed by hydrogenolysis of the benzhydryl group, pivaloylation of the resulting amine and thioamide conversion. Access to starting *N*-benzhydrylazetidin-3-ol (**106**) can be made using the same ring forming procedure with benzhydrylamine (**18**) instead of *tert*-butylamine (**21**) (Scheme 2.5, see also p. 6).



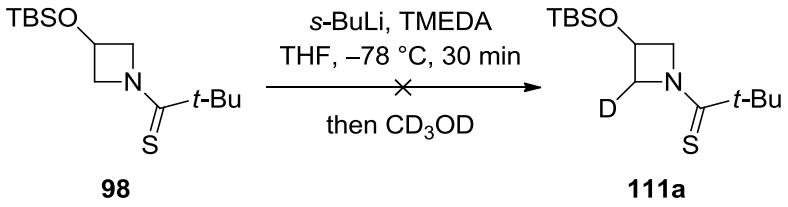
Scheme 2.5 Synthesis of thioamide **98** from benzhydrylamine **18**

In the event, *N*-benzhydrylazetidin-3-ol (**106**) was obtained in 73% yield from epichlorohydrin (**22**) and benzhydrylamine (**18**). Subsequent silylation using TBSCl and imidazole in CH_2Cl_2 gave silyl ether **107** in 92% yield.

Literature hydrogenolysis of an *N*-benzhydryl group requires a high pressure of hydrogen.[82] Fortunately, with no access to equipment necessary to carry out this reaction, hydrogenolysis with ammonium formate[83] in the presence of Pd/C in refluxing methanol gave desired TBSO-azetidine **108** (NH peak at 2.26 ppm in ^{1}H NMR spectrum and HRMS parent ion of 188.1460 $[M+H]^+$) and diphenylmethane **109** (CH_2 peak at 4.01 ppm in ^{1}H NMR spectrum and 41.9 ppm in ^{13}C NMR spectrum). Amine **108** was subsequently acylated with pivCl in the presence of DMAP in CH_2Cl_2 to give amide **110** (C=O 1628 cm^{-1} in the IR spectrum) in 70% yield over two steps. Conversion to thioamide **98** (C=S 1470 cm^{-1} in the IR spectrum) was achieved with P_2S_5 in pyridine at 75 °C to give test substrate **98** in an excellent 86% yield, with an overall yield from benzhydrylamine (**18**) of 40% (over 5 steps). In subsequent identical preparations to generate more test substrate, benzhydryl azetidinol **106** was synthesised in 81% yield, silylation and thionation steps were achieved in quantitative yield, hydrogenation and acylation steps were achieved in yields up to 90% over two steps, to give an overall yield from benzhydrylamine (**18**) of up to 72%.

2.1.2 Initial results

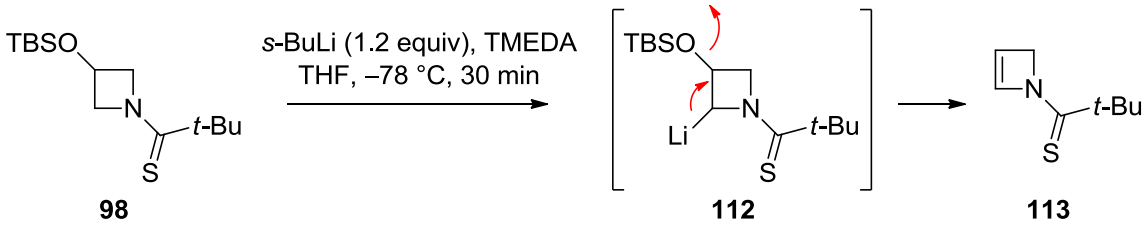
With TBS thioamide **98** in hand, a test lithiation–deuteration was carried out using the same procedure for α-deprotonation–electrophile trapping of azetidine **94**[80] (Scheme 2.6).



98 **111a**

Scheme 2.6 Test lithiation and deuteration of thioamide azetidinol **98**

TLC analysis of the crude reaction mixture indicated two products were present; one, expected to be deuterated azetidinol **111a** with the same R_f as the starting material, and another product slightly more polar than the starting material. Unfortunately, ^{1}H NMR and mass spectroscopic analysis did not indicate any deuterium incorporation into TBS thioamide **98**. However, surprisingly, the more polar product was identified as 2-azetine **113**; confirmed by the presence of sp^2 carbons in the ^{13}C NMR spectrum at 139.4 and 118.0 ppm, the loss of two protons in the azetidine region of the ^{1}H NMR spectrum combined with loss of coupling patterns between the protons, and a parent ion of m/z 155. 2-Azetine formation had not been anticipated, given the strained nature of the 2-azetine ring and the low temperature of lithiation, but is presumably formed by elimination of TBSO$^-$ from lithiated intermediate **112** (Scheme 2.7). Azetine **113** was present in the crude mixture in a ratio of 81:19 azetine **113**: TBS thioamide **98** by ^{1}H NMR spectrum analysis, and isolated in up to 26% yield (see Table 2.1, p. 32). It is interesting to note that the initial crude ratio of azetine **113**: TBS azetidine **98** was 81:19, however, on purification and isolation the relative proportion of azetine **113** to TBS azetidine **98** is significantly reduced possibly indicating an instability of azetine **113** to silica.



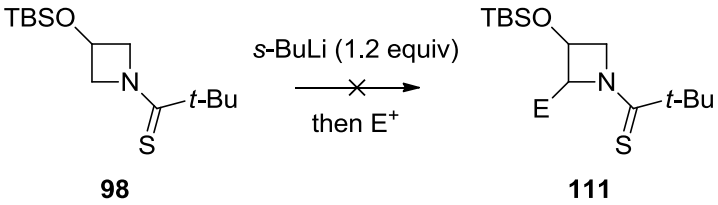
Scheme 2.7 2-Azetine **113** formation from lithiated azetidine **112**

While generation of this unusual and rarely studied class of azacycle was interesting (see Chapter 3, p. 89 for further details), unfortunately access was not achieved to the desired deuterated azetidine **111a**.

2.1.3 Attempted electrophile trapping of 2-lithioazetidine 112

A number of experiments were carried out in order to assess if the electrophile trapping pathway could be favoured over the elimination (Table 2.1).

Table 2.1 Attempted lithiation and electrophile trapping of thioamide azetidinol **98**

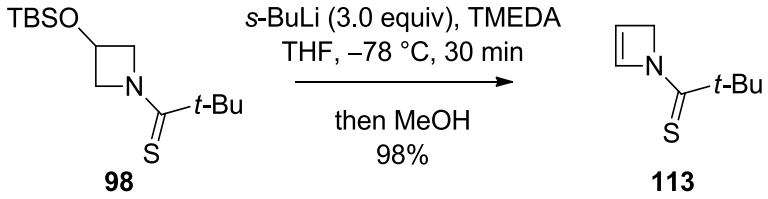


Entry no.	Solvent	Ligand	Temp (°C)	Time (min)	Electrophile	Recovered SM (%)	Azetine 113 yield (%)
1	THF	TMEDA	–78	15	CD_3OD	30	14 [a]
2	THF	-	–78	30	CD_3OD	36	26 [a]
3	THF	TMEDA	–100	30	CD_3OD	36	20 [a]
4	THF	TMEDA	–78	15	MeI	40	8
5	Et_2O	TMEDA	–78	30	CD_3OD	42	16 [a]
6	Et_2O	TMEDA	–78	30	TMSCl *in situ*	74	14

[a] Reanalysis of ^1H NMR spectra of azetines isolated after trapping with CD_3OD did reveal partial deuteration of the azetine to give deuterated azetine **149a**, see Section 3.1.1, p. 93 for further details.

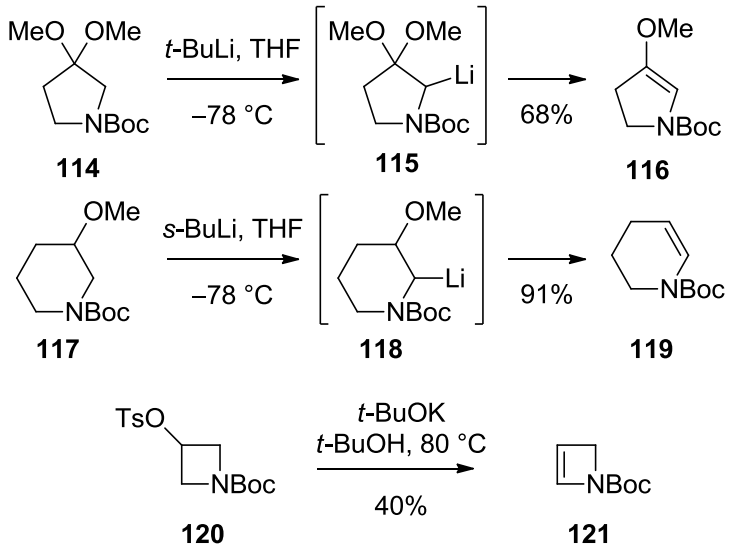
Unfortunately, all conditions attempted failed to give any trapped products. In the case of attempted deuterations (entries 1–3, 5), all recovered TBS azetidine **98** did not display any deuterium incorporation. Reducing the lithiation time (Table 2.1, entry 1) had no significant effect on the results; likewise, removing the ligand (entry 2) or reducing the temperature to –100 °C (entry 3) did not prevent azetine **113** forming. Changing the electrophile to MeI (entry 4) did reduce the amount of azetine **113** isolated, to 8%, but no methylated product was observed. Switching solvents to Et_2O (entry 5) with CD_3OD trapping did not give any deuterated azetidine. Finally, an attempted α-lithiation with *in situ* TMSCl was carried out with the aim of trapping lithiated species **112** immediately on formation. However, once again, only recovered starting material **98** and azetine **113** were recovered from the reaction mixture, suggesting that, following lithiation, the elimination process is extremely facile.

Azetine **113** can be synthesised in up to 98% yield with 3 equiv *s*-BuLi and quenching the reaction with MeOH (Scheme 2.8).



Scheme 2.8 High yielding synthesis of azetine **113**

Related eliminations are known. For five-membered[84] or larger rings,[60b] eliminations are observed (Scheme 2.9), but given the reduction of ring strain, the five- and six-membered rings can accommodate the double bond to a much greater extent. For four-membered rings, forcing conditions are required, namely heating with potassium *tert*-butoxide (Scheme 2.9)[85], making the observed elimination worthy of further exploration (see Chapter 3, p. 89).

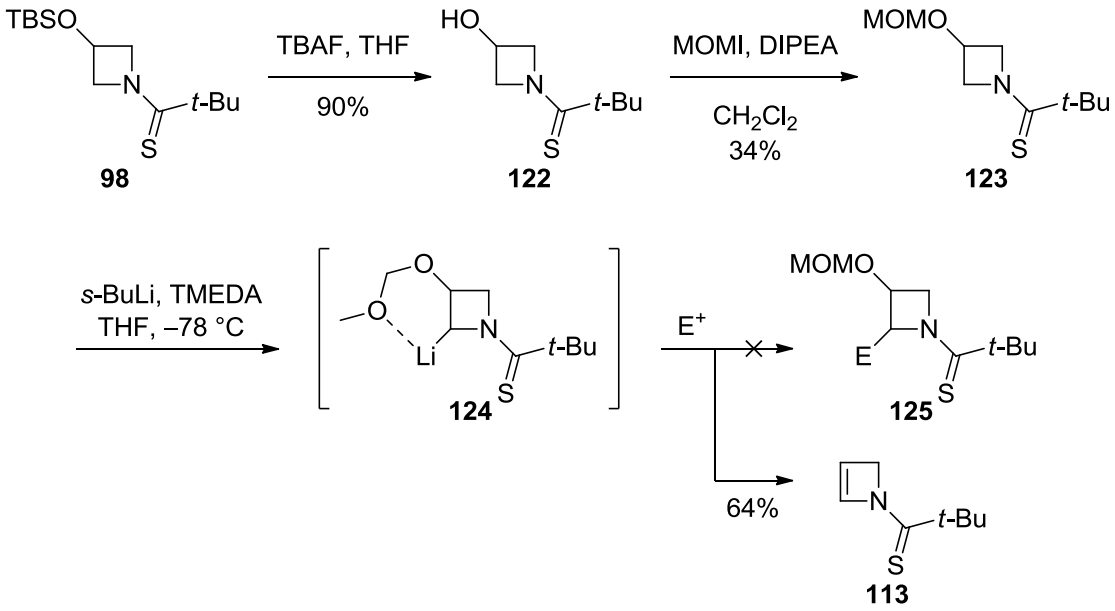


Scheme 2.9 Examples of eliminations of α-metallated azacycles

2.1.4 Other substrates

It was considered that further stabilisation of the lithiated species might slow down the elimination of the TBSO group and therefore allow electrophile trapping. With this in mind, 3-methoxymethyl ether **123** was synthesised in the hope that, on lithiation, the methyl ether would chelate to the lithium and therefore stabilise lithiated intermediate **124** (Scheme 2.10).

MOM analogue **123** was synthesised by TBAF-induced desilylation of TBS thioamide **98** in 90% yield, and subsequent treatment with MOMI and DIPEA, in 34% yield. However, attempted lithiation–deuteration of **123** resulted in only recovered undeuterated starting material **123** and azetine **113** in 5% and 64% yields, respectively (Scheme 2.10).



Scheme 2.10 Synthesis and lithiation of MOM azetidinol **123**

2.2 Free alcohol substrate

With elimination of protected alcohol derivatives of azetidinol **122** being favoured over electrophile trapping, use of the free alcohol **122** itself was considered as a way to prevent elimination.[86] In this case, double the equivalents of BuLi would be required, first to deprotonate the alcohol and secondly to deprotonate the ring. However, if the azetidine could be doubly lithiated, this could potentially raise difficulties of solubility of the dilithiated azetidine in certain reaction solvents. Furthermore, in forming the lithiated alkoxide a mixture of *C*- and *O*- trappings may be possible (Figure 2.2).

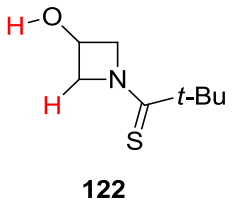
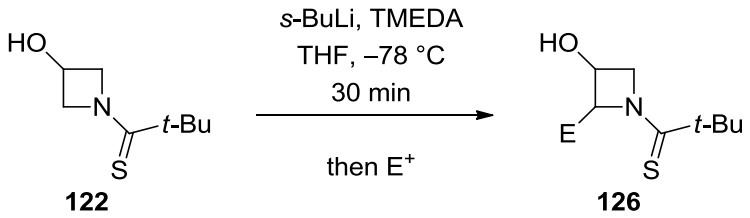


Figure 2.2 Possible reaction sites on azetidinol **122**

2.2.1 Initial results

With free alcohol **122** having been already synthesised in small quantity (Scheme 2.10), a test deuteration and methylation was carried out to assess if free alcohol **122** could undergo double

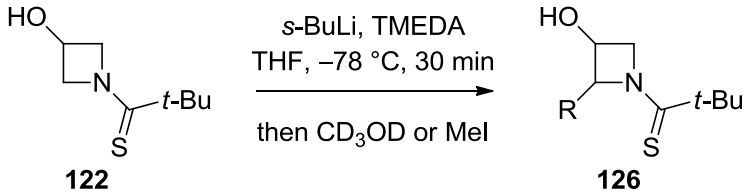
lithiation and electrophile trapping. Lithiation was carried out at –78 °C in THF for 30 min, with an increase in both the *s*-BuLi and TMEDA to 2.4 and 4.8 equiv respectively, to accommodate the presence of the alcohol. The lithiated intermediate was subsequently trapped with deuterated methanol as well as with methyl iodide (Scheme 2.11).



122 **126**

Scheme 2.11 Initial lithiation and electrophile trapping of azetidinol **122**

With deuterated methanol trapping, it was pleasing to see only one product was observed by TLC analysis with the same R_f as the starting material. Isolation by chromatography gave 92% recovery of azetidinol **122** (R = H)/ **126a** (R = D) with 53% deuterium incorporation and 94:6 dr (Scheme 2.12), as calculated from ^{1}H NMR spectrum integration values (see Section 2.2.5.2, p. 63 for further information regarding %D and dr assignment and calculations). Trapping with MeI gave two products, one being recovered starting material **122** and the other identified, following purification, as the inseperable diastereoisomers of methyl azetidine **126b** (R = Me) in 36% yield and 77:23 trans:cis dr. Identification was supported by mass spectrometry with a parent ion of m/z 188.07. Diastereoisomers were confirmed by coupling constant analysis of $^3J_{C2\text{-}H–C3\text{-}H}$ found to be 3.0 and 6.6 Hz respectively, diastereomeric ratio was calculated via integration of respective *t*-Bu peaks at 1.32 and 1.30 ppm.



122 **126**

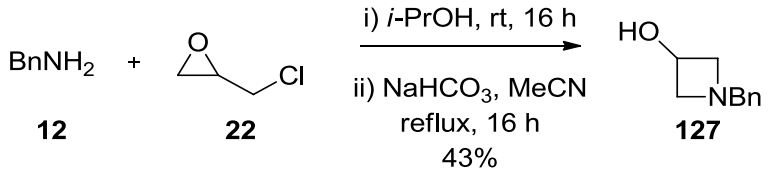
CD_3OD: 92% recovery **122**/**126a**,
53% D, 94:6 dr
MeI: R = Me, 36%, 76:22 dr

Scheme 2.12 Initial lithiation and electrophile trapping results

2.2.2 Substrate synthesis

With very pleasing initial results from use of free alcohol **122** under α-deprotonation–electrophile trapping conditions a new synthesis of test substrate **122** was attempted. While free alcohol **122** can be accessed in high yields (85–90%) by desilylation of TBS thioamide **98** and up to 65% overall yield from benzhydrylamine (**18**), use of the TBS group became undesirable for scale-up purposes (>70 mmol scale). Therefore, a couple of different strategies were attempted for accessing free alcohol **122** to reduce the number of synthetic steps and overall cost of substrate synthesis.

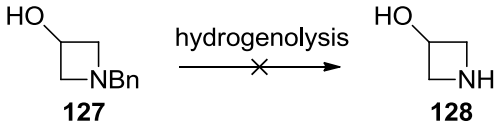
Firstly, *N*-benzhydrylazetidin-3-ol (**106**) was used as the initial source of azetidine in substrate synthesis. As discussed previously (Section 2.1.1, p. 27), synthesis of this class of azetidine requires use of a bulky amine to effect the cyclisation.[20,21] However, a recent report indicated that less bulky, and cheaper, amines such as benzylamine (**12**) could be used in place of benzhydrylamine (**18**) by using $NaHCO_3$ in refluxing MeCN for the ring-closing step (Scheme 2.13).[22] It was decided this would be a more suitable substrate for initial azetidine formation, especially as the functionality on the amine is lost during hydrogenolysis after ring formation.



Scheme 2.13 Azetidinol **127** formation from epichlorohydrin (**22**) and benzylamine (**12**)

The recent report stated that up to 93% yields can be achieved for this transformation;[22] however, in my hands, only a 43% yield of **127** was achieved. With *N*-benzylazetidin-3-ol **127** in hand, hydrogenolysis of the benzyl group was attempted with ammonium formate (Scheme 2.14), as previously used for benzhydryl hydrogenolysis (Scheme 2.5, p. 30). Unfortunately, these hydrogenolysis conditions were not able to remove the benzyl group. Similar to hydrogenolysis of the benzhydryl group, a large majority of literature references regarding this transformation require high pressure hydrogen (typically greater than 4 atm). Further attempts to effect hydrogenolysis with Pd/C

in the presence of ammonium formate, formic acid or a balloon of hydrogen all failed to give desired product **128** (Scheme 2.14).

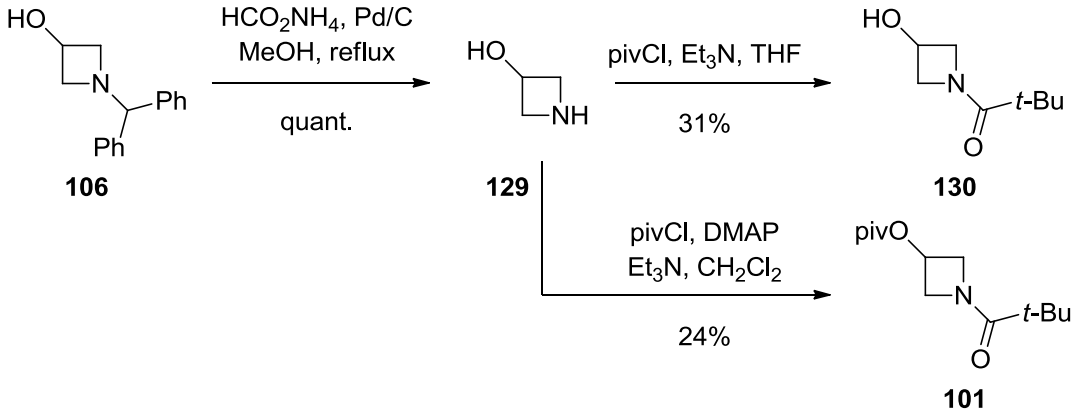


Scheme 2.14 Attempted benzyl hydrogenolysis of azetidinol **127**

With the inability to remove the benzyl group under mild conditions, *N*-benzhydrylazetidin-3-ol (**106**) was used as the source of azetidine.

Further attempts were made to improve the synthesis of thioamide **122** by carrying out the amide formation and thioamide conversion without protection of the alcohol, to determine if these steps are not affected by the presence of a free alcohol.

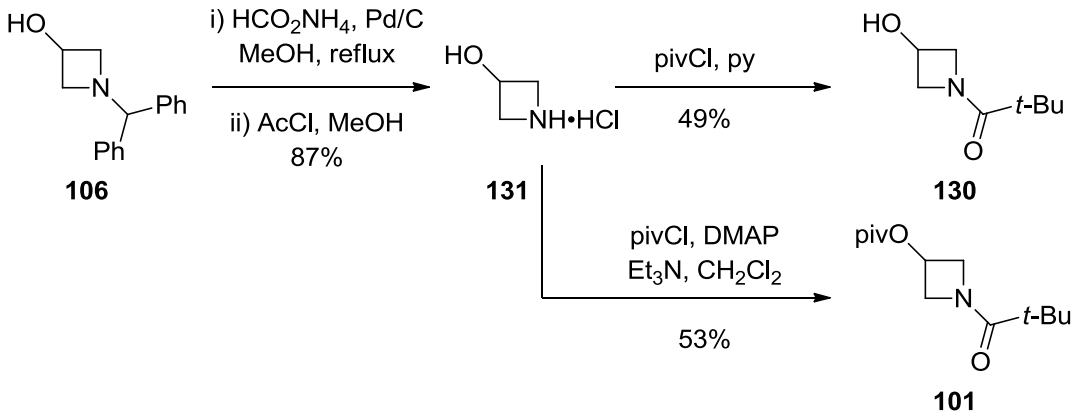
Hydrogenolysis of the benzhydryl group gave free azetidin-3-ol (**129**) in quantitative yield, however, attempts to selectively pivaloylate the amine were not successful when carried out with pivCl in pyridine, or in DMF with Et_3N. A 31% yield of amide **130** (C=O, 1594 cm^{-1} in the IR spectrum) was obtained when using 1.1 equiv pivCl with Et_3N in THF, whereas, a 24% yield of dipivaloylated azetidinol **101** (OC=O, 1733 cm^{-1} and NC=O, 1618 cm^{-1} in the IR spectrum) was observed when using 2.3 equiv pivCl with DMAP and Et_3N in CH_2Cl_2 (Scheme 2.15).



Scheme 2.15 Synthesis of acylated and diacylated azetidines

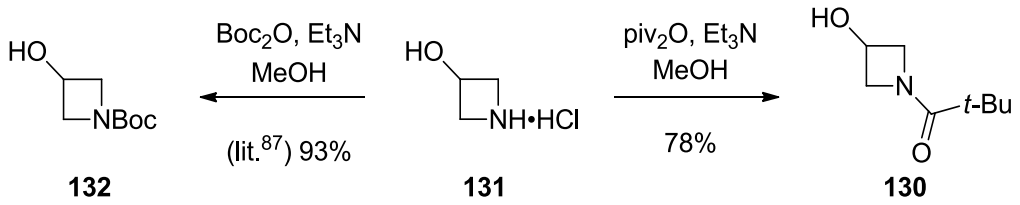
130 and **101** from *N*-benzhydrylazetidin-3-ol (**106**)

Unfortunately neither of these results were sufficiently high yielding. Alternatively, azetidin-3-ol hydrochloride (**131**) was obtained by treating azetidin-3-ol (**129**) with methanolic HCl post hydrogenolysis. Forming hydrochloride salt **131** allowed purification by washing with Et_2O, which gave an 87% yield of hydrochloride **131** (Scheme 2.16), where the purity of hydrochloride **131** was greater than that of previously used azetidin-3-ol (**129**). Treating azetidinol hydrochloride **131** with pivCl in pyridine gave desired amide **130** in 49% yield, while use of previously successful pivCl in THF with Et_3N conditions unfortunately did not give any amide **130**. Treatment of hydrochloride **131** with pivCl in CH_2Cl_2 with DMAP and Et_3N gave dipivaloylated azetidin-3-ol **101** in 53% yield (Scheme 2.16). While these yields are greater than previously observed, they remain undesirable for scale up purposes, with poor solubilisation of hydrochloride **131** in the reaction solvents being a likely cause for the modest yields.



Scheme 2.16 Synthesis of acylated and diacylated azetidines **130** and **101** from azetidine hydrochloride **131**

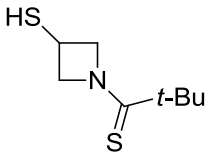
Poor solubility of azetidinol hydrochloride **131** was observed even under basic conditions. A literature procedure, used to install a Boc group onto azetidin-3-ol hydrochloride **131** in high yield (lit.[87] 93%), was carried out in methanol with Et_3N; allowing complete dissolution of azetidinol hydrochloride **131**. Carrying out an analogous experiment with piv_2O gave access to amide **130** in a much more pleasing 78% yield (Scheme 2.17) presumably aided significantly by increased dissolution of the starting material.



132 **131** **130**

Scheme 2.17 Boc and piv protection of azetidinol hydrochloride **131**

Initial attempts to access test substrate thioamide **122** by thionation of amide **130** with P_2S_5 gave no identifiable products, except for a possible trace of thioamide thiol **133** (Figure 2.3) in GC-MS analysis of the crude reaction mixture as indicated by a $[M+H]^+$ peak at m/z 190.

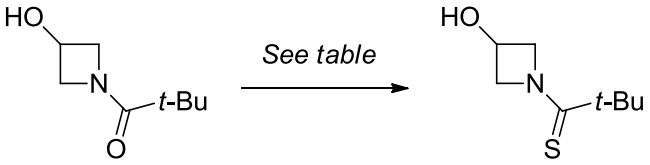


133

Figure 2.3 Thioamide thiol **133**

Subsequently, thioamide formation was attempted with Lawesson's reagent[88] and using alternative conditions with P_2S_5 to access desired thioamide **122** (Table 2.2).

Table 2.2 Attempted thionation of amide **130** to give test substrate thioamide **122**



130 **122**

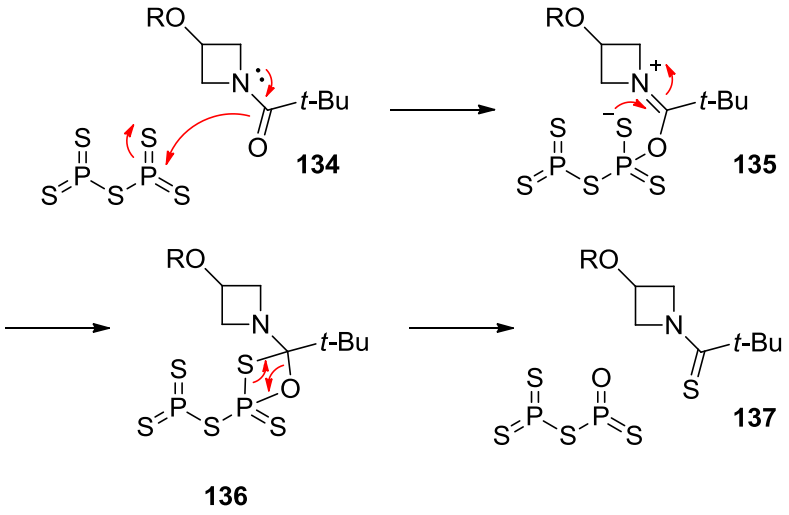
Entry no.	Sulfur source	Reagents	Temp (°C)	Reaction time (h)	Yield	Comments
1	1.5 equiv Lawesson's	Toluene	Reflux	2	0	Unidentifiable product
2	0.5 equiv Lawesson's	Toluene	Reflux	3	0	Unidentifiable product
3	0.25 equiv Lawesson's	Toluene	Reflux	0.5	0	Unidentifiable product

4	0.5 equiv Lawesson's	Toluene	rt	2	0	Unidentifiable product
5	0.5 equiv Lawesson's	Pyridine	rt	9	0	Unidentifiable product
6	0.6 equiv P_2S_5	$NaHCO_3$ THF	rt	7	0	
7	0.6 equiv P_2S_5	CH_2Cl_2	Reflux	7	0	
8	0.6 equiv P_2S_5	Toluene	Reflux	1.5	0	
9	1.2 equiv P_2S_5	Pyridine	75	2	9	
10	1.0 equiv P_2S_5	Pyridine	75	1.5	30	
11	0.6 equiv P_2S_5	Pyridine	75	1.5	40	
12	0.6 equiv P_2S_5	Pyridine	75	1.5	15	
13	0.6 equiv P_2S_5	Pyridine	75	0.5	35	
14	0.25 equiv P_2S_5	Pyridine	75	9	Trace	
15	0.25 equiv P_2S_5	Pyridine	rt	9	0	No product by TLC
16	0.6 equiv P_2S_5	Pyridine	rt → 50	12	-	Poor conversion
17	0.6 equiv P_2S_5	Pyridine	rt → 50	9	-	Poor conversion
18	0.6 equiv P_2S_5	Pyridine	120 Microwave	1	-	Poor conversion
19	0.6 equiv P_2S_5	TMSCl Pyridine	rt → 75	1	-	Poor conversion

Use of Lawesson's reagent[89] with variation of equivalents and temperatures (entries 1–5) did not give the desired product. The only isolable product was a large mass recovery of a colourless sulfur smelling viscous syrup believed to be a complex of Lawesson's reagent and starting alcohol **130**, as indicated by the ^{1}H NMR spectrum of purified samples displaying aromatic and methoxy peaks corresponding to Lawesson's reagent together with *t*-Bu and azetidine peaks corresponding to starting material **130** in a 1:2 ratio. All attempts to break down or push this 'complex' to completion failed to give the desired product.

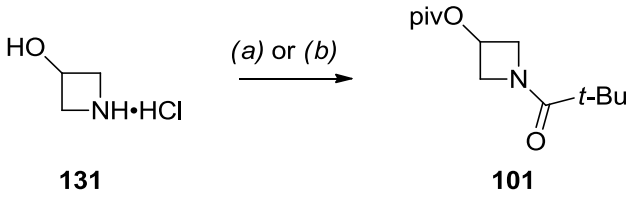
Application of three alternative literature procedures[90,91,92] for thioamide synthesis with P_2S_5 in non-pyridine solvents (entries 6–8) also did not give the desired product. However, reverting back to P_2S_5, in varying equivalents, in pyridine at different temperatures (entries 9–14), did give the desired alcohol in trace–40% yields. While a 40% yield was achieved (entry 11), attempts to replicate this result (entries 12–13) gave differing yields, indicating this transformation is not reproducible. Further attempts at rt (entry 15), stepwise warming (entry 16–17), microwave irradiation (entry 18) and attempted *in situ* alcohol protection by means of silylation followed by acidic desilylation during reaction work–up all failed to give the desired product.

Further attempts at alcohol **130** thionation were abandoned due to the unreliable nature of the transformations and poor yields. A literature review of this transformation indicated that thionation in the presence of an alcohol is rare,[93] and of those that exist many suffer from poor yields,[94] or the alcohol is on an aromatic system,[95] or the alcohol itself is converted into the corresponding thiol.[93] Several examples of simple protection of the alcohol, followed by thionation and deprotection of the alcohol were found in the literature[96] (similar to the attempted *in situ* silylation Table 2.2, entry 19, p. 40). Given that reaction with P_2S_5 and Lawesson's reagent require nucleophilic addition of the amide to the P=S bond in order to form the thiaoxaphosphetane intermediate **136** before breakdown to the desired thioamide **137** (Scheme 2.18), it is likely that the alcohol could act as a competitive nucleophile, resulting in irreversible binding as the thiaoxaphosphetane is unable to form.



Scheme 2.18 Mechanism of thionation with P_2S_5

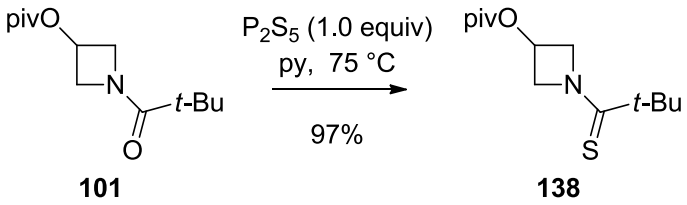
With this in mind, dipivaloylated azetidine **101** was re-examined as a potential alcohol protected substrate obtained in one step from azetidinol **131**. Dipivaloylated azetidine **101** was previously obtained from hydrochloride **131** in 53% yield by pivaloylation using pivCl in CH_2Cl_2 with DMAP and Et_3N (Scheme 2.16, p. 39). On repeating this pivaloylation the yield increased slightly to 57%, but it was noted again that not all the reagents were completely solubilised, possibly preventing higher yields from being achieved. A 75% yield was achieved by briefly heating hydrochloride **131** with Et_3N in CH_2Cl_2, and ensuring any 'lumps' were broken up before addition of pivCl and DMAP. Carrying out the reaction in pyridine, again with brief heating before addition of pivCl and DMAP, before stirring overnight, resulted in a much higher 93% yield of dipivaloylated azetidine **101** (Scheme 2.19).



Reagents and conditions: (a) Et_3N, CH_2Cl_2, Δ, then pivCl, DMAP, rt, 75%; *(b)* py, Δ, then pivCl, DMAP, rt, 93%

Scheme 2.19 Dipivaloylation experiments from azetidinol hydrochloride **131**

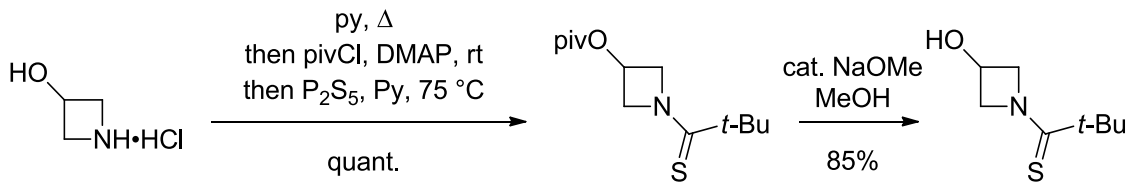
With a high yielding route to dipivaloylated azetidine **101** established, thionation with P_2S_5 was carried out and it was very pleasing to isolate desired thioamide **138** (C=S, 1484 cm^{-1} in the IR spectrum), in 97% without affecting the ester (C=O, 1781 cm^{-1} in the IR spectrum) (Scheme 2.20).



101 **138**

Scheme 2.20 Thionation of dipivaloylated azetidine **101**

Given that both the acylation and thionation steps were carried out in pyridine, combination of the steps was examined. It was found that the dipivaloylation goes to completion in 1 h, after which time P_2S_5 was added to give desired thioamide **138** in very pleasing quantitative yield over two steps. Simple de-esterification was carried out with catalytic NaOMe in MeOH to give test substrate **122** in 85% yield, with an overall yield of 85% from hydrochloride **131** (Scheme 2.21).



131 **138** **122**

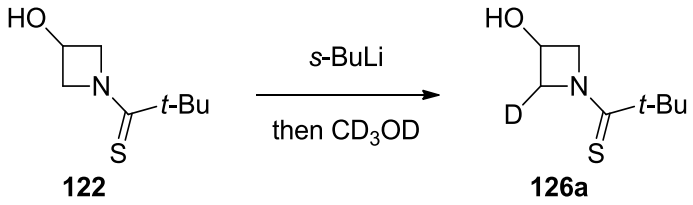
Scheme 2.21 Method to thioamide **122**, including one-pot dipivaloylation and thionation

While access to thioamide **122** could not be achieved directly from amide **130**, use of pivCl to doubly pivaloylate azetidine hydrochloride **131** provided a cheap and efficient method towards protected azetidinol amide **101** which can be successfully thionated and de-esterified in high yields.

2.2.3 α-Deprotonation–electrophile trapping optimisation

With an efficient route to quantities of azetidinol **122** in hand, an extensive optimisation of the lithiation and trapping procedure (Scheme 2.22) was carried out. Deuteration was initially used for test purposes, given the simplicity in purification and %D calculated directly by ^1H NMR integration

analysis of the crude/purified product spectra (see Section 2.2.5.2, p. 63 for further information regarding %D and dr assignment and calculations). Percentage recovery in optimisation tables represents the recovery of inseperable starting azetidinol **122** and deuterated azetidinol **126a**. Percentage deuteration (%D) represents the proportion of this recovery corresponding to **126a**, and dr represents the diastereomeric ratio of **126a** in this mixture.



122 **126a**

Scheme 2.22 Lithiation and deuteration of thioamide **122**

2.2.3.1 Deuteration experiments

Deuteration experiments used 5.0 equivalents of CD_3OD during the trapping step. Analysis of resulting deuterated azetidinol **126a** was carried out by ^1H NMR analysis. Deuteration only occurred α- to nitrogen; no deuteration was observed at C_3.

2.2.3.2 NMR spectroscopic studies

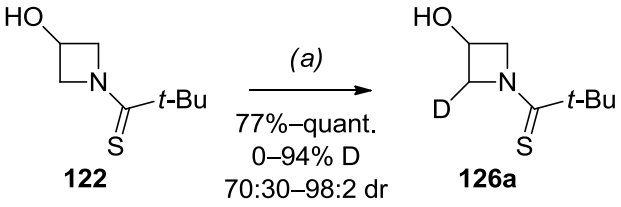
Analysis was carried out by ensuring the *tert*-butyl group protons and the carbinol carbon methine proton integrated as close to 9 and 1, respectively, as possible. The combined integration of ring protons, when subtracted from the original four protons gave the percentage incorporation. Detailed information regarding NMR interpretation and diastereoselectivity calculations are found in Section 2.2.5.2 (p. 63).

2.2.3.3 Solvent and concentration effects

A small range of solvents are typically used in lithiation procedures, but primarily ethereal[97] and hydrocarbon solvents are preferable. Looking ahead to a possible asymmetric variant of this work, less coordinating solvents were considered desirable if a chiral ligand was going to be the source of asymmetric induction;[98] in such cases, diethyl ether and hydrocarbon solvents work well.[99] As a

result, diethyl ether was the first solvent tested and subsequent experiments used THF (Table 2.3). Early experiments used THF dried and distilled over sodium with benzophenone indicator, later experiments used THF degassed and dried over activated alumina (for further details see Experimental Section 4.1, General details, p. 119).

Table 2.3 Optimisation of solvent and concentration



Reagents and conditions: (a) s-BuLi (2.4 equiv), TMEDA (4.8 equiv), Solvent (see table), –78 °C, Time (see table), then CD_3OD

Entry no.	Solvent	Concentration (mmol/mL)	Lithiation time (min)	%D	dr (cis:trans)	Recovery of 122/126a (%)
1	Et_2O	0.1	60	10	70:30	78
2	Et_2O	0.1	45	48	79:21	77
3	Et_2O	0.1	30	47	72:28	79
4	Et_2O	0.1	30	0	-	92
5	THF	0.1	45	44	93:7	quant.
6	THF	0.1	30	53	94:6	94
7	THF	0.15	30	74	98:2	88
8	THF	0.3	30	94	90:10	94
9	THF	0.6	30	73	96:4	94
10	THF	0.6	120	92	80:20	94
11	Et_2O	0.3	30	23	96:4	94

In Et_2O experiments (entries 1–4) a solid appeared during each run, which was suspected to be the

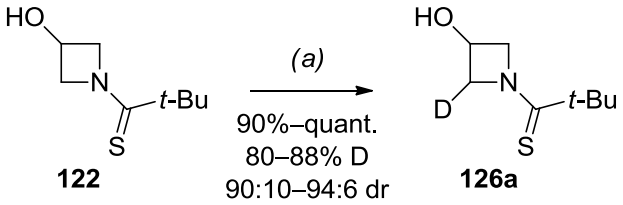
lithiated/dilithiated azetidine precipitating out of solution. These experiments showed a maximum deuterium incorporation of 48% regardless of lithiation time, at the relatively dilute concentration of 0.1 mmol/mL. In entry 4, an exact repetition of entry 3, no deuterium incorporation was observed possibly indicating poor double lithiation in Et_2O. As a result of this, hydrocarbon solvents were not tested, suspecting lack of solubility would be an even greater issue. Using THF (entries 5–6), deuterium incorporations and yields immediately increased to 44% and up to 53%, respectively.

A more striking change was observed when, perhaps against what would be expected, the reaction mixture was concentrated (entries 7–10). In the first two cases (entries 7–8), a 1.5x and 3x concentration of the reaction mixture was carried out. Pleasingly, this resulted in 74% and 94% deuterium incorporation, respectively. On concentrating further to 0.6 mmol/mL a similar deuterium incorporation was observed (entry 9), although longer lithiation time (entry 10) appeared to increase the deuterium incorporation to 92%, albeit to the detriment of the diastereoselectivity. A concentration (to 0.3 mmol/mL) using Et_2O (entry 11) gave, as expected (due to solubility issues), a low deuterium incorporation of 23%.

The major diastereoisomer for deuterated azetidinol **126a** was confirmed as cis by analysis of *J* values for the C_2-H and C_4-H ring protons. With deuterated azetidinol **126a**, the peaks with the lowest integration, indicating deuterium incorporation, dispayed a ring coupling constant of 3.9 Hz corresponding to a position cis to the alcohol (for further details regarding %D and dr assignments and calculations see Section 2.2.5.2, p. 63).

For further testing, Table 2.3, entry 8 was used as the standard conditions due to an acceptable balance of high deuterium incorporation and dr. Keeping concentration at 0.3 mmol/mL, it was decided that verifying the promising experiments in the previous table would be helpful; so four experiments were carried out in an attempt to check the reproducibility of the result in Table 2.3, entry 8 (Table 2.4).

Table 2.4 Verification of previously obtained results



Reagents and conditions: (a) s-BuLi (2.4 equiv), TMEDA (4.8 equiv), THF (0.3 mmol/mL), –78 °C, 30 min, then CD_3OD

Entry no.	Concentration (mmol/mL)	Temp (°C)	Reaction time (min)	%D	dr (cis:trans)	Recovery of 122/126a (%)
1	0.3	–78	30	81	93:7	quant.
2	0.3	–78	30	81	91:9	96
3	0.3	–78	30	88	90:10	90
4	0.3	–78	30	80	94:6	96

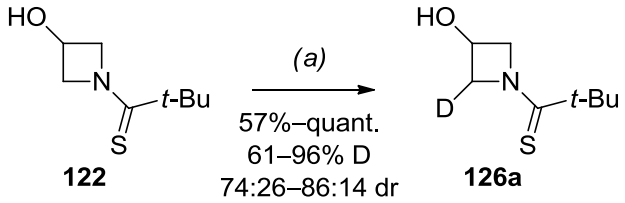
The results obtained here display a slight drop in deuterium incorporation but an increase in the diastereoselectivity, but are generally consistent with each other.

2.2.3.4 Temperature effect

With concentration and solvent parameters examined, both warmer and cooler reaction conditions were then evaluated to assess the effect on deuterium incorporation and dr (Table 2.5).

Firstly, experiments were carried out at a warmer temperature, utilising a warm-cool cycle[84b,86] (entries 1–3), whereby *s*-BuLi was added to the reaction mixture at –78 °C then warming of the reaction mixture to –46 °C and holding at this temperature for the stated amount of time before cooling to –78 °C for deuterium trapping.

Table 2.5 Effect of lithiation using warm–cool cycles on deuterium incorporation and dr



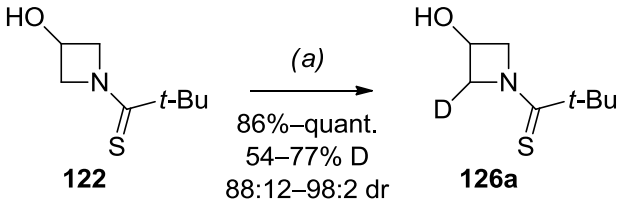
Reagents and conditions: (a) s-BuLi (2.4 equiv), TMEDA (4.8 equiv), THF, Temp (see table), Time (see table), then CD_3OD

Entry no.	Concentration (mmol/mL)	Temp (°C)	Reaction time (min)	%D	dr (cis:trans)	Recovery of 122/126a (%)
1	0.6	–78 → –46	120	96	74:26	quant.
2[a]	0.6	–78 → –46	120	75	85:15	quant.
3	0.6	–78 → –46	30 → 120	90	86:14	98
4	0.3	0	30	61	82:18	57

[a] Repetition of entry 1

While difficulty was encountered in maintaining sufficient agitation during the warming stage due to the required use of a large cooling bath, pleasingly, high deuterium incorporations were observed; however, diastereoselectivities appeared marginally less selective than those obtained at –78 °C (entries 1–2). This was even the case when stirring at –78 °C for 30 min before warming and holding at –46 °C for 120 min (entry 3). Warming further to 0 °C (entry 4), gave a significantly lower deuterium incorporation with a similar dr, but the yield of deuterated azetidinol **126a** was much lower than in other entries, possibly indicating a partial decomposition of the lithiated species at warmer temperatures (only 57% yield obtained) and protonation from the solvent (only 61% D). Therefore, reaction efficiency at the lower temperature of –98 °C was also evaluated (Table 2.6).

Table 2.6 Lithiation–deuteration at –98 °C

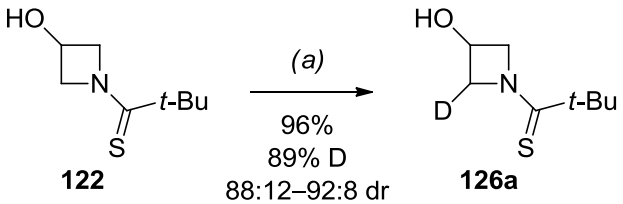


Reagents and conditions: (a) s-BuLi (2.4 equiv), TMEDA (4.8 equiv), THF, –98 °C, Time (see table), then CD_3OD

Entry no.	Concentration (mmol/mL)	Temp (°C)	Reaction time (min)	%D	dr (cis:trans)	Recovery of 122/126a (%)
1	0.3	–98	30	63	95:5	quant.
2	0.3	–98	30	63	98:2	98
3	0.3	–98	30	54	98:2	86
4	0.3	–98	120	62	97:3	98
5	0.6	–98	30	77	88:12	quant.

While diastereoselectivities for these experiments were generally slightly better than at –78 °C, the deuterium incorporations dropped below those previously observed (entries 1–3); this was also the case when extending the lithiation time to 120 min (entry 4), and concentrating the reaction mixture to 0.6 mmol/mL (entry 5). With the diastereoselectivities of deuterated azetidinols formed at –98 °C being favourable, it was decided to increase the equivalents of *s*-BuLi to see if deuterium incorporation could be increased while maintaining the observed diastereoselectivities (Table 2.7).

Table 2.7 Lithiation at –98 °C with excess *s*-BuLi



Reagents and conditions: (a) s-BuLi (4.8 equiv), TMEDA (9.6 equiv), THF (0.3 mmol/mL), –98 °C, Time (see table), then CD_3OD

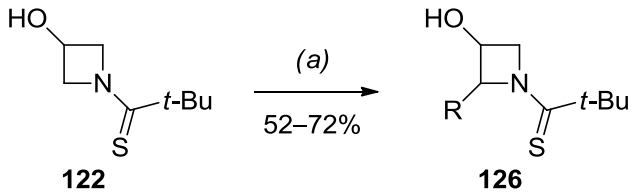
Entry no.	Concentration (mmol/mL)	*s*-BuLi (equiv)	Temp (°C)	Reaction time (min)	%D	dr (cis:trans)	Recovery of 122/126a (%)
1	0.3	4.8	–98	30	89	92:8	96
2	0.3	4.8	–98	60	89	88:12	96

Use of excess *s*-BuLi did indeed increase the deuterium incorporation, with similar diastereoselectivities to those found in previous experiments at –98 °C. On carrying out the same experiment with excess (4.8 equiv) *s*-BuLi, but at –78 °C for 30 min, it was pleasing to observe a 100% deuterium incorporation with a dr of 89:11, in 92% yield.

2.2.3.5 Early test of procedure with other electrophiles

With an early high yielding result in hand, a small number of test experiments with other electrophiles were carried out to obtain an early indication of the procedure's compatibility with other classes of electrophiles (Table 2.8): simple alkyl halides (MeI, BuBr, BnBr), and a carbonyl-based electrophile PhCHO. Trapping with all these electrophiles proceeded well, with good yields of isolated substituted azetidinols **126**.

Table 2.8 Trapping with a small range of electrophiles



122 **126**

Reagents and conditions: (a) s-BuLi (4.8 equiv), TMEDA (9.6 equiv) THF (0.3 mmol/mL), –78 °C, 30 min, then E^+

Entry no.	Concentration (mmol/mL)	*s*-BuLi (equiv)	Temp (°C)	Electrophile	dr (cis:trans)	Yield (%)	Yield brsm (%)
1	0.3	4.8	–78	MeI	30:70	72	83
2	0.3	4.8	–78	BuBr	0:100	58	75
3	0.3	4.8	–78	BnBr	0:100	57	73
4	0.3	4.8	–78	PhCHO	0:100 66:34 (new stereocentre)	52[a]	approx. 63%[a]

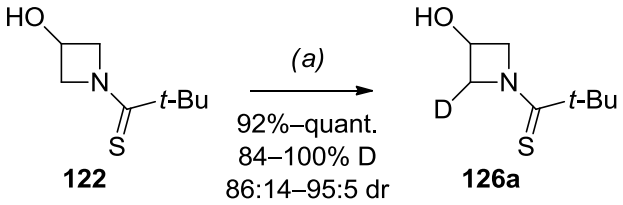
[a] Yield corrected for inseparable starting material (17% as determined by ^{1}H NMR analysis)

Reaction with MeI (entry 1) gave methylated azetidinol **126b** (R = Me) in 72% yield as a 30:70 cis:trans mixture of diastereoisomers (for further details of stereochemical assignment of configuration see Section 2.2.5, p. 62). Reaction with the other three electrophiles gave substituted azetidinols **126c** (R = Bu), **126d** (R = Bn), and **126i** (R = CH(OH)Ph) in 52–58% yields (entries 2–4). In each case, approximately 15% recovered starting azetidinol **122** was isolated after chromatography. Confident that trapping with other classes of electrophile would be possible based on satisfactory results from this small compatibility study, further optimisation of α-deprotonation–electrophile trapping conditions was attempted.

2.2.3.6 Stoichiometry effect

Although use of a large excess of *s*-BuLi (4.8 equiv) gave substituted azetidinols **126** in good yields, the theoretical amount of *s*-BuLi required for this transformation is only 2.0 equivalents. Results thus far using 2.4 equiv *s*-BuLi did not achieve complete deuterium incorporation; it was therefore possible that an amount of *s*-BuLi between 2.4 equiv, used in early optimisations, and the large excess of 4.8 equiv, used in the latter part of Section 2.2.3.4 (p. 50), would be sufficient for complete α-deprotonation. It may be the case that a slight excess is required to account for small water traces in the reaction mixture, or any differences between the titrated and actual concentration of *s*-BuLi used. A brief evaluation of the required stoichiometry of *s*-BuLi was therefore carried out (Table 2.9).

Table 2.9 Examination of required *s*-BuLi stoichiometry



Reagents and conditions: (a) s-BuLi (see table), TMEDA, THF (0.3 mmol/mL), –78 °C, 30 min, then CD_3OD

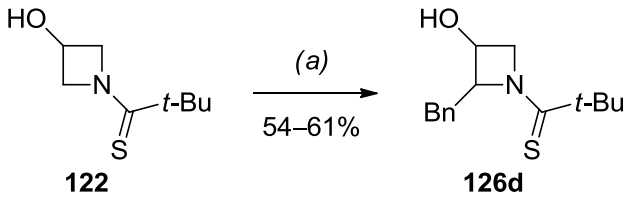
Entry no.	Concentration (mmol/mL)	*s*-BuLi (equiv)	Temp (°C)	Reaction time (min)	%D	dr (cis:trans)	Recovery of 122/126a (%)
1	0.3	2.4	–78	30	84	93:7	quant.
2	0.3	2.7	–78	30	95	86:14	98
3	0.3	2.7	–78	30	84	95:5	quant.
4	0.3	3.0	–78	30	97	86:14	98
5	0.3	3.0	–78	30	95	89:11	98
6	0.3	3.5	–78	30	97	88:12	quant.
7	0.3	4.8	–78	30	100	89:11	92

These results do indicate a general trend of increased %D, up to 100% incorporation, with increasing stoichiometry of *s*-BuLi at –78 °C, while maintaining diastereoselectivities around 90:10 cis:trans. A disadvantage of using excess *s*-BuLi, even if it is required for complete lithiation to occur, is any unreacted *s*-BuLi still present at the trapping stage is likely to react competitively with the electrophile, which is undesirable if an expensive or complex electrophile is used. A compromise of 3.0 equivalents of *s*-BuLi (Table 2.9, entries 4–5) was selected as the optimum conditions giving high deuterium incorporation and dr. Generally, all subsequent experiments were carried out with 3.0 equiv *s*-BuLi, 6.0 equiv TMEDA in THF at –78 °C for 30 min.

2.2.3.7 Ligand effect

With a high yield, high deuterium incorporation and good dr obtained by using 3.0 equiv *s*-BuLi, a brief examination of the effect of TMEDA stoichiometry, used as a de-aggregation ligand, was carried out (Table 2.10). Use of TMEDA is widely used with *s*-BuLi reactions,[57,60b,67] although THF is also known to behave as a ligand to *s*-BuLi.[100] With deuteration giving near 100% incorporation already these effects were investigated with a poorer yielding electrophile, in this case BnBr (see Table 2.8, entry 3, p. 51), with variation of TMEDA to evaluate the effect on the yield of benzyl azetidine **126d**.

Table 2.10 Examination of required TMEDA stoichiometry



122 **126d**

Reagents and conditions: (a) s-BuLi (3.0 equiv), TMEDA (see table) THF (0.3 mmol/mL), –78 °C, 30 min, then BnBr

Entry no.	*s*-BuLi (equiv)	TMEDA (equiv)	Yield (%)	Yield brsm (%)
1	3.0	6.0	60	66
2	3.0	3.0	61	68
3	3.0	0.3	57	66
4	3.0	0	54	64

Variation of the equivalents of TMEDA from 6.0 to 0 led to only a very slight drop in yield of benzyl azetidinol **126d** being observed; along with this trend, slightly greater levels of unreacted starting material **122** were recovered as the equivalents of TMEDA were reduced. The use of 1:2 molar equivalents *s*-BuLi:TMEDA originated from early development of substituted azetidine work[80] (discussed further in Section 1.4, p. 25), and for this reason TMEDA was kept at 6.0 equiv for the

continuation of this work (although clearly its presence is not an essential requirement for lithiation–electrophile trapping).

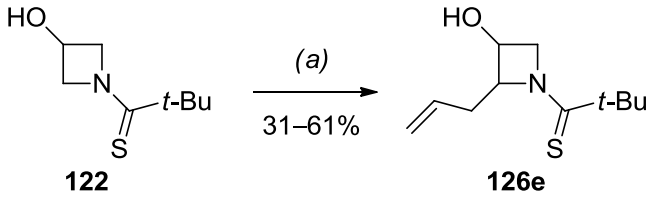
2.2.3.8 Electrophile effect

With the main lithiation parameters now having been examined, post-lithiation conditions were turned to: the effect of stoichiometry of the electrophile, reaction time after electrophile addition, temperature of trapping and speed of electrophile addition on the outcome of the experiment, with particular interest in reducing levels of recovered azetidinol **122**.

In an allyl bromide trapping experiment using 3.0 equiv *s*-BuLi, 6.0 equiv TMEDA, THF, –78 °C a moderate 53% yield of allyl azetidinol **126e** was obtained, with 16% recovered starting material, (Table 2.11, entry 1). For the following set of experiments allyl bromide was used as the test electrophile as the relative proportion of recovered starting material to product was higher than with other electrophiles (see Table 2.8, p. 51 for results with other electrophiles).

Using allylation, equivalents of electrophile was examined (Table 2.11, entries 1–3), followed by trapping time (entries 4–8), and finally effects of equivalents and rate of *s*-BuLi and electrophile addition (entries 9–11).

Table 2.11 Examination of required electrophile stoichiometry



122 **126e**

Reagents and conditions: (a) s-BuLi (3.0 equiv), TMEDA (6.0 equiv) THF (0.3 mmol/mL), –78 °C, 30 min, then allyl bromide (see table)

Entry no.	*s*-BuLi (equiv)	Allyl bromide (equiv)	Conditions post electrophile addition		Yield (%)	Yield brsm (%)
1	3.0	3.0	30 min, –78 °C	30 min, rt	53	63
2	3.0	5.0	30 min, –78 °C	30 min, rt	58	67
3	3.0	7.0	30 min, –78 °C	30 min, rt	51	58
4	3.0	3.0	10 min, –78 °C	30 min, rt	39	49
5	3.0	3.0	30 min, –78 °C	30 min, rt	53	63
6	3.0	3.0	60 min, –78 °C	30 min, rt	61	72
7	3.0	3.0	90 min, –78 °C	30 min, rt	56	65
8	3.0	3.0	30 min, –78 °C	0 min, rt	49	59
9	6.0	6.0	30 min, –78 °C	30 min, rt	44	49
10	3.0 v. slow addn.	3.0 v. slow addn.	30 min, –78 °C	30 min, rt	49	54
11	3.0	3.0 v. fast addn.	30 min, –78 °C	30 min, rt	42	59

To test the required level of allyl bromide, firstly, equimolar amounts of allyl bromide and *s*-BuLi were used (entry 1) and incrementing upwards (entries 2–3), but a variation of only 7% was observed in the yield of allyl azetidinol **126e**. Checking post electrophile addition parameters, the stirring time at –78 °C was varied (10, 30, 60 and 90 min, entries 4–7). A greater degree of difference was observed in this series, with the highest yield being observed after 60 min trapping time (entry 6). In all these experiments, after the allotted time at –78 °C had passed the reaction mixture was allowed to

warm to rt and stir for 30 min. Carrying out an experiment with 30 min at –78 °C followed by work up without pre-warming to rt gave a slightly reduced yield of 49% (entry 8).

In the experiments up to this point, the yield of allyl azetidinol **126e** did not increase as much as hoped, and starting azetidinol **122** was still being recovered. High deuterium incorporations in previous optimisations suggested that >95% of the azetidinol is C_2-lithiated. This indicates that either allyl bromide trapping is particularly inefficient, or an alternative proton source (potentially the solvent or the electrophile itself) is quenching the lithiated species, possibly during warming to rt if trapping had not occurred.

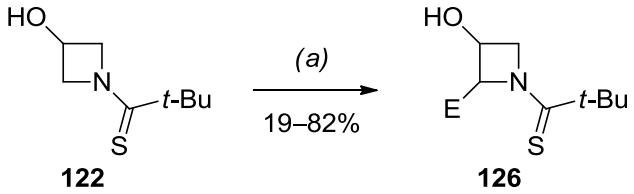
While these speculations are difficult to verify, a lithiation with a large excess of *s*-BuLi was carried out in an attempt to quench any early-stage proton sources in the reaction mixture (entry 9); however, only a lower yield of allyl azetidinol **126e** was obtained. Furthermore, two experiments were carried out examining effect of addition rates, one, with dropwise addition of *s*-BuLi and allyl bromide using a syringe pump to prevent micro environments of high concentration during the experiment (entry 10), and the second, with fast addition of allyl bromide in an attempt to expose the lithiated azetidinol to the electrophile as quick as possible (entry 11). Unfortunately, in both cases, similarly modest yields of allyl azetidinol **126e** were observed.

As a result of this study, it is still not known how to boost yields further and consequently reduce levels of recovered starting material. It is likely that certain classes of electrophile suffer from poor reactivity and as such will result in poor yields with higher than desired levels of recovered starting material.

2.2.4 Electrophile scope

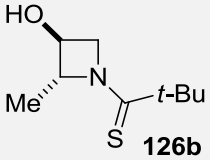
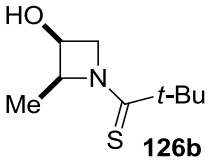
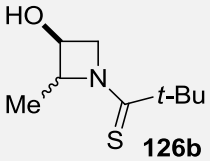
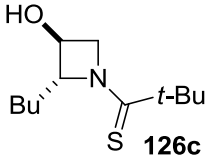
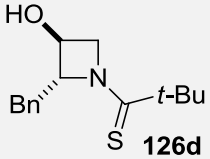
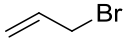
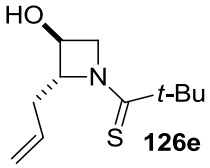
With a reasonably optimised procedure in hand, the scope of the reaction was investigated with a range of electrophiles (Table 2.12).

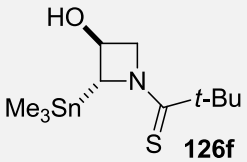
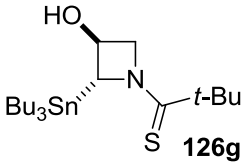
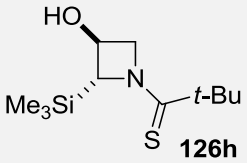
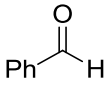
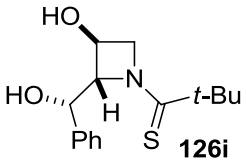
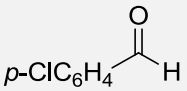
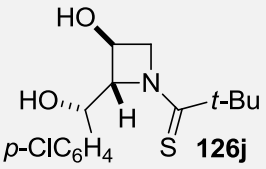
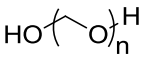
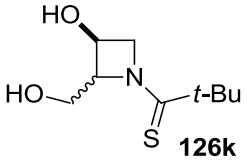
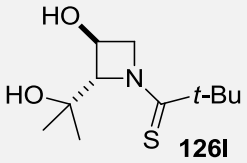
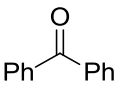
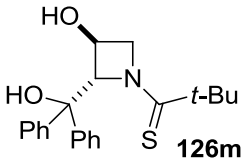
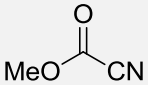
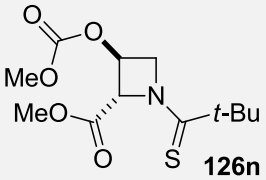
Table 2.12 Electrophile scope



122 **126**

Reagents and conditions: (a) s-BuLi (3.0 equiv), TMEDA (6.0 equiv) THF (0.3 mmol/mL), –78 °C, 30 min, then E^+

Entry No.	Electrophile	2,3-Disubstituted azetidine 126	Yield (%)	Notes
1	MeI	 **126b**	72	69:31 trans:cis Major diastereoisomer shown
2	Me_2SO_4	 **126b**	69	44:56 trans:cis Major diastereoisomer shown
3	MeOTf	 **126b**	19	50:50 trans:cis
4	BuI	 **126c**	68	-
5	BnBr	 **126d**	74	-
6		 **126e**	61	-

7	Me_3SnCl	 **126f**	41	57% yield brsm
8	Bu_3SnCl	 **126g**	82	-
9	Me_3SiCl	 **126h**	35	Further ~20% doubly silylated (*C*- and *O*-) azetidinol isolated
10		 **126i**	72	75:25 Mixture of epimers at side-chain carbinol. Major diastereoisomer shown
11		 **126j**	81	57:43 Mixture of epimers at side-chain carbinol. Major diastereoisomer shown
12		 **126k**	29	50:50 trans:cis
13		 **126l**	30	91% yield brsm
14		 **126m**	11	15% yield brsm
15		 **126n**	68	93:7 trans:cis Major diastereoisomer shown

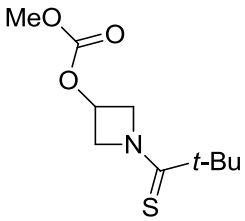
Alkylation (entries 1–6), including methylation (entries 1–3), benzylation and allylation (entries 5 and 6), all proceeded to give the corresponding 2,3-disubstituted azetidines **126b-e**. Different methylating agents did affect the diastereoselectivity of trapping. Use of MeI (entry 1) gave methyl azetidinol **126b** in high yield and reasonable dr (72%, 69:31 trans:cis); however, use of Me_2SO_4 (entry 2) and MeOTf (entry 3) gave a high yield in the former case, but for both electrophiles poor dr was observed. In the case of Me_2SO_4 a slight reversal of the typical trans diastereoselectivity was observed, as determined by ^{1}H NMR analysis (69% yield, 44:56 trans:cis) [for further details of stereochemical assignment see Section 2.2.5, p. 62].

Reaction with stannyl halides (Me_3SnCl and Bu_3SnCl, entries 7–8) proceeded well, giving **126f-g** in yields of 41% and 82%, respectively, albeit with 50% recovered starting material **122** in the former case; however, silylation (entry 9) suffered from competing silyl ether formation. In silylation experiments a mixture of *C*- and *O*-disilylated, *C*-monosilylated and *O*-monosilylated azetidinols were observed, leading to the lower yield of desired *C*-monosilylated azetidinol **126h**. Trapping with carbonyl-based electrophiles gave a wide range of results; aromatic aldehydes (benzaldehyde and *para*-chlorobenzaldehyde, entries 10–11) gave only the trans diastereoisomers **126i-j** with variation only at the newly formed chiral carbinol carbon (75:25 and 57:43, respectively). Reactions with paraformaldehyde (entry 12), acetone (entry 13) and benzophenone (entry 14) gave the desired azetidines **126k-m** in poor yields. In the case of paraformaldehyde, low solubility of the polymer in the reaction mixture could be contributing to the low yield. With acetone, it seems probable that enolisation of the ketone is competing with electrophile trapping thereby reducing the yield of acetone azetidinol **126l**, as indicated by 91% yield brsm. With benzophenone, a deep blue colour was instantly seen on electrophile addition, indicating ketyl formation resulting in poorer availability of the electrophile for trapping. However, reaction with Mander's reagent (entry 15) very pleasingly gave *C*– and *O*– methoxycarbonylated azetidine **126n**, which provides potential access to azetidine amino acids and mugineic acid–type natural products **9** (see Figure 1.1, p. 3).[14a]

Aside from methylation (entries 1–3) and reaction with paraformaldehyde (entry 12), very good trans diastereoselectivity was observed. These stereochemical assignments are based on X-ray

crystallographic analysis of the minor epimer *epi*-**126i** (epimeric to **126i** at the side-chain benzylic position, see Section 2.2.5.1, p. 62 for further details) derived from benzaldehyde, and proton coupling constant analysis by analogy to all the other substituted azetidinols. Further details of stereochemical assignment of configuration can be found in Section 2.2.5 (p. 62).

Aside from the successful electrophiles mentioned above, some other electrophiles examined failed to provide the desired substituted azetidines (Table 2.13). Attempted trappings with other carbonyl-based electrophiles, phenyl isocyanate and DMF, did not give any substituted azetidine products, whereas reaction with methyl chloroformate resulted in only *O*-addition to give **139** in 16% yield (Figure 2.4) and recovered starting material **122** (24%).

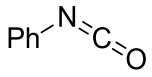
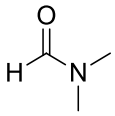
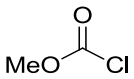
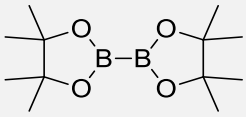


139

Figure 2.4 *O*-Acylated product of methyl chloroformate trapping

Reaction with CO_2 was believed to have occurred successfully, based on an almost instant loss of colour of the reaction mixture on CO_2 introduction which has been a characteristic indication of successful trapping with a majority of other electrophiles, but, after several attempts, the corresponding acid azetidine was not isolated. Reaction with bis(pinacolato)diboron[101] was attempted to access potential cross coupling partners, but unfortunately no boronated azetidine was observed.

Table 2.13 Unsuccessful electrophiles

2.2.5 Configurational support

In the previous section, nearly all the synthesised azetidinols were assigned with trans stereochemistry; these assignments were made through coupling constant analysis compared to the coupling constants determined for the minor epimer of benzaldehyde trapping *epi*-**126i** of known stereochemistry, see below.

2.2.5.1 X-ray

While nearly all of the substituted azetidinols synthesised were syrups or oils, fortunately the minor epimer of benzaldehyde addition crystallised into X-ray suitable crystals. X-ray crystallographic analysis (Figure 2.5, see Appendix 6.1, p. 219 for more information) confirmed trans stereochemistry, which was previously assumed based on literature coupling constants for four-membered rings.[102]

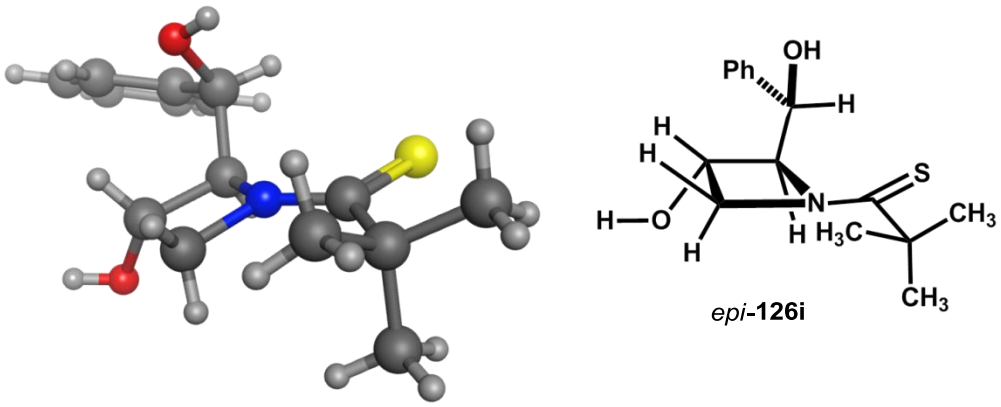


Figure 2.5 X-ray crystal structure of *epi*-**126i**

Analysis of the H-C-C-H torsion angles in the X-ray crystal structure indicated an almost perfect cis relationship with a torsion angle of 3.4° (6.6 Hz), while the trans torsion angle is 134.3° (3.3 Hz), significantly away from the optimum 180 °C with regard to coupling constant magnitude (Figure 2.6).

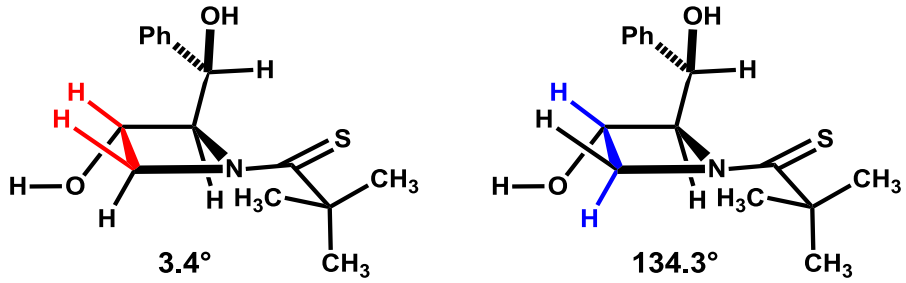


Figure 2.6 Diagrammatic display of cis and trans H-C-C-H torsion angles

As a result of this X-ray crystal structure, it was possible to determine that the large azetidine vicinal coupling corresponds to cis coupling, and the smaller azetidine vicinal coupling corresponds to trans coupling (see Figure 2.7, p. 64 for a diagrammatic representation of azetidine ring vicinal coupling constants).

2.2.5.2 NMR spectroscopy

Due to restriction of rotation around the thioamide N-C bond[103] on the NMR timescale all the ring protons in unsubstituted azetidinol **122** and deuterated azetidinol **126a** used in optimisation studies are distinct, this is also true in 2-substituted azetidinols **126**. In–house calculations of activation energy and half-life of thioamide rotation for unsubstituted thioamide azetidine **94** (p. 25) were carried out by variable temperature ^{1}H NMR spectroscopy. Line-shape analysis gave approximate activation parameters $\Delta H^{\ddagger}$ 82.2 kJmol^{-1} and $\Delta S^{\ddagger}$ 19.6 JK^{-1}mol^{-1}. The half-life of rotation was calculated to be $t_{1/2}$ ~3 s at 25 °C, and ~5 years at –78 °C (compared to $\Delta H^{\ddagger}$ 62.4 kJmol^{-1} and $\Delta S^{\ddagger}$ 16.3 JK^{-1}mol^{-1} for corresponding amide **228** (see Appendix 6.2.2, p. 223), with calculated half-lives of rotation $t_{1/2}$ ~0.001 s at 25 °C, and ~21 min at –78 °C) indicating that for unsubstituted azetidine **94** essentially no rotation occurs at this reaction temperature (for further information regarding thioamide rotation barrier calculations see Appendix 6.2, p. 221). The higher rotational barrier for thioamides compared to amides has been ascribed to greater charge transfer from N to S. [103] It can be considered as

originating from a greater contribution of the resonance structure containing $^{+}N{=}C{-}S^{-}$, with the weaker C=S π bond not present, and sulfur's large size (polarisability), allowing it to accommodate the negative charge.

The vicinal coupling constants between the ring protons C_2-H and C_3-H, and a long range coupling also observed, for unsubstituted (and deuterated) azetidinol **122**/**126a** and *epi*-**126i** are listed below in both tabular (Table 2.14) and diagrammatic (Figure 2.7) forms.

Table 2.14 Coupling constant comparison of substituted and unsubstituted azetidinols

Coupling	Unsubstituted and deuterated azetidinol 122/126a	Benzaldehyde azetidinol *epi*-126i
$^{3}J_{C3\text{-}C4cis}$	6.6 Hz	6.6 Hz
$^{3}J_{C2\text{-}C3trans}$	3.9 Hz	3.3 Hz
$^{4}J_{C2\text{-}C4trans}$	2.0-2.3 Hz	1.9 Hz

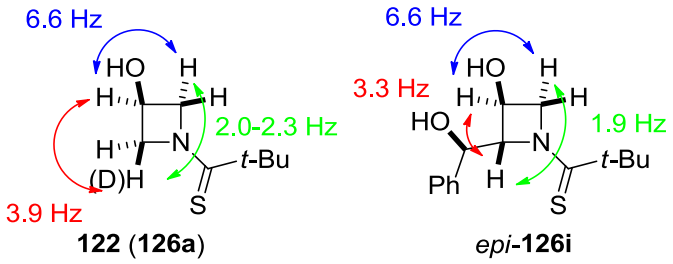


Figure 2.7 Diagrammatic display of coupling constants

The identification of these *J* values for the C_2-H and C_3-H protons allowed stereochemical assignments to be made for the other substituted azetidinols synthesised, by analogy to benzaldehyde azetidinol *epi*-**126i**. ^{1}H NMR resonances for the C_3-H proton in particular show all the vicinal coupling constants about the ring. The C_3-H resonance for unsubstituted azetidinol **122** and deuterated azetidinol **126a** are shown below (Figure 2.8).

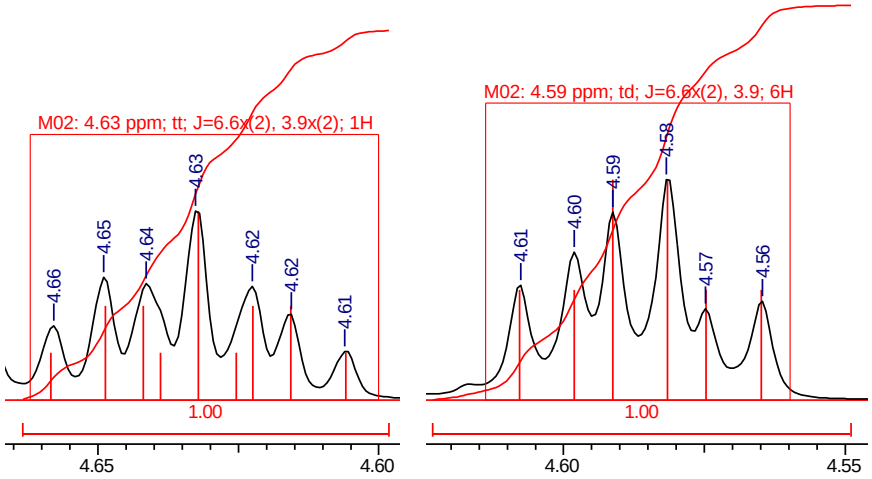


Figure 2.8 ^{1}H NMR appearance of C_3-H for undeuterated and deuterated azetidinols **122** and **126a**

For unsubstituted azetidinol **122** a triplet of triplets is observed with 6.6 & 3.9 Hz couplings. In the case of deuterated azetidinol **126a** (100% D, 90:10 cis:trans dr) a triplet of doublets is observed with 6.6 & 3.9 Hz couplings indicating the loss of one 3.9 Hz coupling corresponding to a proton cis to the alcohol (Figure 2.8).

This type of analysis, together with the calculation of the corresponding coupling in the C_2-H resonance, by analogy to the confirmed coupling constants of benzaldehyde azetidinol *epi*-**126i**, allowed assignment of all other substituted azetidinols.

While altering the substituents at the C_2 position could affect the conformation of the ring and therefore the coupling constants, the *J* values observed for all the substituted azetidinols remained similar to that of *epi*-**126i**. Trans $^{3}J_{C2\text{-}H\text{–}C3\text{-}H}$ couplings were found to be in the range of 2.6-3.9 Hz, while cis $^{3}J_{C3\text{-}H\text{–}C4\text{-}H}$ were found to be in the range of 5.8-7.5 Hz

Calculation of %D incorporation for deuterium optimisation experiments was carried out by careful integration of proton resonances in the ^{1}H NMR spectrum of deuterated azetidinols. Deuterium incorporation was calculated as follows:

$$\%D = 100 \times \left(No.protons\ \alpha-\ to\ N - (Sum\ of\ integrations\ of\ protons\ \alpha-\ to\ N)\right)$$

Equation 2.1 Percentage deuterium incorporation for deuterated azetidinols

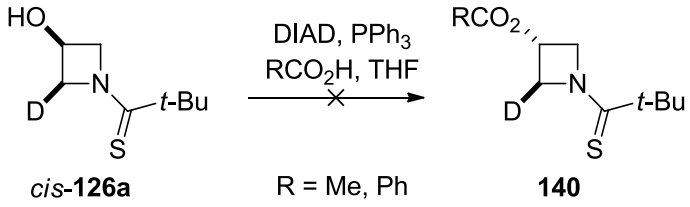
The dr was calculated following deuterium incorporation calculations and peak assignment. %cis deuterium was calculated as follows:

$$\%cis = \frac{(No.cis\ protons\ \alpha-\ to\ N - sum\ of\ integrations\ of\ cis\ protons) \times 10000}{D\%}$$

Equation 2.2 Calculation of dr for deuterated azetidinols

2.2.5.3 Inversion of alcohol

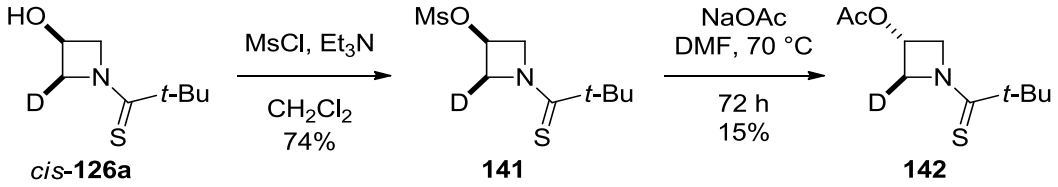
Attempted inversion of the alcohol in deuterated azetidine **126a** (*cis*-**126a**) to give the opposite diastereoisomer was anticipated to help further confirm the earlier stereochemical assignments, by changes in integration and multiplet fine structure. However, attempted Mitsunobu inversions[104] on deuterated azetidinol *cis*-**126a** did not give any inversion (Scheme 2.23).



cis-**126a** **140**

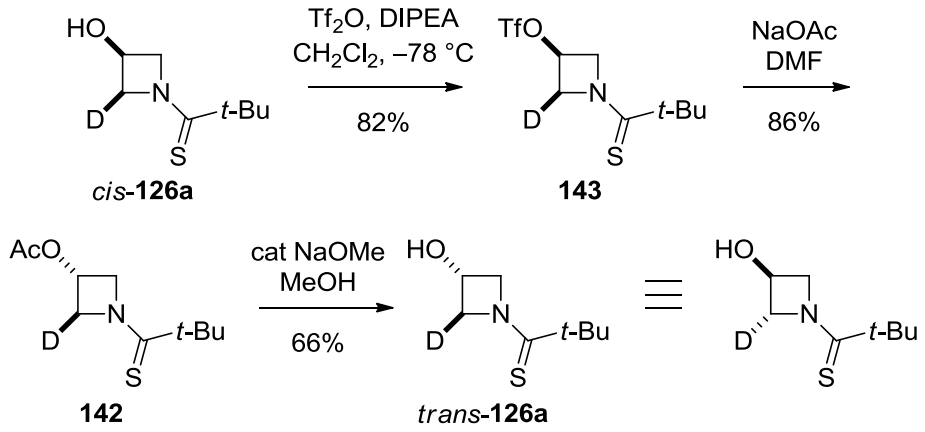
Scheme 2.23 Attempted Mitsonobu inversion of azetidinol *cis*-**126a**

An alternative approach of mesyl activation of the alcohol to give **141** followed by heating with NaOAc[105] did give inverted ester **142**, but only in 15% yield after 72 h (Scheme 2.24). Recovery of a large amount of starting material **141** (69%) indicated that possible deprotonation (at $MeSO_2$) was occurring over displacement.



Scheme 2.24 Mesylation and inversion of azetidinol *cis*-**126a**

An analogous reaction with tosyl activation similarly appeared slow. However, reaction of alcohol *cis*-**126a** with triflic anhydride at –78 °C[18] did give desired triflate **143** in 82% yield (reaction at 0 °C and –20 °C gave 0% and 17% yields, respectively), and treatment of this intermediate with NaOAc very pleasingly gave inverted ester **142** in 86% yield. De-esterification with catalytic NaOMe in MeOH gave the desired inverted α-deuterated azetidinol *trans*-**126a**, in 89% yield (Scheme 2.25).



Scheme 2.25 Triflation and inversion of azetidinol *cis*-**126a**

^{1}H NMR analysis of inverted α-deuterated azetidinol *trans*-**126a** indicated a shift in resonance integration and a corresponding change in the fine structure of ring proton resonances (Figure 2.9 and Figure 2.10).

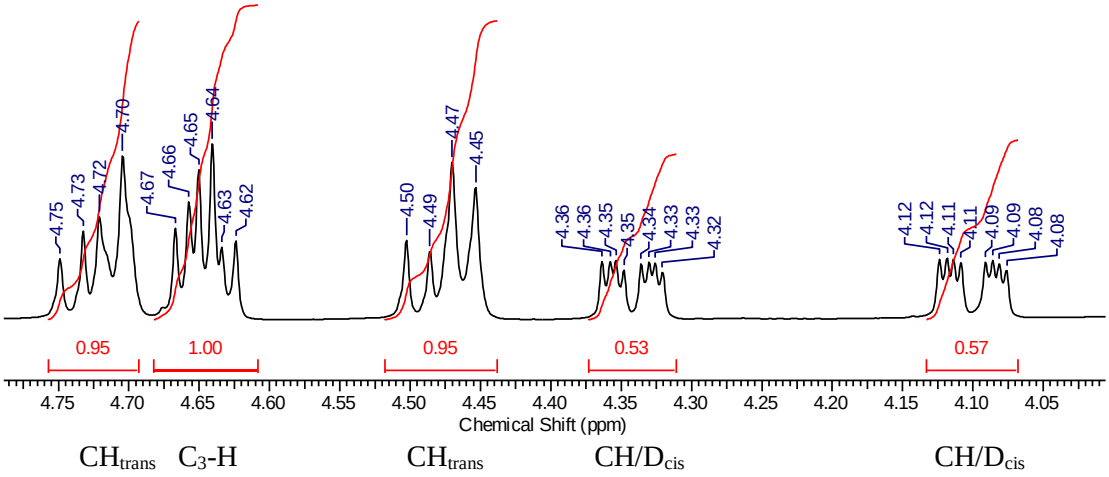


Figure 2.9 ^{1}H NMR spectrum of azetidine region of deuterated azetidinol *cis*-**126a**

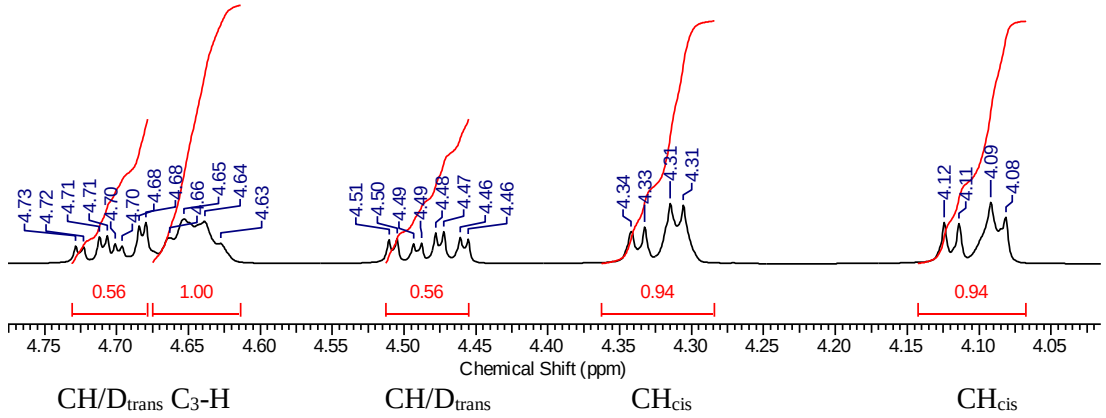


Figure 2.10 ^{1}H NMR spectrum of azetidine region of inverted deuterated azetidinol *trans*-**126a**

As shown in Figure 2.10, the integration values almost perfectly swap over from cis–deuterated azetidinol *cis*-**126a** (Figure 2.9), and the fine structure which is lost in the left hand peaks for deuterated azetidinol *cis*-**126a** are regained for inverted deuterium azetidinol *trans*-**126a**. The same is true for the right hand resonances. The resonance for C_3-H also shifts from a triplet of doublets (6.6 and 3.9 Hz) to a doublet of triplets (6.6 and 3.9 Hz) after inversion, displaying the loss of cis coupling thereby confirming the deuterium was on the opposite side of the ring to C_3-H following initial lithiation–deuteration (Figure 2.11).

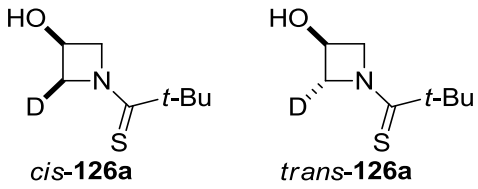


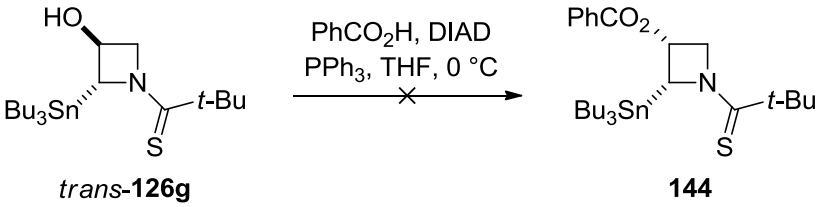
Figure 2.11 Deuterated and inverted deuterated azetidines *cis*-**126a** and *trans*-**126a**

2.2.6 Mechanistic studies

Coupling constant analysis allowed relative stereochemistry assignments to be made by analogy for all other substituted azetidinols. After stereochemical assignment of deuterated azetidinols *cis*-**126a** and *trans*-**126a**, an unusual switch was noted from general trans diastereoselectivity for most electrophiles shown in Table 2.12 (p. 58), except for small electrophiles (such as MeI and paraformaldehyde, where diastereoselectivities were closer to 50:50 trans:cis), to predominantly cis trapping for deuteration (90:10 cis:trans diastereoselectivity). These observations prompted an investigation into the stereoselectivity of the lithiation and electrophile trapping steps.[106] Initial studies were conducted with tin–lithium exchange, followed by deuterium trapping of stannylated azetidinol **126g**. Subsequent work focused on the behaviour of deuterated azetidinols *cis*-**126a** and *trans*-**126a** on re-lithiation and further trapping.

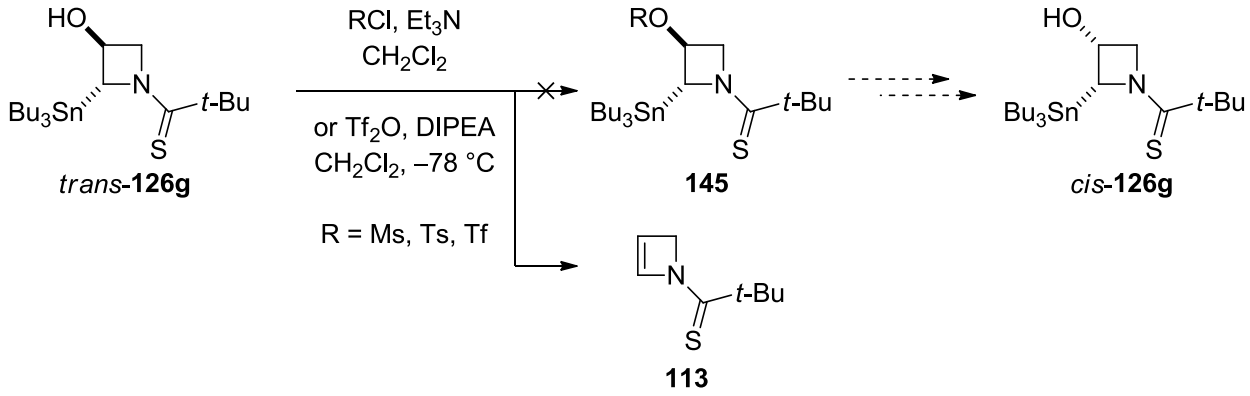
2.2.6.1 Tin–lithium exchange

Access was first required to inverted stannyl azetidinol *cis*-**126g** for comparison to stannylated azetidinol **126g** (*trans*-**126g**) in tin–lithium exchange experiments to determine the stability of the lithiated species in the reaction environment and the selectivity of electrophile trapping.[106, 107] However, attempted Mitsunobu alcohol inversion with stannylated azetidinol *trans*-**126g** unfortunately resulted in an unidentifiable mixture of products (Scheme 2.26).



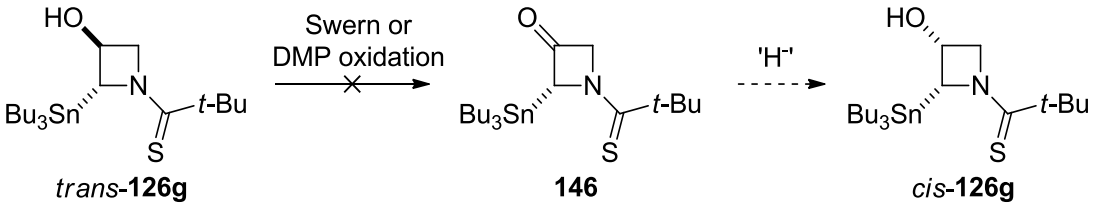
Scheme 2.26 Attempted Mitsonobu inversion of stannyl azetidinol *trans*-**126g**

Subsequently, attempts were made to carry out a similar type of inversion as achieved with deuterium azetidinol *cis*-**126a** (Section 2.2.5.3, p. 66). Unfortunately, attempts to access mesyl-, tosyl- or triflyl-activated stannyl azetidinol **145**, in order to carry out a displacement with NaOAc, all failed to give the corresponding activated alcohols (Scheme 2.27): in all three cases thioamide azetine **113** was isolated, in 42%, ~13% and trace yields, respectively. It is currently not known how azetine **113** forms, it was considered that it was possibly due to a Peterson-type elimination of the α-stannyl alcohol[108] in which Bu_3SnCl and RO^- would be eliminated to give azetine **113**.



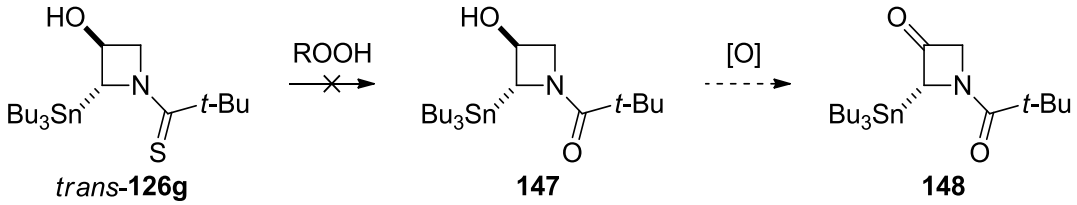
Scheme 2.27 Attempted activation of stannyl azetidinol *trans*-**126g** for NaOAc inversion

Further routes to inverted stannyl azetidinol *cis*-**126g** were studied, including oxidation of the alcohol then followed by diastereoselective reduction (Scheme 2.28). Unfortunately, both Swern and DMP oxidations failed to give intermediate ketone **146**; attempted Swern oxidation resulted in the reaction mixture turning black, while DMP oxidation gave an unidentifiable mixture of products. It was suspected that sulfur's susceptibility to oxidation may have prevented the desired product from being formed.



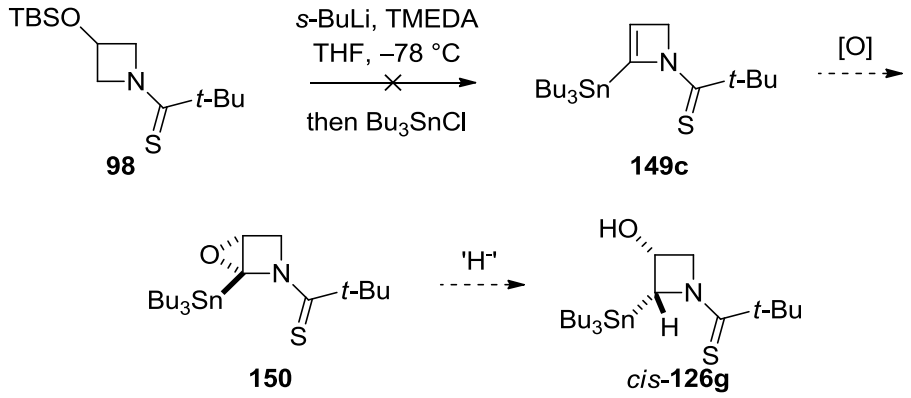
Scheme 2.28 Attempted stannyl azetidinol oxidation for selective reduction of azetidinone **146**

Alternatively, to avoid potential sulfur oxidation, attempted conversion of thioamide *trans*-**126g** to amide **147** was carried out before alcohol oxidation and reduction (Scheme 2.29). Unfortunately, despite using a range of conditions ($MeCO_3H$, *m*-CPBA or H_2O_2), no desired amide was isolated; in several cases stannyl residues were observed, in other cases complete decomposition of the reaction mixture had occurred.



Scheme 2.29 Attempted thioamide to amide conversion of *trans*-**126g**

A final, ambitious, strategy considered was to form α-stannylated thioamide azetine **149c** through lithiation–elimination of TBS azetidine **98**, followed by relithiation and trapping with Bu_3SnCl. Azetine **149c** could then be epoxidised to give **150** and subsequently reductively ring-opened to give desired inverted stannyl azetidinol *cis*-**126g** (Scheme 2.30).



Scheme 2.30 Inverted stannyl azetidinol *cis*-**126g** via stannyl azetine **149c**

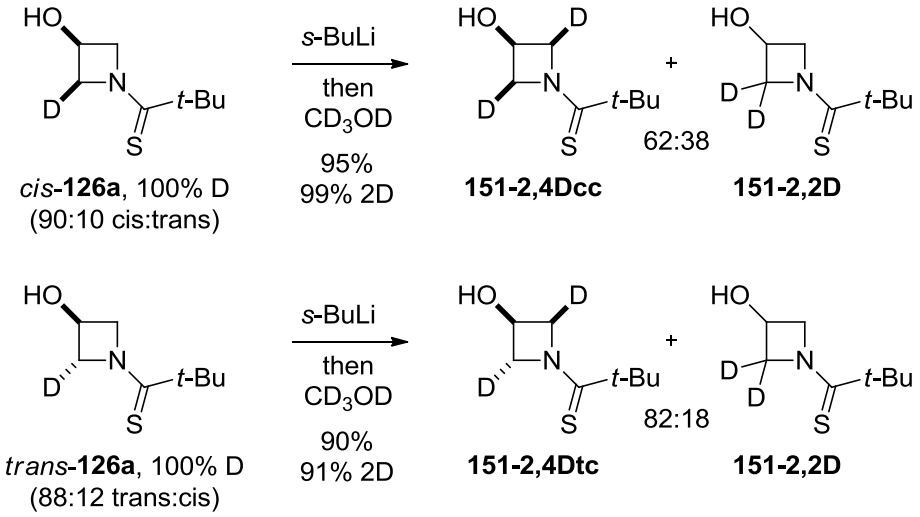
Unfortunately, while stannyl thioamide azetine **149c** was observed in the crude ^{1}H NMR spectrum (as indicated by the loss of the α-azetine peak and the shift and loss of rotameric peaks for the C_3-H and C_4-H_2 protons, see Section 3.1.1, p. 93 for further discussion), on purification stannyl azetine **149c** remained inseparable from Bu_3SnCl residues. However, if stannyl azetine **149c** had been isolated, it was likely that further issues would have arisen during oxidation of the double bond due to the presence of the thioamide, as previously encountered in attempted oxidations (Scheme 2.28, p. 71).

With the synthesis of inverted stannyl azetidinol *cis*-**126g** proving elusive and manipulation of stannyl azetidinol *trans*-**126g** leading to elimination in some cases, alternative ways to probe lithiation and configurational stability issues were considered.

2.2.6.2 Deuterated substrate studies

As access had been made to both diastereoisomers of deuterated azetidinol **126a**, this opened up further possibilities to analyse the effects of relithiation of deuterated azetidinols by following any changes in the configuration with respect to the deuterium and the electrophile used in trapping.

Using deuterated azetidinol *cis*-**126a** and inverted deuterated azetidinol *trans*-**126a**, the preference for proton removal (cis or trans to OLi under the reaction conditions) was examined by lithiation–deuteration of deuterated azetidinols *cis*-**126a** and *trans*-**126a** to give dideuterated azetidinols **151** (Scheme 2.31).

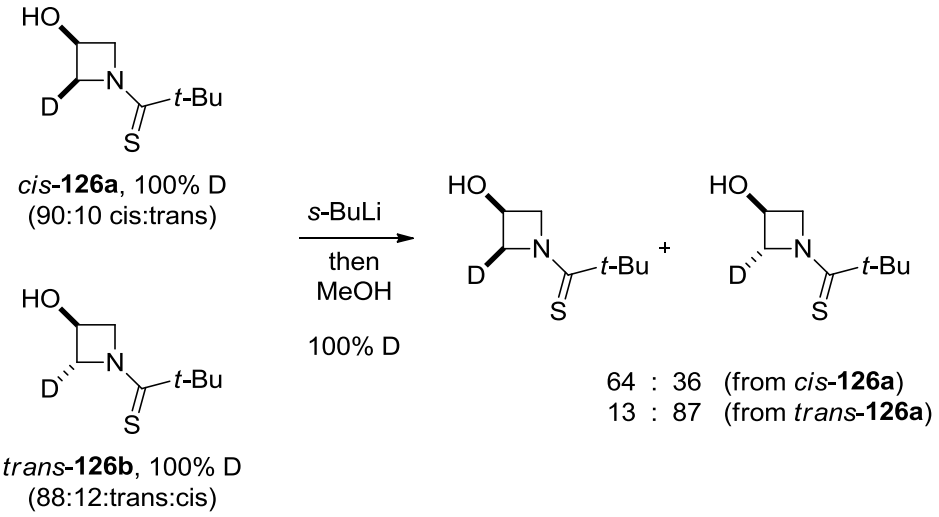


Scheme 2.31 Lithiation–deuteration of deuterated azetidinols *cis*-**126a** and *trans*-**126a**

2,4-Dideuterated azetidinol **151-2,4D** was present in a greater proportion from reaction with inverted deuterated azetidinol *trans*-**126a** (2,4-:2,2-, 82:18) than from deuterated azetidinol *cis*-**126a** (2,4-:2,2-, 62:38), indicating a preference for trans deprotonation. In the case of inverted deuterated azetidinol *trans*-**126a** the trans proton is blocked at C_2 by the presence of the trans deuterium, assuming a high primary kinetic isotope effect at the reaction temperature of –78 °C. While cis deprotonation is less preferable to trans deprotonation, cis deprotonation did occur competitively, as indicated by the formation of 2,2-dideuterated azetidinol **151-2,2D** from inverted deuterated azetidinol *trans*-**126a**, and the unequal ratio of dideuterated azetidinol from deuterated azetidinol *cis*-**126a**, assuming the presence of the deuterium does not deactivate deprotonation by a secondary kinetic isotope effect.

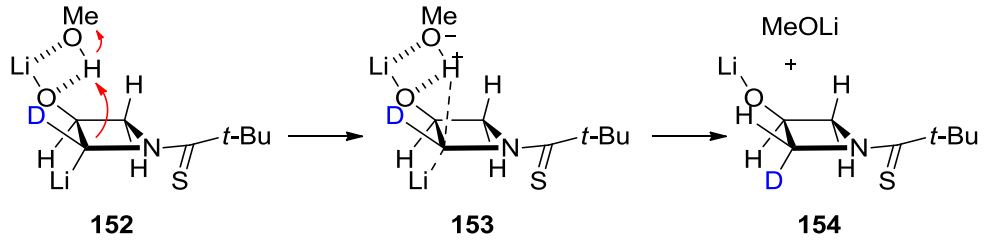
Present in both starting deuterated azetidinols **126a** is approximately 10% of the opposite diastereoisomer and while this 10% will likely lead to formation of small amounts of opposite dideuterated azetidinols the fate of these minor diastereoisomers is not detectable or analysable by ^{1}H NMR spectroscopy. However, the general trends observed here remain helpful despite the expected slight changes in the ratios as a result of these minor diastereoisomers.

Lithiation–protonation resulted in a change in dr from 90:10 to 64:36 cis:trans with deuterated azetidinol *cis*-**126a**, and no change in dr with inverted deuterated azetidinol *trans*-**126a** (Scheme 2.32).



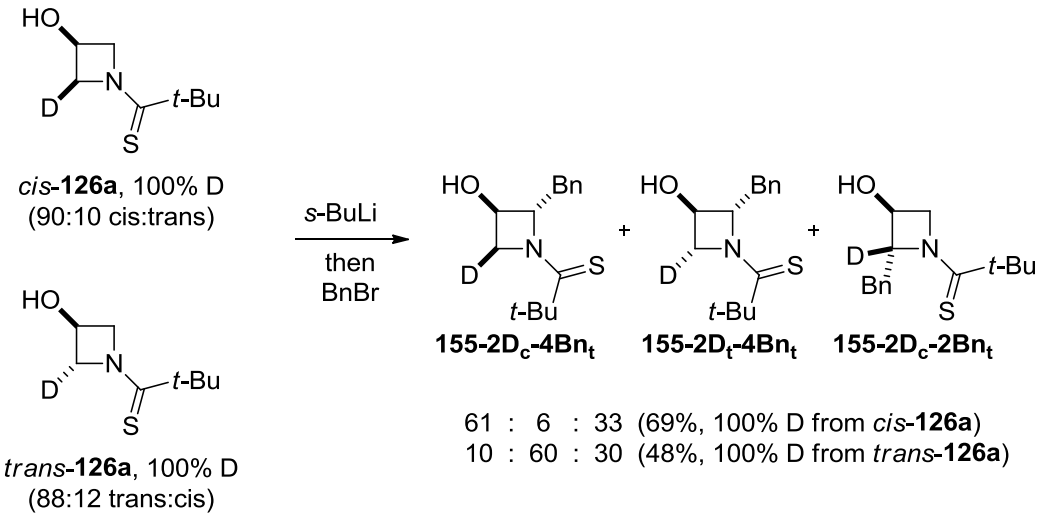
Scheme 2.32 Lithiation–protonation of deuterated azetidinols *cis*-**126a** and *trans*-**126a**

Earlier dideuteration results with deuterated and inverted deuterated azetidinols *cis*-**126a** and *trans*-**126a** (Scheme 2.31) indicated that the regioselectivity of the deprotonation between the C_4 and C_2 positions was approximately 6:4 and 8:2 respectively, in favour of lithiation and trapping on the C_4 position. With lithiation–protonation of deuterated azetidinol *cis*-**126a** (Scheme 2.32), the C_4-lithiated intermediate representing approximately 60% of the total lithiated azetidinol (as indicated by previous ratios) will, on protonation, regenerate starting deuterated azetidinol *cis*-**126a**, whereas the C_2-lithiated species representing the other approximately 40% of the total lithiated azetidinol gave inverted deuterated azetidinol *trans*-**126a**. However, for lithiation–protonation of inverted deuterated azetidinol *trans*-**126a**, both the C_4-and C_2-lithiated components of the total lithiated azetidinol regenerate only starting inverted deuterated azetidinol *trans*-**126a**. These results therefore suggest that there is a strong bias for cis protonation and deuteration, regardless of whether a cis or trans proton is originally removed. It is possible that intermediate alkoxide **153** may be involved in directing the protonation (and deuteration) cis to itself (Scheme 2.33).[109]



Scheme 2.33 Suggested alkoxide-directed proton (and deuterium) trapping of lithiated-deutero intermediate **152**

Lithiation–benzylation of both deuterated azetidinols *cis*-**126a** and *trans*-**126a** resulted in a mixture of the two possible regioisomers: cis and trans C_2–deuterated C_4–benzylated derivatives (**155-2D$_c$-4Bn$_t$** and **155-2D$_t$-4Bn$_t$**), and C_2-benzylated-deuterated derivative (**155-2,D$_c$-2Bn$_t$**) (Scheme 2.34).



Scheme 2.34 Lithiation–benzylation of deuterated azetidinols *cis*-**126a** and *trans*-**126a**

The cis and trans C_2-C_4–derivatives (**155-2D$_c$-4Bn$_t$** and **155-2D$_t$-4Bn$_t$**) likely derive directly from C_4-lithiation of the major and minor diastereoisomeric azetidinols. This is supported by the approximate 90:10 ratios of the cis and trans C_2-C_4-derivatives for both deuterated azetidinols **126a** which comprise the starting material. Unlike with deuteration and protonation of deuterated azetidinols *cis*-**126a** and *trans*-**126a**, in this case the fate of the minor diastereoisomer in each case could be determined, due to benzyl desymmetrisation of the azetidine ring allowing assignment relative to the newly installed benzyl group. Benzylation from C_2–lithiation from either deuterated or inverted

deuterated azetidinols *cis*-**126a** and *trans*-**126a** gave only trans-2-benzylated azetidinol **155-2D$_c$-2Bn$_t$**; confirmed by ^{1}H NMR comparison of benzyl azetidinol **126d** (*trans*-**126d**) and inverted benzyl azetidinol *cis*-**126d** (see Section 2.2.7.1, p. 77 for synthesis of inverted benzyl azetidinol *cis*-**126d** synthesis). These observations indicate there is a strong bias for electrophile trapping, when the electrophile is not a proton or deuterium, to occur trans to the C_3 lithium alkoxide, regardless of whether a cis or trans proton is initially removed at the C_2 position.

Calculation of %D incorporation in doubly deuterated experiments (p. 72) was carried out in a similar fashion to calculations of singly deuterated azetidinols (see Equation 2.1, p. 66), while also taking into account the deuterium already present in the starting material. For these azetidinols the deuterium incorporation was calculated as follows:

$$\%D = 100 \times (No.protons\ \alpha-\ to\ N - (Sum\ of\ integrations\ of\ protons\ \alpha-\ to\ N) - \frac{\%D\ of\ starting\ material}{100})$$

Equation 2.3 Percentage second deuterium incorporation for doubly deuterated azetidinols

Calculation of dr for these experiments was more complex, given the diastereoselectivity already calculated for the starting material. For this to be calculated, the integration of each proton α- to nitrogen in the product had to be subtracted from the integration of the equivalent proton in the starting material. The summation of the differences was used in the following dr calculation:

$$\%\text{-}\mathbf{2,4Dcc} = \frac{(Sum\ of\ differences\ in\ cis\ protons) \times 10000}{\%D}$$

Equation 2.4 Calculation of dr of second deuterium installation for doubly deuterated azetidinols

This calculation provides the ratio of deuterium installed on the same carbon (C_2) as the deuterium in the starting material to deuterium installed on the undeuterated (C_4) carbon in the starting material. These calculations are a slight generalisation as they do not account for the approximate 10% of the opposite diastereoisomer **126a** (deuterated azetidine *cis*-**126a** was isolated with ~90:10 cis:trans dr,

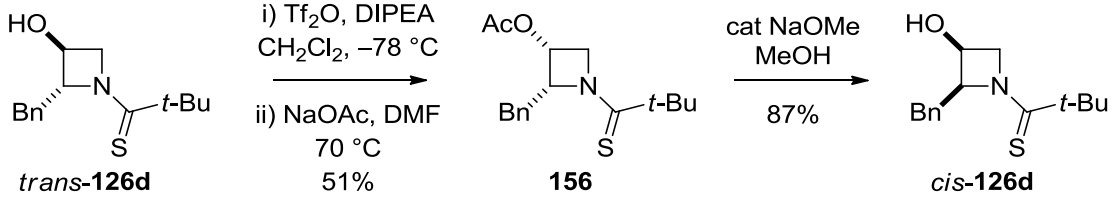
see Table 2.9, p. 53) in the starting material, as the fate of this minor component of the starting material cannot be detected/analysed in the product ^{1}H NMR spectrum.

It was unfortunate that access was not possible to inverted stannyl azetidinol *cis*-**126g** to allow for, in combination with stannyl azetidinol *trans*-**126g**, configuration stability studies of the lithiated azetidinol. However, utilisation of deuterium labelling has given some insight into the lithiation and deuteration steps. Namely, that there is a preference for trans deprotonation, and protonation and deuteration trap predominately cis to the alkoxide, while most other electrophiles trap predominantly trans, regardless of which proton is originally removed. Without tin–lithium exchange experiments it was not possible to make further conclusions regarding whether the electrophile trapping step follows with retention or inversion or via single electron transfer pathways.

2.2.7 Substituted azetidinol manipulations

2.2.7.1 Inverted benzyl azetidinol

For comparison and identification of benzyl-deuterated azetidinols **155** in Scheme 2.34 (p. 75), benzyl azetidinol *trans*-**126d** was inverted using the same procedure followed for deuterated azetidinol *cis*-**126a** (Scheme 2.25, p. 67). Activation of benzyl azetidinol *trans*-**126d** with triflic anhydride and displacement with NaOAc gave inverted acylated azetidinol **156** in 51% yield over two steps. De-esterification with catalytic NaOMe in MeOH gave desired *cis*-benzylated azetidinol *cis*-**126d** in 87% yield (Scheme 2.35).

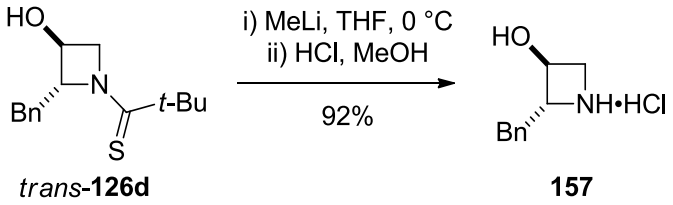


Scheme 2.35 Inversion of benzyl azetidinol *trans*-**126d**

Benzylation of both diastereoisomers of deuterated azetidinol **126a**, as detailed in Section 2.2.6.2 (p. 75), resulted only in *trans*-benzylation. Comparison with the ^{1}H NMR spectrum of *cis*-benzylated azetidinol *cis*-**126d** indicated no presence of this diastereoisomer in the deuterated mixture.

2.2.7.2 Thioamide deprotection and amide conversion

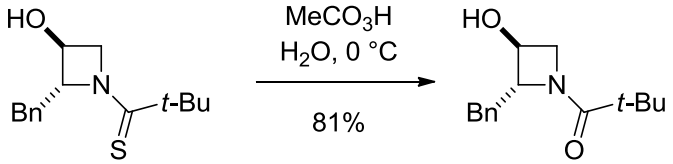
Effective deprotection of an α-substituted azetidinol can be achieved by treatment with MeLi. Benzyl azetidinol hydrochloride **157** was obtained in 92% yield using MeLi in THF with TMEDA at 0 °C of benzyl azetidinol *trans*-**126d**,[80] followed by isolation utilising ion exchange columns and forming the hydrochloride salt by treatment with methanolic HCl (Scheme 2.36).



trans-**126d** **157**

Scheme 2.36 Thioamide deprotection to give free azetidine **157**

Furthermore, conversion of an α-substituted thioamide to the corresponding pivalamide can be achieved by treatment with $MeCO_3H$. Benzyl azetidinol amide **158** (C=O 1595 cm^{-1}) was obtained in 81% yield by treatment of benzyl azetidinol *trans*-**126d** with $MeCO_3H$ (Scheme 2.37).[80,110]



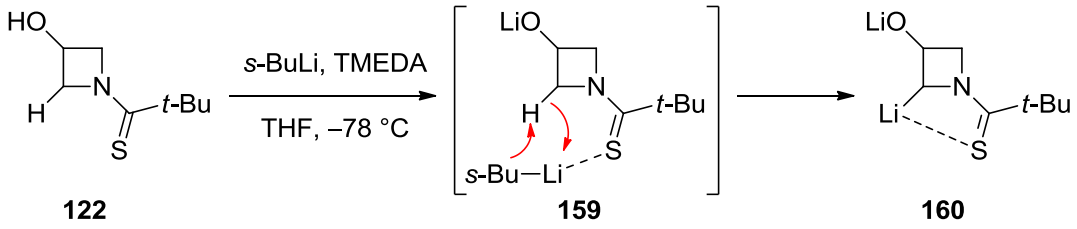
trans-**126d** **158**

Scheme 2.37 Thioamide to amide conversion

2.2.7.3 Re-lithiation of 2-substituted azetidinol

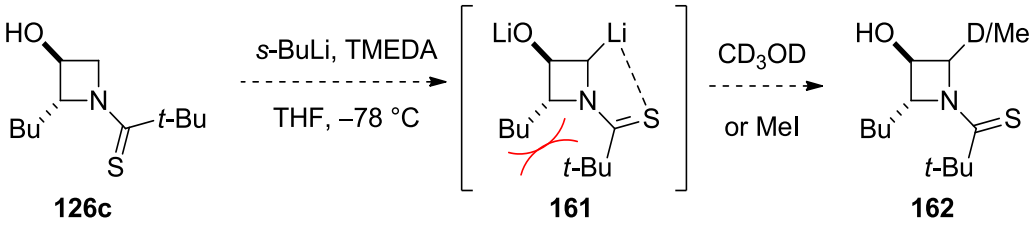
As alluded to previously in ^{1}H NMR analysis of deuterated and methylated azetidinols (Section 2.2.5.2, p. 63), on installation of a group bigger than a proton or deuterium, only one rotameric set of peaks are observed on ^{1}H NMR analysis of 2-substituted azetidines **126**. It was therefore anticipated

that α-deprotonation on the other side of the ring, at –78 °C, was unlikely as the activating group likely forms a pre-lithiation complex with *s*-BuLi (Scheme 2.38, **159**), to bring the *s*-BuLi within proximity of the α-protons for deprotonation. With the equilibrium of thioamide rotation lying on the α-substituted side, the *s*-BuLi is unlikely to be able to form a pre-lithiation complex in close proximity to the α-protons on the other side of the ring.



Scheme 2.38 Pre-lithiation complex **159** induces correct proximity for α-deprotonation

In order to check this theory, butylated azetidinol **126c** was re-subjected to lithiation conditions and trapping with CD_3OD or MeI attempted in order to assess, via ^1H NMR analysis, if any deprotonation is possible on C_4 (Scheme 2.39).



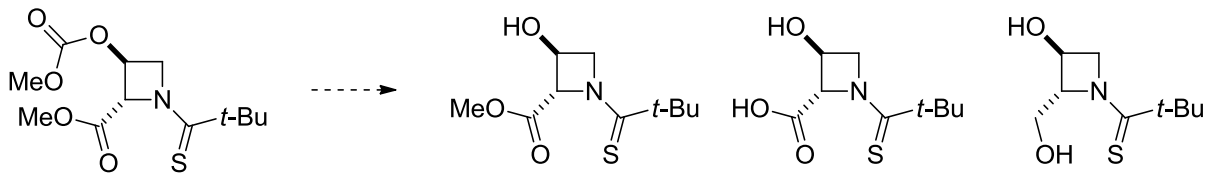
Scheme 2.39 Attempted re-lithiation and trapping of butyl azetidinol **126c**

^1H NMR analysis of the resulting azetidinol from attempted deuteration indicated very little, if any, deuterium incorporation. With methylation, the bulk of the crude mixture was unreacted starting azetidinol **126c**, however, a small amount (~3%) of a different product was obtained. ^1H NMR analysis of this product appeared to indicate methyl installation by loss of one of the ring protons and formation of a 3H doublet in the aliphatic region corresponding to the methyl group (1.67 ppm, J = 6.9 Hz). The doublet multiplicity of the resonance appeared to indicate that the methyl group was installed on the C_4 position to give 2-butyl-4-methyl azetidinol **162** rather than the other regioisomer,

2-butyl-2-methyl azetidinol. Lack of a strong geminal coupling, between the two C_4-H_2 protons if the 2,2- product had been formed, also reinforces this assignment. However, given that only a very minor portion of the crude mixture corresponds to this product, it can be assumed that the other side of the ring cannot be functionalised further by this methodology, most likely due to steric constraints preventing the rotation of the thioamide.

2.2.7.4 Mander's azetidinol manipulations

Given access to *C*- and *O*-methoxycarbonylated azetidinol **126n** in high yield (Table 2.12, entry 15, p. 58), attempts were made to deprotect the carbonate and ester (Scheme 2.40) to allow progression to an interesting class of azetidine amino acids and mugineic acid-type natural products **9** (see Figure 1.1, p. 3).[14a-b]



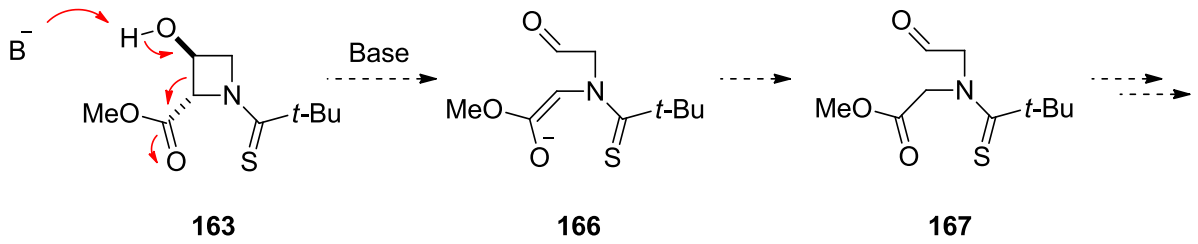
Scheme 2.40 Attempted deprotection of Mander's reagent azetidinol **126n**

Attempted selective carbonate deprotection to give alcohol **163** was carried out by reaction with catalytic NaOMe (MeOH, rt, 20 min). On carrying out this experiment, only a 25% mass recovery of a relatively clean, seemingly complex (18 resonances in the ^{1}H NMR spectrum) product was isolated. ^{1}H NMR analysis indicated the presence of several OMe groups (3.74, 3.73, 3.71, 3.44, 3.40 ppm) and three *t*-Bu groups (1.28, 1.23, 1.22 ppm) possibly indicating desired alcohol **163** underwent further reaction. Furthermore, the loss of coupling and shift of the azetidine ring protons suggested the ring had been opened, but full assignment of this product was not possible.

Treatment of azetidinol **126n** with $MeNH_2$[111] or Pd/C, H_2 gave only recovered starting material, while treatment with methanolic NH_3 resulted in an unidentifiable mixture of products. Similarly, refluxing with KOH[112] in an attempt to deprotect both the carbonate and ester to give acid **164**, and treating with

$NaBH_4$ in an attempt to selectively reduce the ester[113] in the presence of the carbonate only resulted in an unidentifiable mixture of products.

It is likely that on alcohol deprotection, especially in the presence of a base, a retro-aldol reaction[114] takes place, resulting in ring-opening to give acyclic aldehyde **167** which could potentially undergo further chemistries to give complex products (Scheme 2.41).



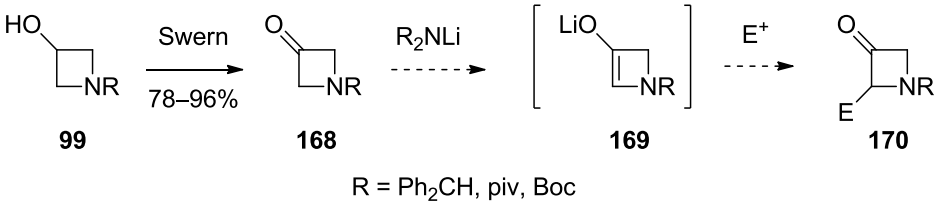
163 **166** **167**

Scheme 2.41 Retro-aldol reaction on deprotection of alcohol carbonate

As a result, unfortunately it was not possible to access free acid **164** with the alcohol functional group present in the 3-position.

2.3 Azetidin-3-one substrates

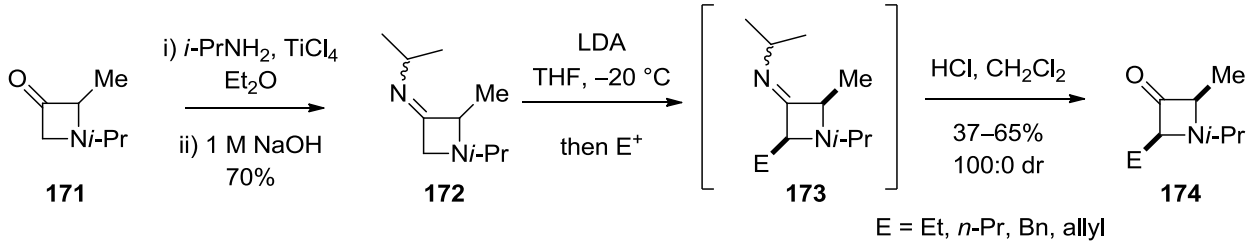
An alternative method examined to access substituted azetidines was utilising azetidin-3-ones **168**, with the intention to deprotonate the ring to form azetidine enolate **169** (Scheme 2.42). The enolate could then be trapped with an electrophile to give 2-substituted azetidin-3-ones **170**. The advantage of this methodology was that while a protecting group on nitrogen is required, the type of group is likely less important, as the deprotonation is tied up in the carbonyl group rather than stabilised with the nitrogen protecting group.



Scheme 2.42 Proposed azetidinone alkylation strategy via enolate formation

To study this chemistry, a small range of azetidin-3-ones (**168**, R = Ph_2CH, piv, Boc) were synthesised by Swern oxidation of the corresponding azetidinols (**106**, **130**, and **132**, respectively), in 78–96% yields. However, all attempts to form enolate **169** with LDA or LTMP and electrophile trap failed to give substituted azetidinones. An attempt to trap any enolate with a silyl chloride also failed to give the desired silyl enol ether. By TLC, most experiments displayed significant, if not complete, decomposition of the azetidinone. ^{1}H NMR analysis of the crude reaction mixtures further indicated significant decomposition.

Research carried out by De Kimpe and co-workers[115] has shown that alkylation of azetidinones **171** is possible, however this was achieved indirectly via the corresponding imine **172**, followed by treatment with a bulky amide base and alkylation with simple alkyl halides (Scheme 2.43).



Scheme 2.43 Alkylation of azetidinones via corresponding imine[115]

Treatment of the resulting substituted azetidine imine **173** with HCl returned the substituted azetidinone **174**. The yields obtained of substituted azetidinones were moderate (37–65%). No mention is made of attempts to directly alkylate azetidinones but the above indirect strategy suggests similar difficulties were encountered.

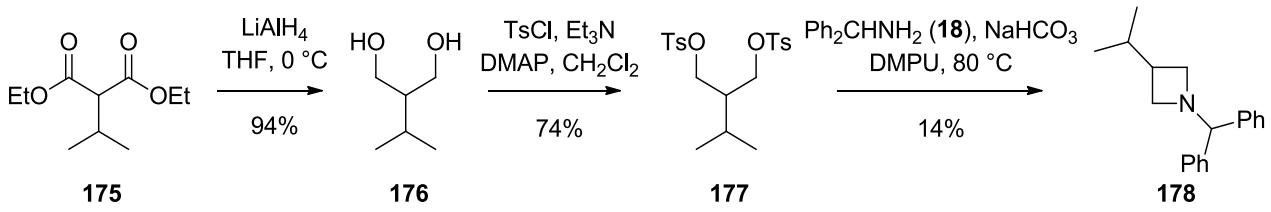
2.4 3-Alkyl azetidines

It was pleasing to discover that functionalisation of an azetidine with an alcohol in the 3-position could be achieved. The alcohol also provides a further handle for functionalisation at a later stage as required. Brief examination of a 3-alkyl azetidine as a test substrate for α-deprotonation–electrophile trapping methodology was also carried out. Unfortunately, here target substrate synthesis requires early stage commitment to the group in the 3-position, which is undesirable for potential future analogue synthesis.

2.4.1 Substrate synthesis

For the purposes of an early indication of the viability of this chemistry it was decided to focus on one example of a 3-alkyl azetidine. The isopropyl group was chosen for the 3-position. It was anticipated, similar to the use of the OTBS group in Section 2.1 (p. 27), that a bulky group may block one face from α-deprotonation resulting in good diastereoselectivity.

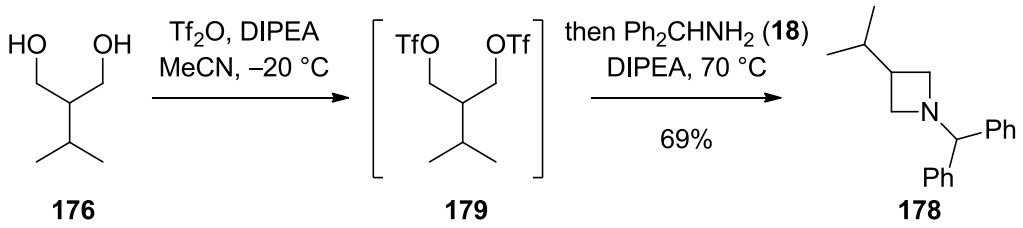
The synthesis commenced with 2-isopropyl diethyl malonate **175**. Reduction to diol **176** (OH, 3329 cm^{-1}, no carbonyl stretch in IR spectrum) with $LiAlH_4$ at 0 °C was achieved in 94% yield. To cyclise to the azetidine, diol **176** was ditosylated to give tosylate **177** (Ts-Me, 6H, 2.45 ppm in the ^1H NMR spectrum and S=O, 1359 and 1174 cm^{-1} in the IR spectrum) in 74% yield. Cyclisation with benzhydrylamine (**18**) and $NaHCO_3$ at 80 °C gave desired azetidine **178** (NC<u>H</u>Ph_2, 4.33 ppm in the ^1H NMR spectrum), albeit in 14% yield (Scheme 2.44).[18]



Scheme 2.44 3-Alkyl azetidine synthesis via ditosylate **177**

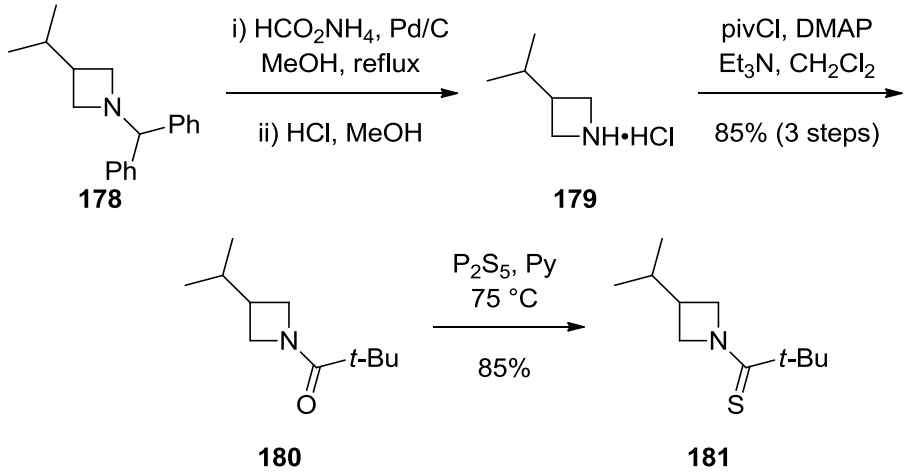
Using a similar triflate activation to that used previously for hydroxyl inversion (see Section 2.2.5.3, p. 66), at –20 °C with Tf_2O and DIPEA, gave ditriflate **179** which was subsequently treated without

isolation with benzhydrylamine (**18**) and further DIPEA and heated to 70 °C; this approach gave azetidine **178** in a much more satisfactory yield of 69% over two steps (Scheme 2.45).[18]



Scheme 2.45 3-Alkyl azetidine synthesis via ditriflate **179**

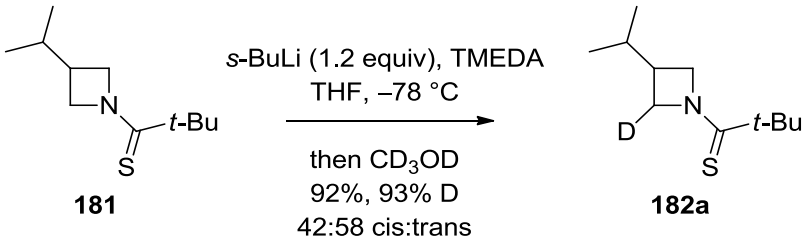
With benzhydryl azetidine **178** in hand, hydrogenolysis with ammonium formate and Pd/C in refluxing methanol gave the free azetidine, which was converted into hydrochloride salt **179** on treatment with methanolic HCl. Amide formation with pivCl and DMAP gave amide **180** (C=O, 1621 cm^{-1} in the IR spectrum) in 85% over three steps. Finally, thioamide conversion was carried out in the standard manner with P_2S_5 in pyridine, to give target test substrate **181** (C=S, 1449 cm^{-1} in the IR spectrum) in 85% yield (Scheme 2.46), 47% from malonate **175** in 7 steps.



Scheme 2.46 Synthesis of 3-alkyl substituted substrate **181**

2.4.2 Initial results

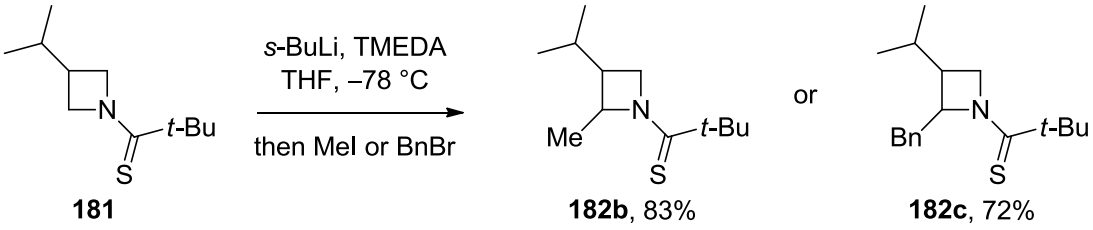
With test thioamide **181** in hand, a standard deuteration experiment was carried out (Scheme 2.47).



Scheme 2.47 Lithiation–deuteration of 3-alkyl substrate **181**

Following ^{1}H NMR analysis, 93% deuterium incorporation was observed. Coupling constants for the cis and trans geminal coupling around the ring were calculated as 8.8 and 5.8 Hz, very similar to the values obtained with substituted azetidinols **126** (see Section 2.2.5.2, p. 63). Consequently, the diastereoselectivity of deuteration with 3-alkyl azetidine **181** was calculated as 42:58 cis:trans. In contrast to the high stereoselectivities observed with azetidinol **122**, reaction with 3-alkyl azetidine **181** displayed significantly poorer dr. Furthermore, with azetidinol **122** preference for cis deuteration was observed, whereas with 3-alkyl azetidine **181** a slight preference for trans deuteration was observed. This provides additional support to the suggestion that in deuteration of azetidinol **122** the deuterium is delivered by the alkoxide during trapping (see Section 2.2.6.2, p. 72).

Testing further, 3-alkyl azetidine **181** was trapped with MeI and BnBr (Scheme 2.48).



Scheme 2.48 Lithiation–methylation/benzylation of 3-alkyl substrate **181**

Both experiments gave two major products, which were identified as the diastereoisomers of the desired substituted azetidines **182**. In the case of methylation (**182b**), a 64:36 ratio of diastereoisomers

was observed by crude ^{1}H NMR analysis. On purification, both diastereoisomers were separable giving a similar 67:33 ratio with a combined yield of 83%. Identification of each diastereoisomer proved difficult due to complexity in the ^{1}H NMR coupling constant analysis. It is likely that the change of the substitution at C_2 altered the conformation of the ring, potentially leading to a greater or lesser degree of puckering, resulting in a change in the coupling constant pattern observed; this therefore made diastereochemical assignment more of a speculative task.

The minor diastereoisomer appeared to fit the coupling constant pattern previously observed with the azetidinol systems for a *trans*-substituted azetidine (see Section 2.2.5.2, p. 63), with geminal couplings of 8.0 and 4.3 Hz (Figure 2.12). However, with the 3-isopropyl group, it is likely that the ring is puckered to relieve strain, so it is unlikely the coupling constant pattern observed for the planar azetidinol **126** system (as confirmed by X-ray crystal analysis, see Section 2.2.5.1, p. 62) would be observed. Furthermore, based on the earlier deuterated azetidine **182a** result in which the minor diastereoisomer was the cis, it could also be rationalised that the minor methyl diastereoisomer is the cis azetidine.

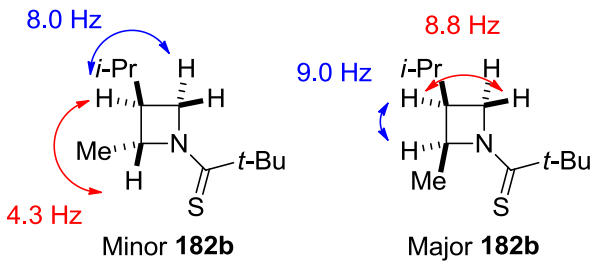


Figure 2.12 Tentative structural assignments for methylation based on coupling constant analysis

Analysis of the major diastereoisomer does not shed further light on the identification. In this case, all three ring coupling constants are between 8.8-9.0 Hz (Figure 2.12), making assignment based on coupling constants impossible. The assumption that there is a puckering of the ring in both diastereoisomers, particularly in the cis diastereoisomer, may make more sense if the major diastereoisomer was the trans-substituted azetidine. However, without further NOE studies or computation of conformer energy levels this remains speculation.

Trapping with BnBr (**182c**) displayed 85:15 dr after crude ^{1}H NMR analysis. Unfortunately, the minor diastereoisomer was not fully separable from the major; however, a sample of the major diastereoisomer was isolated pure (72% total yield was obtained for both diastereoisomers). Interestingly, the major product displayed a similar coupling pattern (8.5 and 4.5 Hz) to that of the minor methyl azetidine (8.0 and 4.3 Hz), possibly indicating a switching of preference between MeI and BnBr trapping (Figure 2.13).

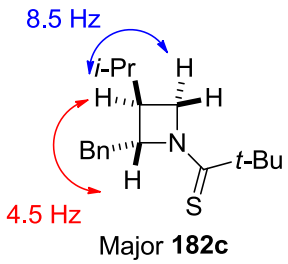


Figure 2.13 Tentative structural assignments for benzylation based on coupling constant analysis

However, a more likely explanation is that methylation and benzylation show the same preference for formation of one diastereoisomer, however conformational effects of the substituents alter the coupling constants resulting in incorrect assignment of one of the diastereoisomers.

It was unfortunate that a greater level of diastereoselectivity was not observed in this system; however, these remain preliminary results. Shifting from an isopropyl group to a *tert*-butyl group may enhance the diastereoselectivity, but in terms of useful functionality at the 3-position, primary centres are likely to be desired, and as such it is predicted that a significantly reduced level of selectivity would be observed when the steric bulk of the group at the 3-position is reduced.

2.5 Summary

Despite initial protected azetidinol experiments leading to undesired azetine **113** rather than 2-substituted azetidinols **111**, readily available *N*-thiopivaloylazetidin-3-ol (**122**) was shown to undergo efficient α-lithiation–electrophile trapping with a range of electrophiles, providing 2-substituted-2-hydroxyazetidines **126** in good yields with generally good trans diastereoselectivity.

Deuterium labelling studies indicate that the α-deprotonation step is preferentially, but not exclusively, *trans*-stereoselective. An exception to this is protonation/deuteration, wherein the proton/deuterium is installed cis, possibly directed by the alkoxide.[109] The stereochemical outcome of trapping with other electrophiles is dependent on the electrophile used, regardless of which cis or trans α-proton is initially removed.

Furthermore, lithiation–trapping using 3-alkyl substituted azetidines can be achieved in high yields, however early results indicate poorer diastereoselectivity compared to that with the azetidinol system.

2.6 Concluding remarks

These studies indicate that functionalised azetidines can be achieved by late stage introduction of functionality from readily available starting materials. This work shows for the first time α-lithiation on a 3-functionalised azetidine, and indicates that further generation of substituted azetidines can be achieved using this methodology.

Potential future work in this area includes:

- Modifying the *N*-protecting/activating group to allow rotation once substituted, to potentially give access to 3-hydroxy-4-lithio-2-substituted azetidines and trapping with electrophiles to give 2,3,4-trisubstituted azetidines.
- Extending the range of substituted azetidines by possible cross-coupling from the lithiated species with a range of cross-coupling partners.
- Trapping with more complex electrophiles, moving towards natural product synthesis.
- Briefly examining the diastereoselectivity of a primary alkyl and *tert*-butyl derivative of the 3-alkyl system to determine if diastereoselectivity is a feature of C_3 steric bulk.
- Examining an asymmetric variant of 2,3-disubstituted azetidine methodology, potentially utilising THF compatible chiral ligands.[66]

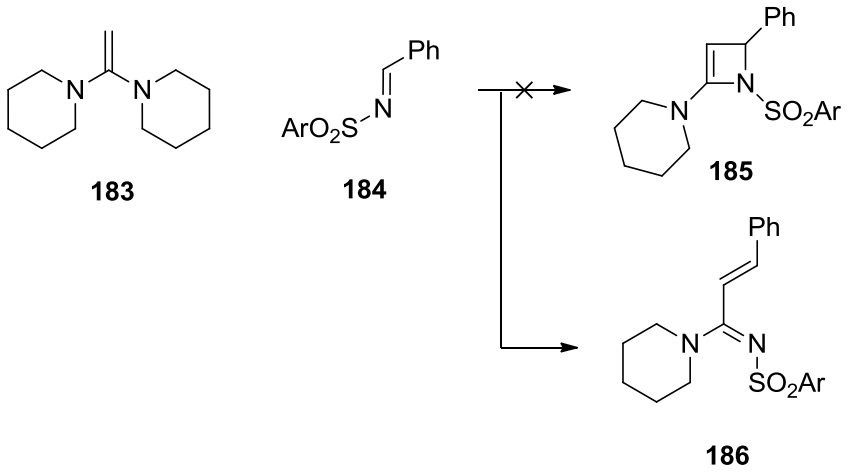
3 Results & Discussion: Azetines

An unusual observation, made during the attempted synthesis of substituted azetidines **111** using TBS-protected azetidinol **98** (see Section 2.1.2, p. 31), was the isolation of 2-azetine **113**, presumably formed through elimination of $TBSO^-$ from lithiated intermediate **112**. This result was unexpected, given the strain in the 2-azetine and the low temperature at which the experiments were carried out.

However, given that it is a potentially interesting sub-class of azacycle, and that access was easily achieved from readily available TBS-protected azetidinol **98**, it was decided that this would be an attractive avenue for further research. Very little research has been carried out with monocyclic azetines when compared to azetidines.

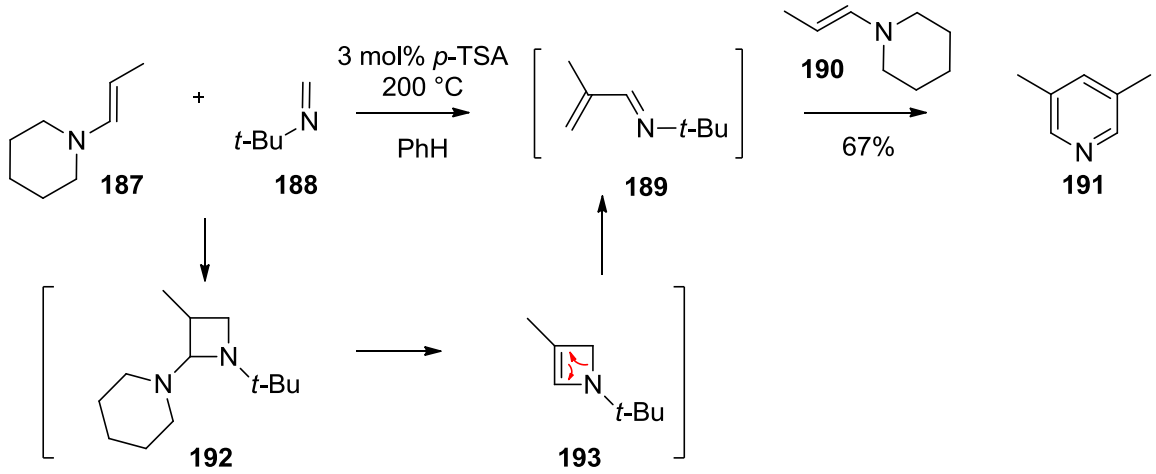
3.1 Introduction

As noted above, very little research has been carried out on 2-azetines. This partly reflects issues of ease of access and stability, namely the tendency to undergo 4e electrocyclic ring-opening to 1-azabutadienes, which is thermodynamically and kinetically favoured.[116] However, a small number of azetines have been synthesised. The first reported 2-azetine was claimed in 1966, formed by [2+2] cycloaddition between ketene aminal **183** and imine **184** to give azetine **185** (Scheme 3.1).[117] However, later analysis of the suspected azetine ^{1}H NMR spectrum indicated seemingly high coupling constants for the double bond indicating an olefinic trans arrangement and giving strong evidence for this compound actually being the ring-opened 1-azabutadiene **186** (Scheme 3.1).[118] However, azetine **185** is still likely to have formed en route to the ring-opened azadiene **186**.



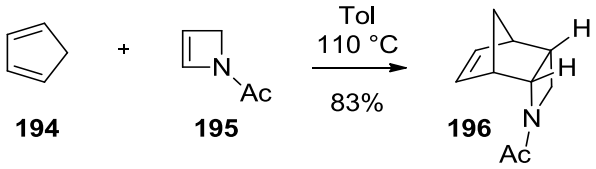
Scheme 3.1 Electrocyclic breakdown of first reported azetine

While the propensity for electrocyclic ring-opening prevents, in some cases, 2-azetines being isolated, 2-azetines have been utilised as masked diene partners for hetero-Diels-Alder reactions using this property. An example is the reaction of enamine **187** with aldimine **188** to give pyridines **191** via azadiene **189** from the breakdown of 2-azetine intermediate **193** (Scheme 3.2).[119]



Scheme 3.2 Azetine **193** as an intermediate in the synthesis of pyridine **191**

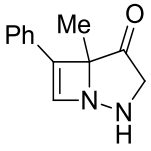
Isolable azetines can be reacted with dienes, such as the reaction of 1-acetyl-2-azetine **195** with cyclopentadiene (**194**) at 110 °C in toluene, to give the corresponding tricyclic cycloadduct **196** (Scheme 3.3).[120]



194 195 196

Scheme 3.3 Diels-Alder reaction of azetine **195** with cyclopentadiene **194**

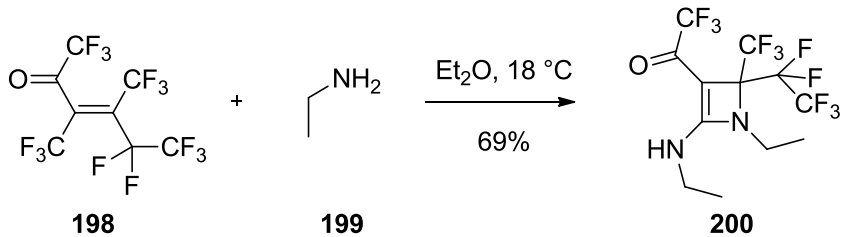
As noted above, ring-opening often prevents isolation of 2-azetines, and as a result very few methods are available for their synthesis.[116c] However, the presence of an electron withdrawing group on the nitrogen can stabilise the azetine ring.[121] Furthermore (and following the conservation of orbital symmetry),[122] ring-opening of azetines occurs by a conrotatory mechanism. This mechanism is unfavourable in fused azetine systems such as azetine **197** (Figure 3.1), resulting in stabilisation.[116b] However, accessing monocyclic azetines, where this effect is not present, presents a significantly greater challenge for synthesis and isolation.



197

Figure 3.1 Fused 2-azetine ring

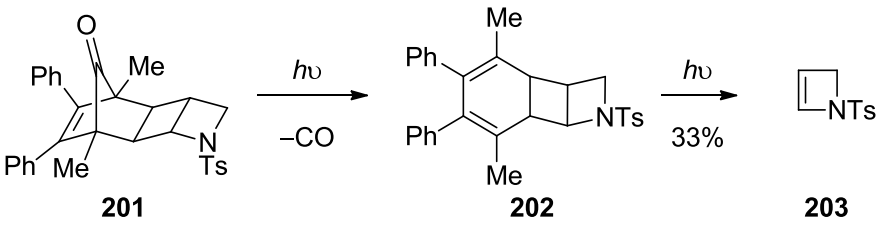
A few methods do exist, however, for the preparation of monocyclic 2-azetines. For example the cyclisation of primary amines with maximally fluorinated enone **198** gives specific fluorinated azetine **200** (Scheme 3.4).[123]



198 199 200

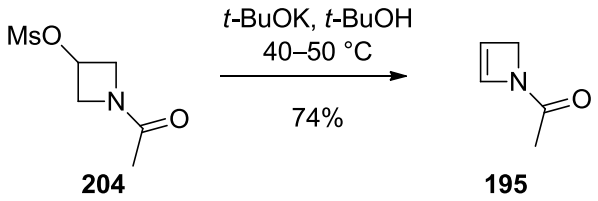
Scheme 3.4 Cyclisation of enone **198** with ethylamine **199**

Photoaromatisation of tetracycle **201** also gives access to monocyclic azetines; in this case 2-azetine **203** was obtained in 33% yield (Scheme 3.5) via cheletropic extrusion of CO followed by light-induced cycloreversion.[124]



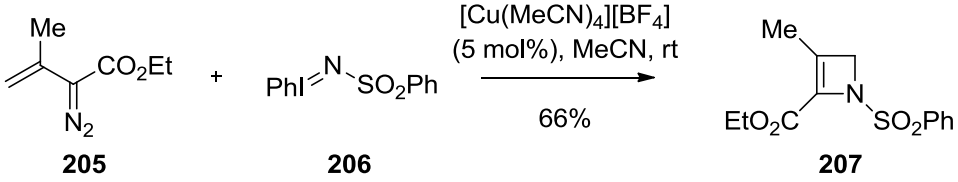
Scheme 3.5 Photofragmentation of **201** to give azetine **203**

One of the simplest methods to monocyclic azetines is elimination of activated alcohols from azetidines, such as the elimination of mesylate **204** with *t*-BuOK to give azetine **195** in good yield (Scheme 3.6).[125] This method for azetine formation is closely related to methods used for azetine formation in this work, and as such is discussed further in Section 3.2.2.1 (p. 96).



Scheme 3.6 Elimination of mesylate **204** to give azetine **195**

In more recent work towards the synthesis of substituted monocyclic azetines, Barluenga and co-workers have shown that copper catalysts provide azetine **207** from stabilised vinyldiazoester **205** and iminoiodinane **206** in good yield (Scheme 3.7).[126]



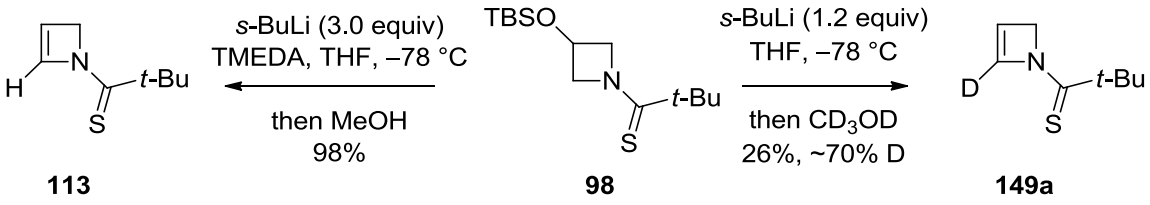
Scheme 3.7 Synthesis of substituted azetine **207** from vinyldiazo **205** and iminoiodinane **206**

Several more isolated examples of monocyclic azetines exist in the literature, but many of them are found in reports concerned with using the azetine as an alkene equivalent,[85,127] or the azetine is merely produced as a minor undesired side-product,[128] or the azetine is a suspected reaction intermediate in the formation of other products.[129]

Very little research has been carried out into the synthesis of azetines and their derivatives. As a result of coming across a facile method towards azetines, an investigation commenced to examine if this method could be utilised to access further substituted azetines by α-deprotonation–electrophile trapping.

3.1.1 Early azetine results

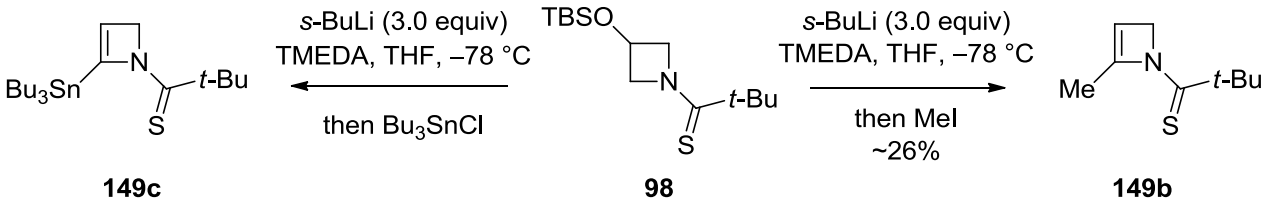
Thioamide azetine **113** was first synthesised by lithiation and elimination of TBS-protected azetidinol **98**. Azetine **113** could be isolated in yields up to 98% with 3.0 equiv *s*-BuLi. Reanalysis of previously isolated azetines formed by elimination of TBS-protected azetidinol **98** when trapped with CD_3OD (see Table 2.1, p. 32) did show partial deuteration of the azetine to give deuterated azetine **149a**, as determined by diminution of the α-alkenyl proton at 6.98 ppm (and associated rotamer peak at 7.35 ppm) in the ^{1}H NMR spectrum, indicating regioselective lithiation at the α-sp^2 position.[130] In the case of Table 2.1, entry 2 (p. 32) a deuterium incorporation of ~70% (by ^{1}H NMR analysis) was observed, which demonstrated that azetine lithiation could occur (Scheme 3.8).



Scheme 3.8 Azetine formation and deuteration from TBSO azetidine **98**

Further experiments in Section 2.2.6.1 (p. 69), attempting to access inverted stannyl azetidinol *cis*-**126g** via stannyl azetine **149c**, illustrated trapping of the lithiated azetine with Bu_3SnCl to give stannylated azetine **149c** (Scheme 2.30, p. 72). While this product was observed after chromatography in the ^{1}H NMR spectrum (peaks at 6.50 NC=C<u>H</u> and 5.06 NCH_2, and loss of NC<u>H</u>=CH peak), it was

significantly contaminated with inseparable tributylstannyl residues (~77% of the mixture, by calculation through ^{1}H NMR analysis) and only obtained in low yield (33% by calculation through ^{1}H NMR analysis). A further preliminary experiment was carried out with MeI trapping, and methyl azetine **149b** was observed by ^{1}H NMR analysis (peaks at 5.79 ppm NC=C<u>H</u>, 4.75 ppm NCH_2 and the CH_3 singlet at 2.44 ppm, together with loss of NC<u>H</u>=CH peak) and isolated in ~26% yield, but with significant impurities, trace amounts of azetine **113** were also observed by ^{1}H NMR analysis (Scheme 3.9).



Scheme 3.9 Stannyl and methyl azetine **149c** and **149b** formation

3.2 Thioamide azetines

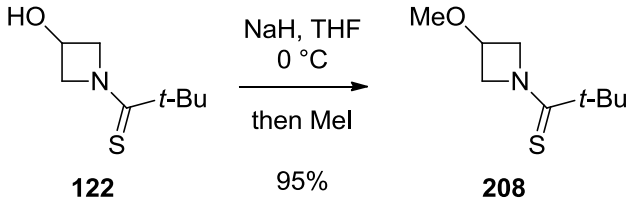
Initially encouraging results of 2-substituted azetine formation with TBS-protected azetidinol **98** with Bu_3SnCl and MeI prompted further investigation towards substituted azetines.

3.2.1 From azetidine

For further studies towards thioamide azetines, MeO-protected azetidinol **208** was used as the test substrate over continued use of TBS-protected azetidinol **98**, for reasons of simplicity, cost effectiveness, and greater atom efficiency in the eventual elimination.

3.2.1.1 Synthesis

Methoxyazetidine **208** was straightforwardly synthesised from azetidinol **122** in 95% yield, by deprotonation with NaH in THF, followed by MeI trapping (Scheme 3.10).

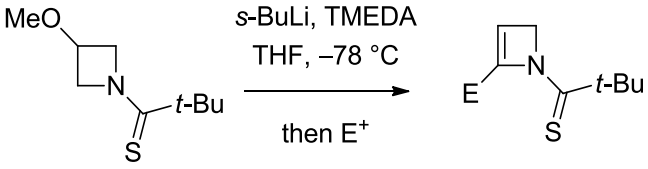


122 208

Scheme 3.10 Synthesis of OMe-protected azetidinol **208**

3.2.1.2 Results

With methoxyazetidine **208** in hand, two test lithiations were carried out, using the same lithiation conditions as for TBS-protected azetidinol **98** followed by trapping with MeI or BnBr (Scheme 3.11).

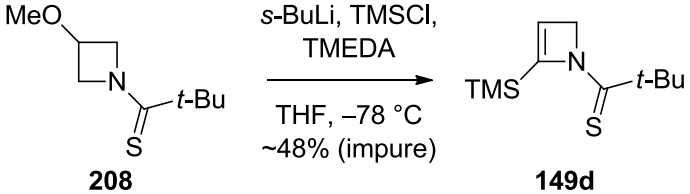


208 149

Scheme 3.11 Attempted methyl and benzyl azetine formation

Crude ^{1}H NMR and TLC analysis indicated possible substituted azetine **149** formation, albeit in low yield (along with recovered unsubstituted azetine **113**). Unfortunately, purification of the crude reaction mixtures did not result in product isolation, possibly indicating azetine instability during chromatography.

Furthermore, an *in situ* silylation, similar to the experiment carried out in Section 2.1.3 (p. 32), to access silylated azetine **149d** was attempted (Scheme 3.12).



208 149d

Scheme 3.12 Attempted *in situ* silyl azetine **149d** formation

^{1}H NMR analysis of the crude reaction mixture indicated an approximate 1:1 ratio of silylated azetine **149d** to unreacted starting material **208**. However, on purification silylated azetine **149d** coeluted with non-polar by-products, similar to observations made in initial stannyl azetine **149c** synthesis (Section 2.2.6.1, p. 72), leading to significant impurities.

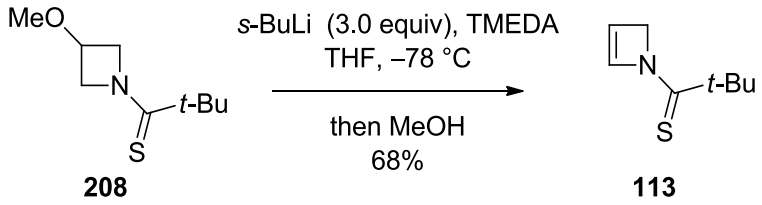
As a result of these poor results, examination with deuterium trapping was carried out to determine if complete lithiation could be achieved. In a small study of reaction parameters the equivalents of *s*-BuLi and TMEDA were examined, together with reaction concentration, duration and method of work–up, in an attempt to optimise the lithiation and trapping procedure. It was observed that crude mass recovery remained consistently high (up to 100%) with high levels of deuteration (up to 100% D), as calculated by ^{1}H NMR analysis. However, on chromatographic purification of the crude products on silica gel, significant amounts of material were lost, resulting in only modest yields (19–38%) of deuterated azetine **149a**.

3.2.2 From azetine

In most of the experiments carried out attempting to access substituted azetines, significant levels of unsubstituted azetine **113** had been either observed in crude ^{1}H NMR spectra, or subsequently isolated on purification. Experiments carried out to this point used azetidinol ethers as starting materials for azetine synthesis, due to their greater stability when compared to the corresponding azetine starting material. However, from observations made during these experiments it was believed that unsubstituted azetine **113** had a greater degree of stability than its substituted azetine analogue **149**. Following this analysis, it was decided to assess unsubstituted azetine **113** itself as the starting material for substituted azetine **149** synthesis, in so doing, the requirement for the initial elimination stage would be removed and thereby hopefully increasing the likelihood of reaction success.

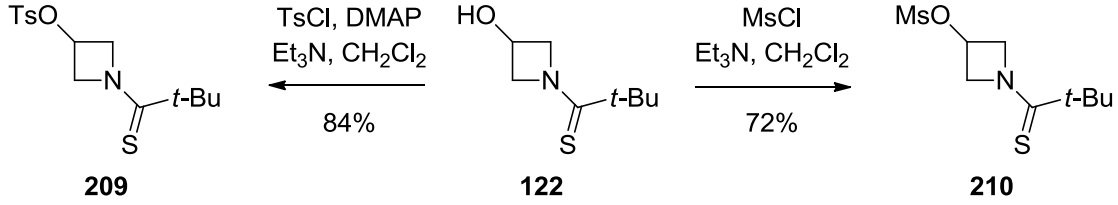
3.2.2.1 Synthesis

Unsubstituted azetine **113** was synthesised in 68% yield from methoxyazetidine **208** by lithiation and quenching with MeOH (Scheme 3.13).



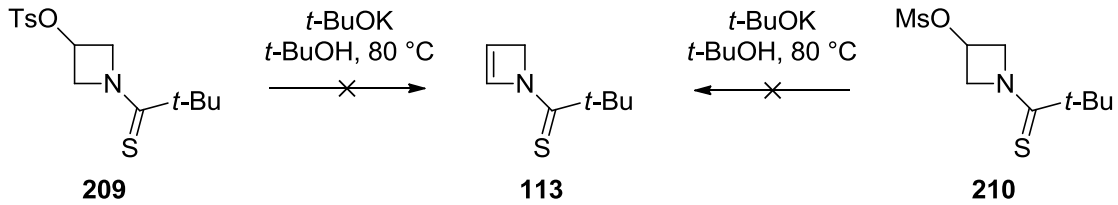
Scheme 3.13 Synthesis of unsubstituted azetine **113**

Synthesis of azetine **113** was also attempted from tosylated and mesylated azetidinols by elimination using *t*-BuOK. Tosylation and mesylation of azetidinol **122** was achieved with the corresponding sulfonyl chloride, Et_3N (and DMAP for tosylation) in CH_2Cl_2 to give tosylate **209** and mesylate **210** in 84% and 72% yields, respectively (Scheme 3.14).



Scheme 3.14 Tosyl and mesyl activation of azetidinol **122**

Sulfonates **209** and **210** were treated with *t*-BuOK in *t*-BuOH at 80 °C in order to try to access unsubstituted azetine **113** (Scheme 3.15).[125]

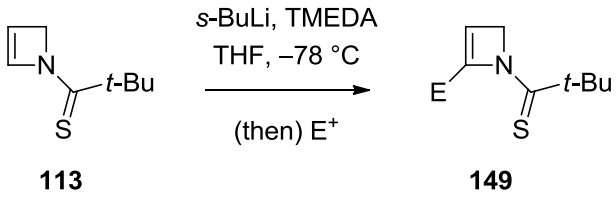


Scheme 3.15 Attempted tosyl and mesyl elimination to give azetine **113**

Unfortunately, in both cases, desired unsubstituted azetine **113** was not isolated. Reaction of both sulfonates with *t*-BuOK gave a complex mixture of products.

3.2.2.2 Results

Unsubstituted azetine **113** (Scheme 3.13, p. 97) was lithiated and trapped with MeI, and with TMSCl *in situ* (Scheme 3.16).



Scheme 3.16 Attempted methyl and silyl azetine **149** synthesis

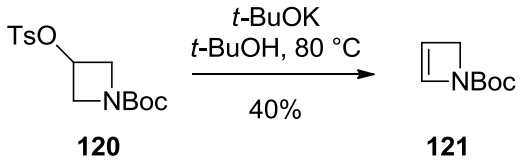
By TLC analysis, MeI and TMSCl trapping appeared to have given the corresponding substituted azetines. However, on purification, as in previous examples, only complex mixtures of products were isolated, possibly containing trace amounts of the desired substituted azetines **149**.

3.3 Boc azetines

Initial experiments were conducted using thioamide azetine **113** as the test candidate, since this had given the first (unsubstituted) azetine observed in these studies. However, all attempted syntheses of substituted thioamide azetines **149** suffered from poor yields, difficulties in purification (coelution of close running non-polar impurities), and susceptibility to decomposition, resulting in only low yields of contaminated products. Due to this limited success, it was decided to evaluate azetines with different *N*-protecting groups. One of the most studied *N*-protecting groups for azacycle lithiation chemistry is Boc, which as discussed in the introductory chapter (pp. 1–26) has found extensive use in lithiations of piperidines,[60b,63,72,131] pyrrolidines,[60,61,66,70,131] and aziridines[73] (including Csp^2 α-lithiation of 1,2,3,4-tetrahydropyridine,[132] 1,2-dihydropyridine[133] and 1,4-dihydropyridine[134]). Boc is a useful protecting group for nitrogen, due to ease of installation and removal, and is sufficiently electron withdrawing to stabilise the aforementioned lithiated species (see Section 1.3.1, p. 14). Early studies of substituted Boc azetidines did not give efficient lithiation and trapping, with possible attack at the Boc group occurring when treated with *s*-BuLi.[80] However, Boc protection was evaluated with an azetine to assess if the change in azacycle led to a more efficient deprotonation and trapping.

3.3.1 From azetine

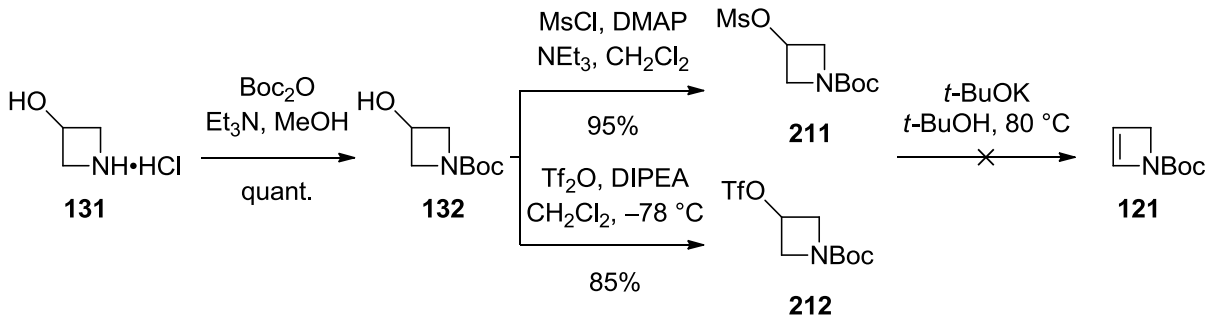
Only one mention is made of Boc azetine **121** in the literature, in which it is used as an alkene equivalent in a rhodium-catalysed asymmetric hydroformylation reaction.[85] The synthesis was achieved from tosyl azetidinol **120**, by elimination with *t*-BuOK in *t*-BuOH at 80 ˚C, in 40% yield (Scheme 3.17).



Scheme 3.17 Literature Boc-azetine **121** synthesis[85]

3.3.1.1 Synthesis

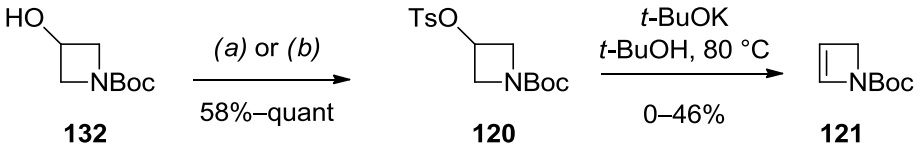
With only a 40% yield, indicated in the literature, it was considered that the corresponding mesylate or triflate might provide azetine **121** in higher yields. The synthesis of these latter substrates was carried out starting from azetidinol hydrochloride **131**. Boc installation with Boc_2O and Et_3N in MeOH[87] gave Boc azetidinol **132** (C=O, 1666 cm^{-1}) in quantitative yield, and subsequent mesylation by treatment with MsCl, DMAP and Et_3N in CH_2Cl_2 gave desired mesylate **211** in 95% yield. Triflation with Tf_2O and DIPEA in CH_2Cl_2 at –78 ˚C gave triflate **212** in 85% yield. However, treating either sulfonate with *t*-BuOK did not give desired azetine **121**, and in the case of mesylate **211** de-mesylation occurred returning starting Boc azetidinol **132** in 78% yield (Scheme 3.18).



Scheme 3.18 Attempted synthesis of Boc-azetine **121** from mesylate **211** and triflate **212**

Consequently, recourse was made to the literature procedure, using tosylate **120** for the elimination.[85] However, repeating the literature result was more complicated than initially expected. The literature claimed that a 100% conversion to tosylate **120** was achieved by reaction *N*-Boc azetidinol (**132**) with TsCl in pyridine at freezer temperatures. The corresponding crude tosylate **120** was treated with *t*-BuOK and eliminated to give desired azetine **121** in 40% yield. In my hands only 65% yield of tosylate **120** was achieved, and 17% yield of azetine **121**.

Tosylations were carried out following the literature procedure,[85] or with TsCl, DMAP and Et_3N in CH_2Cl_2, but in most cases ~20% of starting azetidinol **132** remained in the crude mixture. Elimination using the crude mixture gave azetine **121** yields ranging from 0% to 35%, while elimination using purified tosylate **120** gave yields ranging from 0% to 46% (Scheme 3.19).



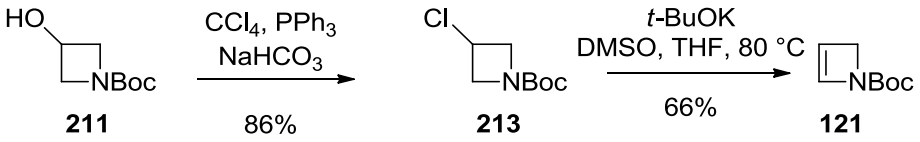
Reagents and conditions: (a) TsCl, py, Freezer, 16 h.
(b) TsCl, DMAP, Et_3N, CH_2Cl_2, 16 h.

Scheme 3.19 Synthesis of Boc-azetine **121** from tosylate **120**

Unfortunately the desired higher yields were not achieved, and the results that were obtained appeared to be unreliable in their reproducibility. Possible volatility of azetine **121** was also noted, which may account for the lower yields during the removal of *t*-BuOH which required the use of lower vacuums and warmer temperatures.

At this stage, the possibility of changing the leaving group to a chloride was considered. The latter was achieved via an Appel reaction[135] giving chloride **213** in 86% yield (m/z 214.1, $[M+Na]^+$). Elimination of chloride **213** with *t*-BuOK in a THF/DMSO solvent mixture pleasingly gave desired azetine **121** in 66% yield (Scheme 3.20); moreover, this process was reproducible in several subsequent syntheses and benefited from the use of DMSO and THF allowing isolation under mild

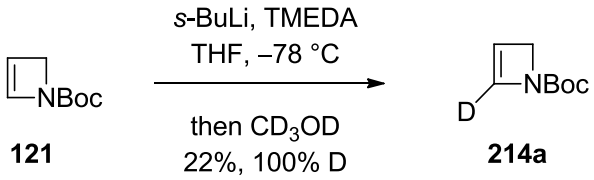
conditions without use of low vacuums, thereby eliminating possible losses due to azetine **121** volatility.



Scheme 3.20 Boc-azetine **121** synthesis via chloride **213**

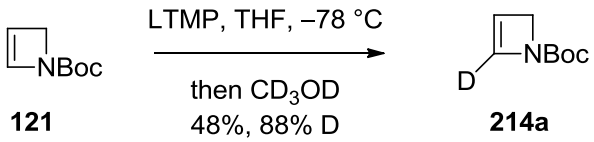
3.3.1.2 Initial results

With satisfactory access to azetine **121** established, a standard lithiation and deuterium trapping with CD_3OD was carried out (Scheme 3.21).



Scheme 3.21 Initial deuteration of Boc-azetine **121**

Only a 22% yield of azetine **214a** was obtained, albeit fully deuterated, as calculated by HRMS. Carrying out the same experiment in Et_2O did not give any product. Attempted trappings with MeI, BnBr, PhCHO and with *in situ* TMSCl all failed to give any substituted azetines, as did lithiations at –98 ˚C and lithiations with substoichiometric quantities of *s*-BuLi (0.9 equiv) to reduce or prevent excess *s*-BuLi being present in the reaction mixture post lithiation. Taking the view that *s*-BuLi was causing decomposition of the starting material, or products, lithiation was then attempted with weaker amide bases. Lithiating azetine **121** with 1.2 equiv LTMP and trapping with CD_3OD gave deuterated azetine **214a** in a much more pleasing yield of 48%, with 88% deuteration, as calculated by HRMS (Scheme 3.22).



121 **214a**

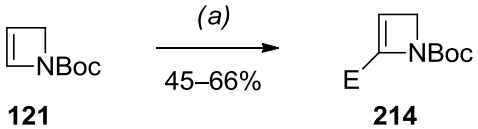
Scheme 3.22 Lithiation and deuteration of Boc-azetine **121** with LTMP

3.3.1.3 Electrophile scope

With *s*-BuLi treatment of Boc-azetine **121** failing to show significant trapping, an early stage examination of Boc-azetine **121** lithiation with LTMP and trapping with a small range of electrophiles was carried out, to determine if this substrate was able to give substituted azetines (Table 3.1)

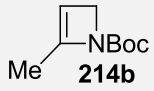
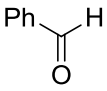
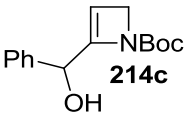
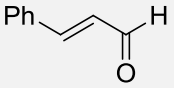
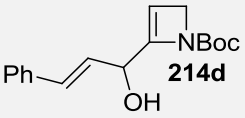
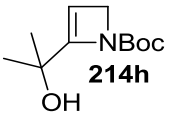
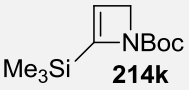
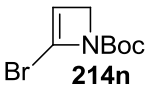
Azetines appeared to show strongly by TLC without the need for heating when stained in $KMnO_4$, and this property was used to identify azetine products and starting materials. Several purifications carried out of these reactions resulted in complex mixtures of products, particularly with methyl and bromo azetines **214b** and **214n**. 2D TLC analysis of these azetines, and other synthesised azetines, indicated, as suspected with previous azetines, a propensity to decomposition on silica to varying degrees. 2D TLC analysis was carried out on each azetine to assess if silica purification was a viable method of isolation. Furthermore, it was discovered that azetine products decompose on contact with an acid wash during work-up, as a result no acid washes were used during subsequent work-ups.

Table 3.1 Electrophile scope with LTMP azetine lithiation



121 **214**

Reagents and conditions: (a) LTMP (1.2-1.4 equiv), THF, –78 °C, 1 h, then E^+

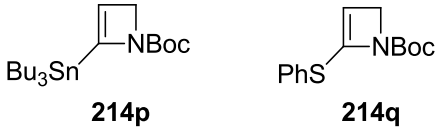
Entry No.	Electrophile	2-Substituted azetine 214	Yield (%)	Notes
1	MeI	 **214b**	-	Product observed but not isolated
2		 **214c**	66	-
3		 **214d**	60	-
4		 **214h**	60	-
5	Me_3SiCl	 **214k**	45	Contaminated with TMS side products
6	$BrCl_2CCBrCl_2$	 **214n**	60	Reverse phase chromatographic purification

Methyl azetine **214b** was observed by TLC using MeI trapping (entry 1) with 1.2 and 1.4 equiv LTMP, but only as a minor component of the crude reaction mixture, with the major component being starting azetine **121**. As indicated above, methyl azetine **214b** is partially unstable to silica, unfortunately leading to a complex mixture of products on attempted purification.

Reaction with carbonyl electrophiles (entries 2–4) proceeded well giving silica-stable azetines. Trapping with PhCHO gave alcohol **214c** in 66% yield (entry 2), cinnamaldehyde gave alcohol **214d** in 60% (entry 4), with no indication of any 1,4-addition product by TLC or ^{1}H NMR analysis, and acetone gave alcohol **214h** in 60% yield (entry 4). Trapping with TMSCl (entry 5) was successful, with silyl azetine **214k** being more stable to silica (as indicated by 2D TLC); a 45% yield was achieved with slight TMS residue contamination.

Finally, trapping with bromine electrophile $BrCl_2CCBrCl_2$ successfully gave bromo azetine **214n** by TLC, but 2D TLC indicated complete decomposition on silica, which was reflected in very little, if any, product being obtained by normal-phase silica chromatography. However, greater stability was observed when utilising reverse-phase column chromatography (octadecylsilanised silica gel, $MeCN/H_2O$ eluent),[136] resulting in a 60% yield of bromo azetine **214n**.

Trappings with Bu_3SnCl and $(PhS)_2$ in attempts to synthesise stannyl- and thiophenyl-substituted azetines **214p** and **214q** (Figure 3.2) appeared to show product by TLC analysis, but the substituted azetines could not be isolated by column chromatography. Attempted reverse phase chromatography of stannyl azetine **214p** resulted in co-elution with tributyltin residues, whereas with thiophenyl azetine **214q**, an unidentifiable mixture of products was obtained.



214p **214q**

Figure 3.2 Stannyl and thiophenyl azetines **214p** and **214q**

Attempted trappings were also carried out with Mander's reagent and methyl chloroformate; however, no product or starting material was observed. Trappings with DMF showed a small amount of possible product by TLC analysis, but was not isolable and only starting material was observed on attempted trapping with BnBr.

3.3.1.4 Limitations

A small number of 2-substituted azetines had been isolated as some of the first examples of substituted monocyclic azetines synthesised by deprotonation α- to nitrogen (Table 3.1, p. 102). While this development confirmed that these structures can exist and be isolated, several limitations were encountered. Some of these limitations have already been mentioned, in that most of the azetines isolated here, and those detailed later on in this report, have a propensity to decompose on contact with acid and silica, and when exposed to temperatures exceeding 40 ˚C.[124]

Furthermore, once isolated, these azetines slowly decompose at varying rates while in storage at freezer temperatures (~ –20 °C). In the subsequent stages of this research, having gained experience with these compounds in terms of production, workup, isolation and storage, it was favoured to store these azetines in basic media which often prevented (or reduced rates of) decomposition. Azetines were usually stored in CH_2Cl_2 over K_2CO_3. Moreover, use of Et_3N eluent doping, or pre-neutralising the silica with Et_3N for column chromatography increased, to a greater extent in some cases but to a significant extent in most, the yields of substituted-azetines.

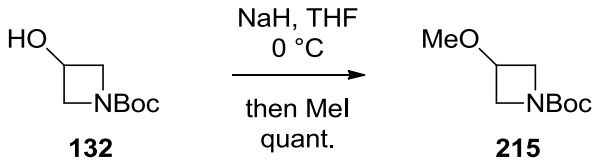
These discoveries were made during the work detailed herein, however, difficulties remained in the handling of stock amounts of azetine starting material **121**. In some of the syntheses of this starting material azetine **121** polymerised immediately after purification. In most cases azetine **121** was stable in the freezer for a few days, but became increasingly viscous as time passed, indicating partial polymerisation. Consequently, it was considered important to develop a more workable procedure, with stable, easily obtainable starting materials, and ideally without the need to also make LTMP fresh each time.

3.3.2 From azetidine

Having gained experience in the issues of handling, purification and storage of azetines, it was decided to reinvestigate *in situ* azetine formation, thereby hopefully removing the somewhat troublesome synthesis and isolation of *N*-Boc azetine **121**.

3.3.2.1 Synthesis

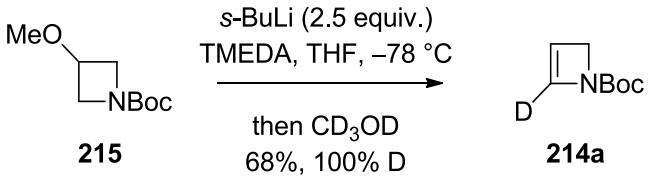
Similar to elimination experiments using thioamide **208** (see Section 3.2.1, p. 94), evaluation of methoxyazetidine **215** was first carried out, the latter being easily accessed from *N*-Boc azetidinol (**132**) by deprotonation with NaH in THF at 0 °C, followed by methylation with MeI, to give methoxyazetidine **215** (in the ^{1}H NMR spectrum: OCH_3, 3.26 ppm) in quantitative yield (Scheme 3.23).



Scheme 3.23 Methyl ether formation from *N*-Boc azetidinol **132**

3.3.2.2 Method comparison

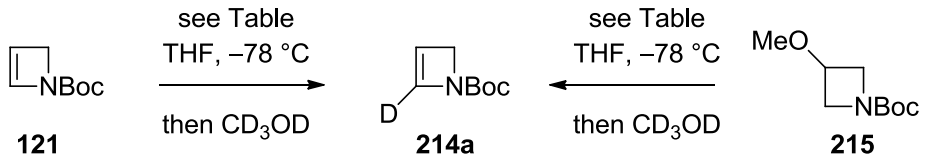
Reaction of methoxyazetidine **215** under standard lithiation conditions, 2.5 equiv *s*-BuLi, with TMEDA in THF at –78 °C, followed by trapping with CD_3OD very pleasingly gave deuterated azetine **214a** in 68% yield with 100% D (Scheme 3.24).



Scheme 3.24 Deuterated azetine **214a** synthesis from MeO-protected azetidinol **215**

With lithiation of azetine **121** using LTMP also giving access to deuterated azetine **214a** in moderate yields, as well as substituted azetines in good yields, a comparison of lithiation procedures was carried out to determine the most efficient overall procedure for accessing substituted azetines (Table 3.2).

Table 3.2 Method comparison to substituted azetines



Entry no.	Starting material	Reaction conditions	Yield
1	**121**	1.2 equiv LTMP	48%[a]
2	**121**	1.4 equiv LTMP	70%
3	**121**	1.2 equiv *n*-BuLi, TMEDA	56%[b]
4	**121**	1.2 equiv *s*-BuLi, TMEDA	54%[b]
5	**121**	1.2 equiv *s*-BuLi	54%
6	**215**	2.5 equiv LTMP, 30 min	48%
7	**215**	2.5 equiv LTMP, 5 h	62%
8	**215**	2.5 equiv *s*-BuLi, TMEDA	68%
9	**215**	2.5 equiv *s*-BuLi, TMEDA[c]	88%
10	**215**	2.5 equiv *s*-BuLi	74%

[a] 88% D. [b] Crude yield. [c] repetition of entry 8.

Deprotonation of azetine **121** can be achieved with LTMP (entries 1–2), although using slightly more LTMP (entry 2) gave a significantly greater yield (70%) of deuterated azetine **214a**. Use of *n*-BuLi (entry 3) and *s*-BuLi (entries 4–5) gave deuterated azetine **214a** in ~55% yield but in the former cases (entries 3–4) were not purified, indicating a likely reduction in yield on purification. α-Deprotonation can also be carried out without TMEDA (entry 5) while maintaining the yield.

Reaction of methoxyazetidine **215** can also be achieved with LTMP (entries 6–7): reaction for 30 min (entry 6) and 5 h (entry 7) gave deuterated azetine **214a** in 48% and 62% yields, respectively. Use of *s*-BuLi initially gave deuterated azetine **214a** in 68% yield (entry 8), a repetition of the same procedure gave an 88% yield (entry 9). Using *s*-BuLi without TMEDA gave a slight drop in yield to 74% (entry 10).

Using the conditions detailed in entry 9 as a basis, attempted eliminations and deuterations were also carried out in different solvents. Use of Et_2O gave only a 54% yield of deuterated azetine **214a**, whereas MTBE gave 50% yield. Toluene resulted in a slightly higher yield (60%), but it was

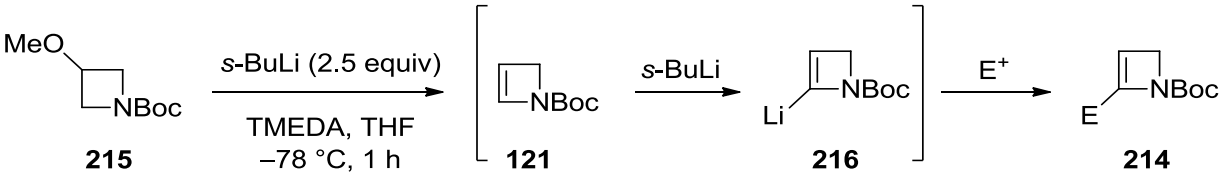
concluded that THF remained the most effective solvent to carry out these eliminations and functionalisations.

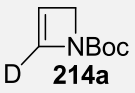
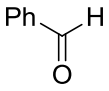
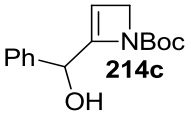
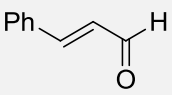
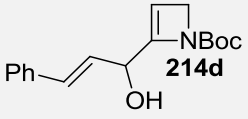
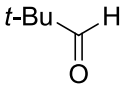
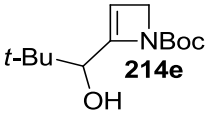
With yields of deuterated azetine **214a** being higher from methoxyazetidine **215**, this approach was used in all subsequent work. This method also benefits from high yielding *in situ* azetine formation, which when performed separately significantly reduced overall yield.

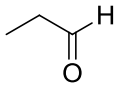
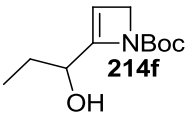
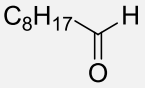
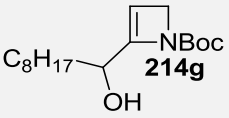
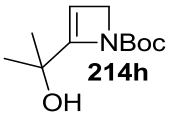
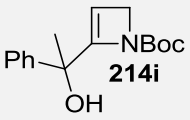
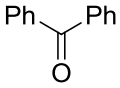
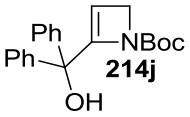
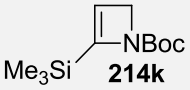
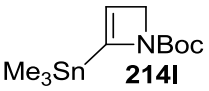
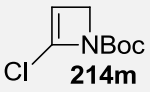
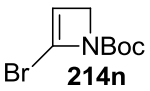
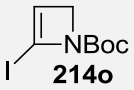
3.3.2.3 Electrophile scope

With a high yielding, efficient method in hand, the scope of this methodology was examined (Table 3.3).

Table 3.3 Electrophile scope



Entry No.	Electrophile	2-Substituted azetine 214	Yield (Previous yield)[a]
1	CD_3OD	 **214a**	88% 100% D
2		 **214c**	97% (66%)
3		 **214d**	78% (60%)
4		 **214e**	84%

5		 **214f**	82%
6		 **214g**	82%
7		 **214h**	44% (60%)
8		 **214i**	54%[b]
9		 **214j**	51%[b]
10	Me_3SiCl	 **214k**	74% (45%)
11	Me_3SnCl	 **214l**	76%
12	Cl_3CCCl_3	 **214m**	63%
13	$BrCl_2CCBrCl_2$	 **214n**	71% (60%)
14	I_2	 **214o**	60%

[a] Previous yield using azetine **121** and LTMP (Table 3.1, p. 102). [b] Yield corrected for inseparable *N*-Boc-azetine **121**, 9% and 10% for substituted azetines **214i** and **214j**, respectively (as calculated by ^{1}H NMR analysis).

As can be observed from comparison with previously obtained yields, the yields achieved in the *in situ* elimination methodology are, in most cases, significantly higher than those from azetine **121**

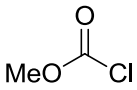
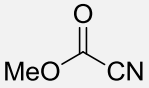
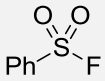
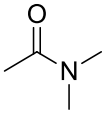
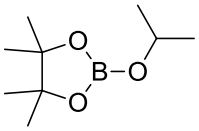
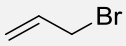
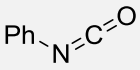
itself, except for the case with acetone trapping giving alcohol **214h** (entry 7), in which the yield dropped slightly. Unfortunately subsequent attempts to increase this yield (greater excess of acetone, and alternative drying methods) were not successful, possibly indicating that under this method acetone has an increased propensity to undergo enolisation rather than trapping.

However, a number of successful trappings were achieved, including simple deuteration (entry 1), which was mentioned earlier (see Section 3.3.2.2, p. 106). Reaction with a number of carbonyl electrophiles (entries 2–9), including aldehydes (entries 2–6), gave access to secondary alcohols **214c-j** in high yields, with particular reference to trapping with benzaldehyde (entry 2), to give alcohol **214c** in 97% yield, and trapping with cinnamaldehyde (entry 3), to give only the 1,2-addition product **214d** in 78% yield. Furthermore, trappings with ketones (entries 7–9), proceeded to give tertiary alcohols **214h-j** in moderate yields. In the case of acetophenone and benzophenone (entries 8–9), difficulty was encountered with co-elution of a small portion of *N*-Boc azetine **121**. The yields for reactions with acetophenone and benzophenone have been corrected for slight *N*-Boc azetine **121** impurity.

Trapping with heteroatom electrophiles (entries 10–14) can also be achieved in high yields. Silylation and stannylation (entries 10–11), gave silylated azetine **214k** and stannylated azetine **214l** in 74% and 76% yields, respectively. Halide installation (entries 12–14) was also achieved in good yields, giving chloride **214m**, bromide **214n** and iodide **214o** in 63%, 71% and 60% yields, respectively. In the latter four cases (entries 11–14) reverse phase chromatography was necessary for product isolation.[136] With stannylation, stannyl azetine **214l** was sufficiently non-polar to render normal phase chromatography unable to separate non-polar by-products from stannyl azetine **214l**. With halide installation, exposure of halide azetines **214m-o** to normal phase silica, even under pre-neutralised and Et_3N-doped conditions, led to complete decomposition of the azetines. Successful purification of these latter azetines was achieved by reverse-phase chromatography.

A number of other electrophile trappings were attempted, but either no trapping was observed, returning unsubstituted azetine **121**, or led only to complete decomposition of the reaction mixture. The electrophiles attempted are displayed in Table 3.4.

Table 3.4 Unsuccessful electrophiles

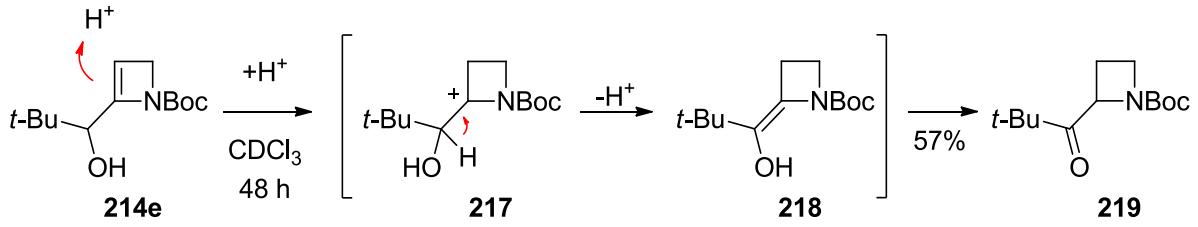
MeI		CO_2	$(PhS)_2$
BuI			$(t\text{-BuS})_2$
BnBr		$B(OMe)_3$	
			

Unfortunately, trappings with alkyl halides all failed to give the desired alkylated azetines. Similarly, treatment with higher oxidation state electrophiles which would have given ester, aldehyde, amide and carboxylate installation lead to decomposition of the reaction mixture. Attempted installation of fluorine, boron and sulfur electrophiles also failed to give the desired heteroatom substituted azetines (Table 3.4).

3.3.2.4 Limitations & observations

A number of unusual observations were made during the synthesis of the azetines present in Table 3.3 (p. 108).

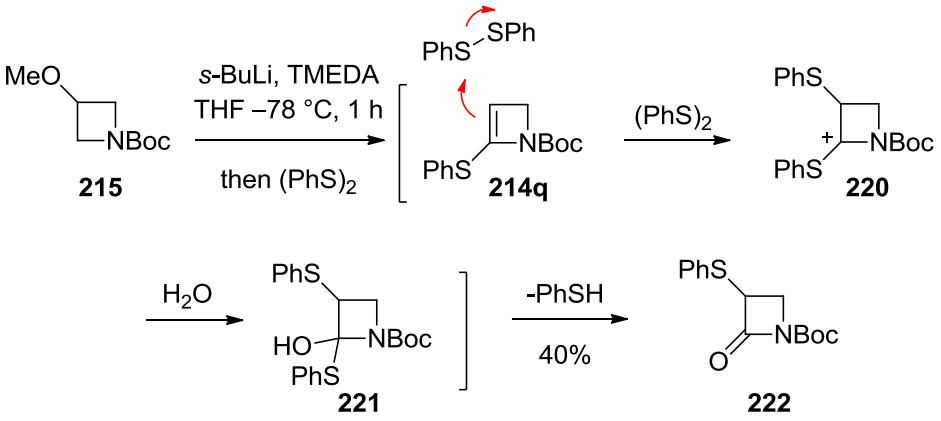
Trapping of the lithiated species with *t*-BuCHO can be achieved in high yield as indicated in Table 3.3, entry 4. However, this was only achievable with Et_3N-doped eluents during column chromatography. Without Et_3N-doping, desired alcohol **214e** present in the crude mixture decomposed, resulting in no isolation of the desired azetine; this example indicates how beneficial the presence of Et_3N can be in purification. Furthermore, when alcohol **214e** was isolated utilising Et_3N-doped eluents and held in $CDCl_3$, which had not been passed through alumina prior to use, a rearrangement occurs, presumably driven by relief of strain, to the corresponding saturated ketone **219**. A possible reaction pathway of this isomerisation is displayed in Scheme 3.25, in which the trace amounts of acid in $CDCl_3$ likely catalyse a prototropic rearrangement.[137] Other aldehyde-derived alcohols did not undergo analogous isomerisations.



Scheme 3.25 Possible mechanism of isomerisation

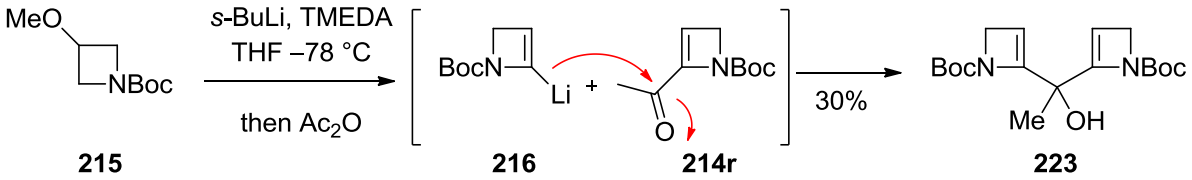
Trapping with $(PhS)_2$, as indicated in the failed electrophile table (Table 3.4, p. 111), did not give the desired 2-thio azetine **214q**. However, it is suspected that the desired 2-thio azetine **214q** was present in the crude mixture (by reaction TLC and crude ^{1}H NMR analysis, trace amounts of *N*-Boc azetine **121** were observed in the ^{1}H NMR spectrum along with two other azetine peaks at 5.31 and 5.13 ppm, suspected to be NCH_2 and NC=CH of 2-thio azetine **214q**). However, on workup and purification the presumed 2-thio azetine **214q** underwent further reaction, resulting in a slight change in R_f by TLC analysis. The resulting product of further reaction was stable to column chromatography, and was isolated and identified as *N*-Boc-α-phenylthio-β-lactam **222**, as indicated by loss of one ring proton, m/z 302.1 peak in the MS, and two carbonyl peaks at 1801 and 1722 cm^{-1} in the IR spectrum. The formation of this product may proceed through initial electrophile trapping, where the resulting electron-rich azetine **214q** undergoes further reaction with the electrophile, followed by hydrolysis

(Scheme 3.26). Unfortunately repeated attempts to isolate what is suspected to be 2-phenylthio azetine **214q** were not successful. Reduction in the quantity of $(PhS)_2$ used (0.9 or 1.0 equiv) to prevent further reaction did not result in recovery of any identifiable products, indicating the need for excess $(PhS)_2$ for eventual β-lactam **222** formation.

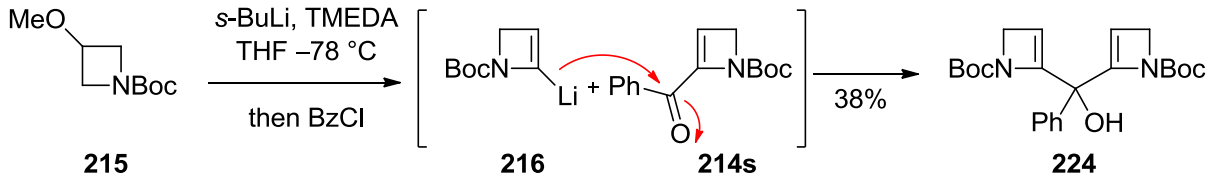


Scheme 3.26 Possible mechanism of β-lactam **222** formation from phenylthio azetine **214q**

Trapping with Ac_2O and BzCl gave what was initially assumed to be acylated and benzoylated azetines **214r** and **214s**. However, on MS and detailed ^{1}H and ^{13}C NMR analysis they were found to be double addition products: the corresponding diazetine alcohols **223** (OH 3367 cm^{-1} br, C(OH)(Me) 67.7 ppm, Scheme 3.27) and **224** (OH 3293 cm^{-1} br, C(OH)(Ph) 72.4 ppm, Scheme 3.28) formed in 30% and 38% yields, respectively. It is believed that these diazetines are generated by slow trapping of the electrophile giving a carbonyl-substituted azetine (**214r/s**) as a more reactive electrophile, which is trapped by a further equivalent of lithiated azetine **216** giving double addition products.



Scheme 3.27 Synthesis of diazetine **223** via acetylated azetine **214r**



Scheme 3.28 Synthesis of diazetine **224** via benzoylated azetine **214s**

These observations were quite intriguing, illustrating the possibility of further transformations of these strained azacycles. However, as indicated by Table 3.4 (p. 111), a number of electrophile classes did not give the desired substituted azetines. This may be a result of further reactivity akin to the examples mentioned here, or that this methodology is not compatible in other ways with these electrophiles.

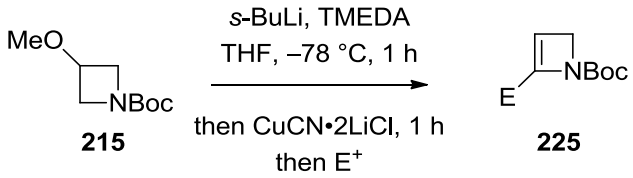
3.3.2.5 Copper modification

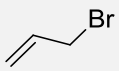
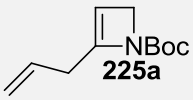
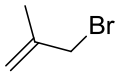
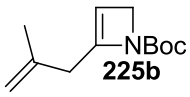
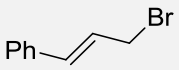
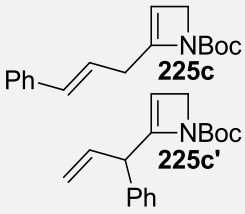
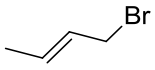
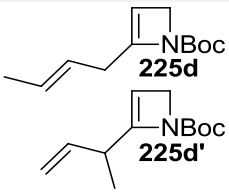
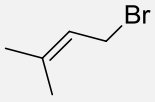
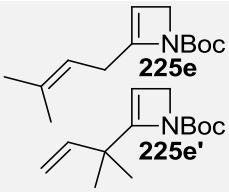
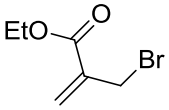
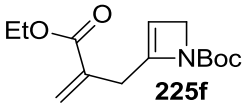
One significant class of electrophile that was problematic was simple alkyl halides. While reaction had been achieved with azetidine **122** (Section 2.2.4, p. 57), only with trapping MeI was any reactivity observed with azetines, and unfortunately in that case only very limited trapping (see Section 3.3.1.3, p. 102). Consequently, alternative methods were sought for installation of these groups. A potential solution to this issue could be transmetallation of the lithium species to copper, as carried out by Dieter [138] and more recently by Coldham. [139] In these examples, the lithiated species was transmetallated to copper by means of stirring with CuCN•2LiCl or CuI and trapped with vinyl ketones or allyl-halide type electrophiles. Encouraged by this reactivity, and the lack of allyl bromide reactivity under direct lithiation methodology (see Table 3.4, p. 111), attempted transmetallation experiments were carried with allyl bromide trapping.

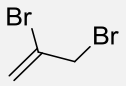
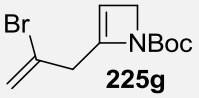
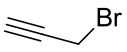
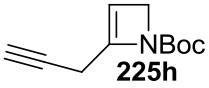
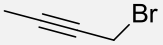
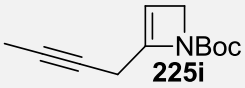
Unfortunately, attempts to trap with methyl vinyl ketone and 1-bromo-1-propene failed to give the corresponding azetines. However, it was delightful to observe that trapping of the copper species could be achieved with allyl bromide (Table 3.5, entry 1). It was noted in the simple allyl bromide cases (entries 1-2) that crude reaction mixtures indicated almost quantitative yields of allylated

azetines **225a-b** and, by ^{1}H NMR analysis, were remarkably clean. As a result, trapping with a range of allyl bromide type electrophiles was carried out (Table 3.5).

Table 3.5 Electrophile scope by transmetallation to copper



Entry no.	Electrophile	2-Substituted azetine 225	Yield
1		 **225a**	60%
2		 **225b**	55%
3		 **225c** **225c'**	50% **225c**:**225c′** 100:0 [a]
4		 **225d** **225d'**	78%[b] **225d**:**225d′** 47:53[a]
5		 **225e** **225e'**	64%[b] **225e**:**225e′** 61:39 [a]
6		 **225f**	15%

7		 **225g**	11%
8		 **225h**	37%
9		 **225i**	46%[b]

[a] Isolated ratio after chromatography. [b] Results obtained by M. Kazmi, University of Oxford, 2013; see Ref. 143 for full details.

Trapping was achieved with a range of allylic bromides (entries 1–7) as well as propargylic bromides (entries 8–9) in good to moderate yields. Unfortunately, while crude yields appeared to be almost quantitative with good purities by crude ^{1}H NMR analyses, these azetines appeared to be particularly susceptible to decomposition on silica, resulting in a drop of yields on purification.

Simple allylation and methylallylation (entries 1–2) proceeded satisfactorily giving allyl and methyl allyl azetines **225a** and **225b** in 60% and 55% yields, respectively. With unsymmetrical cinammyl bromide (entries 3), a mixture of S_N2- and S_N2'- derived azetines **225c** and **225c′** was observed. The crude S_N2:S_N2' ratio by ^{1}H NMR analysis was found to be 91:9 (by integration of peaks at 6.57 ppm (S_N2 (cinnamyl) adduct PhHC=CHCH$_2$) and 4.66 ppm (S_N2' (isocinnamyl) adduct H$_2$C=CHCH(Ph)). On purification, only the S_N2 product was isolated. Reaction with more structurally complex electrophiles ethyl 2-(bromomethyl)acrylate and 2,3-dibromopropene (entries 6–7) gave the corresponding substituted azetines **225f** and **225g** in 15% and 11% yields, respectively. Reaction with propargylic bromides (entries 8–9) proceeded to give exclusively the S_N2 product, giving propargyl azetine **225h** in 37% yield and methylpropargyl azetine **225i** in 46% yield. These two last results contrast with S_N2' regioselectivity giving allenes seen with *N*-Boc-α-aminoalkylcuprates.[139]

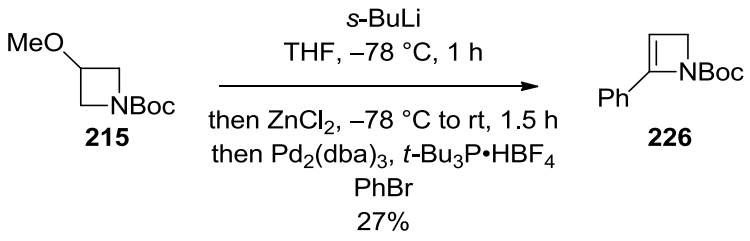
A colleague was also able to trap with unsymmetrical allylic bromides: crotyl bromide and prenyl bromide to give crotyl azetine **225d** and **225d′** in 78% yield (Table 3.5, entry 4) and prenyl azetine **225e** and **225e′** in 64% yield (Table 3.5, entry 5), respectively. Crude S_N2:S_N2' ratios by ^{1}H NMR

analysis were found to be 47:53 (by integration of peaks at 3.09 ppm (S_N2 (crotyl) adduct, $H_3CH_2C{=}CHC\underline{H}_2$) and 3.37 ppm ($S_N2'$ (isocrotyl) adduct, $H_2C{=}CHC\underline{H}(CH_3)$)) and 66:33 (by integration of peaks at 3.11 ppm (S_N2 (prenyl) adduct, $(CH_3)_2C{=}CHC\underline{H}_2$) and 3.12 ppm ($S_N2'$ (isoprenyl) adduct, ($H_2C{=}C\underline{H}C(CH_3)_2$)), respectively. After purification similar ratios were observed: 47:53 and 61:39, respectively.

While limitations were encountered by lack of alkyl halide reactivity with lithiated azetine **216**, it was very pleasing to find the scope of this methodology could be widened further to incorporate previously unreactive allylic bromides via copper transmetallation.

3.3.2.6 Further chemistries

Further cross-coupling experiments were attempted with the aim of widening the range of functional groups that could be installed on the azetine scaffold. However, attempted transmetallations to palladium in Suzuki cross-couplings with bromide **214n** ($PhB(OH)_2$, K_2CO_3, $Pd(OAc)_2$, *t*-Bu_3PHBF_4, THF, H_2O, rt)[140] and Stille couplings with stannane **214l** (PhI, $Pd(PPh_3)_2Cl_2$, CuI, DMF, rt)[141] did not prove viable, giving only complex mixtures of products. However, Negishi coupling, [67,142] achieved by transmetallation from lithium to zinc and then to palladium and coupled with bromobenzene showed phenyl azetine **226** was present in the crude ^{1}H NMR spectrum, and a colleague was able, after significant effort, to isolate phenyl azetine **226** in 27% yield (Scheme 3.29).

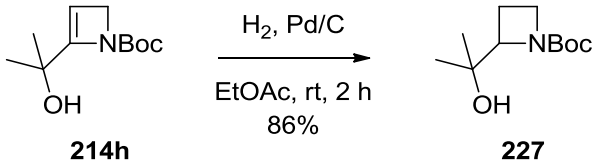


Scheme 3.29 Negishi cross-coupling to give phenyl azetine **226**[143]

Similar to allyl bromide azetines, phenyl azetine **226** also displayed a propensity to decompose on silica, however Et_3N pre-neutralisation of the silica allowed isolation of the azetine. As yet, it has not

been possible to further increase the yield of phenyl azetine **226**. These results represent early stage cross-coupling experiments, with scope for further experimentation.

Hydrogenation of azetines can also be achieved providing straightforward access to substituted *N*-Boc azetidines which cannot by synthesised by α-lithiation–electrophile trapping of *N*-Boc azetidine.[80] Acetone-trapped azetine **214h** gave azetidine alcohol **227** in 86% yield after treatment with Pd/C in EtOAc under a balloon of hydrogen (Scheme 3.30).[126]



214h **227**

Scheme 3.30 Hydrogenation of azetine **214h** to give azetidine **227**

Exposure of *t*-BuCHO azetine **214e** to hydrogenation conditions quickly formed isomerised product **219** (Scheme 3.25, p. 112), indicating again that slight acid traces may be responsible for the rearrangement.

3.4 Summary

While the synthesis of azetines can be difficult due to the highly strained nature of the ring, initial α-deprotonation of commercially available, or easily accessible, *N*-Boc-3-methoxyazetidine (**215**), tends to elimination to form *N*-Boc azetine **121** *in situ*, which can be further α-lithiated regioselectivity at the sp^2 centre, and trapped with a range of electrophiles, or transmetallated to copper and trapped with allylic and propargylic halides, providing a direct entry to 2-substituted azetines **214** and **225**.

3.5 Concluding remarks

These studies indicate that electrophile incorporation can be achieved on simple monocyclic azetines and suggest that further opportunities exist for azetine diversity generation using this strategy, with potential to access substituted azetidines through double bond manipulation.

4 Experimental

4.1 General details

All reactions requiring anhydrous conditions were conducted in flame-dried apparatus under an atmosphere of nitrogen or argon. CH_2Cl_2, MeOH, THF and Et_2O were degassed and dried over activated alumina under nitrogen.[144] TMEDA was distilled over CaH_2; aldehydes were freshly distilled over CaH_2 immediately prior to use; 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 from Sigma-Aldrich.

Thin layer chromatography (TLC) was carried out on aluminium-backed plates pre-coated with silica (0.2 mm, 60 F254 nm, Merck), which were visualised using ultraviolet light (λmax = 254 nm) and/or developed with basic potassium permanganate, PMA or ninhydrin dip solutions with heating. Flash column chromatography was carried out on BDH Si-gel 60 (43-63 μm), Merck Si-gel 60 (40-63 μm) or Sigma C_{18} Si-gel (40-75 μm) in the solvents systems indicated, applying head pressure by means of a low pressure nitrogen line (0.1–0.3 atm). Pet ether refers to the fraction of petroleum ether boiling between 30 °C – 40 °C. Due to varying acid-sensitivity, for the purification of most azetines, either Et_3N eluent-doping or pre-neutralising Si-gel with Et_3N [typically, by stirring in 10% Et_3N in pet ether (40 mL), decanting and eluting with pet ether (50 mL)] was carried out. C_{18} Si-gel was primed by eluting with MeCN, followed by 1:1 MeCN:H_2O before use.

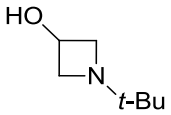
Melting points were obtained in capillary tubes using a Griffin melting point apparatus and are uncorrected. Infra-red spectra were recorded neat using a 1750 FTIR spectrophotometer. The intensity of the peaks are reported as s, m, w, br, denoting strong, medium, weak and broad, respectively. ^1H and ^{13}C NMR spectra were recorded at 25 °C in $CDCl_3$, unless otherwise stated, using DPX200, AVN400, DPX400, DQX400, and AVC500 spectrometers. ^{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), DMSO-D6 (^1H δ 2.50 ppm,

^{13}C δ 39.5 ppm, respectively), CD_3OD (^1H δ 3.31 ppm, ^{13}C δ 49.2 ppm, respectively), toluene-D8 (^1H δ 2.09 ppm, ^{13}C δ 20.4 ppm) or benzene-D6, (^1H δ 7.16 ppm, ^{13}C δ 128.4 ppm, respectively), as the internal standards on the δ scale. 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. Coupling constants *J* are reported to the nearest 0.1 Hz. High resolution mass spectra were obtained by field ionization (FI; Micromass GCT), or by electrospray ionisation (ESI; LCT Premier reflectron TOF and Brüker MicroTOF) 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.

To minimize decomposition, azetines were stored in solution (typically CH_2Cl_2) over K_2CO_3 in a freezer (~ –20 °C).

4.2 Experimental conditions

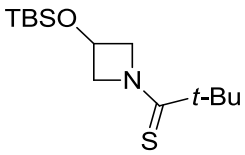
1-(*tert*-Butyl)azetidin-3-ol (**23**)[21]



To a stirred solution of *t*-BuNH$_2$ (**21**) (0.80 g, 11 mmol), in *i*-PrOH (11 mL) at rt was added epichlorohydrin (**22**) (1.10 g, 11.9 mmol) dropwise over 2 min. The reaction mixture was warmed to 30 °C and after 2 d the reaction mixture was concentrated to dryness under reduced pressure, then the residue purified (Si-gel, EtOAc/MeOH 9:1) to give a colourless syrup which solidified on standing. The intermediate was dissolved in MeCN (20 mL) and Et_3N (4.5 mL, 32 mmol) and heated to reflux. After 4 d, the reaction mixture was cooled to 0 °C, filtered to remove salts, and concentrated to dryness under reduced pressure. The residue was redissolved in CH_2Cl_2 (30 mL), washed with aq NaOH (20% w/v, 30 mL), dried (Na_2SO_4), and concentrated to dryness under reduced pressure to give azetidinol **23** as a pale orange syrup (0.82 g, 58%).

- R_f 0.11 (EtOAc/MeOH 4:1);
- **IR** (neat/cm^{-1}) 3115 br, 2964 m, 2861 w, 1478 w,1363 m, 1343 w, 1228 s, 1151 s, 1102 m, 982 w, 807 w, 734 m;
- **^{1}H NMR** (400 MHz, $CDCl_3$) 4.36 (1H, dd, *J* = 6.6, 5.8 Hz, C<u>H</u>OH), 3.42 (2H, td, *J* = 6.6, 1.8 Hz, NC<u>H</u>H), 3.02 (2H, td, *J* = 5.8, 1.8 Hz, NCH<u>H</u>) 0.95 (9H, s, C(CH$_3$)$_3$);
- **^{13}C NMR** (100 MHz, $CDCl_3$) 60.6 (CHOH), 56.1 (NCH_2), 51.8 (<u>C</u>(CH$_3$)$_3$), 24.2 (C(<u>C</u>H$_3$)$_3$);
- **LRMS** (ESI$^+$) 130.11 ([M+H]$^+$, 50%), 259.26 ([2M+H]$^+$, 65%), 520.43 ([4M+4H]$^+$, 90%).

1-(3-(*tert*-Butyldimethylsilyloxy)azetidin-1-yl)-2,2-dimethylpropane-1-thione (**98**)

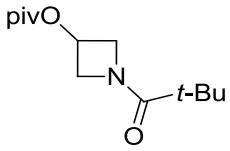


Experimental

To a stirred solution of silyloxyamide **110** (3.65 g, 13.4 mmol) in pyridine (40 mL) at rt was added P_2S_5 (3.70 g, 16.6 mmol). The reaction mixture was heated to 75 °C for 2 h, then after cooling to rt, was concentrated under reduced pressure to ~20 mL. The partially concentrated reaction mixture was poured onto aq HCl (1 M, 100 mL) and stirred vigorously for 10 min. The aq layer was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were washed with aq HCl (1 M, 100 mL), H_2O (100 mL), then brine (100 mL), dried (Na_2SO_4), and concentrated to dryness under reduced pressure. Purification (Si-gel, pet ether/Et_2O 1:0 → 9:1) gave silyloxythioamide **98** as a colourless solid (3.60 g, 93%).

- R_f 0.57 (pet ether/Et_2O 9:1);
- **mp** 56–58 °C;
- **IR** (neat/cm^{-1}) 2960 m, 2929 m, 2858 m, 1487 m, 1470 m, 1128 s, 841 s, 775 m;
- **^{1}H NMR** (400 MHz, $CDCl_3$) 4.67 (1H, ddd, *J* = 10.6, 6.6, 2.0, Hz, NC<u>H</u>H), 4.58 (1H, tt, *J* = 6.6, 4.3 Hz, OC<u>H</u>) , 4.48 (1H, ddd, *J* = 12.4, 6.6, 2.0 Hz, NC<u>H</u>H), 4.24 (1H, ddd, *J* = 10.6, 4.3, 2.0 Hz, NCH<u>H</u>), 4.07 (1H, ddd, *J* = 12.4, 4.3, 2.0 Hz, NCH<u>H</u>), 1.34 (9H, s, C(S)C(C<u>H</u>$_3$)$_3$), 0.89 (9H, s, Si(CH$_3$)$_2$C(C<u>H</u>$_3$)$_3$), 0.074 (3H, s, Si(C<u>H</u>$_3$)$_2$C(CH$_3$)$_3$), 0.066 (3H, s, Si(C<u>H</u>$_3$)$_2$C(CH$_3$)$_3$);
- **^{13}C NMR** (100 MHz, $CDCl_3$) 209.9 (C=S), 66.2 (NCH_2), 66.0 (NCH_2), 60.3 (CHO), 43.2 (C(S)<u>C</u>(CH$_3$)$_3$), 29.7 (C(<u>C</u>H$_3$)$_3$), 25.6 (C(<u>C</u>H$_3$)$_3$), 17.9 (Si(CH$_3$)$_2$<u>C</u>(CH$_3$)$_3$), –5.0 (Si(<u>C</u>H$_3$)$_2$C(CH$_3$)$_3$), -5.1 (Si(<u>C</u>H$_3$)$_2$C(CH$_3$)$_3$);
- **LRMS** (FI^+) 287.17 ($[M]^+$, 100%); **HRMS** (FI^+) calcd for $C_{14}H_{29}NOSSi$: 287.1739, found 287.1737.

1-Pivaloylazetidin-3-yl pivalate (**101**)



Method A

To a stirred slurry of azetidin-3-ol (**129**) (50 mg, 0.7 mmol) in CH_2Cl_2 (4 mL) at rt was added DMAP (33 mg, 0.3 mmol) and Et_3N (275 mg, 3 mmol). The reaction mixture was cooled to –78 °C and PivCl (200 mg, 1.6 mmol) added over 2 min. The reaction mixture was warmed slowly to rt and stirred overnight. After quenching with aq HCl (1 M, 25 mL) the aq layer was extracted with CH_2Cl_2 (2 x 15 mL). The combined organic layers were washed with H_2O (20 mL), dried (Na_2SO_4) and concentrated to dryness under reduced pressure. Purification (Si-gel, pet ether/EtOAc 8:2→7:3) gave amide-ester **101** as a colourless solid (42 mg, 24%).

Method B

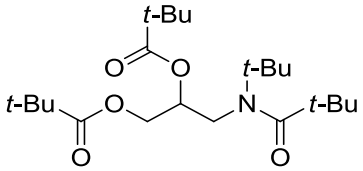
To a stirred slurry of azetidin-3-ol hydrochloride (**131**) (50 mg, 0.5 mmol) in CH_2Cl_2 (3 mL) at rt was added DMAP (22 mg, 0.2 mmol) and Et_3N (184 mg, 2 mmol). The reaction mixture was cooled to –78 °C and pivCl (133 mg, 1.1 mmol) added over 2 min. The reaction mixture was warmed slowly to rt and stirred overnight. The reaction mixture was concentrated to dryness under reduced pressure and purified (Si-gel, pet ether/EtOAc 8:2 →7:3) gave amide-ester **101** as a colourless solid (61 mg, 53%).

Method C

A suspension of azetidin-3-ol hydrochloride (**131**) (250 mg, 2.28 mmol) in py (3 mL) was heated to 50 °C for 5 min, then cooled to rt. DMAP (56 mg, 0.46 mmol), and pivCl (700 µL, 5.70 mmol) were added, after 16 h the reaction mixture was diluted with EtOAc (20 mL) and washed sequentially with aq HCl (2 M, 40 mL), water (20 mL) and brine (20 mL), dried (Na_2SO_4) and concentrated to dryness under reduced pressure. Purification (Si-gel, heptane/EtOAc 1:0→2:3) gave amide-ester **101** as a colourless syrup which solidified on standing (512 mg, 93%).

- R_f 0.61 (pet ether/EtOAc 2:3);
- **mp** 45–46 °C;
- **IR** (neat/cm^{-1}) 2962 m, 1733 m, 1618 m, 1422 w, 1283 w, 1144 s;
- **^{1}H NMR** (400 MHz, $CDCl_3$) 5.11-5.06 (1H, m, CHO), 4.61-3.94 (4H, m, NCH_2), 1.18 (9H, s, $C(CH_3)_3$), 1.15 (9H, s, $C(CH_3)_3$);
- **^{13}C NMR** (100 MHz, $CDCl_3$) 178.0 (C=O), 177.7 (C=O), 63.4 (CHO), 59.9 (NCH_2), 55.6 (NCH_2), 38.5 ($\underline{C}(CH_3)_3$), 38.4 ($\underline{C}(CH_3)_3$), 27.0 ($C(\underline{C}H_3)_3$), 26.9 ($C(\underline{C}H_3)_3$);
- **LRMS** (ESI^+) 505.34 ($[2M+Na]^+$, 100%); **HRMS** (ESI^+) calcd for $C_{13}H_{24}NO_3$: 242.1751, found 242.1743.

3-(*N*-(*tert*-butyl)pivalamido)propane-1,2-diyl bis(2,2-dimethylpropanoate) (**105**)

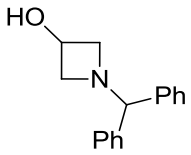


To piv_2O (790 μL, 3.87 mmol) at 0 °C was added azetidine **23** (100 mg, 0.77 mmol) followed by dropwise addition of BF_3•Et_2O (10 μL). The reaction mixture was heated to 115 °C for 24 h, after which the reaction mixture was cooled to rt. Purification of the neat reaction mixture (Si-gel, pet ether/EtOAc 1:0 → 4:1) gave acyclic ester amide **105** as a colourless syrup (229 mg, 87%).

- R_f 0.26 (pet ether/Et_2O 3:2);
- **IR** (neat/cm^{-1}) 2968 w, 2932 w, 2872 w, 1732 s, 1480 m, 1460 w, 1398 w, 1364 w, 1281 m, 1143 s, 1033 w, 938 w, 866 w, 769 w;
- **^{1}H NMR** (400 MHz, $CDCl_3$) 5.07 (1H, qd, *J* = 5.6, 3.4 Hz, CHO), 4.35 (1H, dd, *J* = 12.0, 3.4 Hz, OC$\underline{H}$H), 4.19 (1H, dd, *J* = 12.0, 5.6 Hz, OCH$\underline{H}$), 2.82 (2H, d, *J* = 5.6 Hz, NCH_2), 1.20 (9H, s, $C(CH_3)_3$), 1.19 (18H, s, 2 x $C(CH_3)_3$), 1.11 (9H, s, $C(CH_3)_3$);
- **^{13}C NMR** (100 MHz, $CDCl_3$) 183.7 (C=O), 178.0 (C=O), 177.7 (C=O), 71.4 (CHO), 63.4 (OCH_2), 51.1 ($\underline{C}(CH_3)_3$), 42.4 (NCH_2), 38.8 ($C(O)\underline{C}(CH_3)_3$), 38.8 ($C(O)\underline{C}(CH_3)_3$), 38.6 ($C(O)\underline{C}(CH_3)_3$), 28.4 ($C(CH_3)_3$), 27.2 ($C(O)C(\underline{C}H_3)_3$), 27.1 (2 x $C(O)C(\underline{C}H_3)_3$);

- **LRMS** (ESI$^+$) 316.24 ([M-piv+2H]$^+$, 100%), 529.46 (60%), 803.59 (50%); **HRMS** (ESI$^+$) calcd for $C_{17}H_{34}NO_4$: 316.2482, found 316.2476.

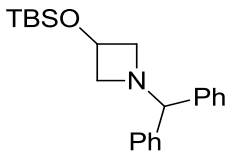
1-Benzhydrylazetidin-3-ol (**106**)[23]



To a stirred solution of Ph_2CHNH_2 (**18**) (94.0 mL, 0.55 mol) in *i*-PrOH (450 mL) at rt was added epichlorohydrin (**22**) (51.2 mL, 0.65 mol) dropwise over 2 min. The reaction mixture was warmed to 30 °C and after 2 d, the reaction mixture was concentrated to dryness under reduced pressure. The residue was redissolved in MeCN (288 mL) and Et_3N (304 mL 2.18 mol) and heated to reflux. After 2 d, the reaction mixture was concentrated to dryness under reduced pressure. The crude residue was dissolved in EtOAc (200 mL) and precipitated with aq HCl (2 M, 200 mL). The solid was filtered, suspended in EtOAc (200 mL) and neutralised with aq NaOH (2 M, 200 mL). The organic layer was washed with H_2O (200 mL), brine (200 mL), dried (Na_2SO_4) and concentrated to dryness under reduced pressure to give azetidinol **106** as a colourless solid (106.1 g, 81%).

- R_f 0.32 (pet ether/EtOAc 3:2);
- **mp** 78–80 °C;
- **IR** (neat/cm^{-1}) 3085 br, 2938 w, 2848 w, 1556 w, 1492 m, 1351 w, 1205 w, 1185 w, 1162 w, 1093 w, 1070 w, 1049 w, 1029 w, 983 w, 846 w, 829 w, 763 m, 743 w, 701s;
- **^{1}H NMR** (400 MHz, $CDCl_3$) 7.41-7.19 (10H, m, Ar), 4.50-4.43 (1H, m, C<u>H</u>OH), 4.36 (1H, s, C<u>H</u>Ph_2), 3.55 (2H, td, *J* = 7.1, 2.0 Hz, NC<u>H</u>H), 2.91 (2H, td, *J* = 7.1, 2.0 Hz, NCH<u>H</u>), 2.62 (1H, br, CHO<u>H</u>);
- **^{13}C NMR** (100 MHz, $CDCl_3$) 142.0 (Ar), 128.5 (Ar), 127.4 (Ar), 127.2 (Ar), 78.5 (N<u>C</u>HPh_2), 63.4 (NCH_2), 62.1 (CHOH);
- **LRMS** (ESI$^+$) 240.15 ([M+H]$^+$, 93%).

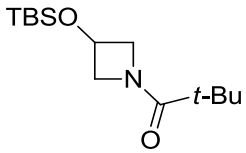
3-((*tert*-Butyldimethylsilyl)oxy)-1-(diphenylmethyl)azetidine (**107**)



To a stirred solution of *N*-benzhydrylazetidin-3-ol (**106**) (3.60 g, 15.0 mmol) and TBSCl (2.73 g, 18.1 mmol) in CH_2Cl_2 (30 mL) at rt was added imidazole (1.23 g, 18.1 mmol). After 30 min, the reaction mixture was filtered, and the filter cake washed with CH_2Cl_2 (10 mL). The filtrate was concentrated to dryness under reduced pressure. Purification (Si-gel, pet ether/Et_2O 1:0 → 9:1) gave silyl ether **107**[145] as an off-white solid (5.30 g, quant).

- ***R*$_f$** 0.83 (pet ether/EtOAc 3:2);
- **mp** 45–47 °C;
- **IR** (neat/cm^{-1}) 2929 w, 2854 w, 2832 w, 1451 w, 1307 w, 1204 m, 1204 m, 1182 m, 1160 w, 880 m, 836 m, 780 m, 703 m;
- **^{1}H NMR** (400 MHz, $CDCl_3$) 7.42-7.18 (10H, m, Ar), 4.47 (1H, quin, *J* = 6.1 Hz, CHO), 4.37 (1H, s, C<u>H</u>Ph_2), 3.55 (1H, dd, *J* = 6.1, 2.0 Hz, NC<u>H</u>H), 3.53 (1H, dd, *J* = 6.1, 2.0 Hz, NC<u>H</u>H), 2.84 (1H, dd, *J* =6.3, 2.0 Hz , NCH<u>H</u>), 2.82 (1H, dd, *J* = 6.3, 2.0 Hz, NCH<u>H</u>), 0.87 (9H, s, $Si(CH_3)_2C(C\underline{H}_3)_3$), 0.03 (6H, s, $Si(C\underline{H}_3)_2C(CH_3)_3$);
- **^{13}C NMR** (100 MHz, $CDCl_3$) 142.3 (Ar), 128.4 (Ar), 127.4 (Ar), 127.0 (Ar), 78.6 (N<u>C</u>HPh_2), 63.8 (NCH_2), 61.8 (CHO), 25.8 ($Si(CH_3)_2C(\underline{C}H_3)_3$), 18.0 ($Si(CH_3)_2\underline{C}(CH_3)_3$), –5.0 ($Si(\underline{C}H_3)_2C(CH_3)_3$);
- **LRMS** (ESI$^+$) 354.20 ([M+H]$^+$, 80%); **HRMS** (ESI$^+$) calcd for $C_{22}H_{32}NOSi$: 354.2248, found 354.2236.

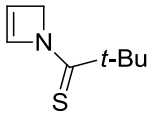
1-(3-((*tert*-Butyldimethylsilyl)oxy)azetidin-1-yl)-2,2-dimethylpropan-1-one (**110**)



To a stirred solution of silyl ether **107** (5.30 g, 15.0 mmol) in MeOH (100 mL) at rt was added ammonium formate (4.73 g, 75.0 mmol) and 10% wt. Pd/C (530 mg). The reaction mixture was heated to reflux. After 2 h, the reaction mixture was cooled to rt, filtered through a pad of celite, then concentrated to dryness under reduced pressure. The crude residue was dissolved in CH_2Cl_2 (75 mL). To the resulting solution was added DMAP (670 mg, 5.5 mmol) and Et_3N (4.2 mL, 30.1 mmol). The reaction mixture was cooled to 0 °C and pivCl (2.2 mL, 17.9 mmol) added dropwise over 5 min. The reaction mixture was warmed slowly to rt and stirred overnight. After quenching with aq HCl (1 M, 75 mL) the aq layer was extracted with CH_2Cl_2 (2 x 50 mL). The combined organic layers were washed with H_2O (75 mL), then brine (75 mL), dried (Na_2SO_4), and concentrated to dryness under reduced pressure. Purification (Si-gel, pet ether/EtOAc 19:1 → 4:1) gave silyloxyamide **110** as a colourless solid (3.65 g, 90%).

- R_f 0.36 (pet ether/Et_2O 3:2);
- **mp** 32–34 °C;
- **IR** (neat/cm^{-1}) 2956 m, 2931 m, 2858 w, 1628 s, 1415 m, 1131 m, 988 m, 836 m, 777 m;
- **^{1}H NMR** (500 MHz, T = 363 K, toluene-D8) 4.21 (1H, m, CHO), 4.05 (2H, dd, *J* = 9.1, 6.9 Hz, NC<u>H</u>H), 3.84 (2H, dd, *J* = 9.1, 4.1 Hz, NCH<u>H</u>), 1.08 (9H, s, C(O)C(CH_3)$_3$), 0.84 (9H, s, Si(CH_3)$_2$C(C<u>H</u>$_3$)$_3$), -0.07 (6H, s, Si(C<u>H</u>$_3$)$_2$C(CH_3)$_3$);
- **^{13}C NMR** (125 MHz, T = 363 K, toluene-D8) 177.1 (C=O), 62.7 (CHO), 61.4 (NCH_2), 38.9 (C(O)<u>C</u>(CH_3)$_3$), 27.7 (C(<u>C</u>H$_3$)$_3$), 26.0 (C(<u>C</u>H$_3$)$_3$), 18.2 (Si(CH_3)$_2$<u>C</u>(CH_3)$_3$), –4.8 (Si(<u>C</u>H$_3$)$_2$C(CH_3)$_3$);
- **LRMS** (ESI^+) 272.2 ($[M+H]^+$, 100%); **HRMS** (ESI^+) calcd for $C_{14}H_{30}NO_2Si$: 272.2040, found 272.2039.

1-(2-Azetinyl)-2,2-dimethylpropane-1-thione (**113**)



Method A

To a stirred solution of silyloxythioamide **98** (100 mg, 0.35 mmol) in THF (1 mL), at –78 °C was added TMEDA (315 μL, 2.10 mmol). *s*-BuLi (777 μL, 1.35 M in cyclohexane/hexane (92/8), 1.05 mmol) was added dropwise to the reaction mixture over 5 min resulting in a characteristic deep yellow colour. After 30 min, MeOH (71 μL, 1.75 mmol) was added and the reaction mixture stirred for 10 min. The cooling bath was removed and the reaction mixture was stirred for another 10 min, quenched with aq HCl (1 M, 5 mL) and extracted with EtOAc (3 x 5 mL). The combined organic layers were washed with H_2O (5 mL) then brine (5 mL), dried (Na_2SO_4), and concentrated to dryness under reduced pressure. Purification (Si-gel, pet ether/Et_2O 9:1) gave azetine **113** as a yellow syrup (53 mg, 98%).

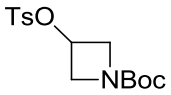
Method B

To a stirred solution of methoxyazetidine **208** (267 mg, 1.43 mmol) in THF (5 mL), at –78 °C was added TMEDA (1.28 mL, 8.55 mmol). *s*-BuLi (3.12 mL, 1.35 M in cyclohexane/hexane (92/8), 4.28 mmol) was added dropwise to the reaction mixture over 1 min resulting in a characteristic deep yellow colour. After 1 h, MeOH (154 μL, 4.28 mmol) was added and the reaction mixture stirred for 10 min. The cooling bath was removed and the reaction mixture was stirred for another 10 min, quenched with aq HCl (1 M, 5 mL) and extracted with EtOAc (3 x 5 mL). The combined organic layers were washed with H_2O (5 mL) then brine (5 mL), dried (Na_2SO_4), and concentrated to dryness under reduced pressure. Purification (Si-gel, pet ether/Et_2O 9:1) gave azetine **113** as a yellow syrup (149 mg, 68%).

- $\boldsymbol{R_f}$ 0.30 (pet ether/Et_2O 9:1);
- **IR** (neat/cm^{-1}) 2968 w, 1456 s, 1364 w, 1137 m, 935 m, 689 m;

- **^{1}H NMR** (400 MHz, $CDCl_3$, 3:1 mixture of rotamers) Major rotamer: 6.98 (1H, s, NCH), 6.04 (1H, s, NCH=C<u>H</u>), 4.67 (2H, s, NCH_2), 1.38 (9H, s, $C(CH_3)_3$); Minor rotamer: 7.35 (1H, s, NCH), 6.14 (1H, s, NCH=C<u>H</u>), 4.86 (2H, s, NCH_2), 1.42 (3H, s, $C(CH_3)_3$);
- **^{13}C NMR** (100 MHz, $CDCl_3$) Major rotamer: 203.8 (C=S), 139.4 (NCH), 118.0 (NCH=<u>C</u>H), 62.0 (NCH_2), 43.0 ($\underline{C}(CH_3)_3$), 30.3 ($C(\underline{C}H_3)_3$); Minor rotamer: 203.8 (C=S), 141.7 (NCH), 118.7 (NCH=<u>C</u>H), 63.9 (NCH_2), 43.0 ($\underline{C}(CH_3)_3$), 31.0 ($C(\underline{C}H_3)_3$);
- **LRMS** (FI^+) 155.08 ($[M]^+$,100%); **HRMS** (FI^+) calcd for $C_8H_{13}NS$: 155.0769, found 155.0767.

***tert*-Butyl 3-(tosyloxy)azetidine-1-carboxylate** (**120**)



To a stirred solution of azetidinol **132** (4.50 g, 26.0 mmol) and DMAP (317 mg, 2.6 mmol) in CH_2Cl_2 (60 mL) was added Et_3N (4.0 mL, 28.6 mmol) and TsCl (5.20 g, 27.3 mmol). After 1 h, the reaction mixture was washed with aq HCl (2 M, 60 mL) and extracted with CH_2Cl_2 (2 x 20 mL). The combined organic layers were washed with brine (40 mL), dried (Na_2SO_4), and concentrated to dryness under reduced pressure. Purification (Si-gel, pet ether/EtOAc 1:0→7:3) gave tosyl azetidine **120**[85] as a colourless solid (5.00 g 59%).

- R_f 0.75 (pet ether/EtOAc 3:2);
- **mp** 47-50 °C;
- **IR** (neat/cm^{-1}) 2977 w, 1700 s, 1598 w, 1393 m, 1365 s, 1299 w, 1255 w, 1177 m, 1150 s, 1090 w, 1019 s, 934 w, 865 m, 812 m, 773 w, 740 w, 661 m;
- **^{1}H NMR** (400 MHz, $CDCl_3$) 7.79 (2H, d, J = 8.3 Hz, Ar), 7.37 (2H, d, J = 8.3 Hz, Ar), 5.01 (1H, tt, J = 6.6, 4.4 Hz, CHO), 4.10 (1H, dd, J = 10.4, 6.6 Hz, $NCH_{cis}\underline{H}_{trans}$), 3.93 (2H, dd, J = 10.4, 4.4 Hz, $NC\underline{H}_{cis}H_{trans}$), 2.47 (3H, s, CH_3), 1.41 (9H, s, $C(CH_3)_3$);
- **^{13}C NMR** (100 MHz, $CDCl_3$) 155.8 (C=O), 145.5 (Ar), 132.9 (Ar), 130.1 (Ar), 127.9 (Ar), 80.2 ($\underline{C}(CH_3)_3$), 67.7 (CHO), 56.2 (NCH_2), 28.2 ($C(\underline{C}H_3)_3$), 21.7 (CH_3);

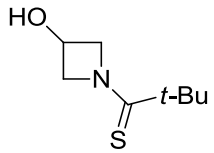
- **LRMS** (ESI^+) 350.1 ($[M+Na]^+$,75 %), 272.1 (100%); **HRMS** (ESI^+) calcd for $C_{15}H_{21}NNaO_5S$: 350.1033, found 350.1027.

***tert*-Butyl azete-1(2*H*)-carboxylate** (**121**)

To a solution of *t*-BuOK (440 mg, 3.92 mmol) in DMSO (5 mL) was added dropwise *N*-Boc-3-chloroazetidine **213** (500 mg, 2.61 mmol) in THF (5 mL). The reaction mixture was then heated to 70 °C for 17 h, then cooled to rt. Water (10 mL) was added and the reaction mixture extracted with Et_2O (2 x 10 mL). The combined organic layers were concentrated to dryness under reduced pressure. Purification (Si-gel, pet ether/EtOAc 2:3) gave azetine **121**[85] as a colourless liquid (266 mg, 66%).

- R_f 0.38 (pet ether/Et_2O 9:1);
- **IR** (neat/cm^{-1}) 3102 w, 2978 w, 1701 s, 1391 m, 1147 s, 1058 w, 955 w, 908 w, 857 w, 763 m, 675 m;
- **^{1}H NMR** (400 MHz, $CDCl_3$ over K_2CO_3) 6.56 (1H, s, NCH), 5.52-5.51 (1H, m, NCH=C<u>H</u>), 4.38-4.38 (2H, m, NCH_2), 1.46 (9H, s, $C(CH_3)_3$);
- **^{13}C NMR** (100 MHz, $CDCl_3$ over K_2CO_3) 151.8 (C=O), 138.5 (NCH), 111.7 (NCH=<u>C</u>H), 80.1 (<u>C</u>$(CH_3)_3$), 58.2 (NCH_2), 28.3 ($C(\underline{C}H_3)_3$);
- **LRMS** (FI) 155.09 ($[M]^+$, 100%); **HRMS** (FI) calcd for $C_8H_{13}NO_2$: 155.0946, found 155.0944.

1-(3-Hydroxyazetidin-1-yl)-2,2-dimethylpropane-1-thione (**122**)



Method A

To a stirred solution of silyl thioamide **98** (4.2 g, 14 mmol) in THF (100 mL) at rt was added TBAF (16 mL, 1 M in THF, 16 mmol) dropwise over 2 min. After 2 h, the reaction mixture was poured onto sat. aq NH_4Cl (250 mL) and extracted with EtOAc (3 x 50 mL). The combined organic layers were dried (Na_2SO_4), and concentrated to dryness under reduced pressure. Purification (Si-gel, pet ether/EtOAc 1:0 →2:3) gave azetidinol **122** as a colourless syrup which solidified on standing (2.3 g, 90%).

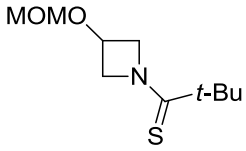
Method B

To a solution of thioamide ester **138** (15.0 g, 58 mmol) in MeOH (20 mL) was added NaOMe (26 mL, 25% wt in MeOH, 117 mmol). After 1 h, the reaction mixture was concentrated to dryness under reduced pressure and the crude residue purified (Si-gel, heptane/EtOAc 1:0→2:3) to give azetidinol **122** as a colourless syrup which solidified on standing (9.6 g, 95%).

- $\boldsymbol{R_f}$ 0.27 (pet ether/EtOAc 3:2);
- **mp** 54-56 °C;
- **IR** (neat/cm^{-1}) 3363 br, 2968 w, 1471 s, 1447 s, 1137 m, 1007 m, 730 s;
- **^{1}H NMR** (400 MHz, $CDCl_3$) 4.69 (1H, ddd, *J* = 11.0, 6.6, 2.0 Hz, NC<u>H</u>H), 4.63 (1H, tt, *J* = 6.6, 3.9 Hz, C<u>H</u>OH), 4.47 (1H, ddd, *J* = 13.1, 6.6, 2.3 Hz, NC<u>H</u>H), 4.31 (1H, ddd, *J* = 11.0, 3.9, 2.3 Hz, NCH<u>H</u>), 4.09 (1H, ddd, *J* = 13.1, 3.9, 2.0 Hz, NCH<u>H</u>), 3.26 (1H, br, OH), 1.32 (9H, s, $C(CH_3)_3$);
- **^{13}C NMR** (100 MHz, $CDCl_3$) 210.0 (<u>C</u>(S)$C(CH_3)_3$), 65.8 (NCH_2), 65.5 (NCH_2), 59.9 (CHOH), 43.2 (<u>C</u>$(CH_3)_3$), 29.6 (C(<u>C</u>$H_3)_3$);

- **LRMS** (FI^+) 173.09 ($[M]^+$, 100%); **HRMS** (FI^+) calcd for $C_8H_{15}NOS$: 173.0874, found 173.0879.

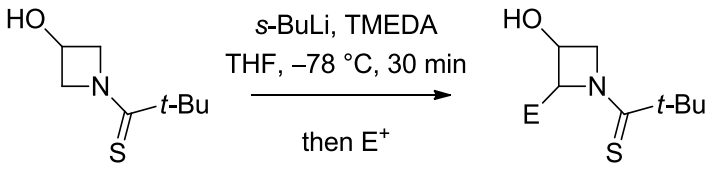
1-(3-(Methoxymethoxy)azetidin-1-yl)-2,2-dimethylpropane-1-thione (**123**)



To a stirred solution of azetidinol **122** (100 mg, 0.6 mmol) in CH_2Cl_2 (20 mL) at rt was added MOMI (147 μL, 1.7 mmol) and DIPEA (1 mL, 6 mmol). After 4 h, the reaction mixture was poured onto aq HCl (1 M, 5 mL) and extracted with CH_2Cl_2 (2 x 5 mL). The combined organic layers were washed with H_2O (5 mL), brine (5 mL), dried (Na_2SO_4), and concentrated to dryness under reduced pressure. Purification (Si-gel, pet ether/EtOAc 1:0 → 4:1) gave MOM–protected azetidinol **123** as a clear syrup (47 mg, 34%).

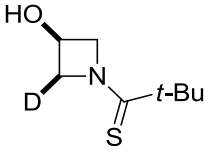
- R_f 0.59 (pet ether/EtOAc 3:2);
- **IR** (neat/cm^{-1}) 2928 w, 2855 w, 1628 w, 1496 w, 1454 m, 1419 s, 1373 w, 1324 w, 1226 w, 1187 w, 1153 m, 1138 m, 1118 w, 1069 m, 1022 m, 986 s, 939 m;
- **^{1}H NMR** (400 MHz, $CDCl_3$) 4.68 (1H, ddd, *J* = 10.9, 6.2, 2.5, NC<u>H</u>H), 4.65 (1H, s, OC<u>H</u>HOCH$_3$), 4.64 (1H, s, OCH<u>H</u>OCH$_3$), 4.49-4.39 (2H, m, NC<u>H</u>H, CHO), 4.33 (1H, ddd, *J* = 10.9, 3.5, 2.0, NCH<u>H</u>), 4.16 (1H, ddd, *J* = 12.1, 3.5, 2.0 Hz, NCH<u>H</u>), 3.38 (3H, s, OCH$_3$), 1.32 (9H, s, C(CH$_3$)$_3$);
- **^{13}C NMR** (100 MHz, $CDCl_3$) 210.1 (C=S), 96.2 (O<u>C</u>H$_2$OCH$_3$), 64.9 (CHO), 63.9 (NCH$_2$), 63.5 (NCH$_2$), 56.0 (OCH$_3$), 43.2 (<u>C</u>(CH$_3$)$_3$), 29.8 (C(<u>C</u>H$_3$)$_3$);
- **LRMS** (ESI^+) 218.13 ($[M+H]^+$, 100%); **HRMS** (ESI^+) calcd for $C_{10}H_{20}NO2S$: 218.1209, found 218.1210.

General Procedure A: α-deprotonation–electrophile trapping of azetidinol 122.



To a stirred solution of azetidinol **122** (100 mg, 0.58 mmol) in THF (2 mL), at –78 °C was added TMEDA (519 μL, 3.46 mmol). *s*-BuLi (1.24 mL 1.40 M in cyclohexane/hexane (92/8), 1.73 mmol) was added dropwise to the reaction mixture over 5 min, resulting in a characteristic deep yellow colour. After 30 min, the electrophile was added and the reaction mixture stirred for 30 min. The cooling bath was removed and the reaction mixture was stirred for another 30 min, quenched with aq HCl (1 M, 5 mL) and extracted with EtOAc (3 x 5 mL). The combined organic layers were washed with H_2O (5 mL) then brine (5 mL), dried (Na_2SO_4), and concentrated to dryness under reduced pressure.

1-(2-Deutero-3-(hydroxy)-azetidin-1-yl)-2,2-dimethylpropane-1-thione (*cis*-**126a**)



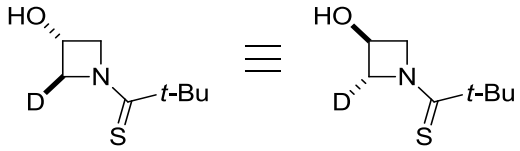
CD_3OD (70 μL, 1.7 mmol) was used following General Procedure A. Purification (Si-gel, pet ether/EtOAc 3:2) gave the deuterated azetidinol *cis*-**126a** as a colourless syrup which solidified on standing (92 mg, 91%, 100% D, 90:10 cis:trans, dr determined by integration at δ_H 4.67 + 4.42 and 4.28 + 4.04).

- ***R*$_f$** 0.27 (pet ether/EtOAc 3:2);
- **mp** 54-56 °C;
- **IR** (neat/cm^{-1}) 3361 br, 2966 m, 1467 s, 1395 w, 1134 s, 1006 m;
- **^{1}H NMR** (400 MHz, $CDCl_3$) 4.73 (0.95H, dd, *J* = 11.0, 6.6 Hz, $NCH_{cis}\underline{H}_{trans}$ and $NCD_{cis}\underline{H}_{trans}$), 4.65 (1H, td, *J* = 6.6, 3.9 Hz, C<u>H</u>OH), 4.48 (0.95H, dd, *J* = 13.1, 6.6 Hz,

$NCH_{cis}\underline{H}_{trans}$ and $NCD_{cis}\underline{H}_{trans}$), 4.34 (0.53H, ddd, *J* = 11.0, 3.9, 2.3 Hz, $NC\underline{H}_{cis}H_{trans}$), 4.10 (0.57H, ddd, *J* = 13.1, 3.9, 2.3 Hz, $NC\underline{H}_{cis}H_{trans}$), 3.81 (1H, br, OH), 1.35 (9H, s, $C(CH_3)_3$);

- **^{13}C NMR** (100 MHz, $CDCl_3$) 209.9 (C=S), 65.8 (NCH_2), 65.5 (T, *J* = 23 Hz, NCHD), 65.4 (NCH_2), 65.1 (T, *J* = 23 Hz, NCHD), 59.6 (CHOH), 59.6 (t, *J* = 7 Hz, CHOH), 43.1 ($\underline{C}(CH_3)_3$), 29.5 ($C(\underline{C}H_3)_3$);
- **LRMS** (ESI^+) 175.11 ($[M+H]^+$, 85%); **HRMS** (ESI^+) calcd for $C_8H_{15}DNOS$: 175.1010, found 175.1011.

1-(2-Deutero-3-(hydroxy)-azetidin-1-yl)-2,2-dimethylpropane-1-thione (*trans*-**126a**)

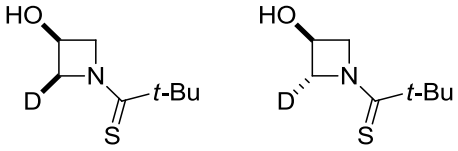


To a stirred solution of acetate **142** (350 mg, 1.62 mmol) in MeOH (10 mL) was added NaOMe (15 drops, 30% in MeOH). After 10 min, the reaction mixture was concentrated to dryness under reduced pressure. The residue was washed with aq HCl (1 M, 10 mL) and extracted with EtOAc (20 mL), the organic layer was washed with H_2O (10 mL), then brine (10 mL), dried (Na_2SO_4), filtered and concentrated to dryness under reduced pressure. Purification (Si-gel, pet ether/EtOAc 3:2→2:3) gave azetidin-3-ol *trans*-**126a** as a colourless syrup which solidified on standing (186 mg, 66%, 100% D, 88:12 trans:cis, dr determined by integration of δ_H 4.70 + 4.48 and 4.32 + 4.10).

- ***R*$_f$** 0.27 (pet ether/EtOAc 3:2);
- **mp** 54-56 °C;
- **IR** (neat/cm^{-1}) 3359 br, 2968 w, 1469 s, 1364 w, 1255 w, 1138 , 1005 m, 951 w, 730 s;
- **^{1}H NMR** (400 MHz, $CDCl_3$) 4.70 (0.56 H, ddd, *J* = 11.1, 6.6, 1.5 Hz, $NCH_{cis}\underline{H}_{trans}$), 4.65 (1H, dt, *J* = 6.6, 3.9 Hz, C<u>H</u>OH), 4.48 (0.56H, ddd, *J* = 12.9, 6.6, 1.5 Hz, $NCH_{cis}\underline{H}_{trans}$), 4.32 (0.94H, dd, *J* = 11.1, 3.9 Hz, $NC\underline{H}_{cis}H_{trans}$ and $NC\underline{H}_{cis}D_{trans}$), 4.10 (0.94H, dd, *J* = 12.9, 3.9 Hz, $NC\underline{H}_{cis}H_{trans}$ and $NC\underline{H}_{cis}D_{trans}$), 3.14 (1H, br, OH), 1.33 (9H, s, $C(CH_3)_3$);

- **^{13}C NMR** (100 MHz, $CDCl_3$) 210.0 (C=S), 65.8 (NCH_2), 65.5 (T, *J* = 23 Hz, NCHD), 65.5 (NCH_2), 65.2 (T, *J* = 23 Hz, NCHD), 59.9-59.7 (m, CHOH), 43.2 ($\underline{C}(CH_3)_3$), 29.6 ($C(\underline{C}H_3)_3$);
- **LRMS** (ESI^+) 175.2 ($[M+H]^+$, 100%); **HRMS** (ESI^+) calcd for $C_8H_{14}DNNaOS$:197.0829, found 197.0825.

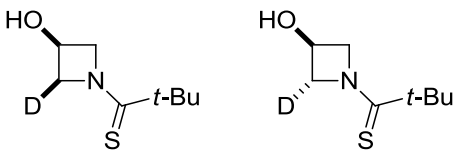
Lithiation–protonation of *cis*-126a: 1-(2-Deutero-3-hydroxyazetidin-1-yl)-2,2-dimethylpropane-1-thione (**126a**)



To a stirred solution of azetidinol *cis*-**126a** (50 mg, 0.29 mmol) in THF (1 mL), at –78 °C was added TMEDA (261 μL, 1.74 mmol). *s*-BuLi (614 μL, 1.40 M in cyclohexane/hexane (92/8), 0.86 mmol) was added very slow dropwise to the reaction mixture over 5 min. After 30 min, MeOH (58 μL, 1.43 mmol) was added and the reaction mixture stirred for 10 min. The cold bath was removed and the reaction mixture was stirred for another 10 min, quenched with aq HCl (1 M, 5 mL) and extracted with EtOAc (3 x 5 mL). The combined organic layers were washed with H_2O (5 mL) then brine (5 mL), dried (Na_2SO_4), and concentrated to dryness under reduced pressure to give azetidinol **126a** as a pale yellow syrup (50 mg, quant, 100% D, 64:36 cis:trans, dr determined by integration of δ_H 4.67 + 4.42 and 4.28 + 4.04).

Characterization data the same as *cis*-**126a**, with the exception of two additional peaks in the ^{13}C NMR spectrum: 65.5 (T, *J* = 23 Hz, NCHD), 65.2 (T, *J* = 23 Hz, NCHD).

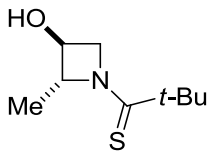
Lithiation–protonation of *trans*-126a: 1-(2-Deutero-3-hydroxyazetidin-1-yl)-2,2-dimethylpropane -1-thione (*trans*-**126a**)



To a stirred solution of azetidinol *trans*-**126a** (50 mg, 0.29 mmol) in THF (1 mL), at –78 °C was added TMEDA (261 μL, 1.74 mmol). *s*-BuLi (614 μL, 1.40 M in cyclohexane/hexane (92/8), 0.86 mmol) was added very slow dropwise to the reaction mixture over 5 min. After 30 min, MeOH (52 μL, 1.45 mmol) was added and the reaction mixture stirred for 10 min. The cold bath was removed and the reaction mixture was stirred for another 10 min, quenched with aq HCl (1 M, 5 mL) and extracted with EtOAc (3 x 5 mL). The combined organic layers were washed with H_2O (5 mL) then brine (5 mL), dried (Na_2SO_4), and concentrated to dryness under reduced pressure to give azetidinol *trans*-**126a** as a pale yellow syrup (43 mg, 86%, 100% D, 87:13 trans:cis, dr determined by integration of δ_H 4.70 + 4.48 and 4.32 + 4.10).

Characterization data the same as *trans*-**126a.**

1-(3-Hydroxy-2-methyl-azetidin-1-yl)-2,2-dimethylpropane-1-thione (**126b**)



Method A

MeI (180 μL, 2.9 mmol) was used following General Procedure A, but on half the scale. Purification (Si-gel, pet ether/EtOAc 4:1) gave methylated azetidinol **126b** as a pale yellow syrup (39 mg, 72%, 69:31 trans:cis, dr determined by integration at δ_H 1.32 and 1.30).

Method B

Me_2SO_4 (164 μL, 1.73 mmol) was used following General Procedure A. Purification (Si-gel, pet ether/EtOAc 9:1 → 2:3) gave methylated azetidinol **126b** as a pale yellow syrup (73 mg, 69%, 44:56 trans:cis, dr determined by integration at δ_H 1.32 and 1.30).

Method C

MeOTf (390 μL, 3.46 mmol) was used following General Procedure A, but on double the scale. Purification (Si-gel, heptane/EtOAc 1:0 → 4:1) gave methylated azetidinol **126b** as a pale yellow syrup (40 mg, 19%, 50:50 trans:cis, dr determined by integration at δ_H 1.32 and 1.30).

- R_f 0.38 (pet ether/EtOAc 3:2);
- **IR** (neat/cm^{-1}) 3364 br, 2965 w, 2929 w, 1461 s, 1434 s, 1364 w, 1135 m;
- **LRMS** (ESI^+) 188.12 ($[M+H]^+$, 40%); **HRMS** (ESI^+) calcd for $C_9H_{18}NOS$: 188.1104, found 188.1105;

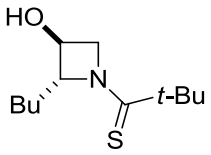
Major diastereoisomer

- **^{1}H NMR** (400 MHz, $CDCl_3$) 4.74 (1H, ddd, *J* = 11.4, 6.1, 2.4 Hz, $NCH_{cis}\underline{H}_{trans}$), 4.59 (1H, qdd, *J* = 6.6, 3.0, 2.4 Hz, NCH), 4.23 (1H, dd, *J* = 11.4, 3.0 Hz, $NC\underline{H}_{cis}H_{trans}$), 4.14 (1H, dt, *J* = 6.1, 3.0 Hz, C<u>H</u>OH), 3.18 (1H, br, OH), 1.56 (3H, d, *J* = 6.6 Hz, CH_3), 1.32 (9H, s, $C(CH_3)_3$);
- **^{13}C NMR** (100 MHz, $CDCl_3$) 211.2 (C=S), 74.0 (NCH), 67.9 (CHOH), 64.6 (NCH_2), 43.5 ($\underline{C}(CH_3)_3$), 29.6 ($C(\underline{C}H_3)_3$), 16.0 ($CH\underline{C}H_3$).

Minor diastereoisomer

- **^{1}H NMR** (400 MHz, $CDCl_3$) 4.97 (1H, quin, *J* = 6.6 Hz, NCH), 4.74 (1H, m, C<u>H</u>OH), 4.67 (1H, ddd, *J* = 10.9, 7.3, 1.0 Hz, $NCH_{cis}\underline{H}_{trans}$), 4.33 (1H, ddd, *J* = 10.9, 5.3, 2.0 Hz, $NC\underline{H}_{cis}H_{trans}$), 2.82 (1H, br, OH), 1.55 (3H, d, *J* = 6.6 Hz, CH_3), 1.30 (9H, s, $C(CH_3)_3$);
- **^{13}C NMR** (100 MHz, $CDCl_3$) 209.3 (C=S), 70.6 (NCH), 64.6 (NCH_2), 61.7 (CHOH), 43.3 ($\underline{C}(CH_3)_3$), 29.5 ($C(\underline{C}H_3)_3$), 10.3 ($CH\underline{C}H_3$).

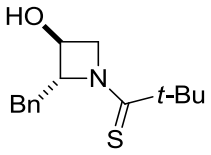
1-(3-Hydroxy-2-butyl-azetidin-1-yl)-2,2-dimethylpropane-1-thione (**126c**)



BuI (986 µL, 8.66 mmol) was used following General Procedure A, but on five times the scale. Purification (Si-gel, pet ether/EtOAc 19:1 →4:1) gave butylated azetidinol **126c** as a pale yellow syrup (451 mg, 68%).

- R_f 0.64 (pet ether/EtOAc 3:2);
- **IR** (neat/cm^{-1}) 3372 br, 2958 w, 2923 m, 2854 m, 1461 s, 1435 m, 1363 w, 1134 m, 737 m;
- **^{1}H NMR** (400 MHz, $CDCl_3$) 4.68 (1H, ddd, *J* = 12.6, 7.5, 1.8 Hz, $NCH_{cis}\underline{H}_{trans}$), 4.52 (1H, m, NCH), 4.24-4.19 (2H, m, C<u>H</u>OH and $NC\underline{H}_{cis}H_{trans}$), 2.90 (1H, br s, OH), 2.41-2.33 (1H, m, C<u>H</u>HCH$_2$CH$_2$CH$_3$), 1.67 (1H, ddt, *J* = 14.7, 7.3, 7.1 Hz, CH<u>H</u>CH$_2$CH$_2$CH$_3$), 1.38-1.24 (4H, m, CH$_2$C<u>H</u>$_2$C<u>H</u>$_2$CH$_3$), 1.33 (9H, s, C(CH$_3$)$_3$), 0.91 (3H, t, *J* = 7.1 Hz, CH$_2$CH$_2$CH$_2$C<u>H</u>$_3$);
- **^{13}C NMR** (100 MHz, $CDCl_3$) 211.3 (C=S), 78.0 (NCH), 66.6 (CHOH), 64.9 (NCH_2), 43.5 (<u>C</u>(CH$_3$)$_3$), 29.7 (C(<u>C</u>H$_3$)$_3$), 28.3 (<u>C</u>H$_2$CH$_2$CH$_2$CH$_3$), 25.9 (CH$_2$<u>C</u>H$_2$CH$_2$CH$_3$), 22.5 (CH$_2$CH$_2$<u>C</u>H$_2$CH$_3$), 14.0 (CH$_2$CH$_2$CH$_2$<u>C</u>H$_3$);
- **LRMS** (ESI^+) 230.17 ($[M+H]^+$, 55%); **HRMS** (ESI^+) calcd for $C_{12}H_{24}NOS$: 230.1573, found 230.1569.

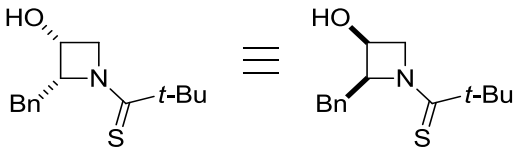
1-(3-Hydroxy-2-benzyl-azetidin-1-yl)-2,2-dimethylpropane-1-thione (**126d**)



BnBr (1.03 mL, 8.66 mmol) was used following General Procedure A, but on five times the scale. Purification (Si-gel, heptane/EtOAc 9:1 →8:2) gave benzylated azetidinol **126d** as a pale yellow syrup (559 mg, 74%).

- ***R**f* 0.64 (pet ether/EtOAc 3:2);
- **IR** (neat/cm^{-1}) 3365 br, 2966 w, 2930 w, 1455 s, 1432 s, 1125 m, 995 m, 702 s;
- **^{1}H NMR** (400 MHz, $CDCl_3$) 7.32-7.22 (5H, m, Ar), 4.83 (1H, dddd, *J* = 7.8, 3.3, 3.0, 2.0 Hz, NCH), 4.28 (1H, dt, *J* = 6.1, 3.0 Hz, C<u>H</u>OH), 4.22 (1H, ddd, *J* = 11.1, 6.1, 2.0 Hz, $NCH_{cis}\underline{H}_{trans}$), 4.10 (1H, dd, *J* = 11.1, 3.0 Hz, $NC\underline{H}_{cis}H_{trans}$), 3.46 (1H, dd, *J* = 13.9, 3.3 Hz, C<u>H</u>HPh), 3.36 (1H, dd, *J* = 13.9, 7.8 Hz, CH<u>H</u>Ph), 1.86 (1H, br, OH), 1.33 (9H, s, $C(CH_3)_3$);
- **^{13}C NMR** (100 MHz, $CDCl_3$) 211.6 (C=S), 136.4 (Ar), 129.7 (Ar), 128.4 (Ar), 126.7 (Ar), 77.5 (NCH), 65.2 (CHOH), 64.7 (NCH_2), 43.6 ($\underline{C}(CH_3)_3$), 33.8 ($\underline{C}H_2Ph$), 29.6 ($C(\underline{C}H_3)_3$);
- **LRMS** (ESI^+) 286.14 ($[M+Na]^+$, 100%); **HRMS** (ESI^+) calcd for $C_{15}H_{22}NOS$: 264.1417, found 264.1414.

1-(2-benzyl-3-hydroxyazetidin-1-yl)-2,2-dimethylpropane-1-thione (*cis*-**126d**)

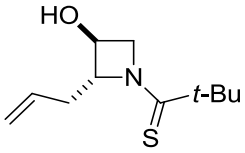


To a stirred solution of inverted acetate **156** (245 mg, 0.80 mmol) in MeOH (3 mL) was added NaOMe (10 drops, 30% in MeOH). After 1 h, the reaction mixture was concentrated to dryness under reduced pressure. The residue was washed with aq HCl (1 M, 10 mL) and extracted with CH_2Cl_2 (10 mL), the organic layer was washed brine (10 mL), dried (Na_2SO_4), filtered and concentrated to dryness under reduced pressure gave *cis*–benzyl substituted azetidine *cis*-**126d** as a pale orange syrup which solidified on standing (184 mg, 87%), diastereoselectivity determined by ^{1}H NMR coupling constant analysis.

- ***R**f* 0.47 (pet ether/EtOAc 4:1);
- **mp** 101-103 °C;
- **IR** (neat/cm^{-1}) 3368 br, 2996 w, 2964 w, 2929 w, 1468 s, 1435 s, 1357 w, 1253 w, 1149 m, 1109 m, 1037 w, 984 w, 829 w, 746 m, 702 m;

- **^{1}H NMR** (400 MHz, $CDCl_3$) 7.42-7.21 (5H, m, Ar), 5.17 (1H, dddd, *J* = 10.4, 7.3, 2.4, 2.0 Hz, NCH), 4.77 (1H, td, *J* = 7.3, 5.6 Hz, C<u>H</u>OH), 4.65 (1H, dd, *J* = 10.8, 7.3 Hz, NC<u>H</u>$_{trans}$H$_{cis}$), 4.23 (1H, ddd, *J* = 10.8, 5.6, 2.0 Hz, NCH$_{trans}$<u>H</u>$_{cis}$), 3.83 (1H, dd, *J* = 13.7, 2.4 Hz, C<u>H</u>HPh), 3.31 (1H, dd, *J* = 13.7, 10.4 Hz, CH<u>H</u>Ph), 2.03 (1H, br, OH), 1.34 (9H, s, C(CH$_3$)$_3$);
- **^{13}C NMR** (100 MHz, $CDCl_3$) 210.2 (C=S), 138.2 (Ar), 129.4 (Ar), 128.5 (Ar), 126.4 (Ar), 74.5 (NCH), 64.7 (NCH$_2$), 62.5 (CHOH), 43.5 (<u>C</u>(CH$_3$)$_3$), 29.6 (C(<u>C</u>H$_3$)$_3$);
- **LRMS** (ESI$^+$) 286.2 ([M+Na]$^+$, 100%); **HRMS** (ESI$^+$) calcd for $C_{15}H_{21}NNaOS$: 286.1236, found 286.1244.

1-(2-Allyl-3-hydroxyazetidin-1-yl)-2,2-dimethylpropane-1-thione (**126e**)

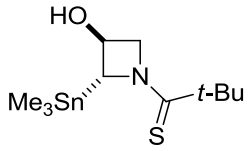


Allyl bromide (75 μL, 0.87 mmol) was used following General Procedure A, but on half the scale. Purification (Si-gel, pet ether/EtOAc 9:1→1:1) gave allylated azetidinol **126e** as a yellow syrup (37 mg, 60%).

- R_f 0.23 (pet ether/EtOAc 4:1);
- **IR** (neat/cm^{-1}) 3369 br, 2966 w, 2872 w, 1460 s, 1395 w, 1135 m, 1001 s, 918 m, 796 w, 732 w;
- **^{1}H NMR** (400 MHz, $CDCl_3$) 5.74 (1H, ddt, *J* = 17.2, 10.1, 7.1 Hz, CH$_2$C<u>H</u>=CH$_{cis}$H$_{trans}$), 5.18 (1H, d, *J* = 17.2 Hz, CH$_2$CH=CH$_{cis}$<u>H</u>$_{trans}$), 5.16 (1H, d, *J* = 10.1 Hz, CH$_2$CH=C<u>H</u>$_{cis}$H$_{trans}$), 4.65-4.61 (2H, m, NCH and NCH$_{cis}$<u>H</u>$_{trans}$), 4.27 (1H, dt, *J* = 6.5, 3.0 Hz, C<u>H</u>OH), 4.22 (1H, dd, *J* = 11.0, 3.2 Hz, NC<u>H</u>$_{cis}$H$_{trans}$), 2.92 (1H, ddd, *J* = 14.5, 7.5, 2.5 Hz, C<u>H</u>HCH=CH$_2$), 2.76 (1H, ddd, *J* = 14.5, 7.5, 7.0 Hz, CH<u>H</u>CH=CH$_2$), 2.66 (1H, br, OH), 1.33 (9H, s, C(C<u>H</u>$_3$)$_3$);
- **^{13}C NMR** (100 MHz, $CDCl_3$) 211.6 (C=S), 131.9 (<u>C</u>H=CH$_2$), 119.0 (CH=<u>C</u>H$_2$), 76.4 (NCH), 65.4 (CHOH), 64.9 (NCH$_2$), 43.6 (<u>C</u>(CH$_3$)$_3$), 32.6 (<u>C</u>H$_2$CH=CH$_2$), 29.7 (C(<u>C</u>H$_3$)$_3$);

- **LRMS** (ESI^+) 214.13 ($[M+H]^+$, 85%); **HRMS** (ESI^+) calcd for $C_{11}H_{19}NNaOS$: 236.1080, found 236.1082.

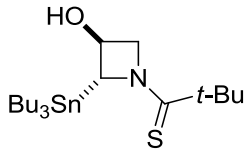
1-(3-Hydroxy-2-(trimethylstannyl)azetidin-1-yl)-2,2-dimethylpropane-1-thione (**126f**)



Me_3SnCl (345 mg, 1.73 mmol) in THF (0.5 mL) was used following General Procedure A. Purification (Si-gel, pet ether/EtOAc 9:1→3:2) gave stannylated azetidinol **126f** as a colourless syrup (80 mg, 41%).

- R_f 0.36 (pet ether/EtOAc 4:1);
- **IR** (neat/cm^{-1}) 3346 br, 2970, 2931 w, 1474 s, 1364 w, 1126 m, 909 m, 767 m, 728 s;
- **^{1}H NMR** (400 MHz, $CDCl_3$) 4.70 (1H, ddd, *J* = 11.4, 5.5, 2.5 Hz, $NCH_{cis}\underline{H}_{trans}$), 4.54 (1H, ddd, *J* = 5.5, 3.8, 3.3 Hz, C<u>H</u>OH), 4.39 (1H, dd, *J* = 3.8, 2.5 Hz, NCH), 4.39 (1H, dd, *J* = 11.4, 3.3 Hz, $NC\underline{H}_{cis}H_{trans}$), 1.34 (9H, s, $C(C\underline{H}_3)_3$), 0.18 (9H, s, $Sn(CH_3)_3$);
- **^{13}C NMR** (100 MHz, $CDCl_3$) 203.2 (C=S), 71.5 (NCH), 66.0 (NCH_2), 64.4 (CHOH), 42.6 ($\underline{C}(CH_3)_3$), 30.0 ($C(\underline{C}H_3)_3$), -7.5 ($Sn(CH_3)_3$);
- **LRMS** (ESI^-) 336.05 ($[M–H]^-$, 87%); HRMS (ESI^-) calcd for $C_{11}H_{22}NOSSn$: 336.0450, found 336.0444.

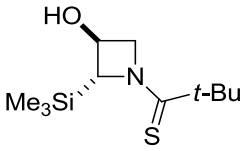
1-(3-Hydroxy-2-(tributylstannyl)azetidin-1-yl)-2,2-dimethylpropane-1-thione (**126g**)



Bu_3SnCl (2.3 mL, 8.48 mmol) was used following General Procedure A, but on five times the scale. Purification (Si-gel, pet ether/EtOAc 39:1→4:1) gave stannylated azetidinol **126g** as a colourless syrup (1.1 g, 82%).

- R_f 0.33 (pet ether/EtOAc 9:1);
- **IR** (neat/cm^{-1}) 3361 br, 2923 w, 2854 w, 1465 s, 1364 w, 1124 w, 910 m, 732 s;
- **^{1}H NMR** (400 MHz, $CDCl_3$) 4.72 (1H, ddd, *J* = 11.6, 5.8, 2.5 Hz, $NCH_{cis}\underline{H}_{trans}$), 4.58 (1H, ddt, *J* = 6.3, 5.8, 3.3 Hz, C<u>H</u>OH), 4.40-4.38 (1H, m, NCH), 4.36 (1H, dd, *J* = 11.6, 3.3. Hz, $NC\underline{H}_{cis}H_{trans}$), 2.30 (1H d, *J* = 6.3 Hz, CHO<u>H</u>), 1.65-1.42 (6H, m, $CH_2C\underline{H}_2CH_2CH_3$), 1.35 (9H, s, $C(CH_3)_3$), 1.36-1.26 (6H, m, $CH_2CH_2C\underline{H}_2CH_3$), 0.97-0.92 (6H, m, $C\underline{H}_2CH_2CH_2CH_3$), 0.90 (9H, t, *J* = 7.3 Hz, $CH_2CH_2CH_2C\underline{H}_3$);
- **^{13}C NMR** (100 MHz, $CDCl_3$) 202.5 (C=S), 71.6 (NCH), 66.0 (NCH_2), 64.9 (CHOH), 42.7 ($\underline{C}(CH_3)_3$), 30.0 ($CH_2\underline{C}H_2CH_2CH_3$), 29.0 ($CH_2CH_2\underline{C}H_2CH_3$), 27.5 ($C(\underline{C}H_3)_3$), 13.7 ($CH_2CH_2CH_2\underline{C}H_3$), 11.5 ($\underline{C}H_2CH_2CH_2CH_3$);
- **LRMS** (ESI^+) 464.20; ($[M+H]^+$, 68%); **HRMS** (ESI^+) calcd for $C_{20}H_{41}NOSSn$: 464.2005, found 464.1991.

1-(3-Hydroxy-2-(trimethylsilyl)azetidin-1-yl)-2,2-dimethylpropane-1-thione (**126h**)

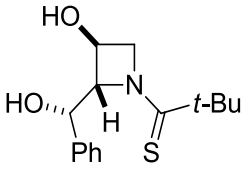


Me_3SiCl (220 µL, 1.73 mmol) was used following General Procedure A. Purification (Si-gel, pet ether/EtOAc 9:1→2:3) gave silylated azetidinol **126h** as a colourless syrup (49 mg, 35%).

- R_f 0.31 (pet ether/EtOAc 4:1);
- **IR** (neat/cm^{-1}) 3261 br, 2961 w, 2901 w, 1472 s, 1246 m, 1136 m, 1077 m, 1009 m, 842 s;
- **^{1}H NMR** (400 MHz, $CDCl_3$) 4.62 (1H, dd, *J* = 11.4, 4.3 Hz, $NCH_{cis}\underline{H}_{trans}$), 4.41-4.37 (2H, m, NCH and C<u>H</u>OH), 4.29 (1H, dd, *J* = 11.4, 3.0 Hz, $NC\underline{H}_{cis}H_{trans}$), 2.71 (1H, br, OH), 1.34 (9H, s, $(C(CH_3)_3$), 0.19 (9H, s, $Si(CH_3)_3$);
- **^{13}C NMR** (100 MHz, $CDCl_3$) 207.5 (C=S), 73.0 (CHOH), 66.1 (NCH_2), 63.3 (NCH), 43.0 ($\underline{C}(CH_3)_3$), 30.0 ($C(\underline{C}H_3)_3$), -1.3 ($Si(CH_3)_3$);

- **LRMS** (ESI$^+$) 268.12 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) calcd for $C_{11}H_{23}NNaOSSi$: 268.1162, found 268.1160.

1-3-Hydroxy-2-(hydroxy(phenyl)methyl)azetidin-1-yl)-2,2-dimethylpropane-1-thione (**126i**)



Benzaldehyde (352 µL, 3.46 mmol) was used following General Procedure A, but on twice the scale. By TLC both diastereoisomers appeared to have the same R_f, with residual starting azetidinol **122** also falling at the same R_f. Purification (Si-gel, heptane/EtOAc 4:1), was achieved using a CombiFlash Companion purification system with UV trace of eluting products. By TLC analysis of fractions no difference could be determined between the products. However, UV analysis of the product–containing fractions showed two distinct products and traces of starting material (Figure 4.1), collected individually, to give both benzaldehyde azetidinol diastereoisomers: *epi*-**126i** as a colourless crystalline solid (60 mg, 19%) and **126i** as a pale yellow syrup (171 mg, 53%). A crystal of *epi*-**126i** for X-ray crystallographic analysis was obtained by slow evaporation from $CDCl_3$.

Peak 1 = *epi*-**126i**

Peak 2 = recovered starting azetidinol **122**

Peak 3 = **126i**

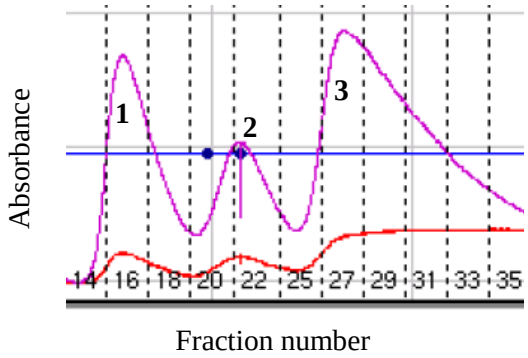
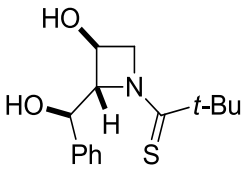


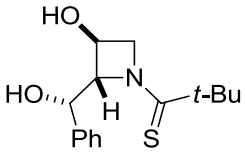
Figure 4.1 UV trace of **126i** purification

Minor diastereoisomer (*epi*-**126i**)



- R_f 0.45 (pet ether/EtOAc 3:2);
- **mp** 145-148 °C;
- **IR** (neat/cm^{-1}) 3444 w, 2964 w, 2928 w, 1486 s, 1362 w, 1180 w, 1106 m, 1008 m, 703 m;
- **^{1}H NMR** (400 MHz, $CDCl_3$) 7.45-7.28 (5H, m, Ar), 5.76 (1H, d, *J* = 1.8 Hz, PhC<u>H</u>(OH)), 4.95 (1H, dt, *J* = 3.3, 1.8 Hz, NCH), 4.44 (1H, dt, *J* = 6.6, 3.3 Hz, C<u>H</u>OH), 4.29 (1H, ddd, *J* = 11.0, 6.6, 1.8 Hz, $NCH_{cis}\underline{H}_{trans}$), 4.09 (1H, dd, *J* = 11.0, 3.3 Hz, $NC\underline{H}_{cis}H_{trans}$), 3.48 (1H, s, OH), 1.34 (9H, s, $C(CH_3)_3$);
- **^{13}C NMR** (100 MHz, $CDCl_3$) 212.8 (C=S), 139.3 (Ar), 128.5 (Ar), 127.8 (Ar), 126.3 (Ar), 82.5 (NCH), 70.8 (Ph<u>C</u>H(OH)), 64.9 (NCH_2), 62.4 (CHOH), 43.7 ($\underline{C}(CH_3)_3$), 29.7 ($C(\underline{C}H_3)_3$);
- **LRMS** (ESI^+) 302.10 ($[M+Na]^+$ 85%); **HRMS** (ESI^+) calcd for $C_{15}H_{21}NNaO_2S$: 302.1185, found 302.1181;
- **X-ray** see Appendix 6.1, p. 219.

Major diastereoisomer (**126i**)

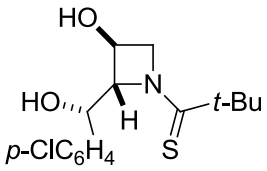


- R_f 0.45 (pet ether/EtOAc 3:2);
- **IR** (neat/cm^{-1}) 3354 br, 2966 w, 2924 w 1455 s, 1433 m, 1364 w, 1244 w, 1130 w, 1041 w, 704 m;
- **^{1}H NMR** (400 MHz, DMSO-D6) 7.35-7.26 (5H, m, Ar), 5.80 (1H, d, *J* = 5.8 Hz, CHO<u>H</u>), 5.73 (1H, d, *J* = 4.3 Hz, PhCH(O<u>H</u>)), 5.72 (1H, dd, *J* = 4.9, 4.3 Hz, PhC<u>H</u>(OH), 4.62 (1H,

ddd, *J* = 4.9, 2.6, 2.0 Hz, NCH), 4.03 (1H, ddt, *J* = 6.3, 5.8, 2.6 Hz, C<u>H</u>OH), 3.84 (1H, dd, *J* = 11.3, 2.6 Hz, NC<u>H</u>$_{cis}$H$_{trans}$), 3.36 (1H, ddd, *J* = 11.3, 6.3, 2.0 Hz, NCH$_{cis}$<u>H</u>$_{trans}$), 1.15 (9H, s, (C(CH$_3$)$_3$);

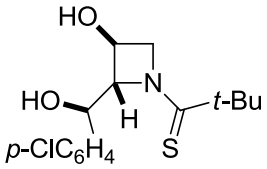
- **^{13}C NMR** (100 MHz, DMSO-D6) 209.6 (C=S), 140.8 (Ar), 127.5 (Ar), 127.1 (Ar), 126.3 (Ar), 80.0 (NCH), 65.5 (NCH$_2$), 65.2 (Ph<u>C</u>H(OH), 60.8 (CHOH), 42.7 (<u>C</u>(CH$_3$)$_3$), 29.2 (C(<u>C</u>H$_3$)$_3$);
- **LRMS** (ESI$^+$) 302.10 ([M+Na]$^+$, 70 %); **HRMS** (ESI$^+$) calcd for $C_{15}H_{21}NNaO_2S$: 302.1185, found 302.1186.

1-(2-((4-Chlorophenyl)(hydroxy)methyl)-3-hydroxyazetidin-1-yl)-2,2-dimethylpropane-1-thione (**126j**)



p-Chlorobenzaldehyde (122 mg, 0.87 mmol) was used following General Procedure A, but on half the scale. Purification (Si-gel, pet ether/EtOAc 9:1→4:1) gave both aldehyde azetidinol diastereoisomers: *epi*-**126j** as a pale yellow syrup (31mg, 34%), and **126j** as a pale yellow syrup (43 mg, 47%).

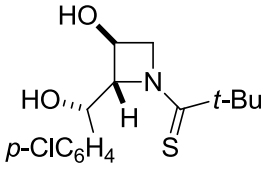
Minor diastereoisomer (*epi*-**126j**)



- ***R**$_f$* 0.54 (pet ether/EtOAc 3:2);
- **IR** (neat/cm^{-1}) 3254 br, 2969 w, 1470 s, 1244 w, 1127 m, 1090 m, 1007 m, 911 m, 854 w, 730 s;

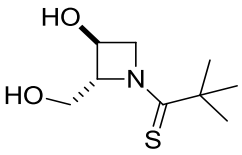
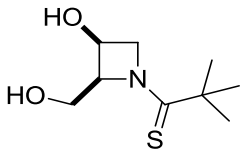
- **^{1}H NMR** (400 MHz, $CDCl_3$) 7.37-7.32 (4H, m, Ar), 5.65 (1H, s, *p*-ClPhC<u>H</u>(OH)), 4.91 (1H, dt, *J* = 3.2, 2.0 Hz, NCH), 4.35 (1H, dt, *J* = 6.5, 3.2 Hz, C<u>H</u>OH), 4.26 (1H, ddd, *J* = 11.0, 6.5, 2.0 Hz, $NCH_{cis}\underline{H}_{trans}$), 4.09 (1H, dd, *J* = 11.0, 3.2 Hz, $NC\underline{H}_{cis}H_{Trans}$), 1.32 (9H, s, $C(C\underline{H}_3)_3$);
- **^{13}C NMR** (100 MHz, $CDCl_3$) 212.9 (C=S), 137.7 (Ar), 133.6 (Ar), 128.6 (Ar), 127.8 (Ar), 82.2 (NCH), 70.5 (*p*-ClPh<u>C</u>H(OH)), 64.9 (NCH_2), 62.3 (CHOH), 43.7 ($\underline{C}(CH_3)_3$), 29.6 ($C(\underline{C}H_3)_3$);
- **LRMS** (ESI^+) 336.10 ($[M+Na]^+$, 100%); **HRMS** (ESI^+) calcd for $C_{15}H_{20}ClNNaO_2S$: 336.0795, found 336.0800.

Major diastereoisomer (**126j**)



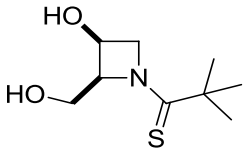
- ***R*$_f$** 0.37 (pet ether/EtOAc 3:2);
- **IR** (neat/cm^{-1}) 3363 br, 2972 w, 1459 s, 1365 w, 1131 m, 1091 m, 906 s, 791 m, 727 s;
- **^{1}H NMR** (400 MHz, $CDCl_3$) 7.33 (4H, s, Ar), 5.47 (1H, d, *J* = 6.8 Hz, *p*-ClPhC<u>H</u>(OH), 4.87 (1H, dd, *J* = 6.8, 1.8 Hz, NCH), 4.14-4.06 (3H, m, C<u>H</u>OH and $NC\underline{H}_{cis}\underline{H}_{trans}$), 1.30 (9H, s, $C(C\underline{H}_3)_3$);
- **^{13}C NMR** (100 MHz, $CDCl_3$) 213.5 (C=S), 137.6 (Ar), 134.0 (Ar), 128.6 (Ar), 128.3 (Ar), 81.5 (NCH), 71.0 (*p*-ClPh<u>C</u>H(OH)), 64.4 (NCH_2), 62.4 (CHOH), 43.8 ($\underline{C}(CH_3)_3$), 29.7 ($C(\underline{C}H_3)_3$);
- **LRMS** (ESI^+) 336.10 ($[M+Na]^+$, 82%); **HRMS** (ESI^+) calcd for $C_{15}H_{20}ClNNaO_2S$: 336.0795, found 336.0800.

1-(3-Hydroxy-2-(hydroxymethyl)azetidin-1-yl)-2,2-dimethylpropane-1-thione (**126k**)

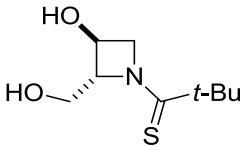
Paraformaldehyde (174 mg, 5.80 mmol) was used following General Procedure A. Purification (Si-gel, pet ether/EtOAc 4:1→2:3) gave *cis*-**126k** (14 mg, 12%) and *trans*-**126k** (20 mg, 17%) each as pale brown syrups.

cis-**126k**



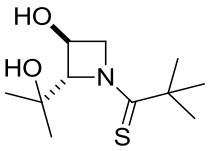
- R_f 0.53 (pet ether/EtOAc 1:4);
- **IR** (neat/cm^{-1}) 3331 br, 2965 w, 2931 w, 1730 w, 1463 s, 1436 m, 1364 m, 1283 w, 1221 w, 1159 w, 1124 m, 1089 m, 1048 m, 982 w, 962 w, 880 w, 799 w;
- **^{1}H NMR** (400 MHz, $CDCl_3$) 4.99-4.94 (1H, m, NCH), 4.79-4.71 (3H, m, C<u>H</u>OH, NC<u>H</u>H and C<u>H</u>HOH), 4.38-4.30 (1H, m, NCH<u>H</u>), 4.03 (1H, dd, *J* = 12.3, 3.2 Hz, CH<u>H</u>OH), 3.28 (2H, br, 2 x OH), 1.35 (9H, s, $C(CH_3)_3$);
- **^{13}C NMR** (100 MHz, $CDCl_3$) 211.0 (C=S), 75.2 (NCH), 67.3 (NCH_2), 63.2 (CHOH), 59.1 (CH_2OH), 53.6 ($\underline{C}(CH_3)_3$), 29.5 ($C(\underline{C}H_3)_3$);
- **LRMS** (ESI^+) 204.1 ($[M+H]^+$, 100%); **HRMS** (ESI^+) calcd for $C_9H_{18}N_2OS$: 204.1053, found 204.1053.

trans-**126k**



- R_f 0.41 (pet ether/EtOAc 1:4);
- **IR** (neat/cm^{-1}) 3735 br, 2966 w, 2873 w, 1704 w, 1461 s, 1433 m, 1364 m, 1300 w, 1224 m, 1197 w, 1131 m, 1093 m, 1032 w, 1004 m, 914 w, 880 w;
- **^{1}H NMR** (400 MHz, $CDCl_3$) 4.68-4.63 (2H, m, NCH and $NCH_{cis}\underline{H}_{trans}$), 4.32 (1H, dt, *J* = 6.6, 4.2 Hz, C<u>H</u>OH), 4.24 (1H, dd, *J* = 11.2, 4.2 Hz, $NC\underline{H}_{cis}H_{trans}$), 4.12 (1H, dd, *J* = 12.3, 2.5 Hz, C<u>H</u>HOH), 3.91 (1H, dd, *J* = 12.3, 5.7 Hz, CH<u>H</u>OH), 1.35 (9H, s, $C(CH_3)_3$);
- **^{13}C NMR** (100 MHz, $CDCl_3$) 212.5 (C=S), 80.4 (NCH), 64.7 (NCH_2), 63.6 (CHOH), 62.5 (CH_2OH), 43.7 ($\underline{C}(CH_3)_3$), 29.7 ($C(\underline{C}H_3)_3$);
- **LRMS** (ESI$^+$) 204.1 ([M+H]$^+$, 100%); **HRMS** (ESI$^+$) calcd for $C_9H_{18}N_2OS$: 204.1053, found 204.1050.

1-(3-Hydroxy-2-(2-hydroxypropan-2-yl)azetidin-1-yl)-2,2-dimethylpropane-1-thione (**126l**)

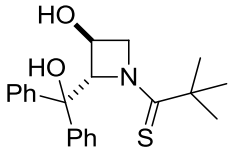


Acetone (256 μL, 3.48 mmol) was used following General Procedure A. Purification (Si-gel, pet ether/EtOAc 4:1→2:3) gave diol **126l** as a colourless solid (39 mg, 29%, 91% brsm).

- R_f 0.15 (pet ether/EtOAc 4:1);
- **mp** 141-142 °C
- **IR** (neat/cm^{-1}) 3312 br, 3088 br, 2966 m, 2917 w, 2851 w, 1462 s, 1423 s, 1381 w, 1362 w, 1306 w, 1288 w, 1251 w, 1214 m, 1174 m, 1140 s, 1122 m, 1082 m, 1047 w, 1026 w, 1003 w, 976 m, 934 m, 900 m, 876 m, 834 w, 795 w, 762 w;

- **^{1}H NMR** (400 MHz, $CDCl_3$) 6.42 (1H, br, OH), 4.68 (1H, dd, *J* = 3.8, 2.0 Hz, NCH), 4.61 (1H, ddd, *J* = 11.0, 6.9, 2.0 Hz, $NCH_{cis}\underline{H}_{trans}$), 4.25 (1H, dd, *J* = 11.0, 3.8 Hz, $NC\underline{H}_{cis}H_{trans}$), 4.20 (1H, dt, *J* = 6.9, 3.8 Hz, C<u>H</u>OH), 3.81 (1H, br, OH), 1.37 (9H, s, $C(CH_3)_3$), 1.28 (3H, s, $C(OH)(C\underline{H}_3)_2$), 1.19 (3H, s, $C(OH)(C\underline{H}_3)_2$);
- **^{13}C NMR** (100 MHz, $CDCl_3$) 213.8 (C=S), 88.0 (NCH), 71.8 ($\underline{C}(OH)(CH_3)_2$), 65.0 ($NCH_2$), 63.9 (CHOH), 44.0 ($\underline{C}(CH_3)_3$), 29.8 ($C(\underline{C}H_3)_3$), 25.0 ($C(OH)(\underline{C}H_3)_2$), 24.1 ($C(OH)(\underline{C}H_3)_2$);
- **LRMS** (ESI^+) 232.1 ($[M+H]^+$, 100%); **HRMS** (ESI^+) calcd for $C_{11}H_{22}NO_2S$: 232.1366, found 232.1364.

1-(3-Hydroxy-2-(hydroxydiphenylmethyl)azetidin-1-yl)-2,2-dimethylpropane-1-thione (**126m**)



Benzophenone (159 mg, 0.87 mmol) in THF (0.5 mL) was used following General Procedure A but on half the scale. Purification (Si-gel, pet ether/EtOAc 9:1→4:1) gave diol **126m** as a colourless solid (11 mg, 11%, 15% brsm, 1:1.2 trans:cis).

- Rf 0.66 (pet ether/EtOAc 3:2);

Cis diastereoisomer

- **^{1}H NMR** (400 MHz, $CDCl_3$) 7.43-7.28 (10H, m, Ar), 6.04 (1H, dd, *J* = 7.3, 2.0 Hz, NCH), 4.87 (1H, ddd, *J* = 8.0, 7.3, 6.3 Hz, C<u>H</u>OH), 4.60 (1H, dd, *J* = 10.2, 8.0 Hz, $NCH_{cis}\underline{H}_{trans}$), 4.26 (1H, ddd, *J* = 10.2, 6.3, 2.0 Hz, $NC\underline{H}_{cis}H_{trans}$), 1.16 (9H, s, $C(C\underline{H}_3)_3$);

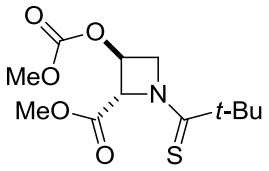
Trans diastereoisomer

- **^{1}H NMR** (400 MHz, $CDCl_3$) 7.43-7.28 (10H, m, Ar), 5.62 (1H, dd, *J* = 2.5, 2.0 Hz, NCH), 4.27 (1H, ddd, *J* = 6.0, 3.0, 2.5 Hz, C<u>H</u>OH), 4.03 (1H, dd, *J* = 11.1, 3.0 Hz, $NC\underline{H}_{cis}H_{trans}$), 3.86 (1H, ddd, *J* = 11.1, 6.0, 2.0 Hz, $NCH_{cis}\underline{H}_{trans}$), 1.17 (9H, s, $C(C\underline{H}_3)_3$);

Discernable data for both diastereoisomers

- **^{13}C NMR** (100 MHz, $CDCl_3$) 213.7 (C=S), 213.3 (C=S), 143.9 (Ar), 143.9 (Ar), 142.6 (Ar), 142.3 (Ar), 130.2 (Ar), 130.1 (Ar), 128.5 (Ar), 128.3 (Ar), 127.9 (Ar), 127.8 (Ar), 127.8 (Ar), 127.8 (Ar), 127.5 (Ar), 127.5 (Ar), 127.3 (Ar), 127.2 (Ar), 86.7 ($Ph_2\underline{C}H(OH)$), 81.7 (NCH), 81.1 (NCH), 65.9 (CHOH), 64.9 (CHOH), 64.9 (NCH_2), 62.9 (NCH_2), 44.0 ($\underline{C}(CH_3)_3$), 43.7 ($\underline{C}(CH_3)_3$), 29.8 ($C(\underline{C}H_3)_3$), 29.6 ($C(\underline{C}H_3)_3$);

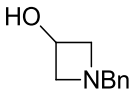
Methyl 1-(2,2-dimethylpropanethioyl)-3-[(methoxycarbonyl)oxy]azetidine-2-carboxylate (**126n**)



Methyl cyanoformate (276 μL, 3.46 mmol) was used following General Procedure A. Purification (Si-gel, pet ether/EtOAc 9:1→4:1) gave azetidine diester **126n** as a pale yellow syrup which solidified on standing (115 mg, 68% 93:7 trans:cis, dr determined by integration of δ_H 5.01 and 4.56).

- R_f 0.70 (pet ether/EtOAc 3:2);
- **mp** 85-87 °C;
- **IR** (neat/cm^{-1}) 2960 w, 1739 s, 1430 s, 1295 m, 1272 m, 1199 m, 1158 m, 992 m, 931 m, 790 m;
- **^{1}H NMR** (400 MHz, $CDCl_3$) 5.01 (1H, dt, *J* = 6.7, 3.4 Hz, CHO), 4.96 (1H, m, NCH), 4.89 (1H, ddd, *J* = 11.1, 6.7, 1.9 Hz, $NCH_{cis}\underline{H}_{trans}$), 4.44 (1H, dd, *J* = 11.1, 3.4 Hz, $NC\underline{H}_{cis}H_{trans}$), 3.83 (3H, s, OCH_3), 3.78 (3H, s, OCH_3), 1.34 (9H, s, $C(CH_3)_3$);
- **^{13}C NMR** (100 MHz, $CDCl_3$) 212.3 (C=S), 167.0 ($NCH\underline{C}(O)$), 154.3 ($CHO\underline{C}(O)$), 72.0, (NCH), 66.5 (CHO), 61.9 (NCH_2), 55.5 (OCH_3), 52.6 (OCH_3), 43.2 ($C(CH_3)_3$), 29.5 ($C(CH_3)_3$);
- **LRMS** (ESI^+) 312.1 ($[M+Na]^+$, 100%); **HRMS** (ESI^+) calcd for $C_{12}H_{19}NNaO_5S$: 312.0876, found 312.0868.

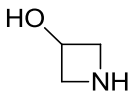
1-Benzylazetidin-3-ol (**127**)[22]



To a stirred solution of $BnNH_2$ (**12**) (22.9 mL, 200 mmol) in *i*-PrOH (200 mL) at rt was added epichlorohydrin (**22**) (22.9 mL, 210 mmol) dropwise over 2 min. After 16 h, the reaction mixture was concentrated to dryness under reduced pressure. The residue was redissolved in MeCN (400 mL) and to it was added $NaHCO_3$ (33.6 g, 400 mmol). The reaction mixture was heated to reflux and after 16 h cooled on ice and filtered. The filter cake was washed with MeCN and the filtrate concentrated to dryness under reduced pressure. Purification (Si-gel, acetone) gave azetidinol **127** as a pale yellow solid (13.9 g, 43%).

- R_f 0.22 (EtOAc/MeOH 9:1);
- **mp** 59–62 °C (lit.[22] 64-65 °C);
- **IR** (neat/cm^{-1}); 3069 br, 2957 w, 2807 m, 1341 m, 1156 m, 794 m, 736 m, 697 m;
- **^{1}H NMR** (400 MHz, $CDCl_3$) 7.33-7.23 (5H, m, $CH_2(C_6\underline{H}_5)$), 4.61 (1H, br s, CHO<u>H</u>), 4.36 (1H, quin, J = 6.0 Hz, C<u>H</u>OH), 3.60 (2H, s, $C\underline{H}_2Ar$), 3.58-3.54 (2H, m, NCH_2), 2.96-2.92 (2H, m, NCH_2);
- **^{13}C NMR** (100 MHz, $CDCl_3$) 137.4 (Ar), 128.5 (Ar), 128.3 (Ar), 127.2 (Ar), 63.8 (NCH_2), 63.5 (CHOH), 61.98 ($N\underline{C}H_2Ar$);
- **LRMS** (ESI^+) 164.10 ($[M+H]^+$, 100%).

A**zetidin-3-ol** (**129**)

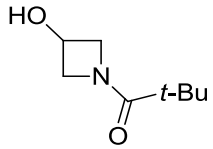


To a stirred solution of *N*-benzhydrylazetidin-3-ol (**106**) (400 mg, 1.7 mmol) in MeOH (10 mL) at rt was added ammonium formate (730 mg, 12 mmol) and 10% wt. Pd/C (40 mg). The reaction mixture was heated to reflux and after 2 h, then on cooling to rt, the reaction mixture was filtered through a pad of celite, washed with MeOH (10 mL), and concentrated to dryness under reduced pressure. The

crude residue was stirred in Et_2O (5 mL) for 5 min, carefully decanted and repeated followed by removal of residual solvent under reduced pressure to give azetidin-3-ol (**129**)[146] as an orange syrup (133 mg, quant).

- **IR** (neat/cm^{-1}) 3281 br, 2435 br, 1579 s, 1344 m, 1116 w;
- **^{1}H NMR** (400 MHz, CD_3OD) 4.63 (1H, quin, *J* = 6.6 Hz, C<u>H</u>OH), 4.00-3.96 (2H, m, NCH_2), 3.76-3.72 (2H, m, NCH_2);
- **^{13}C NMR** (100 MHz, CD_3OD) 64.8 (CHOH), 57.4 (NCH_2);
- **LRMS** (FI^+) 74.06 ($[M]^+$, 55%).

1-(3-hydroxyazetidin-1-yl)-2,2-dimethylpropan-1-one (**130**)



<u>Method A</u>

To a stirred slurry of azetidin-3-ol (**129**) (50 mg, 0.7 mmol) in THF (4 mL) at rt was added Et_3N (104 mg, 1 mmol). The reaction mixture was cooled to –78 °C and pivCl (99 mg, 0.8 mmol) added dropwise over 2 min. The cold bath was removed and after 16 h the reaction mixture was concentrated to dryness under reduced pressure and purified (Si-gel, pet ether/EtOAc 3:2 →0:1) to give alcohol **130** as a colourless syrup (33 mg, 31%).

<u>Method B</u>

To a stirred solution of azetidin-3-ol (**129**) (50 mg, 0.7 mmol) in MeOH (3 mL) at rt was added Et_3N (104 mg, 1 mmol). The reaction mixture was cooled to 0 °C and piv_2O (126 mg, 0.7 mmol) was added dropwise over 2 min. The cold bath was removed and after 6 h the reaction mixture was concentrated to dryness under reduced pressure. Purification (Si-gel, pet ether/EtOAc 2:3 →0:1) gave alcohol **130** as a colourless syrup (54 mg, 50%).

Method C

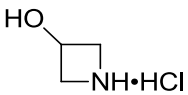
To a stirred slurry of azetidin-3-ol hydrochloride (**131**) (50 mg, 0.5 mmol) in pyridine (3 mL) at rt was added pivCl (61 mg, 0.5 mmol) dropwise over 2 min. After 16 h the reaction mixture was concentrated to dryness under reduced pressure, followed by azeotroping with toluene (2 x 5 ml). Purification (Si-gel, pet ether/EtOAc 2:3 →0:1) gave alcohol **130** as a colourless syrup (36 mg, 49%).

Method D

To a stirred solution of azetidin-3-ol hydrochloride (**131**) (50 mg, 0.5 mmol) in MeOH (3 mL) at rt was added Et_3N (70 mg, 0.7 mmol). The reaction mixture was cooled to 0 °C and piv_2O (85 mg, 0.5 mmol) was added dropwise over 2 min. The cold bath was removed and after 1 h the reaction mixture was concentrated to dryness under reduced pressure. Purification (Si-gel, pet ether/EtOAc 2:3 →0:1) gave alcohol **130** as a colourless syrup (58 mg, 78%).

- R_f 0.47 (EtOAc/MeOH 9:1);
- **IR** (neat/cm^{-1}) 3346 br, 2962 w, 2924 w, 1594 s, 1435 m, 1127 m;
- **^{1}H NMR** (500 MHz, T=363K, tol-D8) 4.24 (1H, quin, *J* = 4.9 Hz, C<u>H</u>OH), 4.09-4.06 (3H, m, NCH_2, CHO<u>H</u>), 3.90-3.87 (2H, m, NCH_2), 1.06 (9H, s, $C(CH_3)_3$);
- **^{13}C NMR** (125 MHz, T=363K, tol-D8) 178.4 (C=O), 62.2 (NCH_2), 61.7 (CHOH), 39.2 ($\underline{C}(CH_3)_3$), 27.8 ($C(\underline{C}H_3)_3$);
- **LRMS** (ESI^+) 337.23 ($[2M+Na]^+$, 100%); **HRMS** (ESI^+) calcd for $C_8H_{16}NO_2$: 158.1176, found 158.1176.

A**zetidin-3-ol hydrochloride** (**131**)

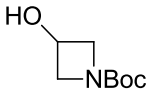


To a stirred solution of *N*-benzhydrylazetidin-3-ol (**106**) (2.0 g, 8.4 mmol) in MeOH (60 mL) at rt was added ammonium formate (2.6 g, 42 mmol) and 10% wt. Pd/C (200 mg). The reaction mixture was heated to reflux and after 3 h, then on cooling to rt, the reaction mixture was filtered through a pad of

celite. The crude reaction mixture was treated with a premixed solution of AcCl (0.9 mL, 13 mmol) in MeOH (10 mL) and stirred for 5 min at rt. The reaction mixture was concentrated to dryness under reduced pressure and the crude residue was stirred in Et_2O (20 mL) for 5 min, carefully decanted and repeated followed by removal of residual solvent under reduced pressure to give hydrochloride **131**[147] as a pale yellow syrup which crystallised on standing (798 mg, 87%).

- **IR** (neat/cm^{-1}) 3306 br, 2966 m, 2460 m, 2275 br, 1431 w, 1335 w, 1153 m, 1056 m;
- **^{1}H NMR** (400 MHz, CD_3OD) 4.72 (1H, quin, *J* = 6.6 Hz, C<u>H</u>OH), 4.27-4.19 (2H, m, NCH_2), 3.97-3.90 (2H, m, NCH_2);
- **^{13}C NMR** (100 MHz, CD_3OD) 63.4 (CHOH), 57.3 (NCH_2);
- **LRMS** (FI) 110.03 ($[M+H]^+$, 75%);

***tert*-Butyl 3-hydroxyazetidine-1-carboxylate** (**132**)[87]

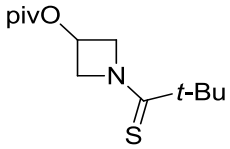


To a stirred solution of azetidin-3-ol hydrochloride (**131**) (12.0 g, 110 mmol) in MeOH (80 mL) was added Et_3N (18.3 mL, 131 mmol). Boc_2O (26.3 g, 121 mmol) in MeOH (40 mL) was added dropwise over 10 min. After 2 h, the reaction mixture was concentrated to dryness under reduced pressure, suspended in CH_2Cl_2, filtered and dry-loaded onto Si-gel. Purification (Si-gel, pet ether/EtOAc 3:2→2:3) gave alcohol **132** as a colourless syrup which solidified on standing (19.0 g, quant).

- R_f 0.81 (pet ether/EtOAc 3:2);
- **mp** 40-43 °C;
- **IR** (neat/cm^{-1}) 3434 br, 2975 w, 2880 w, 1666 s, 1410 m, 1156 m, 1112 m, 772 w;
- **^{1}H NMR** (400 MHz, $CDCl_3$) 4.57 (1H, tdt, *J* = 6.8, 6.1, 4.3 Hz, C<u>H</u>OH), 4.14 (2H, ddd, *J* = 9.6, 6.8, 1.0 Hz, NC<u>H</u>H), 3.80 (2H, ddd, *J* = 9.6, 4.3, 1.0 Hz, NCH<u>H</u>), 3.01 (1H, d, *J* = 6.1 Hz, CHO<u>H</u>), 1.43 (9H, s, C($C\underline{H}_3$)$_3$);

- **^{13}C NMR** (125 MHz, $CDCl_3$) 156.4 (C=O), 79.7 ($\underline{C}(CH_3)_3$), 61.5 (CHOH), 58.9 (NCH_2), 28.3 ($C(\underline{C}H_3)_3$);
- **LRMS** (ES^+) 369.22 ($[2M+Na]^+$ 100%).

1-(2,2-Dimethylpropanethioyl)azetidin-3-yl pivalate (**138**)



Method A

To a stirred solution of ester-amide **101** (5.70 g, 23.6 mmol) in pyridine (60 mL) at rt was added P_2S_5 (5.25 g, 23.6 mmol). The reaction mixture was heated to 75 °C. After 1 h, the reaction mixture was cooled to rt and washed with aq HCl (2 M, 100 mL) and extracted with CH_2Cl_2 (2 x 15 mL). Combined organic layers were washed with H_2O (20 mL), brine (20 mL), dried (Na_2SO_4), and concentrated to dryness under reduced pressure. Purification (Si-gel, heptane/EtOAc 1:0 → 2:3) gave thioamide ester **138** as a colourless syrup which solidified on standing (5.9 g, 97%).

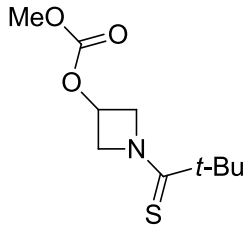
Method B

A suspension of azetidin-3-ol hydrochloride (**131**) (8.0 g, 73 mmol) in py (130 mL) was heated to 40 °C for 5 min, then cooled to rt. DMAP (1.8 g, 15 mmol), and pivCl (22 mL, 179 mmol) were added, and after 1 h P_2S_5 (19 g, 85 mmol) was added and the reaction mixture heated to 75 °C. After 1 h, the reaction mixture was cooled, concentrated to half volume under reduced pressure, diluted with EtOAc (200 mL) and washed with aq HCl (2 M, 500 mL). The organic layer was washed successively with H_2O (200 mL) and brine (200 mL), dried (Na_2SO_4), filtered and concentrated to dryness under reduced pressure. Purification (Si-gel, pet ether/EtOAc 1:0→4:1) gave thioamide ester **138** as a colourless syrup which solidified on standing (20.5 g, quant.).

- $\boldsymbol{R_f}$ 0.45 (heptane/EtOAc 4:1);
- **mp** 50-52 °C;

- **IR** (neat/cm^{-1}) 2965 w, 2872 w, 1781 s, 1484 m, 1465 m, 1321 m, 1139 s, 1004 w, 890 m;
- **^{1}H NMR** (400 MHz, $CDCl_3$) 5.12 (1H, tt, *J* = 6.8, 4.2 Hz, CHO), 4.80 (1H, ddd, *J* = 11.6, 6.8, 2.1 Hz, NC<u>H</u>H), 4.54 (1H, ddd, *J* = 13.3, 6.8, 2.1 Hz, NC<u>H</u>H), 4.27 (1H, ddd, *J* = 11.6, 4.2, 2.1 Hz, NCH<u>H</u>), 4.19 (1H, ddd, *J* = 13.3, 4.2, 2.1 Hz, NCH<u>H</u>), 1.33 (9H, s, $C(CH_3)_3$), 1.21 (9H, s, $C(CH_3)_3$);
- **^{13}C NMR** (100 MHz, $CDCl_3$) 210.6 (C=S), 178.0 (C=O), 63.3 (NCH_2), 62.0 (CHO), 61.9 (NCH_2), 43.2 (C(S)<u>C</u>$(CH_3)_3$), 38.5 (C(O)<u>C</u>$(CH_3)_3$), 29.7 (C(S)C(<u>C</u>$H_3)_3$), 26.9 (C(O)C(<u>C</u>$H_3)_3$);
- **LRMS** (ESI^+) 280.12 ($[M+Na]^+$ 100%); **HRMS** (ESI^+) calcd for $C_{13}H_{23}NNaO_2S$: 280.1342, found 280.1339.

1-(2,2-Dimethylpropanethioyl)azetidin-3-yl methyl carbonate (**139**)

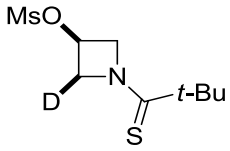


Methylchloroformate (49 μL, 0.64 mmol) was used following General Procedure A but on half the scale. Purification (Si-gel, pet ether/EtOAc 9:1→1:1) gave *O*-acylated azetidine **139** as a yellow syrup (11 mg, 16%).

- R_f 0.39 (Pet ether/EtOAc 4:1);
- **IR** (neat/cm^{-1}) 2963 w, 2873 w, 1749 s, 1435 m, 1363 w, 1256 s, 1142 m, 1026 m, 938 m, 790 w;
- **^{1}H NMR** (400 MHz, $CDCl_3$) 5.16 (1H, tt, *J* = 6.6, 3.8 Hz, CHO), 4.81 (1H, ddd, *J* = 11.6, 6.6, 2.1 Hz, $NCH_{cis}\underline{H}_{trans}$), 4.57 (1H, ddd, *J* = 13.5, 6.6, 2.1 Hz, $NCH_{cis}\underline{H}_{trans}$), 4.44 (1H, ddd, *J* = 11.6, 3.8, 2.1 Hz, $NC\underline{H}_{cis}H_{trans}$), 4.29 (1H, ddd, *J* = 13.5, 3.8, 2.1 Hz, $NC\underline{H}_{cis}H_{trans}$), 3.83 (3H, s, CH_3), 1.35 (9H, s, $C(CH_3)_3$);

- **^{13}C NMR** (100 MHz, $CDCl_3$) 210.9 (C=S), 154.7 (C=O), 64.9 (CHO), 62.9 (NCH_2), 61.7 (NCH_2), 55.3 (CH_3), 42.3 ($\underline{C}(CH_3)_3$), 29.7 ($C(\underline{C}H_3)_3$);
- **LRMS** (ESI^+) 254.10 ($[M+Na]^+$, 53%); **HRMS** (ESI^+) calcd for $C_{10}H_{17}NNaO_3S$: 254.0821, found 254.0816.

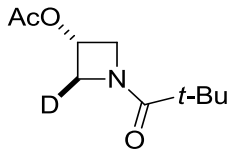
1-(2,2-Dimethylpropanethioyl)-2-deuteroazetidin-3-yl methanesulfonate (**141**)



To a stirred solution of deuterated azetidinol *cis*-**126a** (100 mg, 0.58 mmol) and Et_3N (106 μL, 0.76 mmol) in CH_2Cl_2 (2 mL) at 0 °C was added MsCl (49 μL, 0.63 mmol) dropwise over 1 min and the cold bath removed. After 2 h, the reaction mixture was concentrated to dryness under reduced pressure. Purification (Si-gel, pet ether/EtOAc 1:1) gave mesyl azetidine **141** as a colourless solid (108 mg, 74%).

- R_f 0.54 (pet ether/EtOAc 3:2);
- **mp** 108-109 °C;
- **IR** (neat/cm^{-1}) 2981 w, 2907 w, 1470 m, 1441 w, 1419 w, 1353 s, 1258 w, 1218 w, 1171 m, 1141 m, 1086 w, 1032w, 1008 w, 986 m, 914 m, 849 m, 815 w, 798 w, 770 w, 725 w, 700 w;
- **^{1}H NMR** (400 MHz, $CDCl_3$) 5.25 (1H, td, J = 6.6, 4.3 Hz), 8.84 (0.95H, dd, J = 12.4, 6.6 Hz, $NCH_{cis}\underline{H}_{trans}$ and $NCD_{cis}\underline{H}_{trans}$), 4.63-4.58 (1.43H, m, $NC\underline{H}_{cis}\underline{H}_{trans}$ and $NCD_{cis}\underline{H}_{trans}$), 4.37 (0.48H, ddd, J = 13.9, 4.3, 2.0 Hz, $NC\underline{H}_{cis}H_{trans}$), 3.11 (3H, s, CH_3), 1.34 (9H, s, $C(CH_3)_3$);
- **^{13}C NMR** (100 MHz, $CDCl_3$) 211.2 (C=S), 65.7 (CHO), 63.3 (NCH_2), 61.9 (NCH_2), 43.4 ($\underline{C}(CH_3)_3$), 38.4 (CH_3), 29.7 ($C(\underline{C}H_3)_3$);
- **LRMS** (ESI^+) 275.1 ($[M+Na]^+$, 100%); **HRMS** (ESI^+) calcd for $C_9H_{16}DNNaO_3S_2$: 275.0605, found 275.0605.

2-Deutero-1-(2,2-dimethylpropanethioyl)azetidin-3-yl acetate (**142**)



Method A

To a stirred solution of mesylate **141** (90 mg, 0.36 mmol) in DMF (3 mL) was added NaOAc (1.0 g, 12.2 mmol) and the reaction mixture was heated to 70 °C. After 72 h, the reaction mixture was cooled to rt, washed with H_2O (10 mL) and extracted with EtOAc (3 x 10 mL), the combined organic layers were dried (Na_2SO_4), filtered and concentrated to dryness under reduced pressure. Purification (Si-gel, pet ether/EtOAc 9:1→7:3) gave acetate **142** as a colourless syrup (12 mg, 15%).

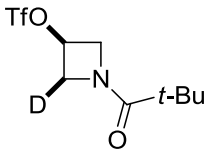
Method B

To a stirred solution of triflate **143** (586 mg, 1.91 mmol) in DMF (10 mL) was added NaOAc (5.3 g, 65 mmol) and the reaction mixture was heated to 70 °C. After 16 h, the reaction mixture was cooled to rt, washed with H_2O (10 mL) and extracted with EtOAc (3 x 10 mL), the combined organic layers were dried (Na_2SO_4), filtered and concentrated to dryness under reduced pressure. Purification (Si-gel, pet ether/EtOAc 9:1→4:1) gave acetate **142** as a colourless syrup (355 mg, 86%).

- $\boldsymbol{R_f}$ 0.41 (pet ether/EtOAc 4:1);
- **IR** (neat/cm^{-1}) 2968 w, 1741 s, 1462 m, 1437 m, 1364 w, 1225 s, 1143 m, 731 m;
- **^{1}H NMR** (400 MHz, $CDCl_3$) 5.15 (1H, dt, *J* = 6.8, 3.8 Hz, CHO), 4.81 (0.59H, ddd, *J* = 11.4, 6.8, 1.3 Hz, $NCH_{cis}\underline{H}_{trans}$), 4.55 (0.60H, ddd, *J* = 13.4, 6.8, 1.3 Hz, $NCH_{cis}\underline{H}_{trans}$), 4.35 (0.93H, dd, *J* = 11.4, 3.8 Hz, $NC\underline{H}_{cis}H_{trans}$ and $NC\underline{H}_{cis}D_{trans}$), 4.23 (0.91H, dd, *J* = 13.4, 3.8 Hz, $NC\underline{H}_{cis}H_{trans}$ and $NC\underline{H}_{cis}D_{trans}$), 2.12 (3H, s, $OC(O)CH_3$), 1.34 (9H, s, $C(CH_3)_3$);
- **^{13}C NMR** (100 MHz, $CDCl_3$) 210.6 (C=S), 170.4 (C=O), 63.3 (NCH_2), 63.0 (T, *J* = 23 Hz, NCHD), 62.0 (CHO), 62.0 (t, *J* = 9 Hz, CHO), 61.8 (NCH_2), 61.6 (T, *J* = 23 Hz, NCHD), 43.3 ($\underline{C}(CH_3)_3$), 29.7 ($C(\underline{C}H_3)_3$), 20.6 (CH_3);

- **LRMS** (ESI^+) 217.1 ($[M+H]^+$, 100%); **HRMS** (ESI^+) calcd for $C_{10}H_{16}DNNaO_2S$:239.0935, found 239.0928.

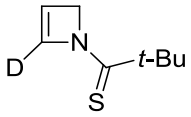
2-Deutero-1-(2,2-dimethylpropanethioyl)-azetidin-3-yl trifluoromethanesulfonate (**143**)



To a stirred solution of deuterated azetidine *cis*-**126a** (417 mg, 2.39 mmol) in CH_2Cl_2 (10 mL) at –78 °C was added DIPEA (538 μL, 3.11 mmol) followed by dropwise addition of Tf_2O (482 μL, 2.87 mmol). After 30 min, MeOH (1 mL) was added and the reaction mixture concentrated to dryness under reduced pressure. Purification (Si-gel, pet ether/EtOAc 19:5→9:1) gave triflate **143** as a pale yellow syrup which solidified on standing (601 mg, 82%).

- R_f 0.27 (pet ether/EtOAc 3:2);
- **mp** 55-57 °C;
- **IR** (neat/cm^{-1}) 2981 w, 2907 w, 1470 m, 1441 m, 1353 s, 1218 m, 1171 m, 986 m, 914 m, 849 m;
- **^{1}H NMR** (400 MHz, $CDCl_3$) 5.49 (1H, td, *J* = 6.4, 3.8 Hz, CHO), 4.91 (0.95 H, dd, *J* = 11.9, 6.9 Hz, $NCH_{cis}\underline{H}_{trans}$ and $NCD_{cis}\underline{H}_{trans}$), 4.73-4.62 (1.51H, m, $NC\underline{H}_{cis}\underline{H}_{trans}$ and $NCD_{cis}\underline{H}_{trans}$), 4.46 (0.58H, ddd, *J* = 13.8, 3.8, 2.1 Hz, $NC\underline{H}_{cis}H_{trans}$), 1.36 (9H, s, $C(CH_3)_3$);
- **^{13}C NMR** (100 MHz, $CDCl_3$) 211.7 (C=S), 118.3 (Q, *J* = 320 Hz, CF_3), 72.9 (CHO), 72.9 (t, *J* = 5 Hz, CHO), 62.7 (NCH_2), 62.4 (T, *J* = 23 Hz, NCHD), 61.7 (NCH_2), 61.4 (T, *J* = 23 Hz, NCHD), 43.6 ($\underline{C}(CH_3)_3$), 29.7 ($C(\underline{C}H_3)_3$);
- **^{19}F NMR** (377 MHz, $CDCl_3$) -74.7 (CF_3);
- **LRMS** (FI^+) 306.04 ($[M]^+$, 100%); **HRMS** (FI^+) calcd for $C_9H_{13}DF_3NO_3S_2$:306.0430, found 306.0432.

2,2-Dimethyl-1-(4-deutroazet-1(2*H*)-yl)propane-1-thione (**149a**)

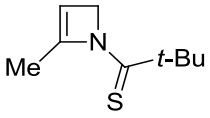


To a stirred solution of methoxyazetidine **208** (50 mg, 0.27 mmol) in THF (1 mL) at –78 °C was added *s*-BuLi (420 μL, 1.4 M in cyclohexane/hexane (92:8), 0.57 mmol) was added dropwise to the reaction mixture over 1 min. After 30 min, CD_3OD (29 μL, 0.80 mmol) was added. The cooling bath was removed and the reaction mixture stirred for a further 5 min. The reaction mixture was washed with sat. aq $NaHCO_3$ (5 mL) and extracted with Et_2O (2 x 5 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated to dryness under reduced pressure. Purification (Si-gel, pet ether/EtOAc 1:0→19:1 with 0.5% Et_3N) gave deuterated azetine **149a** as a yellow syrup (14 mg, 28%, 100%D by ^1H NMR analysis).

Discernable data

- R_f 0.30 (pet ether/Et_2O 9:1);
- **^{1}H NMR** (400 MHz, $CDCl_3$, 3:1 mixture of rotamers) Major rotamer: 6.03 (1H, s, NCD=C<u>H</u>), 4.66 (2H, s, NCH_2), 1.38 (9H, s, $C(CH_3)_3$); Minor rotamer: 6.13 (1H, s, NCD=C<u>H</u>), 4.86 (2H, s, NCH_2), 1.41 (3H, s, $C(CH_3)_3$);
- **^{13}C NMR** (100 MHz, $CDCl_3$) Major rotamer: 203.7 (C=S), 117.8 (NCH=<u>C</u>H), 62.0 (NCH_2), 43.0 (<u>C</u>$(CH_3)_3$), 30.3 (C(<u>C</u>$H_3)_3$); Minor rotamer: 203.8 (C=S), 118.5 (NCH=<u>C</u>H), 63.9 (NCH_2), 43.0 (<u>C</u>$(CH_3)_3$), 31.0 (C(<u>C</u>$H_3)_3$).

2,2-Dimethyl-1-(4-methylazet-1(2*H*)-yl)propane-1-thione (**149b**)



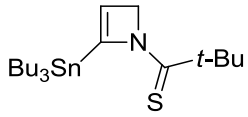
To a stirred solution of silyloxythioamide **98** (65 mg, 0.23 mmol) in THF (1 mL), at –78 °C was added TMEDA (204 μL, 1.36 mmol). *s*-BuLi (496 μL, 1.4 M in cyclohexane/hexane (92/8), 0.68

mmol) was added dropwise to the reaction mixture over 2 min. After 1 h, MeI (42 μL, 0.68 mmol) was added and the reaction mixture stirred for 30 min. The cooling bath was removed and the reaction mixture was stirred for another 1 h, quenched with aq HCl (1 M, 5 mL) and extracted with Et_2O (2 x 5 mL). The combined organic layers were washed with H_2O (5 mL) then brine (5 mL), dried (Na_2SO_4), and concentrated to dryness under reduced pressure. Purification (Si-gel, pet ether/Et_2O 1:0→19:1) gave impure methyl azetine **149b** as a yellow syrup (10 mg, ~26%).

Discernable data

- R_f 0.64 (pet ether/Et_2O 9:1);
- **^{1}H NMR** (400 MHz, $CDCl_3$) 5.79 (1H, s, NCH=C<u>H</u>), 4.75 (2H, s, NCH_2), 2.46-2.43 (3H, m, CH_3), 1.40 (9H, s, $C(CH_3)_3$).

2,2-Dimethyl-1-(4-(tributylstannyl)azet-1(2*H*)-yl)propane-1-thione (**149c**)

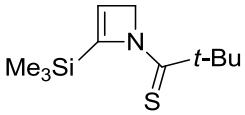


To a stirred solution of silyloxythioamide **98** (65 mg, 0.23 mmol) in THF (1 mL), at –78 °C was added TMEDA (204 μL, 1.36 mmol). *s*-BuLi (496 μL, 1.4 M in cyclohexane/hexane (92/8), 0.68 mmol) was added dropwise to the reaction mixture over 2 min. After 1 h, Bu_3SnCl (184 μL, 0.68 mmol) was added and the reaction mixture stirred for 30 min. The cooling bath was removed and the reaction mixture was stirred for another 1 h, quenched with aq HCl (1 M, 5 mL) and extracted with Et_2O (2 x 5 mL). The combined organic layers were washed with H_2O (5 mL) then brine (5 mL), dried (Na_2SO_4), and concentrated to dryness under reduced pressure. Purification (Si-gel, pet ether/Et_2O 1:0→9:1) gave Bu_3Sn residue contaminated stannyl azetine **149c** as a yellow syrup (217 mg, ~33%, through ^{1}H NMR quantitative analysis of integration values of NCH_2 5.06 ppm (stannyl azetine **149c**) and $Sn(CH_2CH_2CH_2C\underline{H}_3)_3$, 0.92 ppm ($Bu_3Sn$)).

Discernable data

- R_f 0.97 (pet ether/Et_2O 9:1);
- **^{1}H NMR** (400 MHz, $CDCl_3$) 6.50 (1H, s, NCH=C<u>H</u>), 5.06 (2H, s, NCH_2), 1.75-1.22 (18H, m, 3 x C<u>H</u>$_2$C<u>H</u>$_2$C<u>H</u>$_2$CH$_3$), 1.40 (9H, s, C(CH_3)$_3$), 0.94-0.91 (9H, m, 3 x $CH_2CH_2CH_2C$<u>H</u>$_3$).

2,2-Dimethyl-1-(4-(trimethylsilyl)azet-1(2*H*)-yl)propane-1-thione (**149d**)

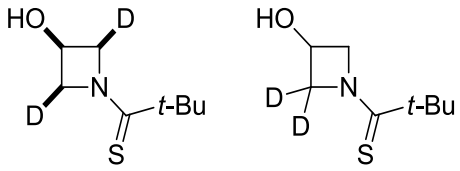


To a stirred solution of methoxyazetidine **208** (50 mg, 0.27 mmol) in THF (1 mL), at –78 °C was added TMSCl (102 μL, 0.80 mmol) and TMEDA (85 μL, 0.57 mmol). *s*-BuLi (420 μL, 1.4 M in cyclohexane/hexane (92/8), 0.57 mmol) was added dropwise to the reaction mixture over 2 min. After 1 h, the cooling bath was removed and the reaction mixture was stirred for another 30 min, washed with sat. aq NH_4Cl (5 mL) and extracted with Et_2O (2 x 5 mL). The combined organic layers were dried (Na_2SO_4), and concentrated to dryness under reduced pressure. Crude ^{1}H NMR analysis indicated silyl azetine **149d**:starting azetidine **208** (61:39) by integration of peaks at 4.94 ppm (silyl azetine **149d**) and 3.31 ppm (starting azetidine **208**). Purification (Si-gel, pet ether/Et_2O 1:0→24:1) gave impure silyl azetine **149d** as a yellow syrup (29 mg, ~48%).

Discernable data

- R_f 0.76 (pet ether/Et_2O 9:1);
- **^{1}H NMR** (400 MHz, $CDCl_3$) 6.49 (1H, s, NCH=C<u>H</u>), 4.94 (2H, s, NCH_2), 1.41 (9H, s, C(CH_3)$_3$) 0.29 (9H, s, Si(CH_3)$_3$);
- **^{13}C NMR** (100 MHz, $CDCl_3$) 202.6 (C=S), 166.2 (NCH), 132.0 (NCH=<u>C</u>H), 65.1 (NCH_2), 43.6 (<u>C</u>(CH_3)$_3$), 31.2 (C(<u>C</u>H$_3$)$_3$) -0.13 (Si(CH_3)$_3$).

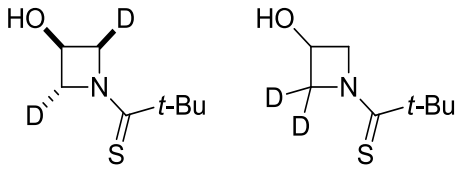
Lithiation–deuteration of *cis*-126a: 1-(2,4-Dideutero-3-hydroxyazetidin-1-yl)-2,2-dimethylpropane-1-thione (151-2,4Dcc) and 1-(2,2-Dideutero-3-hydroxyazetidin-1-yl)-2,2-dimethylpropane-1-thione (151-2,2D)



To a stirred solution of azetidinol *cis*-**126a** (50 mg, 0.29 mmol) in THF (1 mL), at –78 °C was added TMEDA (261 μL, 1.74 mmol). *s*-BuLi (614 μL, 1.40 M in cyclohexane/hexane (92/8), 0.86 mmol) was added very slow dropwise to the reaction mixture over 5 min. After 30 min, CD_3OD (52 μL, 1.45 mmol) was added and the reaction mixture stirred for 10 min. The cold bath was removed and the reaction mixture was stirred for another 10 min, quenched with aq HCl (1 M, 5 mL) and extracted with EtOAc (3 x 5 mL). The combined organic layers were washed with H_2O (5 mL) then brine (5 mL), dried (Na_2SO_4), and concentrated to dryness under reduced pressure to give azetidinol **151** as a pale yellow syrup (50 mg, 95%, 99% 2D, 62:38 2,4-:2,2-, dr determined by integration of δ_H 4.66 + 4.42 and 4.29 + 4.04 in comparison to *cis*-**126a**).

- **IR** (neat/cm^{-1}) 3365 br, 2967 w, 2932 w, 1465 s, 1364 w, 1134 s, 1007 m, 913 m, 730 s;
- **^{1}H NMR** (400 MHz, $CDCl_3$) 4.66 (0.76H, dd, *J* = 11.1, 6.6 Hz, $NCH_{cis}\underline{H}_{trans}$ and $NCD_{cis}\underline{H}_{trans}$), 4.59 (1H, t, *J* = 6.6 Hz, C<u>H</u>OH), 4.42 (0.76H, dd, *J* = 12.9, 6.6 Hz, $NCH_{cis}\underline{H}_{trans}$ and $NCD_{cis}\underline{H}_{trans}$), 4.29 (0.23H, dd, *J* = 11.1, 3.5 Hz, $NC\underline{H}_{cis}H_{trans}$), 4.04 (0.26H, dd, *J* = 12.9, 3.5 Hz, $NC\underline{H}_{cis}H_{trans}$), 3.76 (1H, br s, OH), 1.29 (9H, s, $C(CH_3)_3$);
- **^{13}C NMR** (100 MHz, $CDCl_3$) 209.9 (C=S), 65.8 (NCH_2), 65.5 (T, *J* = 23 Hz, NCHD), 65.4 (NCH_2) 65.1 (T, *J* = 23 Hz, NCHD), 59.5 (CHOH), 59.5 (t, *J* = 8 Hz, CHOH), 43.1 ($\underline{C}(CH_3)_3$), 29.5 ($C(\underline{C}H_3)_3$);
- **LRMS** (ESI^+) 198.08 ($[M+Na]^+$, 93%); **HRMS** (FI^+) calcd for $C_8H_{13}D_2NOS$: 175.1000, found 175.1001.

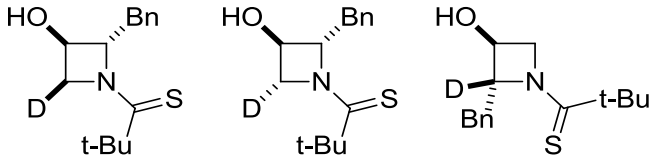
Lithiation–deuteration of *trans*-126a: 1-(2,4-Dideutero-3-hydroxyazetidin-1-yl)-2,2-dimethyl propane-1-thione (151-2,4Dtc) and 1-(2,2-Dideutero-3-hydroxyazetidin-1-yl)-2,2-dimethylpropane-1-thione (151-2,2D)



To a stirred solution of azetidinol *trans*-**126a** (50 mg, 0.29 mmol) in THF (1 mL), at –78 °C was added TMEDA (261 μL, 1.74 mmol). *s*-BuLi (614 μL, 1.40 M in cyclohexane/hexane (92/8), 0.86 mmol) was added very slow dropwise to the reaction mixture over 5 min. After 30 min, CD_3OD (52 μL, 1.45 mmol) was added and the reaction mixture stirred for 10 min. The cold bath was removed and the reaction mixture was stirred for another 10 min, quenched with aq HCl (1 M, 5 mL) and extracted with EtOAc (3 x 5 mL). The combined organic layers were washed with H_2O (5 mL) then brine (5 mL), dried (Na_2SO_4), and concentrated to dryness under reduced pressure to give azetidinol **151** as a pale yellow syrup (45 mg, 90%, 91% 2D, 82:18 2,4-:2,2-, dr determined by integration of δ_H 4.69 + 4.46 and 4.31 + 4.08 in comparison to *trans*-**126a**).

- **IR** (neat/cm^{-1}) 2251 br, 2968 w, 1467 s, 1364 w, 1139 m, 1112 m, 1007 w, 912 w, 730 s;
- **^{1}H NMR** (400 MHz, $CDCl_3$) 4.69 (0.47H, dd, *J* = 11.1, 6.6 Hz, $NCH_{cis}\underline{H}_{trans}$ and $NCD_{cis}\underline{H}_{trans}$), 4.64-4.60 (1H, m, C<u>H</u>OH), 4.46 (0.49H, dd, *J* = 12.9, 6.6 Hz, $NCH_{cis}\underline{H}_{trans}$ and $NCD_{cis}\underline{H}_{trans}$), 4.31 (0.56H, dd, 11.1, 3.9 Hz, $NC\underline{H}_{cis}H_{trans}$ and $NC\underline{H}_{cis}D_{trans}$), 4.08 (0.57H, dd, *J* = 12.9, 3.9 Hz, $NC\underline{H}_{cis}H_{trans}$ and $NC\underline{H}_{cis}D_{trans}$), 3.46 (1H, br, OH), 1.32 (9H, s, $C(CH_3)_3$);
- **^{13}C NMR** (100 MHz, $CDCl_3$) 210.0 (C=S), 65.8 (NCH_2), 65.5 (T, *J* = 23 Hz, NCHD), 65.5 (T, *J* = 23 Hz, NCHD), 65.5 (NCH_2), 65.2 (T, *J* = 23 Hz, NCHD), 65.1 (T, *J* = 23 Hz, NCHD), 59.7 (CHOH), 59.7 (t, *J* = 8 Hz, CHOH), 59.7 (t, *J* = 8 Hz, CHOH), 43.2 ($\underline{C}(CH_3)_3$), 29.6 ($C(\underline{C}H_3)_3$);
- **LRMS** (ESI^+) 198.1 ($[M+Na]^+$, 100%); **HRMS** (ESI^+) calcd for $C_8H_{13}D_2NNaOS$:198.0892, found 198.0893.

Lithiation–benzylation of *cis*-126a: 1-(4-Deutero-3-hydroxy-2-phenylazetidin-1-yl)-2,2-dimethylpropane-1-thione (155-2D$_c$-4Bn$_t$, 155-2D$_t$-4Bn$_t$), 1-(4-Deutero-3-hydroxy-2-phenylazetidin-1-yl)-2,2-dimethylpropane-1-thione (155-2D$_c$-2Bn$_t$)

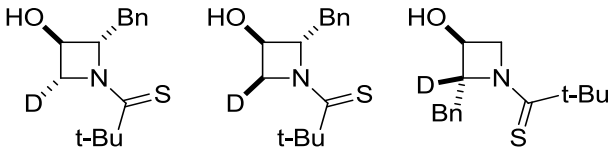


To a stirred solution of azetidinol *cis*-**126a** (50 mg, 0.29 mmol) in THF (1 mL), at –78 °C was added TMEDA (261 µL, 1.74 mmol). *s*-BuLi (614 µL, 1.4 M in cyclohexane/hexane (92/8) , 0.86 mmol) was added very slow dropwise to the reaction mixture over 5 min. After 30 min, BnBr (102 µL, 0.86 mmol) was added and the reaction mixture stirred for 30 min. The reaction mixture was warmed to rt and stirred for another 30 min, quenched with aq HCl (1 M, 5 mL) and extracted with EtOAc (3 x 5 mL). The combined organic layers were washed with H_2O (5 mL) and brine (5 mL), dried (Na_2SO_4), and concentrated to dryness under reduced pressure. Purification (Si-gel, Heptane/EtOAc 1:0→2:3) gave azetidinol **155** as a pale yellow syrup (52 mg, 69%, 100% D, 61:6:33 2D$_c$-4Bn$_t$:2D$_t$-4-Bn$_t$:2D$_c$-2Bn$_t$, dr determined by integration of δ_H 4.80, 4.18 and 4.08).

- ***R**$_f$* 0.64 (pet ether/EtOAc 3:2);
- **IR** (neat/cm^{-1}) 3364 br, 3027 w, 2967 w, 1454 s, 1434 m, 1395 w, 1135 m, 1096 m, 910 m, 730 s, 702 m;
- **^{1}H NMR** (400 MHz, $CDCl_3$) 7.32-7.22 (5H, m, Ar), 4.80 (0.67H, ddd, *J* = 7.6, 3.5, 2.9 Hz, NCH) 4.24 (1H, dd, *J* = 6.3, 2.9 Hz, C<u>H</u>OH), 4.18 (0.94H, dd, *J* = 11.1, 6.3 Hz, NCH$_{Cis}$<u>H</u>$_{Trans}$ and NCD$_{cis}$<u>H</u>$_{trans}$), 4.08 (0.38H, dd, *J* = 11.1, 2.9 Hz, NC<u>H</u>$_{Cis}$H$_{Trans}$ and NC<u>H</u>$_{cis}$D$_{trans}$), 3.43 (1H, dd, *J* = 13.9, 3.5 Hz, C<u>H</u>HPh), 3.35 (0.3H, d, *J* = 13.9 Hz, CDC<u>H</u>HPh), 3.36 (0.7H, dd, *J* = 13.9, 7.6 Hz, CH<u>H</u>Ph), 2.63 (1H, br, OH), 1.31 (9H, s, C(CH$_3$)$_3$);
- **^{13}C NMR** (100 MHz, $CDCl_3$) 211.8 (C=S), 136.5 (Ar), 129.7 (Ar), 128.4 (Ar), 126.7 (Ar), 77.5 (NCH), 65.3 (CHOH), 64.7 (NCH$_2$), 64.4 (T, *J* = 23 Hz, NCDH), 43.6 (<u>C</u>(CH$_3$)$_3$), 33.9 (<u>C</u>H$_2$Ph), 29.7 (C(<u>C</u>H$_3$)$_3$);

- **LRMS** (ESI^+) 287.12 ([M+Na]$^+$, 100%); **HRMS** (ESI^+) calcd for $C_{15}H_{20}DNNaOS$: 287.1299, found 287.1296.

Lithiation–benzylation of *trans*-126a: 1-(4-Deutero-3-hydroxy-2-phenylazetidin-1-yl)-2,2-dimethylpropane-1-thione (155-2D$_t$-4Bn$_t$, 155-2D$_c$-4Bn$_t$), 1-(2-Deutero-3-hydroxy-2-phenylazetidin-1-yl)-2,2-dimethylpropane-1-thione (155-2D$_c$-2Bn$_t$)

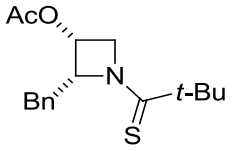


To a stirred solution of azetidinol *trans*-**126a** (26 mg, 0.15 mmol) in THF (0.5 mL), at –78 °C was added TMEDA (135 μL, 0.90 mmol). *s*-BuLi (333 μL, 0.45 mmol, 1.35 M in cyclohexane/hexane (92/8)) was added very slow dropwise to the reaction mixture over 5 min. After 30 min, BnBr (54 μL, 0.45 mmol) was added and the reaction mixture stirred for 30 min. The reaction mixture was warmed to rt and stirred for another 30 min, quenched with aq HCl (1 M, 5 mL) and extracted with EtOAc (3 x 5 mL). The combined organic layers were washed with H_2O (5 mL) and brine (5 mL), dried (Na_2SO_4), and concentrated to dryness under reduced pressure. Purification (Si-gel, pet ether/EtOAc 4:1→2:3) gave azetidinol **155** as a pale yellow syrup (19 mg, 48%, 100% D, 60:10:30 2D$_t$-4Bn$_t$:2D$_c$-4-Bn$_t$:2D$_c$-2Bn$_t$, dr determined by integration of δ_H 4.81, 4.19 and 4.09).

- ***R**$_f$* 0.64; (pet ether/EtOAc 3:2);
- **IR** (neat/cm^{-1}) 3373 br, 2967 w, 1454 s, 1435 m, 1129 m, 1091 m, 997 m, 910 m, 730 s, 702 m;
- **^{1}H NMR** (400 MHz, $CDCl_3$) 7.32-7.23 (5H, m, Ar), 4.81 (0.70H, dt, *J* = 6.6, 2.8 Hz, NCH), 4.25 (1H, m, C<u>H</u>OH), 4.19 (0.40H, dd, *J* = 11.1, 6.8 Hz, NCH$_{Cis}$<u>H</u>$_{Trans}$ and NCD$_{cis}$<u>H</u>$_{trans}$), 4.09 (0.90H, dd, *J* = 11.1, 2.8 Hz, NC<u>H</u>$_{Cis}$H$_{Trans}$ and NC<u>H</u>$_{cis}$D$_{trans}$), 3.43 (1H, dd, *J* = 13.9, 3.5 Hz, C<u>H</u>HPh), 3.35 (0.3H, d, *J* = 13.9 Hz, CDC<u>H</u>HPh), 3.36 (0.7H, dd, *J* = 13.9, 7.6 Hz, CH<u>H</u>Ph), 2.52 (1H, br, OH), 1.32 (9H, s, C(CH$_3$)$_3$);

- **^{13}C NMR** (100 MHz, $CDCl_3$) 211.7 (C=S), 136.5 (Ar), 129.7 (Ar), 128.4 (Ar), 126.8 (Ar), 77.5 (NCH), 65.3 (CHOH), 64.7 (NCH_2), 64.4 (T, *J* = 23 Hz, NCDH), 43.6 ($\underline{C}(CH_3)_3$), 33.9 ($\underline{C}H_2$)Ph), 29.7 ($C(\underline{C}H_3)_3$);
- **LRMS** (ESI^+) 265.1 ($[M+H]^+$, 100%); **HRMS** (ESI^+) calcd for $C_{15}H_{20}DNNaOS$: 287.1299, found 287.1290.

2-Benzyl-1-(2,2-dimethylpropanethioyl)azetidin-3-yl acetate (**156**)

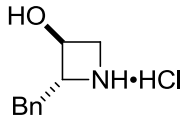


To a stirred solution of benzyl azetidine *trans*-**126d** (412 mg, 1.56 mmol) in CH_2Cl_2 (5 mL) at –78 °C was added DIPEA (351 μL, 2.02 mmol) followed by dropwise addition of Tf_2O (289 μL, 1.72 mmol). After 30 min, MeOH (1 mL) was added and the reaction mixture concentrated to dryness under reduced pressure. The crude triflate was dissolved in DMF (5 mL) and to it was added NaOAc (1.28 g, 16 mmol) and the reaction mixture was heated to 70 °C. After 2 h, the reaction mixture was cooled to rt, washed with H_2O (10 mL) and extracted with EtOAc (3 x 10 mL), the combined organic layers were dried (Na_2SO_4), filtered and concentrated to dryness under reduced pressure. Purification (Si-gel, pet ether/EtOAc 39:1→9:1) gave inverted acetate **156** as a colourless syrup (245 mg, 51%).

- $\boldsymbol{R_f}$ 0.44 (pet ether/EtOAc 9:1);
- **IR** (neat/cm^{-1}) 2968 w, 2872 w, 1742 s, 1455 m, 1431 m, 1364 w, 1224 s, 1155 w, 1111 m, 1007 w, 910 m, 729 s, 700 m;
- **^{1}H NMR** (400 MHz, $CDCl_3$) 7.36-7.19 (5H, m, Ar), 5.36-5.28 (2H, m, NCH and C$\underline{H}$OH), 4.75 (1H, ddd, *J* = 10.9, 7.3, 1.0 Hz, NC$\underline{H}_{trans}H_{cis}$), 4.20 (1H, ddd, *J* = 10.9, 5.3, 1.5 Hz, $NCH_{trans}\underline{H}_{cis}$), 3.78 (1H, dd, *J* = 13.8, 1.6 Hz, C$\underline{H}$HPh), 3.30 (1H, dd, *J* = 13.8, 9.2 Hz, CH$\underline{H}$Ph), 2.09 (3H, s, CH_3), 1.32 (9H, s, $C(CH_3)_3$);

- **^{13}C NMR** (100 MHz, $CDCl_3$) 210.7 (C=S), 170.0 (C=O), 137.3 (Ar), 129.5 (Ar), 128.1 (Ar), 126.4 (Ar), 72.4 (NCH), 63.6 (CHOH), 63.3 (NCH_2), 43.6 ($\underline{C}(CH_3)_3$), 30.4 ($N\underline{C}H_2Ph$), 29.6 ($C(\underline{C}H_3)_3$), 20.6 (CH_3);
- **LRMS** (ESI^+) 306.2 ($[M+H]^+$, 100%); **HRMS** (ESI^+) calcd for $C_{17}H_{23}NNaO_2S$: 328.1342, found 328.1337.

2-Benzylazetidin-3-ol hydrochloride (**157**)

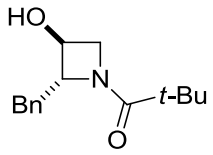


To a solution of benzylated azetidinol *trans*-**126d** (69 mg, 0.26 mmol) in THF at 0 °C was added TMEDA (196 μL, 1.31 mmol) and MeLi (873 μL, 1.50 M in Et_2O, 1.31 mmol). After 4 h, the reaction mixture was quenched with MeOH (few drops) and concentrated to dryness under reduced pressure. The crude residue was dissolved in a minimum of MeOH and loaded onto a SCX-2 ion exchange column. The column was washed through with CH_2Cl_2 (20 mL) and collected. The amine product was released with NH_3 (10 mL, 7 M in MeOH) followed by CH_2Cl_2 (20 mL) and collected. The basic fractions were concentrated to dryness under reduced pressure, redissolved in MeOH (2 mL) and treated with HCl (2 M in Et_2O, 2 mL), followed by concentrating to dryness under reduced pressure to isolate the crude hydrochloride salt. The crude product was suspended in acetone (2 mL) and decanted to remove organic impurities, giving azetidine hydrochloride salt **157** as a pale yellow solid (48 mg, 92%).

- **mp** 127-131 °C;
- **IR** (neat/cm^{-1}) 3306 br, 2956 w, 2938 w, 2458 m, 2184 br, 1454 w, 1173 m, 1117 m, 1031 w, 977 w, 747 m, 702 s;
- **^{1}H NMR** (400 MHz, CD_3OD) 7.38-7.25 (5H, m, Ar), 4.53 (1H, q, *J* = 7.4 Hz, C$\underline{H}$OH), 4.40 (1H, ddd, *J* = 8.9, 7.4, 6.8 Hz, NCH), 4.07 (1H, dd, *J* = 10.5, 7.4 Hz, NC$\underline{H}$H), 3.74 (1H, dd, *J* = 10.5, 7.4 Hz, NCH$\underline{H}$), 3.24 (1H, dd, *J* = 14.4, 6.8 Hz, C$\underline{H}$HPh), 3.17 (1H, dd, *J* = 14.4, 8.9 Hz, CH$\underline{H}$Ph);

- **^{13}C NMR** (100 MHz, CD_3OD) 136.5 (Ar), 130.2 (Ar), 130.1 (Ar), 128.5 (Ar), 73.0 (NCH), 68.4 (CHOH), 53.1, (NCH_2), 38.1 ($\underline{C}H_2Ph$);
- **LRMS** (ESI^+) 164.09 ($[M\text{-}HCl+H)]^+$, 40%); **HRMS** (ESI^+) calcd for $C_{10}H_{14}NO$: 164.1070, found 164.1070.

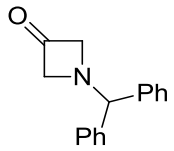
1-(2-Benzyl-3-hydroxyazetidin-1-yl)-2,2-dimethylpropan-1-one (**158**)



To an ice-cold stirred solution of AcOH (3 mL) and H_2O_2 (4 mL, 35% in H_2O) was added benzylated azetidinol *trans*-**126d** (59 mg, 0.24 mmol) in CH_2Cl_2 (1 mL). After 4 h at 0 °C, the reaction mixture was poured onto sat. aq $NaHCO_3$ (30 mL), and extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with sat. aq $NaHCO_3$ (10 mL), H_2O (10 mL), then brine (10 mL), dried (Na_2SO_4), filtered and concentrated to dryness under reduced pressure to give pivalamide **158** as a colourless syrup (45 mg, 81%).

- $\boldsymbol{R_f}$ 0.23 (pet ether/EtOAc 3:2);
- **IR** (neat/cm^{-1}) 2359 br, 2963 w, 1595 s, 1412 m, 1364 w, 1232 w, 1129 w, 736 w, 702 m;
- **^{1}H NMR** (400 MHz, $CDCl_3$) 7.32-7.20 (5H, m, Ar), 4.44 (1H, ddd, *J* = 7.8, 3.7, 3.3 Hz, NCH), 4.18 (1H, dt, *J* = 6.8, 3.7 Hz, C$\underline{H}$OH), 4.10 (1H ddd, *J* = 9.3, 6.8, 1.0 Hz, $NCH_{cis}\underline{H}_{trans}$), 3.95 (1H, dd, *J* = 9.3, 3.7 Hz, $NC\underline{H}_{cis}H_{trans}$), 3.20, (1H, dd, *J* = 13.9, 3.3 Hz, C$\underline{H}$HPh), 3.02 (1H, dd, *J* = 13.9, 7.8 Hz, CH$\underline{H}$Ph), 1.15 (9H, s, $C(CH_3)_3$);
- **^{13}C NMR** (100 MHz, $CDCl_3$) 179.1 (C=O), 136.7 (Ar), 129.6 (Ar), 128.3 (Ar), 126.4 (Ar), 71.7 (NCH), 65.7 (CHOH), 60.1 (NCH_2), 38.7 ($\underline{C}(CH_3)_3$), 36.7 ($\underline{C}H_2Ph$), 27.0 ($C(\underline{C}H_3)_3$);
- **LRMS** (ESI^+) 270.12 ($[M+Na]^+$, 78%); **HRMS** (ESI^+) calcd for $C_{15}H_{21}NNaO_2$: 270.1465, found 270.1466.

1-Benzhydrylazetidin-3-one (**168a**)

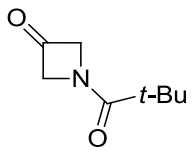


To a stirred solution of oxalylchloride (370 μL, 4.4 mmol) in CH_2Cl_2 (2 mL) at –78 °C was added DMSO (620 μL, 8.8 mmol) cautiously over 2 min. Azetidinol **106** (350 mg, 1.5 mmol) in CH_2Cl_2 (2 mL) was added dropwise to the reaction mixture over 2 min. After 30 min Et_3N (1.8 mL, 13.2 mmol) was added dropwise to the reaction mixture over 4 min, and the cold bath removed. After 30 min the reaction mixture was poured onto H_2O (10 mL) and extracted with CH_2Cl_2 (2 x 5 mL). The combined organic layers were washed with brine (10 mL), dried (Na_2SO_4), and concentrated to dryness under reduced pressure. Purification (Si-gel, pet ether/EtOAc 1:0→19:1) gave azetidinone **168a**[148] as a pale yellow syrup which crystallised on standing (333 mg, 96%).

- R_f 0.90 (Pet ether/EtOAc 3:2);
- **mp** 74–76 °C;
- **IR** (neat/cm^{-1}) 2947 w, 2806 w, 1808 s, 1490 m, 1008 m, 755 m, 702 m;
- **^{1}H NMR** (400 MHz, $CDCl_3$) 7.51-7.22 (10H, m, Ar), 4.62 (1H, s, C<u>H</u>Ph_2), 4.02 (4H, s, NCH_2);
- **^{13}C NMR** (100 MHz, $CDCl_3$) 201.0 (C=O), 142.3 (Ar), 128.7 (Ar), 127.5 (Ar), 127.2 (Ar), 77.8 (<u>C</u>HPh_2), 74.2 (NCH_2);

LRMS (ESI^-) 236.12 ($[M-H]^-$, 96%); **HRMS** (ESI^+) calcd for $C_{15}H_{15}NONa$: 260.1046, found 260.1045.

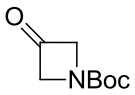
1-Pivalamido azetidin-3-one (**168b**)



To a stirred solution of oxalylchloride (1.2 mL, 14.4 mmol) in CH_2Cl_2 (6 mL) at -78 °C was added DMSO (2.0 mL, 28.7 mmol) cautiously over 2 min. Azetidinol **130** (830 mg, 4.8 mmol) in CH_2Cl_2 (6 mL) was added dropwise to the reaction mixture over 2 min. After 30 min Et_3N (6.0 mL, 43.1 mmol) was added dropwise to the reaction mixture over 4 min, and the cold bath removed. After 30 min the reaction mixture was poured onto H_2O (20 mL) and extracted with CH_2Cl_2 (2 x 25 mL). The combined organic layers were washed with brine (20 mL), dried (Na_2SO_4), and concentrated to dryness under reduced pressure. Purification (Si-gel, pet ether/EtOAc 9:1→7:3) gave azetidinone **168b** as a pale yellow syrup which crystallised on standing (605 mg, 72%).

- R_f 0.59 (Pet ether/EtOAc 1:4);
- **mp** 36-39 °C;
- **IR** (neat/cm^{-1}) 2976 w, 2919 w, 1824 s, 1612 s, 1414 m, 1364 m, 1063 m, 898 m;
- **^{1}H NMR** (400 MHz, $CDCl_3$) 4.82 (4H, s, NCH_2), 1.18 (9H, s, $C(CH_3)_3$);
- **^{13}C NMR** (100 MHz, $CDCl_3$) 196.2 (C=O), 177.6 (NC=O), 71.6 (NCH_2), 38.7 ($\underline{C}(CH_3)_3$), 27.1 ($C(\underline{C}H_3)_3$);
- **LRMS** (FI^+) 155.09 ($[M]^+$ 100%); **HRMS** (FI^+) calcd for $C_8H_{13}NO_2$: 155.0946, found 155.0943.

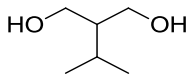
***tert*-Butyl 3-oxoazetidine-1-carboxylate (168c)**



To a stirred solution of oxalylchloride (900 μL, 10.6 mmol) in CH_2Cl_2 (5 mL) at –78 °C was added DMSO (1.5 mL μL, 21.2 mmol) cautiously over 2 min. Azetidinol **132** (610 mg, 3.5 mmol) in CH_2Cl_2 (5 mL) was added dropwise to the reaction mixture over 2 min. After 30 min Et_3N (4.4 mL, 31.8 mmol) was added dropwise to the reaction mixture over 4 min, and the cold bath removed. After 30 min the reaction mixture was poured onto H_2O (20 mL) and extracted with CH_2Cl_2 (2 x 10 mL). The combined organic layers were washed with brine (20 mL), dried (Na_2SO_4), and concentrated to dryness under reduced pressure. Purification (Si-gel, pet ether/EtOAc 1:0→19:1) gave azetidinone **168c**[149] as a pale yellow syrup which crystallised on standing (473 mg, 78%).

- R_f 0.80 (Pet ether/EtOAc 3:2);
- **mp** 44–47 °C;
- **IR** (neat/cm^{-1}) 3003 w, 2930 w, 1819 m, 1695 s, 1364 s, 1154 m, 1118 m, 763 m;
- **^{1}H NMR** (400 MHz, $CDCl_3$) 4.66 (4H, s, NCH_2), 1.46 (9H, s, $C(CH_3)_3$);
- **^{13}C NMR** (100 MHz, $CDCl_3$) 196.6 (C=O), 155.9 (NC=O), 80.8 ($\underline{C}(CH_3)_3$), 70.9 (NCH_2), 28.2 ($C(\underline{C}H_3)_3$);
- **LRMS** (FI^+) 171.09 ($[M]^+$ 100%); **HRMS** (FI^+) calcd for $C_8H_{13}NO_3$: 171.0895, found 171.0891.

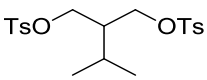
2-Isopropylpropane-1,3-diol (**176**)[150]



To a stirred solution of isopropylmalonate **175** (2.00 g, 9.89 mmol) in THF (25 mL) at 0 °C was carefully added $LiAlH_4$ (750 mg, 20 mmol) portion-wise. The cold bath was removed and after 30 min the reaction mixture was quenched very carefully dropwise with H_2O (40 mL). The aq layer was extracted with EtOAc (2 x 40 mL), dried (Na_2SO_4), and concentrated to dryness under reduced pressure. Purification (Si-gel, pet ether/EtOAc 4:1 → 0:1) gave diol **176** as a clear syrup (1.10 g, 94%).

- R_f 0.21 (pet ether/EtOAc 2:3);
- **IR** (neat/cm^{-1}) 3329 br, 2958 m, 2876 w, 1468 w, 1017 s, 733 m;
- **^{1}H NMR** (400 MHz, $CDCl_3$) 3.80 (2H, dd, *J* = 10.5, 3.5 Hz, 2 x C<u>H</u>HOH), 3.71 (2H, dd, *J* = 10.5, 7.8 Hz, 2 x CH<u>H</u>OH), 3.71 (2H, br, s, OH), 1.70 (1H, dsept, *J* = 7.8, 6.8 Hz, C<u>H</u>$(CH_3)_2$), 1.50 (1H, qt, *J* = 7.8, 3.5 Hz, C<u>H</u>$(CH_2OH)_2$), 0.90 (6H, d, *J* = 6.8 Hz, CH(C<u>H</u>$_3)_2$);
- **^{13}C NMR** (100 MHz, $CDCl_3$) 64.5 (CH_2OH), 47.8 (<u>C</u>H$(CH_2OH)_2$), 26.3 (<u>C</u>H$(CH_3)_2$), 20.2 (CH(<u>C</u>H$_3)_3$);
- **LRMS** (FI^+) 188.10 ($[M]^+$,100%); HRMS (FI^+) calcd for $C_6H_{14}O_2$: 118.0994, found 118.0998.

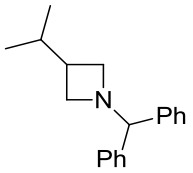
2-Isopropylpropane-1,3-diyl bis(4-methylbenzenesulfonate) (**177**)



To a stirred solution of diol **176** (200 mg, 1.69 mmol) in CH_2Cl_2 (4 mL) at 0 °C was added Et_3N (950 µL, 6.8 mmol), DMAP (19 mg, 0.17 mmol) and TsCl (1.13 g, 5.92 mmol). The cold bath was removed and after 16 h the reaction mixture was concentrated to dryness under reduced pressure. Purification (Si-gel, pet ether/EtOAc 1:0→3:2) gave ditosylate **177** as a colourless oil (550 mg, 74%).

- R_f 0.47 (pet ether/EtOAc 4:1);
- **IR** (neat/cm^{-1}) 2966 w, 1359 s, 1174 s, 949 m, 813 m, 665 m;
- **^{1}H NMR** (400 MHz, $CDCl_3$) 7.73 (4H, d, *J* = 8.1 Hz, Ar), 7.34 (4H, d, *J* = 8.1 Hz, Ar), 4.1 (2H, dd, *J* = 9.9, 4.0 Hz, CH(C<u>H</u>HOTs)$_2$), 3.95 (2H, dd, *J* = 9.9, 6.1 Hz, CH(CH<u>H</u>OTs)$_2$), 2.45 (6H, s, 2 x ArC<u>H</u>$_3$), 1.77-1.66 (2H, m, C<u>H</u>(CH$_3$)$_2$ & C<u>H</u>(CH$_2$OTs)$_2$), 0.81 (6H, d, *J* = 6.3 Hz, CH(C<u>H</u>$_3$)$_2$);
- **^{13}C NMR** (100 MHz, $CDCl_3$) 145.0 (Ar), 132.5 (Ar), 130.0 (Ar), 127.9 (Ar), 67.6 (CH_2O), 43.8 (<u>C</u>H(CH$_2$OTs)$_2$), 25.9 (<u>C</u>H(CH$_3$)$_2$), 21.7 (Ar<u>C</u>H$_3$), 19.8 (CH(<u>C</u>H$_3$)$_2$);
- **LRMS** (ESI^+) 875.29 ($[2M+Na]^+$, 100%); **HRMS** (ESI^+) calcd for $C_{20}H_{27}O_6S_2$: 427.1244, found 427.1238.

1-Benzhydryl-3-isopropyl-azetidine (**178**)



<u>Method A</u>

To a stirred solution of the ditosylate **177** (500 mg, 1.17 mmol) in DMPU (5 mL) was added Ph_2CHNH_2 (214 mg, 1.17 mmol) and $NaHCO_3$ (295 mg, 3.51 mmol). The reaction mixture was heated to 80 °C. After 16 h, the reaction mixture was cooled to rt, diluted with EtOAc (20 mL) and washed with brine (3 x 15 mL), dried (Na_2SO_4), and concentrated to dryness under reduced pressure. Purification (Si-gel, pet ether/Et_2O 1:0→24:1) gave azetidine **178** as a colourless syrup (45 mg, 14%).

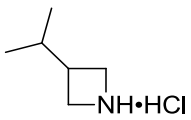
<u>Method B</u>

To a stirred solution of the diol **176** (0.78 g, 6.60 mmol) in MeCN (15 mL) at –20 °C was added Tf_2O (2.4 mL, 14.5 mmol) dropwise over 5 min and DIPEA (3.0 mL, 17.1 mmol). After 30 min, further DIPEA (3.0 mL, 17.1 mmol) was added followed by Ph_2CHNH_2 (1.14 mL, 6.60 mmol). The reaction mixture was then heated to 70 °C. After 6 h, the reaction mixture was cooled to rt and concentrated to

dryness under reduced pressure. Purification (Si-gel, pet ether/Et_2O 1:0→19:1) gave azetidine **178** as an orange syrup (1.20 g, 69%)

- R_f 0.28 (pet ether/Et_2O 19:1);
- **IR** (neat/cm^{-1}) 2952 w, 2810 w, 1452 w, 1205, 742 m, 700 s;
- **^{1}H NMR** (400 MHz, $CDCl_3$) 7.45 (4H, d, *J* = 7.3 Hz, Ar), 7.30 (4H, t, *J* = 7.3 Hz, Ar), 7.21 (2H, t, *J* = 7.3 Hz, Ar), 4.33 (1H, s, C<u>H</u>Ph_2), 3.40 (2H, t, *J* = 7.7 Hz, 2 x NC<u>H</u>H), 2.74 (2H, t, *J* = 7.7 Hz, NCH<u>H</u>), 2.16 (1H, dquin, *J* = 9.6, 7.7 Hz, C<u>H</u>CH$(CH_3)_2$), 1.68 (1H, dsept, *J* = 9.6, 6.6 Hz, C<u>H</u>$(CH_3)_2$), 0.82 (6H, d, *J* = 6.6 Hz, CH(C<u>H</u>$_3)_2$);
- **^{13}C NMR** (100 MHz, $CDCl_3$) 142.6 (Ar), 128.5 (Ar), 127.6 (Ar), 127.1 (Ar), 78.7 (C<u>H</u>Ph_2), 58.8 (NCH_2), 37.8 (<u>C</u>HCH$(CH_3)_2$), 33.4 (<u>C</u>H$(CH_3)_2$), 19.8 (C$(CH_3)_2$);
- **LRMS** (ESI^+) 266.20 ($[M+H]^+$, 75%); **HRMS** (ESI^+) calcd for $C_{19}H_{24}N$: 266.1903, found 266.1897.

3-Isopropyl-azetidine hydrochloride (**179**)

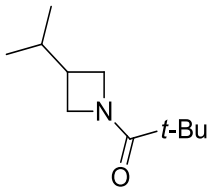


To a stirred solution of azetidine **178** (1.00 g, 3.77 mmol) in MeOH (25 mL) was added ammonium formate (1.20 g, 18.8 mmol) and 10% wt. Pd/C (100 mg). The reaction mixture was heated to reflux. After 8 h, the reaction mixture was cooled to rt and filtered through a pad of celite. The crude reaction mixture was treated with a premixed solution of AcCl (500 µL) in MeOH (5 mL) and stirred for 5 min at rt. The reaction mixture was concentrated to dryness under reduced pressure and the crude residue was stirred in Et_2O (15 mL) for 5 min, carefully decanted. This was repeated, followed by removal of residual solvent under reduced pressure to give azetidine hydrochloride **179** as a colourless solid (651 mg, quant).

- **mp** 112-125 °C;

- **^{1}H NMR** (400 MHz, CD_3OD) 4.10 (2H, t, *J* = 9.1 Hz, NC<u>H</u>H), 3.88 (2H, t, *J* = 9.1 Hz, NCH<u>H</u>), 2.64 (1H, dquin, *J* = 9.5, 9.1 Hz, C<u>H</u>CH$(CH_3)_2$), 1.92 (1H, dseptd, *J* = 9.5, 6.6, 2.0 Hz, C<u>H</u>$(CH_3)_2$), 0.90 (6H, d, *J* = 6.6 Hz, CH(C<u>H</u>$_3)_2$);
- **^{13}C NMR** (100 MHz, CD_3OD) 51.7 (NCH_2), 40.6 (<u>C</u>HCH$(CH_3)_2$), 33.3 (<u>C</u>H$(CH_3)_2$), 19.3 (CH(<u>C</u>H$_3)_2$);
- **IR** (neat/cm^{-1}) 3398 br, 2957 w, 2204 br, 2061 w, 1063 w;
- **LRMS** (ESI$^+$) 100.10 ([M-HCl+H]$^+$, 80%); HRMS (ESI$^+$) calcd for $C_6H_{14}N$: 100.1121, found 100.1123.

1-(3-Isopropylazetidin-1-yl)-2,2-dimethylpropan-1-one (**180**)

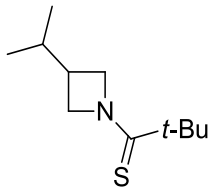


To a stirred slurry of the azetidine hydrochloride **179** (500 mg, 3.69 mmol) in CH_2Cl_2 (20 mL) was added DMAP (180 mg, 1.47 mmol) and Et_3N (1.50 mL, 11.1 mmol). The reaction mixture was cooled to 0 °C and pivCl (544 μL, 4.42 mmol) added dropwise over 2 min. The cold bath was removed and after 16 h the reaction mixture was quenched with aq HCl (1 M, 40 mL) and extracted with CH_2Cl_2 (2 x 25 mL). The combined organic layers were washed sequentially with H_2O (30 mL) and brine (30 mL), dried (Na_2SO_4), and concentrated to dryness under reduced pressure. Purification (Si-gel, pet ether/EtOAc 1:0→3:2) gave amide **180** as a colourless liquid (580 mg, 85%).

- R_f 0.34 (pet ether/Et_2O 3:2);
- **IR** (neat/cm^{-1}) 2957 m, 2874 m, 1621 s, 1415 m, 1361 m, 1154 m, 730 m;
- **^{1}H NMR** (500 MHz, T=363K, tol-D8) 3.85 (2H, dd, *J* = 9.0, 8.5 Hz, NC<u>H</u>H), 3.54 (2H, dd, *J* = 9.0, 5.8 Hz, NCH<u>H</u>), 1.69 (1H, dtt, *J* = 9.5, 8.5, 5.8 Hz, C<u>H</u>CH$(CH_3)_2$), 1.29 (1H, dsept, *J* = 9.5, 6.6 Hz, C<u>H</u>$(CH_3)_2$), 1.12 (9H, s, C(C<u>H</u>$_3)_3$), 0.59 (6H, d, *J* = 6.6 Hz, CH(C<u>H</u>$_3)_2$);

- **^{13}C NMR** (125 MHz, T=363K, tol-D8) 177.0 (C=O), 54.9 (NCH_2), 38.8 ($\underline{C}(CH_3)_3$), 37.2 ($\underline{C}HCH(CH_3)_2$), 32.2 ($\underline{C}H(CH_3)_2$), 27.6 ($C(\underline{C}H_3)_3$), 19.1 ($CH(\underline{C}H_3)_2$);
- **LRMS** (ESI^+) 389.33 ($[2M+Na]^+$, 100%); **HRMS** (ESI^+) calcd for $C_{11}H_{22}NO$: 184.1696, found 184.1695.

1-(3-Isopropylazetidin-1-yl)-2,2-dimethylpropane-1-thione (**181**)

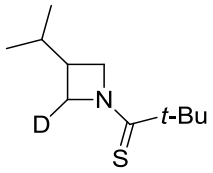


To a stirred solution of amide **180** (550 mg, 3.00 mmol) in pyridine (10 mL) was added P_2S_5 (833 mg, 3.75 mmol). The reaction mixture was heated to 75 °C and after 3 h was concentrated under reduced pressure to ~5 mL. The partially concentrated reaction mixture was poured onto aq HCl (1 M, 50 mL) and extracted with CH_2Cl_2 (2 x 25 mL). The combined organic layers were washed with sequentially with aq HCl (1 M, 50 mL), H_2O (50 mL), and brine (50 mL), dried (Na_2SO_4), and concentrated to dryness under reduced pressure. Purification (Si-gel, pet ether/Et_2O 1:0→9:1) gave thioamide **181** as a colourless liquid (505 mg, 85%).

- $\boldsymbol{R_f}$ 0.35 (pet ether/Et_2O 19:1);
- **IR** (neat/cm^{-1}) 2956 m, 2890 w, 1449 s, 1393 w, 1362 m, 1260 m, 1148 m, 1013 m;
- **^{1}H NMR** (400 MHz, $CDCl_3$) 4.52 (1H, ddd, J = 10.4, 8.5, 1.5 Hz, $NCH_{cis}\underline{H}_{trans}$), 4.28 (1H, ddd, J = 12.4, 8.5, 1.5 Hz, $NCH_{cis}\underline{H}_{trans}$), 4.11 (1H, ddd, J = 10.4, 5.9, 1.5 Hz, $NC\underline{H}_{cis}H_{trans}$), 3.94 (1H, ddd, J = 12.4, 5.9, 1.5 Hz, $NC\underline{H}_{cis}H_{trans}$), 2.25 (1H, dtt, J = 9.8, 8.5, 5.9 Hz, $C\underline{H}CH(CH_3)_2$), 1.75 (1H, dsept, J = 9.8, 6.8 Hz, $C\underline{H}(CH_3)_2$), 1.35 (9H, s, $C(CH_3)_3$), 0.91 (3H, d, J = 6.8 Hz, $CH(C\underline{H}_3)(CH_3)$), 0.89 (3H, d, J = 6.8 Hz, $CH(CH_3)(C\underline{H}_3)$;
- **^{13}C NMR** (100 MHz, $CDCl_3$) 209.5 (C=S), 60.7 (NCH_2), 59.9 (NCH_2), 43.1 ($\underline{C}(CH_3)_3$), 35.1 ($\underline{C}HCH(CH_3)_2$), 32.1 ($\underline{C}H(CH_3)_2$), 29.7 ($C(\underline{C}H_3)_3$), 19.5 ($CH(\underline{C}H_3)(CH_3)$), 19.0 ($CH(CH_3)(\underline{C}H_3)$;

- **LRMS** (ESI^+) 200.15 ($[M+H]^+$, 100%); **HRMS** (ESI^+) calcd for $C_{11}H_{22}NS$: 200.1467, found 200.1468.

1-(2-Deutero-3-isopropyl-azetidin-1-yl)-2,2-dimethylpropane-1-thione (**182a**)



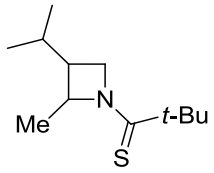
To a stirred solution of thioamide **181** (50 mg, 0.25 mmol) THF (1 mL) at –78 °C was added TMEDA (90 μL, 0.60 mmol). *s*-BuLi (230 μL, 1.3 M in cyclohexane/hexane (92:8), 0.30 mmol) was added dropwise to the reaction mixture over 2 min. After 30 min, CD_3OD (51 μL, 1.30 mmol) was added and the reaction mixture stirred for a further 10 min. The cooling bath was then removed and the reaction mixture was stirred for a further 30 min, washed with aq HCl (1 M, 5 mL), and extracted with EtOAc (3 x 5 mL). The combined organic layers were washed with H_2O (5 mL) and brine (5 mL), dried (Na_2SO_4), and concentrated to dryness under reduced pressure to give deuterated azetidine **128a** as a pale red syrup (46 mg, 92%, 95%D, 61:39 trans:cis).

- R_f 0.35 (pet ether/Et_2O 19:1);
- **IR** (neat/cm^{-1}) 2957 w, 2871 w, 1465 s, 1448 s, 1393 w, 1362 m, 1315 w, 1255 w, 1146 m, 1014 w, 916 w, 856 w, 732 m;
- **^{1}H NMR** (400 MHz, $CDCl_3$) 4.50 (0.72H, dd, *J* = 10.6, 8.8 Hz, $NCH_{cis}\underline{H}_{trans}$ and $NCD_{cis}\underline{H}_{trans}$), 4.26 (0.70H, dd, *J* = 12.1, 8.8 Hz, $NCH_{cis}\underline{H}_{trans}$ and $NCD_{cis}\underline{H}_{trans}$), 4.09 (0.86H, dd, *J* = 10.6, 5.8 Hz, $NC\underline{H}_{cis}H_{trans}$ and $NC\underline{H}_{cis}D_{trans}$), 3.91 (0.77H, dd, *J* = 12.1, 5.8 Hz, $NC\underline{H}_{cis}H_{trans}$ and $NC\underline{H}_{cis}D_{trans}$), 2.22 (1H, dddd, *J* = 9.9, 8.8, 7.3, 5.8 Hz, $C\underline{H}CH(CH_3)_2$), 1.73 (1H, dsept, *J* = 9.9, 6.6 Hz, $C\underline{H}(CH_3)_2$), 1.33 (9H, s, $C(C\underline{H}_3)_3$), 0.89 (3H, d, *J* = 6.6 Hz, $CH(C\underline{H}_3)(CH_3)$), 0.87 (3H, d, *J* = 6.6 Hz, $CH(CH_3)(C\underline{H}_3)$);
- **^{13}C NMR** (100 MHz, $CDCl_3$) 209.4 (C=S), 60.7 (NCH_2), 60.4 (T, *J* = 23 Hz, NCHD), 60.4 (T, *J* = 23 Hz, NCHD), 59.8 (NCH_2), 59.5 (T, *J* = 23 Hz, NCHD), 59.5 (T, *J* = 23 Hz,

NCHD), 43.0 (C(CH$_3$)$_3$), 34.9 (CHCH(CH$_3$)$_2$), 32.0 (CH(CH$_3$)$_2$), 29.6 (C(CH$_3$)$_3$), 19.5 (CH(CH$_3$)(CH$_3$)), 19.0 (CH(CH$_3$)(CH$_3$));

- **LRMS** (ESI$^+$) 223.14 ([M+Na]$^+$, 45%), 498.16 (100%); **HRMS** (ESI$^+$) calcd for $C_{11}H_{20}DNNaS$: 223.1350, found 223.1347.

1-(3-Isopropyl-2-methylazetidin-1-yl)-2,2-dimethylpropane-1-thione (**182b**)



To a stirred solution of thioamide **181** (50 mg, 0.25 mmol) THF (1 mL) at –78 °C was added TMEDA (90 μL, 0.60 mmol). *s*-BuLi (230 μL, 1.3 M in cyclohexane/hexane (92:8), 0.30 mmol) was added dropwise to the reaction mixture over 2 min. After 30 min, MeI (78 μL, 1.25 mmol) was added and the reaction mixture stirred for a further 10 min. The cooling bath was then removed and the reaction mixture was stirred for a further 30 min, washed with aq HCl (1 M, 5 mL), and extracted with EtOAc (3 x 5 mL). The combined organic layers were washed with H_2O (5 mL) and brine (5 mL), dried (Na_2SO_4), and concentrated to dryness under reduced pressure. Purification (Si-gel, pet ether/Et_2O 1:0→97:3) gave both diastereoisomers of methylated azetidine **182b** as colourless syrups (15 mg, 28% and 30 mg, 55%).

Minor diastereoisomer

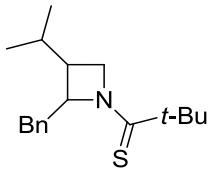
- $\boldsymbol{R_f}$ 0.55 (pet ether/Et_2O 19:1);
- **IR** (neat/cm^{-1}) 2958 w, 2927 w, 2872 w, 1463 w, 1428 s, 1393 w, 1362 m, 1327 w, 1254 m, 1149 m, 1053 w, 1017 w, 993 w;
- **^{1}H NMR** (400 MHz, $CDCl_3$) 4.57 (1H, dd, *J* = 10.4, 8.0 Hz, NCH$_{cis}$H$_{trans}$), 4.50 (1H, qd, *J* = 6.3, 4.3 Hz, NCH), 4.04 (1H, dd, *J* = 10.4, 4.3 Hz, NCH$_{cis}$H$_{trans}$), 1.82-1.61 (2H, m, CHCH(CH$_3$)$_2$), 1.58 (3H, d, *J* = 6.3 Hz, CH$_3$), 1.34 (9H, s, C(CH$_3$)$_3$), 0.91 (3H, d, *J* = 6.3 Hz, CH(CH$_3$)(CH$_3$)), 0.87 (3H, d, *J* = 6.3 Hz, CH(CH$_3$)(CH$_3$));

- **^{13}C NMR** (100 MHz, $CDCl_3$) 210.2 (C=S), 68.5 (NCH), 59.4 (NCH_2), 44.1 ($\underline{C}HCH(CH_3)_2$), 43.3 ($\underline{C}(CH_3)_3$), 31.5 ($\underline{C}H(CH_3)_2$), 29.6 ($C(\underline{C}H_3)_3$), 19.6 ($CH(\underline{C}H_3)(CH_3)$), 19.0 ($CH(CH_3)(\underline{C}H_3)$), 18.6 ($CH_3$);
- **LRMS** (ESI^+) 236.14 ($[M+Na]^+$, 95%); **HRMS** (ESI^+) calcd for $C_{12}H_{24}NS$: 214.1624, found 214.1628.

Major diastereoisomer

- R_f 0.42 (pet ether/Et_2O 19:1);
- **IR** (neat/cm^{-1}) 2959 m, 2926 m, 2868 w, 1728 w, 1464 s, 1431 s, 1360 m, 1329 w, 1276 w, 1249 m, 1195 w, 1153 m, 1130 w, 1052 m, 1016 m, 984 m, 883 w, 800 w;
- **^{1}H NMR** (400 MHz, $CDCl_3$) 4.93 (1H, dq, *J* = 9.0, 6.6 Hz, NCH), 4.43 (1H, dd, *J* = 10.4, 9.0 Hz, $NC\underline{H}H$), 4.13 (1H, dd, *J* = 10.4, 8.8 Hz, $NCH\underline{H}$), 2.44 (1H, dtd, *J* = 11.5, 9.0, 8.8 Hz, $C\underline{H}CH(CH_3)_2$), 1.93 (1H, dsept, *J* = 11.5, 6.6 Hz, $C\underline{H}(CH_3)_2$), 1.52 (3H, d, *J* = 6.6 Hz, CH_3), 1.31 (9H, s, $C(CH_3)_3$), 0.89 (3H, d, *J* = 6.6 Hz, $CH(C\underline{H}_3)(CH_3)$), 0.82 (3H, d, *J* = 6.6 Hz, $CH(CH_3)(C\underline{H}_3)$);
- **^{13}C NMR** (100 MHz, $CDCl_3$) 207.8 (C=S), 66.8 (NCH), 60.2 (NCH_2), 43.1 ($\underline{C}(CH_3)_3$), 40.4 ($\underline{C}HCH(CH_3)_2$), 29.5 ($C(\underline{C}H_3)_3$), 26.8 ($\underline{C}H(CH_3)_2$), 21.3 ($CH(\underline{C}H_3)(CH_3)$), 20.0 ($CH(CH_3)(\underline{C}H_3)$), 11.0 ($CH_3$);
- **LRMS** (ESI^+) 236.14 ($[M+Na]^+$, 95%); **HRMS** (ESI^+) calcd for $C_{12}H_{24}NS$: 214.1624, found 214.1621.

1-(2-Benzyl-3-isopropylazetidin-1-yl)-2,2-dimethylpropane-1-thione (**182c**)



To a stirred solution of thioamide **181** (50 mg, 0.25 mmol) THF (1 mL) at –78 °C was added TMEDA (90 μL, 0.60 mmol). *s*-BuLi (230 μL, 1.3 M in cyclohexane/hexane (92:8), 0.30 mmol) was added

dropwise to the reaction mixture over 2 min. After 30 min, BnBr (149 μL, 1.25 mmol) was added and the reaction mixture stirred for a further 10 min. The cooling bath was then removed and the reaction mixture was stirred for a further 30 min, washed with aq HCl (1 M, 5 mL), and extracted with EtOAc (3 x 5 mL). The combined organic layers were washed with H_2O (5 mL) and brine (5 mL), dried (Na_2SO_4), and concentrated to dryness under reduced pressure. Crude ^{1}H NMR analysis indicated 85:15 dr, by integration of peaks at 1.91 ppm (major diastereoisomer) and 2.58-2.48 (minor diastereoisomer, tentatively assigned as 85:15 trans:cis). Purification (Si-gel, pet ether/Et_2O 1:0→97:3) gave major diastereoisomer pure and a mixture of both diastereoisomers of benzylated azetidine **182c** as colourless syrups (34 mg, 48% pure and 17 mg, 24% (50:50 mixture by ^{1}H NMR analysis).

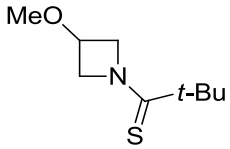
Major diastereoisomer

- R_f 0.65 (pet ether/Et_2O 19:1);
- **IR** (neat/cm^{-1}) 2958 w, 2929 w, 2871 w, 1461 w, 1454 s, 1392 w, 1362 m, 1345 w, 1269 w, 1231 w, 1143 m, 1116 w, 1076 w, 1001 m, 844 w, 743 m, 701 s;
- **^{1}H NMR** (400 MHz, $CDCl_3$) 7.31-7.21 (5H, m, Ar), 4.70-4.65 (1H, m, NCH), 3.97 (1H, dd, *J* = 10.4, 8.5 Hz, $NCH_{cis}\underline{H}_{trans}$), 3.89 (1H, dd, *J* = 10.4, 4.5 Hz, $NC\underline{H}_{cis}H_{trans}$), 3.48 (1H, dd, *J* = 13.4, 7.3 Hz, C<u>H</u>HPh), 3.24 (1H, dd, *J* = 13.4, 2.5 Hz, CH<u>H</u>Ph), 1.91 (1H, tt, *J* = 8.5, 4.5 Hz, C<u>H</u>CH$(CH_3)_2$), 1.65 (1H, dsept, *J* = 8.5, 6.6 Hz, C<u>H</u>$(CH_3)_2$), 1.32 (9H, s, C$(CH_3)_3$), 0.77 (3H, d, *J* = 6.6 Hz, CH(C<u>H</u>$_3$)(CH_3)), 0.67 (3H, d, *J* = 6.6 Hz, CH(CH_3)(C<u>H</u>$_3$));
- **^{13}C NMR** (100 MHz, $CDCl_3$) 210.2 (C=S), 137.0 (Ar), 130.1 (Ar), 128.1 (Ar), 126.5 (Ar), 72.2 (NCH), 59.5 (NCH_2), 43.3 (<u>C</u>$(CH_3)_3$), 40.2 (<u>C</u>HCH$(CH_3)_2$), 35.6 (<u>C</u>H_2Ph), 31.1 (<u>C</u>H$(CH_3)_2$), 29.5 (C(<u>C</u>$H_3)_3$), 19.4 (CH(<u>C</u>H_3)(CH_3)), 18.8 (CH(CH_3)(<u>C</u>H_3));
- **LRMS** (ESI$^+$) 312.17 ([M+Na]$^+$, 100%); **HRMS** (ESI$^+$) calcd for $C_{18}H_{28}NS$: 290.1937, found 290.1939.

Discernable data for minor diastereoisomer

- R_f 0.45 (pet ether/Et_2O 19:1);
- **^{1}H NMR** (400 MHz, $CDCl_3$) 5.24-5.19 (1H, m, NCH), 4.42-4.37 (1H, m, NCHH), 4.27-4.18 (1H, m, NCHH), 3.67 (1H, dd, *J* = 14.4, 13.4 Hz, CHHPH), 3.19 (1H, dd, *J* = 14.4, 9.6 Hz, CHHPh), 2.58-2.48 (1H, m, CHCH(CH_3)$_2$), 2.07 (1H, dsept, *J* = 10.8, 6.6 Hz, CH(CH_3)$_2$), 1.35 (9H, s, C(CH_3)$_3$), 0.77 (3H, d, *J* = 6.6 Hz, CH(CH_3)(CH_3)), 0.51 (3H, d, *J* = 6.6 Hz, CH(CH_3)(CH_3));
- **^{13}C NMR** (100 MHz, $CDCl_3$) 208.0 (C=S), 138.4 (Ar), 129.4 (Ar), 128.2 (Ar), 126.2 (Ar), 71.8 (NCH), 60.5 (NCH_2), 43.2 (C(CH_3)$_3$), 42.1 (CHCH(CH_3)$_2$), 38.7 (CH(CH_3)$_2$), 31.1 (CH_2Ph), 29.6 (C(CH_3)$_3$), 21.7 (CH(CH_3)(CH_3)), 20.1 (CH(CH_3)(CH_3));

1-(3-Methoxyazetidin-1-yl)-2,2-dimethylpropane-1-thione (**208**)

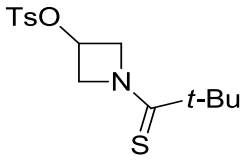


To a stirred ice cold solution of azetidinol **122** (3.00 g, 17.3 mmol) in THF (30 mL) was added NaH (831 mg, 60% in mineral oil, 20.8 mmol) portion-wise. The cold bath was removed and after 15 min MeI (1.29 mL, 2.08 mmol) was added dropwise. After 2 h, the reaction mixture was quenched with MeOH (300 μL) and concentrated to dryness under reduced pressure. Purification (Si-gel, pet ether/EtOAc 1:0→3:2) gave methoxyazetidine **208** as a pale yellow liquid (3.09 g, 95%).

- R_f 0.74 (pet ether/EtOAc 3:2);
- **IR** (neat/cm^{-1}) 2966 w, 2932 w, 2829 w, 1466 m, 1633 s, 1363 m, 1263 w, 1222 m, 1141 s, 1123 s, 1076 w, 1039 w, 1008 m, 933 w, 806 w;
- **^{1}H NMR** (400 MHz, $CDCl_3$) 4.62 (1H, dd, *J* = 10.0, 5.7 Hz, NCHH), 4.39 (1H, dd, *J* = 11.5, 4.7 Hz, NCHH), 4.30-4.27 (1H, m, NCHH), 4.18-4.10 (2H, m, NCHH, CHOCH_3), 3.31 (3H, s, CH_3), 1.32 (9H, s, C(CH_3)$_3$);

- **^{13}C NMR** (100 MHz, $CDCl_3$) 210.2 (C=S), 67.7 ($\underline{C}HOCH_3$), 63.3 (NCH_2), 62.6 (NCH_2), 56.2 ($\underline{C}H_3$), 43.1 ($\underline{C}(CH_3)_3$), 29.7 ($C(\underline{C}H_3)_3$);
- **LRMS** (ESI^+) 188.1 ($[M+H]^+$, 40%), 391.3 (100%); **HRMS** (ESI^+) calcd for $C_9H_{18}NOS$: 188.1104, found 188.1108.

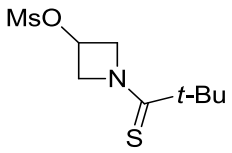
1-(2,2-Dimethylpropanethioyl)azetidin-3-yl 4-methylbenzenesulfonate (**209**)



To a stirred solution of azetidinol **122** (2.00 g, 11.5 mmol) and DMAP (134 mg, 1.2 mmol) in CH_2Cl_2 (40 mL) was added Et_3N (1.77 mL, 12.7 mmol). The reaction mixture was cooled to 0 °C and TsCl (2.42 g, 12.7 mmol) added in one portion. The cold bath was removed and after 6 h was washed with aq HCl (1 M, 40 mL) and extracted with CH_2Cl_2 (20 mL). The organic layer was washed with brine (40 mL), dried (Na_2SO_4), and concentrated to dryness under reduced pressure. Purification (Si-gel, pet ether/EtOAc 1:0→4:1) gave tosyl azetidine **209** as a colourless solid (3.16 g, 84%).

- R_f 0.49 (pet ether/EtOAc 4:1);
- **mp** 108-109 °C;
- **IR** (neat/cm^{-1}) 2957 w, 1472 m, 1437 s, 1356 s, 1264 w, 1193 w, 1169 m, 1133 m, 1098 w, 1082 w, 1060 m, 1032 w, 996 w, 929 s, 904 m, 849 s, 809 m, 765 m, 663 s;
- **^{1}H NMR** (400 MHz, $CDCl_3$) 7.81 (2H, d, *J* = 8.1 Hz, Ar), 7.39 (2H, d, *J* = 8.1 Hz, Ar), 5.05 (1H, tt, *J* = 6.8, 4.0 Hz, CHO), 4.76 (1H, ddd, *J* = 11.7, 6.8, 2.1 Hz, $NCH_{cis}\underline{H}_{trans}$), 4.55 (1H, ddd, *J* = 11.7, 4.0, 2.1 Hz, $NC\underline{H}_{cis}H_{trans}$), 4.43 (1H, ddd, *J* = 13.6, 6.8, 2.1 Hz, $NCH_{cis}\underline{H}_{trans}$), 4.18 (1H, ddd, *J* = 13.6, 4.0, 2.1 Hz, $NC\underline{H}_{cis}H_{trans}$), 2.48 (3H, s, CH_3), 1.32 (9H, s, $C(CH_3)_3$);
- **^{13}C NMR** (100 MHz, $CDCl_3$) 211.0 (C=S), 145.8 (Ar), 132.5 (Ar), 130.2 (Ar), 127.9 (Ar), 66.4 (CHO), 63.1 (NCH_2), 61.8 (NCH_2), 43.3 ($C(CH_3)_3$), 29.7 ($C(\underline{C}H_3)_3$), 21.7 (CH_3);
- **LRMS** (ESI^+) 328.1 ($[M+H]^+$,100 %); **HRMS** (ESI^+) calcd for $C_{15}H_{21}NNaO_3S_2$: 350.0855, found 350.0847.

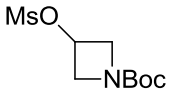
1-(2,2-Dimethylpropanethioyl)azetidin-3-yl methanesulfonate (**210**)



To a stirred solution of azetidinol **122** (3.36 g, 19.4 mmol) and Et_3N (3.25 mL, 23.3 mmol) in CH_2Cl_2 (20 mL) at 0 °C was added MsCl (1.65 mL, 21.4 mmol) dropwise over 5 min. After 2 h, the reaction mixture was washed with H_2O (20 mL), dried (Na_2SO_4), and concentrated to dryness under reduced pressure. Purification (Si-gel, heptane/EtOAc 1:0→2:3) gave mesyl azetidine **210** as a pale yellow syrup which solidified on standing (3.53 g, 72%).

- R_f 0.31 (pet ether/EtOAc 4:1);
- **mp** 101-103 °C;
- **IR** (neat/cm^{-1}) 2980 w, 2907 w, 2870 w, 1473 m, 1442 m, 1420 w, 1352 s, 1262 w, 1163 s, 1141 m, 1092 w, 1057 m, 1032 m, 1005 w, 986 m, 935 s, 895 m, 842 s, 805 m, 727 m;
- **^{1}H NMR** (400 MHz, $CDCl_3$) 5.25 (1H, tt, *J* = 6.5, 4.1 Hz, CHO), 4.84 (1H, ddd, *J* = 11.7, 6.5, 2.0 Hz, $NCH_{cis}\underline{H}_{trans}$), 4.63-4.58 (2H, m, $NC\underline{H}_{cis}\underline{H}_{trans}$), 4.37 (1H, ddd, *J* = 13.9, 4.1, 2.0 Hz, $NC\underline{H}_{cis}H_{trans}$), 3.10 (3H, s, CH_3), 1.35 (9H, s, $C(CH_3)_3$);
- **^{13}C NMR** (100 MHz, $CDCl_3$) 211.1 (C=S), 65.8 (CHO), 63.2 (NCH_2), 61.9 (NCH_2), 43.4 ($\underline{C}(CH_3)_3$), 38.4 (CH_3), 29.7 ($C(\underline{C}H_3)_3$);
- **LRMS** (FI) 251.07 ($[M]^+$, 100%); **HRMS** (FI^+) calcd for $C_9H_{17}NO_3S_2$: 251.0650, found 251.0658.

***tert*-Butyl 3-((methylsulfonyl)oxy)azetidine-1-carboxylate** (**211**)

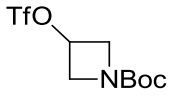


To an ice-cold stirred solution of azetidinol **132** (200 mg, 1.15 mmol) in CH_2Cl_2 (4 mL) was added Et_3N (194 μL, 1.39 mmol) and MsCl (107 μL, 1.39 mmol) added dropwise over 2 min. The cooling

bath was removed and after 3 h was purified neat (Si-gel, pet ether/EtOAc 7:3→4:6) to give mesyl azetidine **211**[151] as a colourless syrup (278 mg, 95%).

- R_f 0.49 (pet ether/EtOAc 3:2);
- **IR** (neat/cm^{-1}) 2976 w, 2931 w, 1697 s, 1400 m, 1358 m, 1344 m, 1145 s, 1007 m, 971 w, 882 m, 815 w, 788 w, 768 w, 726 w;
- **^{1}H NMR** (400 MHz, $CDCl_3$) 5.16 (1H, tt, *J* = 6.7, 4.2 Hz, CHO), 4.24 (2H, ddd, *J* = 10.3, 6.7, 1.0 Hz, $NCH_{cis}\underline{H}_{trans}$), 4.05 (2H, ddd, *J* = 10.3, 4.2, 1.0 Hz, $NC\underline{H}_{cis}H_{trans}$), 3.03 (3H, s, CH_3), 1.40 (9H, s, $C(CH_3)_3$);
- **^{13}C NMR** (100 MHz, $CDCl_3$) 155.7 (C=O), 80.1 ($\underline{C}(CH_3)_3$), 67.2 (CHO), 56.3 (NCH_2), 38.2 (CH_3), 28.1 ($C(\underline{C}H_3)_3$);
- **LRMS** (ESI^+) 274.1 ($[M+Na]^+$,100 %); **HRMS** (ESI^+) calcd for $C_9H_{17}NNaO_5S$: 274.0720, found 274.0723.

***tert*-Butyl 3-(((trifluoromethyl)sulfonyl)oxy)azetidine-1-carboxylate** (**212**)

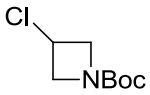


To a stirred solution of azetidinol **132** (500 mg, 2.89 mmol) in CH_2Cl_2 (10 mL) at –78 °C was added DIPEA (648 μL, 3.75 mmol) followed by Tf_2O (540 μL, 3.18 mmol) dropwise over 2 min. After 20 min, the cold bath was removed, and after a further 15 min the reaction mixture was quenched with MeOH (200 μL) and concentrated to half the volume under reduced pressure. Purification (Si-gel, pet ether/EtOAc 9:1) gave triflate **212**[152] as a pale yellow oil (748 mg, 85%).

- R_f 0.77 (pet ether/EtOAc 4:1);
- **IR** (neat/cm^{-1}) 2983 w, 1692 s, 1394 s, 1367 w, 1203 m, 1139 m, 1005 m, 933 m, 893 m, 775 w;
- **^{1}H NMR** (400 MHz, $CDCl_3$) 5.42 (1H, tt, *J* = 6.6, 4.2 Hz, CHO), 4.33 (2H, ddd, *J* = 10.8, 6.6, 1.2 Hz, $NCH_{cis}\underline{H}_{trans}$), 4.16 (2H, dd, *J* = 10.8, 4.2, 1.2 Hz, $NC\underline{H}_{cis}H_{trans}$), 1.44 (9H, s, $C(CH_3)_3$);

- **^{13}C NMR** (100 MHz, $CDCl_3$) 155.6 (C=O), 118.4 (Q, *J* = 320 Hz, CF_3), 80.8 ($\underline{C}(CH_3)_3$), 74.4 (CHO), 56.3 (NCH_2), 28.2 ($C(\underline{C}H_3)_3$);
- **LRMS** (FI) 305.06 ($[M]^+$, 100%); **HRMS** (FI) calcd for $C_9H_{14}F_3NO_5S$: 305.0545, found 305.0551.

***tert*-Butyl 3-chloroazetidine-1-carboxylate** (**213**)



To a solution of azetidinol **132** (8.00 g, 46.2 mmol) in CCl_4 (50 mL) was added Ph_3P (12.1 g, 46.2 mmol) and $NaHCO_3$ (30 mg). The reaction mixture was heated to reflux, and after 2 h further Ph_3P (1.2 g, 4.6 mmol, 0.1 equiv) was added. After 17 h, the reaction mixture was cooled to rt, concentrated to dryness under reduced pressure, suspended in pet ether (50 mL) and filtered. The solid was re-suspended in pet ether (50 mL) and filtered. The combined pet ether washings were concentrated to dryness under reduced pressure. Purification (Si-gel, pet ether/Et_2O 1:0→4:1) gave chloride **213** as a colourless oil (6.83 g, 77%).

- R_f 0.28 (pet ether/Et_2O 9:1);
- **IR** (neat/cm^{-1}) 2977 w, 2887 w, 1699 s, 1387 s, 1366 m, 1128 m, 981 w, 771 w, 629 w;
- **^{1}H NMR** (400 MHz, $CDCl_3$) 4.50 (1H, tt, *J* = 7.1, 4.6 Hz, CHCl), 4.36 (2H, ddd, *J* = 9.5, 7.1, 1.0 Hz, $NC\underline{H}_{trans}H_{cis}$), 4.02 (2H, ddd, *J* = 10.0, 4.6, 1.2 Hz, $NCH_{trans}\underline{H}_{cis}$), 1.42 (9H, s, $C(CH_3)_3$);
- **^{13}C NMR** (100 MHz, $CDCl_3$) 155.7 (C=O), 80.0 ($\underline{C}(CH_3)_3$), 59.7 (NCH_2), 45.0 (CHCl), 28.2 ($C(\underline{C}H_3)_3$);
- **LRMS** (ESI^+) 136.1 (100%), 214.1($[M+Na]^+$,70 %); **HRMS** (ESI^+) calcd for $C_8H_{14}ClNNaO_2$: 214.0605, found 214.0606.

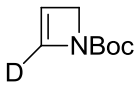
General Procedure B. Synthesis of 2-substituted azetines 214 via LTMP lithiation of azetine 121

To a stirred solution of TMP (81 μL, 0.48 mmol) in THF (2 mL) at –78 °C was added *n*-BuLi (180 μL, 2.5 M in hexanes, 0.45 mmol) dropwise over 1 min. After 20 min, the cooling bath was removed. After a further 20 min the reaction mixture was cooled to –78 °C and azetine **121** (50 mg, 0.32 mmol) in THF (0.5 mL) was added dropwise over 5 min. After 30 min, the electrophile was added and the reaction mixture stirred for a further 1 h. The cooling bath was then removed and the reaction mixture stirred for a further 30 min, washed with H_2O (5 mL) and extracted with Et_2O (2 x 5 mL). The combined organic layers were dried (Na_2SO_4), and concentrated to dryness under reduced pressure.

General Procedure C. Synthesis of 2-substituted azetines 214 via *s*-BuLi lithiation of azetidine 215

To a stirred solution of methoxyazetidine **215** (120 mg, 0.64 mmol) in THF (4 mL) at –78 °C was added TMEDA (248 μL, 1.66 mmol). *s*-BuLi (1.15 mL, 1.4 M in cyclohexane/hexane (92:8), 1.6 mmol) was added dropwise to the reaction mixture over 1 min, resulting in a pale yellow colour. After 1 h, the electrophile was added and the reaction mixture stirred for a further 1 h. The cooling bath was then removed and the reaction mixture was stirred for a further 1 h, washed with sat. aq $NaHCO_3$ (5 mL) and extracted with Et_2O (2 x 5 mL). The combined organic layers were dried (Na_2SO_4), and concentrated to dryness under reduced pressure.

***tert*-Butyl 4-deuteroazete-1(2*H*)-carboxylate** (**214a**)



Method A

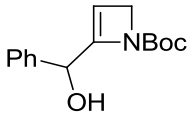
CD_3OD (65 μL, 1.60 mmol, 5 equiv) was used following General Procedure B. Purification (Si-gel, pet ether/Et_2O 9:1) gave deuterated azetine **214a** as a colourless oil (35 mg, 70%).

Method B

CD_3OD (65 μL, 1.60 mmol, 5 equiv) was used following General Procedure C on half the scale. Purification (Si-gel, pet ether/Et_2O 9:1) gave deuterated azetine **214a** as a colourless oil (44 mg, 88%).

- R_f 0.38 (pet ether/Et_2O 9:1);
- **IR** (neat/cm^{-1}) 2979 w, 1700 s, 1389 s, 1366 m, 1275 w, 1257 w, 1145 s, 1089 w, 978 m, 911 w, 855 w, 767 w;
- **^{1}H NMR** (400 MHz, $CDCl_3$ over K_2CO_3) 5.51 (1H, s, CD=C<u>H</u>), 4.38 (2H, s, NCH_2), 1.46 (9H, s, $C(CH_3)_3$);
- **^{13}C NMR** (100 MHz, $CDCl_3$ over K_2CO_3) 151.7 (C=O), 138.3 (T, *J* = 29.4 Hz, <u>C</u>D=CH), 111.4 (CD=<u>C</u>H), 80.1 (<u>C</u>$(CH_3)_3$), 58.2 (NCH_2), 28.3 ($C(\underline{C}H_3)_3$);
- **LRMS** (ESI^+) 157.1 ($[M+H]^+$, 100%); **HRMS** (ESI^+) calcd for $C_8H_{12}DNNaO_2$: 179.0901, found 179.0909.

***tert*-Butyl 4-(hydroxy(phenyl)methyl)azete-1(2*H*)-carboxylate** (**214c**)



Method A

PhCHO (46 μL, 0.45 mmol, 1.4 equiv) was used following General Procedure B. Purification (Si-gel, pet ether/Et_2O 1:0→4:1) gave alcohol **214c** as a pale yellow oil (48 mg, 66%).

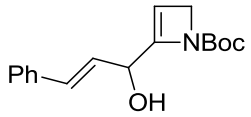
Method B

PhCHO (163 μL, 1.60 mmol, 2.5 equiv) was used following General Procedure C. Purification (Si-gel, pet ether/Et_2O 1:0→39:1 with 0.5% Et_3N) gave alcohol **214c** as a pale yellow oil (163 mg, 97%).

- R_f 0.23 (pet ether/Et_2O 9:1);

- **IR** (neat/cm^{-1}) 3368 br, 2977 w, 1701 s, 1669 s, 1452 w, 1392 m, 1367 m, 1251 m, 1155 m, 1137 s, 1052 w, 916w, 863 w, 831 w, 762 w, 734 w, 699 m;
- **^{1}H NMR** (400 MHz, $CDCl_3$ over K_2CO_3) 7.48-7.46 (2H, m, Ar), 7.39-7.32 (3H, m, Ar), 5.72 (1H, br, OH), 5.43-5.42 (1H, m, C<u>H</u>OH), 5.08 (1H, s, C=CH), 4.26-4.24 (2H, m, NCH_2), 1.50 (9H, s, $C(CH_3)_3$);
- **^{13}C NMR** (100 MHz, $CDCl_3$ over K_2CO_3) 152.8 (N<u>C</u>=CH), 152.4 (C=O), 138.4 (Ar), 128.2 (Ar), 127.9 (Ar), 126.7 (Ar), 107.9 (NC=<u>C</u>H), 81.4 (<u>C</u>$(CH_3)_3$), 68.8 (CHOH), 55.7 (NCH_2), 28.3 (C(<u>C</u>$H_3)_3$);
- **LRMS** (ESI^+) 284.2 ($[M+Na]^+$, 95%), 545.3 (100%); **HRMS** (ESI^+) calcd for $C_{15}H_{19}NNaO_3$: 284.1257, found 284.1248.

(*E*)-*tert*-Butyl 4-(1-hydroxy-3-phenylallyl)azete-1(2*H*)-carboxylate (**214d**)



<u>Method A</u>

Cinnamaldehyde (57 μL, 0.45 mmol, 1.4 equiv) was used following General Procedure B. Purification (Si-gel, pet ether/Et_2O 1:0→17:3) gave alcohol **214d** as a yellow oil (55 mg, 60%).

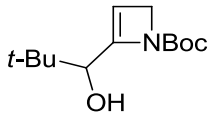
<u>Method B</u>

Cinnamaldehyde (60 μL, 0.48 mmol, 1.5 equiv) was used following General Procedure C on half the scale. Purification (Si-gel, pet ether/Et_2O 1:0→17:3 with 0.5% Et_3N) gave alcohol **214d** as a yellow oil (72 mg, 78%).

- R_f 0.38 (pet ether/Et_2O 9:1) 0.12;
- **IR** (neat/cm^{-1}) 3368 br, 2978 w, 1811 s, 1795 s, 1408 m, 1392 m, 1251 w, 1159 s, 1138 s, 968 w, 876 w, 751 m, 694 m;

- **^{1}H NMR** (400 MHz, $CDCl_3$ over K_2CO_3) 7.35-7.33 (2H, m, Ar), 7.25-7.23 (2H, m, Ar), 7.19-7.17 (1H, m, Ar), 6.68 (1H, d, *J* = 16.0 Hz, PhC<u>H</u>=CH), 6.24 (1H, dd, *J* = 16.0, 6.2 Hz, PhCH=C<u>H</u>), 5.32 (1H, s, NC=C<u>H</u>), 4.93-4.90 (1H, m, C<u>H</u>OH), 4.23-4.16 (2H, m, NCH_2), 1.42 (9H, s, $C(CH_3)_3$);
- **^{13}C NMR** (100 MHz, $CDCl_3$ over K_2CO_3) 152.7 (N<u>C</u>=CH), 151.5 (C=O), 136.5 (Ph<u>C</u>H=CH), 132.3 (Ar), 128.5 (Ar), 127.8 (Ar), 126.6 (Ar), 126.0 (PhCH=<u>C</u>H), 107.1 (NC=<u>C</u>H), 81.4 (<u>C</u>$(CH_3)_3$), 67.3 (CHOH), 56.0 (NCH_2), 28.3 ($C(\underline{C}H_3)_3$);
- **LRMS** (ESI^+) 310.1 ($[M+Na]^+$, 100 %); **HRMS** (ESI^+) calcd for $C_{17}H_{21}NNaO_3$: 310.1414, found 310.1403.

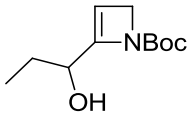
***tert*-Butyl 4-(1-hydroxy-2,2-dimethylpropyl)azete-1(2*H*)-carboxylate** (**214e**)



PivCHO (174 μL, 1.60 mmol, 2.5 equiv) was used following General Procedure C. Purification (Si-gel, pet ether/Et_2O 1:0→39:1 with 0.5% Et_3N) gave alcohol **214e** as a pale yellow oil (130 mg, 84%).

- R_f 0.25 (pet ether/Et_2O 9:1);
- **IR** (neat/cm^{-1}) 3468 br, 3008 w, 1718 s, 1521 w, 1503 w, 1480 w, 1392 m, 1366 m, 1251 w, 1174 s, 1148 s, 1076 w, 1054 w, 1018 w, 960 w, 906 w, 862 w, 774 w, 733 w, 648 w;
- **^{1}H NMR** (400 MHz, C_6D_6) 5.80 (1H, br, OH), 4.85-4.85 (1H, m, NC=CH), 3.99 (1H, d, *J* = 7.8 Hz, C<u>H</u>OH), 3.92-3.86 (2H, m, NCH_2), 1.31 (9H, s, $C(CH_3)_3$), 1.10 (9H, s, $C(CH_3)_3$);
- **^{13}C NMR** (100 MHz, C_6D_6) 153.2 (N<u>C</u>=CH), 152.9 (C=O), 108.5 (NC=<u>C</u>H), 81.1 (O<u>C</u>$(CH_3)_3$), 76.0 (COH), 56.5 (NCH_2), 35.9 (C(OH)<u>C</u>$(CH_3)_3$), 28.5 (OC($\underline{C}H_3)_3$), 26.8 (C(OH)C($\underline{C}H_3)_3$);
- **LRMS** (ESI^+) 264.2 ($[M+Na]^+$, 100%); **HRMS** (ESI^+) calcd for $C_{13}H_{23}NNaO_3$: 264.1570, found 264.1573.

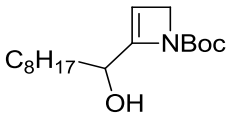
***tert*-Butyl 4-(1-hydroxypropyl)azete-1(2*H*)-carboxylate** (**214f**)



Propanal (58 μL, 0.80 mmol, 2.5 equiv) was used following General Procedure C on half the scale. Purification (Si-gel, pet ether/Et_2O 1:0→9:1 with 0.5% Et_3N) gave alcohol **214f** as a colourless oil (56 mg, 82%).

- R_f 0.26 (pet ether/Et_2O 9:1);
- **IR** (neat/cm^{-1}) 3396 br, 2975 w, 2936 w, 2878 w, 1673 s, 1508 w, 1393 s, 1367 m, 1251 w, 1165 m, 1142 s, 1111 m, 1042 w, 977 w, 862 w, 765 w;
- **^{1}H NMR** (400 MHz, C_6D_6) 5.30 (1H, br, OH), 4.86 (1H, s, NC=CH), 4.22-4.17 (1H, m, C<u>H</u>OH), 3.94-3.87 (2H, m, NCH_2), 1.85-1.65 (2H, m, $CH_3C\underline{H}_2$), 1.32 (9H, s, $C(CH_3)_3$), 1.01 (3H, t, J = 7.5 Hz, CH_3);
- **^{13}C NMR** (100 MHz, C_6D_6) 154.8 (N<u>C</u>=CH), 153.1 (C=O), 105.9 (NC=<u>C</u>H), 81.0 (<u>C</u>$(CH_3)_3$), 68.4 (CHOH), 56.2 (NCH_2), 28.6 ($C(\underline{C}H_3)_3$), 27.3 ($CH_3\underline{C}H_2$), 10.7 ($\underline{C}H_3CH_2$);
- **LRMS** (ESI^+) 449.3 ($[2M+Na]^+$, 100%); **HRMS** (ESI^+) calcd for $C_{11}H_{19}NNaO_3$: 236.1257, found 236.1252.

***tert*-Butyl 4-(1-hydroxynonyl)azete-1(2*H*)-carboxylate** (**214g**)

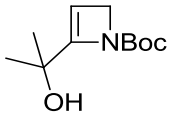


Nonanal (275 μL, 1.60 mmol, 2.5 equiv) was used following General Procedure C. Purification (Si-gel, pet ether/Et_2O 1:0→19:1 with 0.5% Et_3N) gave alcohol **214g** as a colourless oil (157 mg, 82%).

- R_f 0.24 (pet ether/Et_2O 9:1);
- **IR** (neat/cm^{-1}) 3408 br, 2925 m, 2855 w, 1675 s, 1455 w, 1410 s, 1368 w, 1256 w, 1142 s, 1051 w, 863 w, 765 w;

- **^{1}H NMR** (400 MHz, $CCCl_3$) 5.34 (1H, s, NC=CH), 4.24 (1H, s, NCH_2), 4.24-4.19 (1H, m, C<u>H</u>OH), 1.72-1.66 (2H, m, CH(OH)C<u>H</u>$_2$(CH_2)$_6$$CH_3$), 1.48 (9H, s, C(CH3)3), 1.34-1.24 (12H, m, CH(OH)C<u>H</u>$_2$(C<u>H</u>$_2$)$_6$$CH_3$), 0.88 (3H, t, *J* = 6.4 Hz, CH(OH)C<u>H</u>$_2$(CH_2)$_6$C<u>H</u>$_3$);
- **^{13}C NMR** (100 MHz, $CDCl_3$) 153.5 (C=O), 152.5 (N<u>C</u>=CH), 105.9 (NC=<u>C</u>H), 81.0 (<u>C</u>(CH_3)$_3$), 66.4 (CHOH), 55.8 (NCH_2), 33.2 (C_2), 31.9 (C_3), 29.5 (C_4), 29.5 (C_5), 29.2 (C_6), 28.3 (C(<u>C</u>H$_3$)$_3$), 25.6 (C_7), 22.7 (C_8), 14.1 (C_9).
- **LRMS** (ESI^+) 320.3 ($[M+Na]^+$, 100%); **HRMS** (ESI^+) calcd for $C_{17}H_{31}NNaO_3$: 320.2196, found 320.2193.

***tert*-Butyl 4-(2-hydroxypropan-2-yl)azete-1(2*H*)-carboxylate** (**214h**)



<u>Method A</u>

Acetone (33 μL, 0.45 mmol, 1.4 equiv) was used following General Procedure B. Purification (Si-gel, pet ether/Et_2O 1:0→9:1) gave tertiary alcohol **214h** as a colourless oil (41 mg, 60%).

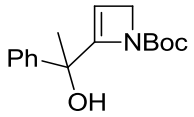
<u>Method B</u>

Acetone (35 μL, 0.48 mmol, 1.5 equiv) was used following General Procedure C on half the scale. Purification (Si-gel, pet ether/Et_2O 1:0→19:1) gave tertiary alcohol **214h** as a colourless oil (30 mg, 44%).

- R_f 0.29 (pet ether/Et_2O 9:1);
- **IR** (neat/cm^{-1}) 3390 br, 2979 w, 2935 w, 1709 w, 1668 s, 1456 w, 1395 s, 1367 m, 1252 w, 1160 s, 1107 w, 1039 m, 959 m, 934 w, 862 w, 765 w, 623 w;
- **^{1}H NMR** (400 MHz, $CDCl_3$ over K_2CO_3) 5.40 (1H, br, OH), 5.28 (1H, s, NC=CH), 4.20-4.20 (2H, m, NCH_2), 1.48 (9H, s, C(CH_3)$_3$), 1.43 (6H, s, C(CH_3)$_2$);

- **^{13}C NMR** (100 MHz, $CDCl_3$ over K_2CO_3) 156.9 (N<u>C</u>=CH), 152.5 (C=O), 104.0 (NC=<u>C</u>H), 81.1 (<u>C</u>$(CH_3)_3$), 66.7 (<u>C</u>$(CH_3)_2$), 55.3 (NCH_2), 28.3 (C(<u>C</u>$H_3)_3$), 26.7 (C(<u>C</u>$H_3)_2$);
- **LRMS** (ESI^+) 236.1 ($[M+Na]^+$, 100%); **HRMS** (ESI^+) calcd for $C_{11}H_{19}NNaO_3$: 236.1257, found 236.1265.

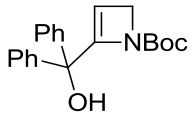
***tert*-Butyl 4-(1-hydroxy-1-phenylethyl)azete-1(2*H*)-carboxylate (214i)**



Acetophenone (93 μL, 0.80 mmol 2.5 equiv) was used following General Procedure C on half the scale. Purification (Si-gel, pet ether/Et_2O 1:0→93:7) gave slightly impure tertiary alcohol **214i** as a colourless oil (52 mg, 91:9 tertiary alcohol **214i**: azetine **121** through ^{1}H NMR analysis, 54%).

- R_f 0.34 (pet ether/Et_2O 9:1);
- **IR** (neat/cm^{-1}) 3316 br, 2979 w, 2933w, 1685 s, 1448 w, 1407 m, 1367 m, 1266 w, 1150 s, 1064 w, 1023 m, 910 w, 860 w, 762 m, 732 w, 701 m;
- **^{1}H NMR** (400 MHz, $CDCl_3$ over K_2CO_3) 7.49-7.40 (2H, m, Ar), 7.28-7.24 (2H, m, Ar), 7.20-7.16 (1H, m, Ar), 6.16 (1H, br, OH), 5.34 (1H, s, NC=CH), 4.22-4.15 (2H, m, NCH_2), 1.58 (3H, s, CH_3), 1.30 (9H, s, $C(CH_3)_3$);
- **^{13}C NMR** (100 MHz, $CDCl_3$ over K_2CO_3) 155.1 (N<u>C</u>=CH), 151.7 (C=O), 144.5 (Ar), 128.0 (Ar), 127.0 (Ar), 125.0 (Ar), 111.7 (NC=<u>C</u>H), 81.2 (<u>C</u>$(CH_3)_3$), 71.3 (<u>C</u>Ph(OH)(CH_3)), 55.3 (NCH_2), 28.1 (C(<u>C</u>$H_3)_3$), 27.7 (CH_3);
- **LRMS** (ESI^+) 298.1 ($[M+Na]^+$, 100%); **HRMS** (ESI^+) calcd for $C_{16}H_{21}NNaO_3$: 298.1414, found 298.1413.

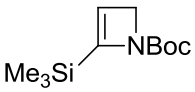
***tert*-Butyl 4-(hydroxydiphenylmethyl)azete-1(2*H*)-carboxylate** (**214j**)



Benzophenone (58 mg, 0.32 mmol, 1 equiv) in THF (0.5 mL) was used following General Procedure C on half the scale. Purification (Si-gel, pet ether/Et_2O 1:0→199:1 with 0.5% Et_3N) gave slightly impure tertiary alcohol **214j** as a colourless solid (66 mg, 89:11 tertiary alcohol **214j**: azetine **121** through ^1H NMR analysis, 55%).

- R_f 0.53 (pet ether/Et_2O 9:1);
- **mp** 151-153 °C;
- **IR** (neat/cm^{-1}) 3316 br, 2978 w, 1707 m, 1667 s, 1450 m, 1405 s, 1368 m, 1293 w, 1255 w, 1142 s, 1059 w, 1038 w, 949 w, 908 w, 881 w, 858 w, 759 m, 699 m;
- **^{1}H NMR** (400 MHz, $CDCl_3$ over K_2CO_3) 7.46-7.25 (10H, m, Ar), 5.10 (1H, s, NC=CH), 4.33 (2H, s, NCH_2), 1.40 (9H, br s, $C(CH_3)_3$);
- **^{13}C NMR** (125 MHz, $CDCl_3$ over K_2CO_3) 153.6 (N<u>C</u>=CH), 152.6 (C=O), 143.1 (Ar), 127.9 (Ar) 127.4 (Ar), 126.8 (Ar), 110.3 (NC=<u>C</u>H), 81.3 (<u>C</u>$(CH_3)_3$), 76.2 (Ph_2<u>C</u>OH), 55.3 (NCH_2), 28.2 (C(<u>C</u>$H_3)_3$);
- **LRMS** (ESI^+) 320.2 (100%), 360.1 ($[M+Na]^+$, 50%); **HRMS** (ESI^+) calcd for $C_{21}H_{23}NNaO_3$: 360.1570, found 360.1571.

***tert*-Butyl 4-(trimethylsilyl)azete-1(2*H*)-carboxylate** (**214k**)



<u>Method A</u>

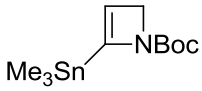
Me_3SiCl (57 μL, 0.45 mmol, 1.4 equiv) was used following General Procedure B on half the scale. Purification (Si-gel, pet ether/Et_2O 1:0→99:1) gave silane **214k** as a colourless oil (33 mg, 45%).

Method B

Me_3SiCl (102 μL, 0.80 mmol, 2.5 equiv) was used following General Procedure C on half the scale. Purification (Si-gel, pet ether/Et_2O 1:0→9:1) gave silane **214k** as a colourless oil (54 mg, 74%).

- R_f 0.68 (pet ether/Et_2O 9:1);
- **IR** (neat/cm^{-1}) 2977 w, 1699 s, 1391 s, 1366 m, 1247 m, 1165 m, 1140 m, 1022 w, 1022 w, 839 s, 764 w, 734 w, 699 w, 633 w;
- **^{1}H NMR** (400 MHz, $CDCl_3$ over K_2CO_3) 5.89 (1H, s, NC=CH), 4.49-4.49 (2H, m, NCH_2), 1.49 (9H, s, $C(CH_3)_3$), 0.20 (9H, s, $Si(CH_3)_3$);
- **^{13}C NMR** (100 MHz, $CDCl_3$ over K_2CO_3) 160.5 (N<u>C</u>=CH), 151.8 (C=O), 123.7 (NC=<u>C</u>H), 80.0 (<u>C</u>$(CH_3)_3$), 59.5 (NCH_2), 28.5 ($C(\underline{C}H_3)_3$), –2.3 ($Si(CH_3)_3$);
- **LRMS** (FI^+) 227.1 ($[M]^+$, 100%); **HRMS** (FI^+) calcd for $C_{11}H_{21}NO_2Si$: 227.1342, found 227.1343.

***tert*-Butyl 4-(trimethylstannyl)azete-1(2*H*)-carboxylate (214l)**

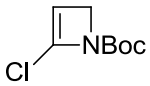


Me_3SnCl (96 mg, 0.48 mmol, 1.5 equiv) in THF (0.5 mL) was used following General Procedure C on half the scale. The crude residue was purified (C_{18} Si-gel, H_2O/MeCN 1:1→3:7), the product containing fractions were combined and washed with brine (50 mL), the organic layer was separated and the aq layer extracted with Et_2O (20 mL). The combined organic layers were washed again with brine (50 mL), dried (Na_2SO_4), filtered and concentrated to dryness under reduced pressure to give stannane **214l** as a colourless oil (77 mg, 76%).

- R_f 0.67 (pet ether/Et_2O 9:1);
- **IR** (neat/cm^{-1}) 2979 w, 2361 w, 2341 w, 1689 s, 1524 w, 1479 w, 1393 m, 1366 w, 1333 w, 1254 m, 1160 s, 1140 m, 992 w, 924 w, 859 w, 765 s;

- **^{1}H NMR** (400 MHz, $CDCl_3$ over K_2CO_3) 5.88 (1H, s, NC=CH), 4.62 (2H, s, NCH_2), 1.47 (9H, s, $C(CH_3)_3$), 0.25 (9H, s, $J_{119Sn-C}$ = 58 Hz, $J_{117Sn-C}$ = 56 Hz, $Sn(CH_3)_3$);
- **^{13}C NMR** (100 MHz, $CDCl_3$ over K_2CO_3) 159.8 (NC=CH), 151.9 (C=O), 125.0 (NC=CH), 80.0 ($\underline{C}(CH_3)_3$), 60.8 (NCH_2), 28.5 ($C(\underline{C}H_3)_3$), -9.1 ($J_{119Sn-C}$ = 381 Hz, $J_{117Sn-C}$ = 363 Hz, $Sn(CH_3)_3$);
- **LRMS** (ESI^+) 264.1 (100%), 320.1 ($[M+H]^+$, 40%); **HRMS** (ESI^+) calcd for $C_{11}H_{21}NNaO_2Sn$: 342.0488, found 342.0482.

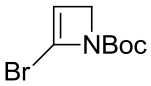
***tert*-Butyl 4-chloroazete-1(2*H*)-carboxylate** (**214m**)



Cl_3CCCl_3 (227 mg, 0.96 mmol, 1.5 equiv) in THF (0.5 mL) was used following General Procedure C. The crude residue was purified (C_{18} Si-gel, H_2O/MeCN 1:1→1:4), the product-containing fractions were combined and washed with brine (50 mL), the organic layer was separated and the aq layer extracted with Et_2O (20 mL). The combined organic layers were washed again with brine (50 mL), dried (Na_2SO_4), filtered and concentrated to dryness under reduced pressure to give chloride **214m** as a colourless oil (76 mg, 63%).

- R_f 0.59 (pet ether/Et_2O 9:1);
- **IR** (neat/cm^{-1}) 2980 w, 1712 s, 1572 w, 1479 w, 1459 w, 1459 w, 1367 s, 1279 m, 1253 m, 1153 s, 1072 m, 1006 m, 915 w, 849 w, 768 m, 679 w;
- **^{1}H NMR** (400 MHz, $CDCl_3$ over K_2CO_3) 5.48 (1H, s, NC=CH), 4.21 (2H, s, NCH_2), 1.49 (9H, s, $C(CH_3)_3$);
- **^{13}C NMR** (100 MHz, $CDCl_3$ over K_2CO_3) 151.9 (C=O), 127.9 ($N\underline{C}$=CH), 108.2 (NC=$\underline{C}$H), 81.4 ($C(\underline{C}H_3)_3$), 54.4 (NCH_2), 28.2 ($C(\underline{C}H_3)_3$);
- **LRMS** (FI^+) 189.1 ($[M]^+$, 100%); **HRMS** (FI^+) calcd for $C_8H_{12}ClNO_2$: 189.0557, found 189.0549.

***tert*-Butyl 4-bromoazete-1(2*H*)-carboxylate (214n)**



Method A

$BrCl_2CCBrCl_2$ (228 mg, 0.70 mmol, 1.1 equiv) in THF (3 mL) was used following General Procedure B on twice the scale with 1.1 equiv LTMP. The crude residue was purified (C_{18} Si-gel, H_2O/MeCN 3:1→1:3), the product-containing fractions were combined and washed with brine (50 mL), the organic layer was separated and the aq layer extracted with Et_2O (20 mL). The combined organic layers were washed again with brine (50 mL), dried (Na_2SO_4), filtered and concentrated to dryness under reduced pressure to give bromide **214n** as a pale orange liquid (91 mg, 60%).

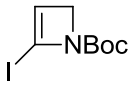
Method B

$BrCl_2CCBrCl_2$ (260 mg, 0.80 mmol, 2.5 equiv) in THF (0.5 mL) was used following General Procedure C on half the scale. The crude residue was purified (C_{18} Si-gel, H_2O/MeCN 1:1→3:7), the product-containing fractions were combined and washed with brine (50 mL), the organic layer was separated and the aq layer extracted with Et_2O (20 mL). The combined organic layers were washed again with brine (50 mL), dried (Na_2SO_4), filtered and concentrated to dryness under reduced pressure to give bromide **214n** as a colourless oil (53 mg, 71%).

- $\boldsymbol{R_f}$ 0.50 (pet ether/Et_2O 9:1);
- **IR** (neat/cm^{-1}) 2978 w, 2934 w, 1708 s, 1558 w, 1478 w, 1455 w, 1366 s, 1271 m, 1253 m, 1150 s, 1067 m, 992 m, 910 w, 843 w, 764 m, 728 w, 688 w;
- **^{1}H NMR** (400 MHz, $CDCl_3$ over K_2CO_3) 5.73 (1H, s, NC=CH), 4.32 (2H, s, NCH_2), 1.49 (9H, s, $C(CH_3)_3$);
- **^{13}C NMR** (100 MHz, $CDCl_3$ over K_2CO_3) 151.8 (C=O), 114.6 (N<u>C</u>=CH), 113.6 (NC=<u>C</u>H), 81.4 (<u>C</u>$(CH_3)_3$), 57.0 (NCH_2), 28.2 (C(<u>C</u>$H_3)_3$);

- **HRMS** (FI^+) 57.0670 (100%), $[M\text{-}C_5H_9O]^+$ requires: 147.9398 and 149.9378, found 147.9398 (30%) and 149.9388 (30%) with a 1:1 ratio.

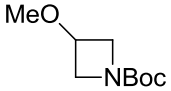
***tert*-Butyl 4-iodoazete-1(2*H*)-carboxylate** (**214o**)



I_2 (244 mg, 0.96 mmol, 1.5 equiv) in THF (0.5 mL) was used following General Procedure C. The crude residue was purified (C_{18} Si-gel, H_2O/MeCN 1:1→1:4), the product-containing fractions were combined and washed with brine (50 mL), the organic layer was separated and the aq layer extracted with Et_2O (20 mL). The combined organic layers were washed again with brine (50 mL), dried (Na_2SO_4), filtered and concentrated to dryness under reduced pressure to give iodide **214o** as a colourless oil (109 mg, 60%).

- R_f 0.55 (pet ether/Et_2O 9:1);
- **IR** (neat/cm^{-1}) 2978 w, 2934 w, 1672 s, 1448 w, 1394 s, 1367 m, 1265 w, 1151 s, 1122 w, 1065 w, 1023 m, 912 w, 860 w, 762 m, 732 w, 700 m;
- **^{1}H NMR** (400 MHz, $CDCl_3$ over K_2CO_3) 6.10 (1H, s, NC=CH), 4.54 (2H, s, NCH_2), 1.47 (9H, s, $C(CH_3)_3$);
- **^{13}C NMR** (100 MHz, $CDCl_3$ over K_2CO_3) 151.7 (C=O), 123.2 (NC=<u>C</u>H), 84.4 (N<u>C</u>=CH), 81.3 (<u>C</u>$(CH_3)_3$), 60.3 (NCH_2), 28.2 (C(<u>C</u>$H_3)_3$);
- **LRMS** (ESI^+) 304.0 ($[M+Na]^+$, 100%); **HRMS** (ESI^+) calcd for $C_8H_{12}INNaO_2$: 303.9805, found 303.9805.

***tert*-Butyl 3-methoxyazetidine-1-carboxylate** (**215**)

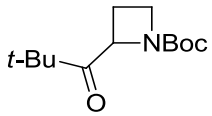


To a stirred ice cold solution of azetidinol **132** (2.00 g, 11.5 mmol) in THF (20 mL) was added NaH (554 mg, 60% in mineral oil, 13.9 mmol) portion-wise. The reaction mixture was warmed to rt and

after 1 h MeI (865 µL, 13.9 mmol) was added dropwise. After 2 h, the reaction mixture was quenched with MeOH (200 µL) and concentrated to dryness under reduced pressure. The residue was suspended in CH_2Cl_2, filtered and concentrated to dryness under reduced pressure. Purification (Si-gel, pet ether/EtOAc 1:0→4:1) gave methoxyazetidine **215**[153] as a colourless liquid (2.22 g, quant).

- R_f 0.48 (pet ether/EtOAc 4:1);
- **IR** (neat/cm^{-1}) 2976 w, 2934 w, 2883 w, 1698 s, 1391 s, 1365 m, 1157 m, 1113 m, 1078 m, 990 w, 932 w, 863 w, 774 w;
- **^{1}H NMR** (400 MHz, $CDCl_3$) 4.11 (1H, tt, *J* = 6.4, 4.2 Hz, C<u>H</u>OCH_3), 4.04 (2H, dd, *J* = 9.9, 6.4 Hz, $NCH_{cis}\underline{H}_{trans}$), 3.79 (2H, dd, *J* = 9.9, 4.2 Hz, $NC\underline{H}_{cis}H_{trans}$), 3.26 (3H, s, OCH_3), 1.41 (9H, s, $C(CH_3)_3$);
- **^{13}C NMR** (100 MHz, $CDCl_3$) 156.3 (C=O), 79.4 (<u>C</u>$(CH_3)_3$), 69.0 (<u>C</u>HOCH_3), 56.2 (NCH_2), 55.9 (OCH_3), 28.3 ($C(\underline{C}H_3)_3$);
- **LRMS** (FI) 131.05 (100%), 187.12 ($[M]^+$, 50%); **HRMS** (FI) calcd for $C_9H_{17}NO_3$: 187.1208, found 187.1207.

***tert*-Butyl 2-pivaloylazetidine-1-carboxylate** (**219**)

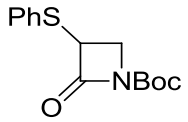


Alcohol **214e** (46 mg, 0.19 mmol) was dissolved in untreated $CDCl_3$ (0.5 mL) and allowed to stand. After 48 h, clean conversion was observed by crude ^{1}H NMR analysis. The reaction mixture was concentrated to dryness under reduced pressure. Purification (Si-gel, pet ether/Et_2O 4:1→3:2) gave ketone **219** as a colourless oil (26 mg, 57%).

- R_f 0.42 (pet ether/EtOAc 4:1);
- **IR** (neat/cm^{-1}) 2971 w, 2893 w, 1716 s, 1700 s, 1478 w, 1390s, 1366 m, 1293 w, 1250 w, 1143 s, 1075 w, 1054 w, 1017 w, 959 w, 9106 w, 863 w, 772 w;

- **^{1}H NMR** (400 MHz, $CDCl_3$) 5.12 (1H, dd, *J* = 9.3, 5.4 Hz, NC<u>H</u>C(O)C$(CH_3)_3$), 3.97 (1H, td, *J* = 8.4, 6.4 Hz, NC<u>H</u>$_{cis}$H$_{trans}$), 3.85 (1H, td, *J* = 8.4, 5.4 Hz, NCH$_{cis}$<u>H</u>$_{trans}$), 2.48-2.39 (1H, m, NCHCH$_{cis}$<u>H</u>$_{trans}$), 1.89 (1H, ddt, *J* = 10.9, 8.4, 5.4 Hz, NCHC<u>H</u>$_{cis}$H$_{trans}$), 1.39 (9H, s, C(O)C$(CH_3)_3$), 1.15 (9H, s, C$(CH_3)_3$);
- **^{13}C NMR** (125 MHz, $CDCl_3$) 210.4 (CH<u>C</u>=O), 155.4 (NC=O), 79.7 (NC=O<u>C</u>$(CH_3)_3$), 62.2 (N<u>C</u>HC(O)C$(CH_3)_3$), 46.3 (NCH_2), 42.9 (NCHC(O)<u>C</u>$(CH_3)_3$), 28.3 (NCHC(O)C(<u>C</u>$H_3)_3$), 25.9 (NC=OC(<u>C</u>$H_3)_3$), 21.3 (NCH<u>C</u>H_2);
- **LRMS** (ESI^+) 186.1 (100%), 264.2 ($[M+Na]^+$, 95%); **HRMS** (ESI^+) calcd for $C_{13}H_{23}NNaO_3$: 264.1570, found 264.1576.

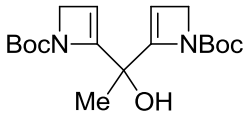
***tert*-Butyl 2-oxo-3-(phenylthio)azetidine-1-carboxylate** (**222**)



$(PhS)_2$ (175 mg, 0.80 mmol, 2.5 equiv) was used following General Procedure C on half the scale and washing with H_2O, rather than sat. aq $NaHCO_3$, in the aq work–up. Purification (Si-gel, pet ether/Et_2O 1:0→7:3) gave β-lactam **222** as a pale yellow syrup (36 mg, 40%).

- R_f 0.19 (pet ether/EtOAc 9:1);
- **IR** (neat/cm^{-1}) 2979 w, 1801 s, 1722 s, 1583 w, 1477 w, 1369 w, 1330 s, 1295 w, 1258 w, 1150 s, 1040 m, 951 w, 844 w, 771 w, 740 m, 691 m;
- **^{1}H NMR** (400 MHz, $CDCl_3$) 7.54-7.51 (2H, m, Ar), 7.36-7.32 (3H, m, Ar), 4.36 (1H, dd, *J* = 6.4, 3.4 Hz, C<u>H</u>SPh), 3.91 (1H, dd, *J* = 7.3, 6.4 Hz, NCH$_{cis}$<u>H</u>$_{trans}$), 3.41 (1H, dd, *J* = 7.3, 3.4 Hz, NC<u>H</u>$_{cis}$H$_{trans}$), 1.49 (9H, s, C$(CH_3)_3$);
- **^{13}C NMR** (100 MHz, $CDCl_3$) 163.6 (NC=O), 147.6 (N<u>C</u>=OC$(CH_3)_3$), 132.7 (Ar), 131.3 (Ar), 129.3 (Ar), 128.4 (Ar), 83.7 (<u>C</u>$(CH_3)_3$), 50.9 (<u>C</u>HSPh), 45.3 (NCH_2), 27.9 (C(<u>C</u>$H_3)_3$);
- **LRMS** (ESI^+) 302.1 ($[M+Na]^+$, 70%), 581.2 (100%); **HRMS** (ESI^+) calcd for $C_{14}H_{17}NNaO_3S$: 302.0821, found 302.0827.

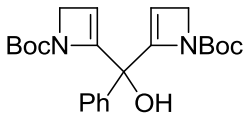
Di-*tert*-butyl 4,4'-(1-hydroxyethane-1,1-diyl)bis(azete-1(2*H*)-carboxylate) (**223**)



Ac_2O (45 μL, 0.48 mmol, 1.5 equiv) was used following General Procedure C on half the scale and washing with H_2O, rather than sat. aq $NaHCO_3$, in the aq work–up. Purification (Si-gel, pet ether/Et_2O 1:0→7:3) gave diazetine **223** as a colourless oil (17 mg, 30%).

- R_f 0.10 (pet ether/Et_2O 9:1);
- **IR** (neat/cm^{-1}) 3367 br, 2977 w, 2934 w, 1703 s, 1517 w, 1393 w, 1367 w, 1251 w, 1163 s;
- **^{1}H NMR** (400 MHz, $CDCl_3$) 5.55 (2H, s, 2 x NC=CH), 4.26-4.18 (4H, m, 2 x NCH_2), 1.75 (3H, s, CH_3), 1.46 (18H, s, 2 x $C(CH_3)_3$);
- **^{13}C NMR** (100 MHz, $CDCl_3$) 152.2 (C=O), 151.9 (N<u>C</u>=CH), 108.2 (NC=<u>C</u>H), 80.7 (<u>C</u>$(CH_3)_3$), 67.7 (<u>C</u>(OH)(CH_3)), 55.3 (NCH_2), 28.3 ($C(\underline{C}H_3)_3$), 22.9 (CH_3);
- **LRMS** (ESI^+) 375.2 ($[M+Na]^+$, 100%).

Di-*tert*-butyl 4,4'-(hydroxy(phenyl)methylene)bis(azete-1(2*H*)-carboxylate) (**224**)



BzCl (93 μL, 0.80 mmol, 2.5 equiv) was used following General Procedure C on half the scale and washing with H_2O, rather than sat. aq $NaHCO_3$, in the aq work–up. Purification (Si-gel, pet ether/Et_2O 1:0→7:3) gave diazetine **224** as a pale yellow oil (25 mg, 38%).

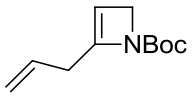
- R_f 0.57 (pet ether/EtOAc 4:1);
- **IR** (neat/cm^{-1}) 3293 br, 2978 w, 2935 w, 1690 m, 1667 s, 1478 w, 1450 w, 1392 s, 1367 m, 1256 w, 1140 s, 1055 w, 905 w, 856 w, 762 w, 700 m;
- **^{1}H NMR** (400 MHz, $CDCl_3$) 7.59-7.27 (5H, m, Ar), 6.50 (1H, br, OH), 5.30 (2H, s, 2 x NC=CH), 4.30-4.23 (4H, m, 2 x NCH_2), 1.36 (18H, s, 2 x $C(CH_3)_3$);

- **^{13}C NMR** (100 MHz, $CDCl_3$) 151.9 (C=O), 150.7 (N<u>C</u>=CH), 139.2 (Ar), 127.8 (Ar), 127.7 (Ar), 126.8 (Ar), 110.5 (NC=<u>C</u>H), 80.8 (<u>C</u>(CH_3)$_3$), 72.4 (<u>C</u>(OH)(Ph)), 54.9 (NCH_2), 28.2 (C(<u>C</u>H_3)$_3$);
- **LRMS** (FI^+) 414.22 ([M]$^+$, 100%); **HRMS** (FI^+) calcd for $C_{23}H_{30}N_2NaO_5$: 414.2155, found 414.2166.

General Procedure D. Synthesis of 2-allylated and 2-propargylated azetines 225

To a stirred solution of methoxyazetidine **215** (120 mg, 0.64 mmol) in THF (4 mL) at –78 °C was added TMEDA (248 μL, 1.66 mmol). *s*-BuLi (1.15 mL, 1.4 M in cyclohexane/hexane (92:8), 1.6 mmol) was added dropwise to the reaction mixture over 1 min, resulting in a pale yellow colour. After 1 h, a solution of CuCN•2LiCl [prepared by adding CuCN (29 mg, 0.32 mmol) to LiCl (27 mg, 0.64 mmol, flame-dried under vacuum, then placed under argon) in THF (2 mL) and the mixture stirred until dissolved (10 min)], was added dropwise over 1 min via syringe. After 1 h, the electrophile was added and the reaction mixture stirred for a further 1 h. The cooling bath was then removed and the reaction mixture was stirred for a further 1 h, washed with sat. aq $NaHCO_3$ (5 mL) and extracted with Et_2O (2 x 5 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated to dryness under reduced pressure.

***tert*-Butyl 4-allylazete-1(2*H*)-carboxylate** (**225a**)

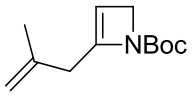


Allyl bromide (138 μL, 1.60 mmol, 2.5 equiv) was used following General Procedure D. Purification (pre-neutralised Si-gel, pet ether/Et_2O 1:0→49:1) gave allylated azetine **225a** as a colourless oil (75 mg, 60%).

- R_f 0.41 (pet ether/Et_2O 9:1);
- **IR** (neat/cm^{-1}) 2978 w, 1700 s, 1479 w, 1452 w, 1382 s, 1365 m, 1257 w, 1150 m, 1112 s, 1045 w, 991 w, 919 w, 863 w, 763 m, 686 w;

- **^{1}H NMR** (400 MHz, $CDCl_3$ over K_2CO_3) 5.86 (1H, ddt, *J* = 17.1, 10.0, 6.7 Hz, $CH_2C\underline{H}=CH_{cis}H_{trans}$), 5.25-5.24 (1H, m, NC=CH), 5.17 (1H, dq, *J* = 17.1, 1.6 Hz, $CH_2CH=C\underline{H}_{cis}H_{trans}$), 5.12 (1H, dq, *J* = 10.0, 1.4 Hz, $CH_2CH=CH_{cis}\underline{H}_{trans}$), 4.21-4.20 (2H, m, NCH_2), 3.16-3.14 (2H, m, $C\underline{H}_2CH=CH_{cis}H_{trans}$),1.47 (9H, s, $C(CH_3)_3$);
- **^{13}C NMR** (100 MHz, $CDCl_3$ over K_2CO_3) 152.0 (C=O), 150.8 ($N\underline{C}$=CH), 132.0 ($CH_2\underline{C}H=CH_2$), 117.6 ($CH_2CH=\underline{C}H_2$), 106.1 (NC=$\underline{C}$H), 80.0 ($\underline{C}(CH_3)_3$), 55.3 (NCH_2), 33.0 ($\underline{C}H_2CH=CH_2$), 28.4 ($C(\underline{C}H_3)_3$);
- **LRMS** (ESI^+) 140.1 (100%), 218.1 ($[M+Na]^+$, 70%); **HRMS** (ESI^+) calcd for $C_{11}H_{17}NNaO_2$: 218.1151, found 218.1154.

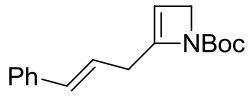
***tert*-Butyl 4-(2-methylallyl)azete-1(2*H*)-carboxylate** (**225b**)



Methylallyl bromide (161 μL, 1.60 mmol, 2.5 equiv) was used following General Procedure D. Purification (pre-neutralised Si-gel, pet ether/Et_2O 1:0→19:1) gave methylallylated azetine **225b** as a colourless oil (75 mg, 55%).

- R_f 0.59 (pet ether/Et_2O 9:1);
- **IR** (neat/cm^{-1}) 2977 w, 2933 w, 1701 s, 1620 w, 1504 w, 1455 w, 1389 m, 1366 m, 1251 w, 1148 s, 1042 w, 963 w, 895 w, 777 w;
- **^{1}H NMR** (400 MHz, $CDCl_3$ over K_2CO_3) 5.26-5.26 (1H, m, NC=CH), 4.87-4.84 (2H, m, $CH_2C(CH_3)=C\underline{H}_2$), 4.22-4.21 (2H, m, NCH_2), 3.11 (2H, s, $C\underline{H}_2C(CH_3)=CH_2$), 1.79 (3H, s, $CH_2C(C\underline{H}_3)=CH_2$), 1.47 (9H, s, $C(CH_3)_3$);
- **^{13}C NMR** (100 MHz, $CDCl_3$ over K_2CO_3) 152.1 (C=O), 150.6 (NC=CH), 140.4 ($CH_2\underline{C}(CH_3)=CH_2$), 112.8 ($CH_2C(CH_3)=C\underline{H}_2$), 106.9 (NC=CH), 80.0 ($\underline{C}(CH_3)_3$), 55.2 ($NCH_2$), 36.9 ($\underline{C}H_2C(CH_3)=CH_2$), 28.4 ($C(\underline{C}H_3)_3$), 22.5 ($CH_2C(\underline{C}H_3)=CH_2$);
- **LRMS** (ESI^+) 232.2 ($[M+Na]^+$, 40%), 252.1 (100%); **HRMS** (ESI^+) calcd for $C_{12}H_{19}NNaO_2$: 232.1308, found 232.1311.

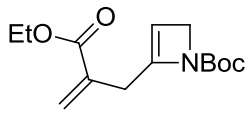
***tert*-Butyl 4-cinnamylazete-1(2*H*)-carboxylate (225c)**



Cinnamyl bromide (315 mg, 1.60 mmol, 2.5 equiv) was used following General Procedure D. Crude ^{1}H NMR analysis indicated S_N2:S_N2' 91:9, by integration of peaks at 6.57 ppm (S_N2 (cinnamyl) adduct PhHC=CHCH$_2$) and 4.66 ppm (S_N2' (isocinnamyl) adduct H$_2$C=CHCH(Ph)). Purification (pre-neutralised Si-gel, pet ether/Et$_2$O 1:0→19:1) gave cinnamylated azetine **225c** as a colourless oil (87 mg, 50%).

- R_f 0.39 (pet ether/Et$_2$O 9:1);
- **IR** (neat/cm^{-1}) 2978 w, 2932 w, 1701 s, 1496 w, 1452 w, 1390 m, 1366 m, 1251 w, 1167 s, 1151 m, 967 w, 911 w, 854 w, 774 m, 750 w, 695 m;
- **^{1}H NMR** (400 MHz, CDCl$_3$ over K$_2$CO$_3$) 7.43-7.28 (5H, m, Ar), 6.57 (1H, d, *J* = 15.9 Hz, CH=CHPh), 6.30 (1H, dt, *J* = 15.9, 6.8 Hz, CH=CHPh), 5.34-5.34 (1H, m, NC=CH), 4.29-4.28 (2H, m, NCH$_2$), 3.38-3.36 (2H, CH$_2$CH=CHPh), 1.55 (9H, s, C(CH$_3$)$_3$);
- **^{13}C NMR** (100 MHz, CDCl$_3$ over K$_2$CO$_3$) 152.0 (C=O), 150.7 (NC=CH), 137.1 (Ar), 132.6 (CH=CHPh), 128.5 (Ar), 127.3 (Ar), 126.1 (Ar), 123.5 (CH=CHPh), 106.3 (NC=CH), 80.1 (C(CH$_3$)$_3$), 55.4 (NCH$_2$), 32.2 (CH$_2$CH=CHPh), 28.4 (C(CH$_3$)$_3$);
- **LRMS** (ESI$^+$) 294.3 ([M+Na]$^+$, 95%), 401.3 (100%); **HRMS** (ESI$^+$) calcd for C$_{17}$H$_{21}$NNaO$_2$: 294.1465, found 294.1455.

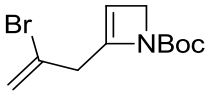
***tert*-Butyl 4-(2-(ethoxycarbonyl)allyl)azete-1(2*H*)-carboxylate (225f)**



Ethyl 2-(bromomethyl)acrylate (221 μL, 1.60 mmol, 2.5 equiv) was used following General Procedure D. Purification (pre-neutralised Si-gel, pet ether/Et_2O 1:0→19:1) gave allyl azetine **225f** as a colourless syrup (26 mg, 15%).

- R_f 0.26 (pet ether/Et_2O 9:1);
- **IR** (neat/cm^{-1}) 2977 w, 2934 w, 2898 w, 1712 s, 1478 w, 1457 w, 1388 m, 1365 m, 1254 m, 1147 s, 1094 w, 1024 w, 971 w, 920 w, 861 w, 760 w, 731 m;
- **^{1}H NMR** (400 MHz, $CDCl_3$ over K_2CO_3) 6.31-6.30 (1H, m, C=C$\underline{H}_{cis}H_{trans}$), 5.74-5.73 (1H, m, C=C$H_{cis}\underline{H}_{trans}$), 5.26 (1H, s, NC=CH), 4.22 (2H, q, *J* = 7.1 Hz, C$\underline{H}_2CH_3$), 4.3-4.22 (2H, m, NCH_2), 3.42 (2H, s, C$\underline{H}_2C=CH_2$), 1.45 (9H, s, $C(CH_3)_3$), 1.30 (3H, t, *J* = 7.1 Hz, $CH_2C\underline{H}_3$);
- **^{13}C NMR** (100 MHz, $CDCl_3$ over K_2CO_3) 166.5 ($\underline{C}(O)OCH_2CH_3$), 152.0 (C=O), 149.5 (N$\underline{C}$=CH), 135.5 ($\underline{C}$=$CH_2$), 126.8 (C=$\underline{C}H_2$), 107.5 (NC=$\underline{C}$H), 80.1 ($\underline{C}(CH_3)_3$), 60.8 ($\underline{C}H_2CH_3$), 55.3 ($NCH_2$), 30.8 ($\underline{C}H_2C=CH_2$), 28.3 ($C(\underline{C}H_3)_3$), 14.2 ($CH_2\underline{C}H_3$);
- **LRMS** (ESI^+) 557.2 ($[2M+Na]^+$, 100%); **HRMS** (ESI^+) calcd for $C_{28}H_{42}N_2NaO_8$: 557.2833, found 557.2852.

***tert*-Butyl 4-(2-bromoallyl)azete-1(2*H*)-carboxylate (225g)**

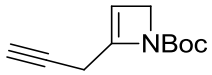


2,3-Dibromopropene (195 μL, 1.60 mmol, 80 % purity, 2.5 equiv) was used following General Procedure D. Purification (pre-neutralised Si-gel, pet ether/Et_2O 1:0→19:1) gave allyl azetine **225g** as a pale yellow syrup (20 mg, 11%).

Discernable data

- R_f 0.42 (pet ether/Et_2O 9:1);
- **IR** (neat/cm^{-1}) 2978 w, 2934 w, 1711 s, 1600 w, 1520 w, 1478 w, 1457 w, 1367 s, 1319 w, 1298 w, 1253 w, 1149 s, 856 w, 761 w;
- **^{1}H NMR** (400 MHz, $CDCl_3$ over K_2CO_3) 5.78-5.77 (1H, m, C=C$H_{cis}$$\underline{H}_{trans}$), 5.57-5.57 (1H, m, C=C$\underline{H}_{cis}H_{trans}$), 5.45-5.45 (1H, m, NC=CH), 4.26-4.25 (2H, m, NCH_2), 3.55 (2H, s, $C\underline{H}_2C(Br)=CH_2$), 1.48 (9H, s, $C(CH_3)_3$);
- **^{13}C NMR** (100 MHz, $CDCl_3$ over K_2CO_3) 152.0 (C=O), 147.6 (N$\underline{C}$=CH), 126.9 ($\underline{C}$=CH_2), 119.2 (C=$\underline{C}H_2$), 108.6 (NC=$\underline{C}$H), 80.4 ($\underline{C}(CH_3)_3$), 55.7 (NCH_2), 40.6 ($\underline{C}H_2C(Br)=CH_2$), 28.4 ($C(\underline{C}H_3)_3$);

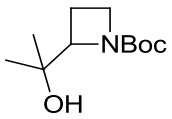
***tert*-Butyl 4-(prop-2-yn-1-yl)azete-1(2*H*)-carboxylate** (**225h**)



Propargyl bromide (178 μL, 1.60 mmol, 80 wt%, 2.5 equiv) was used following General Procedure D. Purification (pre-neutralised Si-gel, pet ether/Et_2O 1:0→19:1) gave propargylated azetine **225h** as a colourless oil (46 mg, 37%).

- R_f 0.48 (pet ether/Et_2O 9:1);
- **IR** (neat/cm^{-1}) 3313 w, 3257 w, 2977 w, 2934 w, 1712s, 1666 m, 1478 w, 1456 w, 1382 s, 1366 s, 1323 w, 1253 w, 1152 s, 1052 w, 859 m, 761 m, 639 w;
- **^{1}H NMR** (400 MHz, $CDCl_3$ over K_2CO_3) 5.49 (1H, s, NC=CH), 4.23-4.21 (2H, m, NCH_2), 3.35 (2H, s, $C\underline{H}_2C{\equiv}CH$), 2.11 (1H, t, J = 2.7 Hz, $CH_2C{\equiv}C\underline{H}$), 1.46 (9H, s, $C(CH_3)_3$);
- **^{13}C NMR** (100 MHz, $CDCl_3$ over K_2CO_3) 152.0 (C=O), 146.2 (N$\underline{C}$=CH), 107.3 (NC=CH), 80.4 ($\underline{C}(CH_3)_3$), 77.6 ($CH_2\underline{C}{\equiv}CH$), 70.3 ($CH_2C{\equiv}\underline{C}H$), 55.3 ($NCH_2$), 28.3 ($C(\underline{C}H_3)_3$), 19.3 ($\underline{C}H_2C{\equiv}CH$);
- **LRMS** (ESI^+) 216.1 ($[M+Na]^+$, 60%), 313.3 (100%); **HRMS** (ESI^+) calcd for $C_{11}H_{15}NNaO_2$: 216.0995, found 216.1005.

***tert*-Butyl 2-(2-hydroxypropan-2-yl)azetidine-1-carboxylate** (**227**)



To a solution of tertiary alcohol **214h** (22 mg, 0.10 mmol) in EtOAc (1 mL) was added Pd/C (2 mg, 10 %). The suspension was stirred under H_2 for 2 h, filtered through celite, washed with MeOH (2 mL) and concentrated to dryness under reduced pressure. Purification (Si-gel, pet ether/EtOAc 1:0→17:3) gave azetidine **227** as a colourless oil (19 mg, 86%).

- R_f 0.48 (pet ether/EtOAc 4:1);
- **IR** (neat/cm^{-1}) 3400 br, 2974 w, 2932 w, 2893 w, 1698 m, 1668 s, 1407 s, 1366 m, 1249 w, 1152 s, 1060 w, 1014 w, 992 w, 936 w, 858 w, 774 w;
- **^{1}H NMR** (400 MHz, $CDCl_3$) 4.77 (1H, br, OH), 4.24 (1H, dd, *J* = 8.8, 6.9 Hz, NCH), 3.85 (1H, td, *J* = 8.8, 6.9 Hz, $NCH_{cis}\underline{H}t_{rans}$), 3.72 (1H, td, *J* = 8.8, 5.2 Hz, $NC\underline{H}_{cis}H_{trans}$), 2.18 (1H, dtd, *J* = 11.3, 8.8, 5.2 Hz, $NCH_2CH_{cis}\underline{H}_{trans}$), 1.87 (1H, ddt, *J* = 11.3, 8.8, 6.9 Hz, $NCH_2C\underline{H}_{cis}H_{trans}$), 1.45 (9H, s, $C(CH_3)_3$), 1.24 (3H, s, CH_3), 1.09 (3H, s, CH_3);
- **^{13}C NMR** (125 MHz, $CDCl_3$) 157.3 (C=O), 80.4 ($\underline{C}(CH_3)_3$), 71.6 (COH), 70.9 (NCH), 46.5 (NCH_2), 28.3 ($C(\underline{C}H_3)_3$), 24.6 (CH_3), 22.6 (CH_3), 18.9 ($NCH_2\underline{C}H_2$);
- **LRMS** (ESI^+) 238.2 ($[M+Na]^+$, 100%); **HRMS** (ESI^+) calcd for $C_{11}H_{21}NNaO_3$: 238.1414, found 238.1417.

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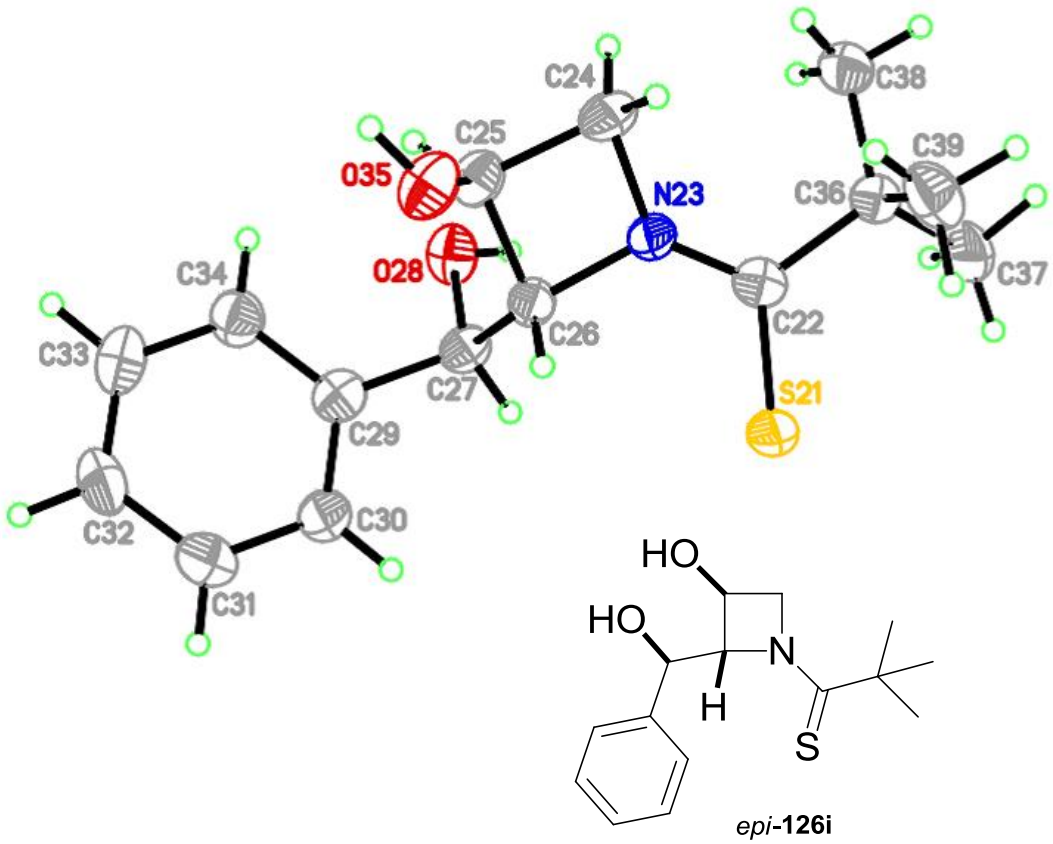
6 Appendices

6.1 Crystal data and structure refinement for epi-126i [1]

Single crystal diffraction data[2] was solved with SuperFlip[3] and further refined.[4] The material is a chiral racemate (crystallizes in a Sohnke space group with both hands in the asymmetric unit such that it fails to make use of the inversion symmetry); examples are rare.[5]



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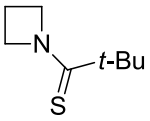
Empirical formula	$C_{15}H_{21}NO_2S$
Formula weight	279.40
Temperature	150 K
Wavelength	0.71073 Å
Crystal system	Orthorhombic
Space group	P 21 21 21
Unit cell dimensions	a = 9.2047(1) Å, α= 90°.
	b = 12.9635(2) Å, β= 90°.
	c = 24.7453(3) Å, γ = 90°.
Volume	2952.74(7) $Å^3$
Z	8
Density (calculated)	1.257 Mg/m^3
Absorption coefficient	0.217 mm^{-1}
F(000)	1200
Crystal size	1.000 x 0.500 x 0.500 mm^3
Theta range for data collection	5.188 to 27.516°.
Index ranges	-11<=h<=11, -16<=k<=16, -31<=l<=32
Reflections collected	26570
Independent reflections	6668 [R(int) = 0.087]
Completeness to theta = 25.590°	98.7 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.90 and 0.49
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4006 / 0 / 344
Goodness-of-fit on F^2	0.9936
Final R indices [I>2sigma(I)]	R1 = 0.0412, wR2 = 0.1009
R indices (all data)	R1 = 0.0506, wR2 = 0.1052
Absolute structure parameter	-0.04(9)
Largest diff. peak and hole	0.29 and -0.32 $e.Å^{-3}$

6.2 Calculation of rotation barriers

All experiments and associated calculations concerned with rotation barriers of thioamide **94** and amide **228** are previously unpublished and were carried out in-house.[6]

6.2.1 Thioamide 94

A sample of thioamide **94** in tol-D8 was placed in an NMR tube and this sample was warmed gradually from 27 °C to 97 °C.



94

Figure 6.1 Unsubstituted thioamide azetidine **94**

Warming allowed coalescence of the CH_2NCH_2 signals (Figure 6.2).

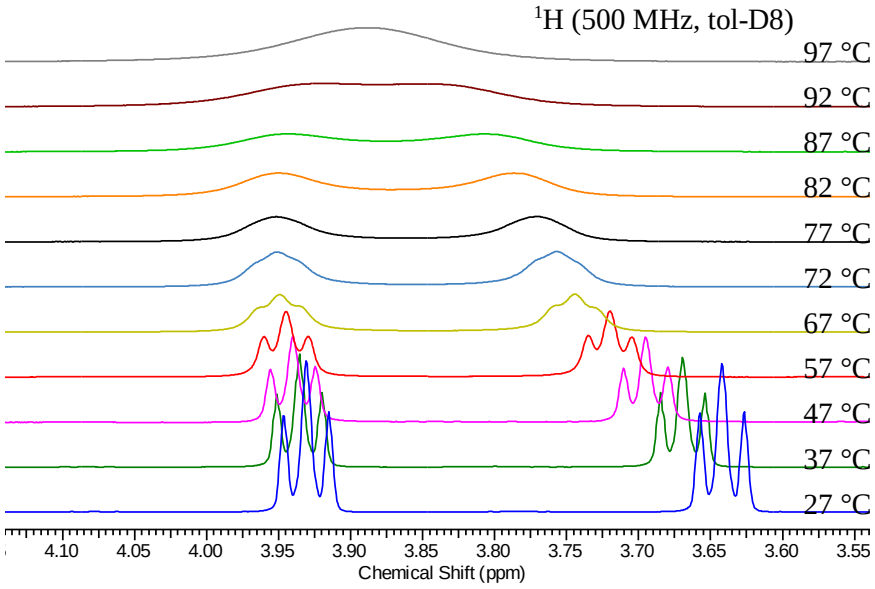


Figure 6.2 Effect of temperature variation ^1H NMR spectrum of thioamide **94** (CH_2NCH_2 region)

[6] Results obtained by T. D. W. Claridge, University of Oxford, 2010.

Due to the unusual temperature dependence of the peak positions, predictions of peak positions had to be calculated when the system approached fast exchange (red values). Rate constants (*k*) were calculated directly from line-shape simulations (green values) using gNMR (Table 6.1).

Table 6.1 Experimental, and simulated peak positions and rate constants for thioamide **94**

T (K)	1/T	δ_A	δ_B	δ_A (sim)	δ_B (sim)	*k*	ln(*k*/T)
300	0.003333333	3.931	3.6424				
310	0.003225806	3.9358	3.6696				
320	0.003125000	3.9403	3.6954	3.9403	3.6954	3	-4.66971
330	0.003030303	3.945	3.7201	3.945	3.7201	6	-4.00733
340	0.002941176	3.9496	3.74656	3.9496	3.7445	17.3	-2.97824
345	0.002898551	3.951925	3.759505	3.952	3.756	27.7	-2.52211
350	0.002857143	3.95425	3.77245	3.954	3.772	41.2	-2.13949
355	0.002816901	3.956575	3.785395	3.956	3.786	62.6	-1.73535
360	0.002777778	3.9589	3.79834	3.959	3.798	92.5	-1.3589
365	0.002739726	3.961225	3.811285	3.961	3.8049	142	-0.94407
370	0.002702703	3.96355	3.82423	3.963	3.816	202	-0.60524

The Eyring plot of 1/T against ln(*k*/T) is shown below (Figure 6.3).

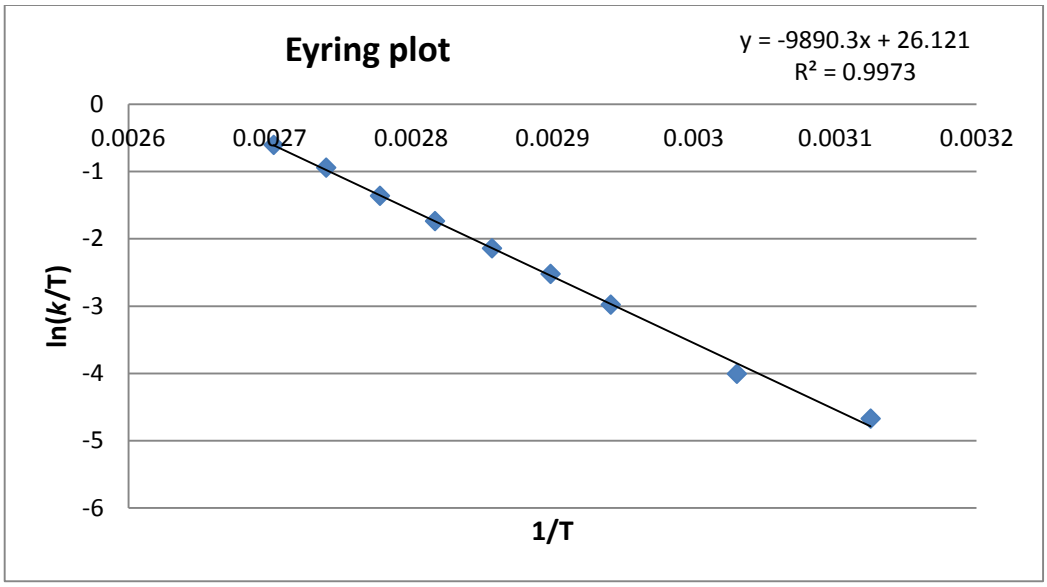


Figure 6.3 Eyring plot for thioamide **94**

From the Eyring plot it can be determined:

$\Delta H^{\ddagger} \approx 82.2$ kJmol^{-1}

$\Delta S^{\ddagger} \approx 19.6$ JK^{-1}mol^{-1}

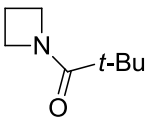
These values provide:

$\Delta G^{\ddagger} \approx 76.4$ kJmol^{-1} at 25 °C, $k = 2.517 \times 10^{-1}$ s^{-1}, $t_{1/2} = 3$ s.

$\Delta G^{\ddagger} \approx 78.4$ kJmol^{-1} at –78 °C, $k = 4.102 \times 10^{-9}$ s^{-1}, $t_{1/2} = 5$ years.

6.2.2 Amide 228

A sample of amide **228** in tol-D8 was placed in an NMR tube and this sample was warmed gradually from –73 °C to 32 °C.



228

Figure 6.4 Unsubstituted amide azetidine **228**

Warming allowed coalescence of the CH_2NCH_2 signals (Figure 6.5).

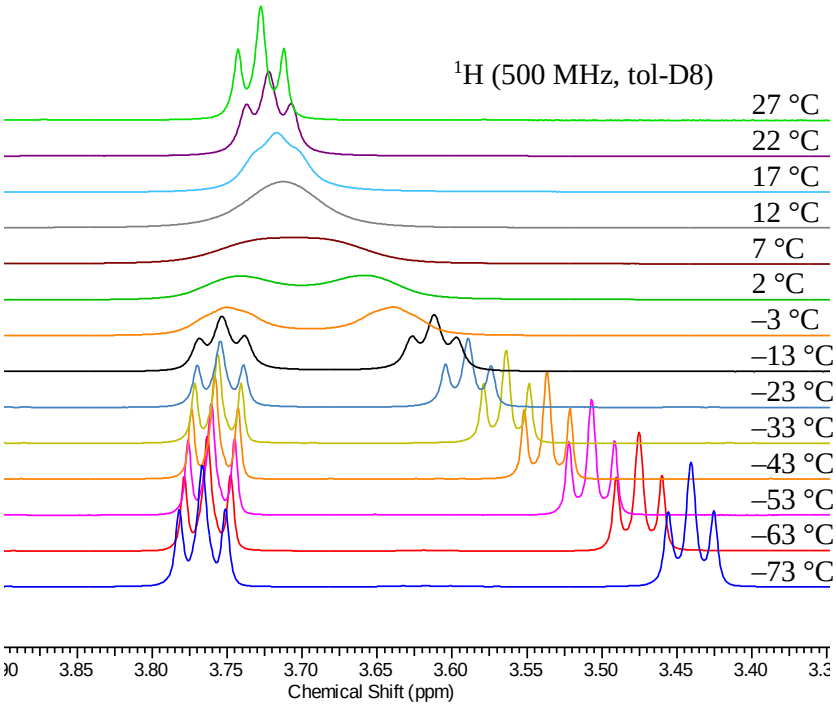


Figure 6.5 Effect of temperature variation ^{1}H NMR spectrum of amide **228** (CH_2NCH_2 region)

Due to the unusual temperature dependence of the peak position, predictions of peak positions had to be calculated when the system approached fast exchange (red values). Rate constants (*k*) were calculated directly from line-shape simulations (green values) using gNMR (Table 6.2).

Table 6.2 Experimental, and simulated peak positions and rate constants for amide **228**

T (K)	1/T	δ_A	δ_B	δ_A (sim)	δ_B (sim)	*k*	ln(*k*/T)
200	0.005000	3.7670	3.4409				
210	0.004762	3.7637	3.4755				
220	0.004545	3.7609	3.5070				
230	0.004348	3.7587	3.5369				
240	0.004167	3.7566	3.5641				
250	0.004000	3.7550	3.5896				

260	0.003846	3.7539	3.6122	3.7539	3.6120	11	-3.16279
270	0.003706	3.7531	3.6326	3.7531	3.6370	33.9	-2.07427
275	0.003636	3.7529	3.6424	3.7529	3.6485	59.3	-1.53416
280	0.003571	3.7528	3.6513	3.7528	3.6614	94.9	-1.08197
285	0.003509	3.7528	3.6596	3.7528	3.6738	142	-0.69666
290	0.003448	3.7529	3.6674	3.7529	3.6812	247	-0.16049
295	0.003390	3.7531	3.6745	3.7531	3.6923	366	0.215658
300	0.003333	3.7533	3.6811	3.7533	3.7026	651	0.774727

The Eyring plot of 1/T against ln(*k*/T) is shown below (Figure 6.6).

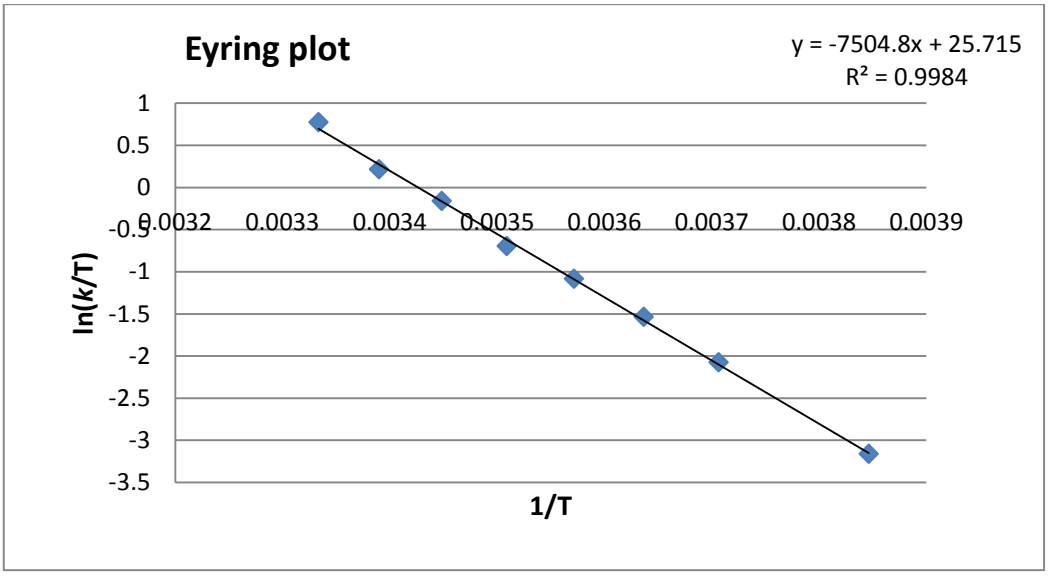


Figure 6.6 Eyring plot for amide **228**

From the Eyring plot it can be determined:

$\Delta H^{\ddagger} \approx 62.4$ kJmol^{-1}

$\Delta S^{\ddagger} \approx 16.3$ JK^{-1}mol^{-1}

These values provide:

$\Delta G^{\ddagger} \approx 57.5$ kJmol^{-1} at 25 °C, $k = 5.086 \times 10^{2}$ s^{-1}, $t_{1/2} = 0.001$ s.

$\Delta G^{\ddagger} \approx 59.2$ kmol^{-1} at –78 °C, $k = 5.554 \times 10^{-4}$ s^{-1}, $t_{1/2} = 21$ min.

6.3 Published reports

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α-Lithiation–Electrophile Trapping of *N*-Thiopivaloylazetidin-3-ol: Stereoselective Synthesis of 2-Substituted 3-Hydroxyazetidines

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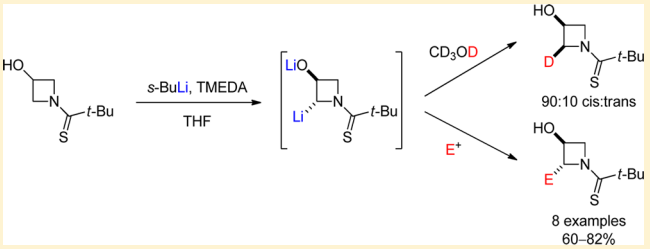
Supporting Information

ABSTRACT: α-Lithiation of *N*-thiopivaloylazetidin-3-ol and subsequent electrophile trapping provides access to a range of 2-substituted 3-hydroxyazetidines with generally good *trans*-diastereoselectivity, aside from deuteration, which gives the *cis*-diastereoisomer. Deuterium labeling studies indicate that the initial α-deprotonation occurs preferentially, but not exclusively, in a *trans*-selective manner. These studies also suggest that the stereochemical outcome of the electrophile trapping depends on the electrophile used but is independent of which α-proton (*cis* or *trans* to the hydroxyl group) is initially removed.



INTRODUCTION

Azetidines have received significantly less attention from the synthesis community in comparison with the larger and smaller azacycles.[1] However, azetidines are being increasingly incorporated into drug candidates[2] and are also finding utility as ligands in metal-catalyzed transformations.[3] In particular, the 3-hydroxy- or 3-alkoxyazetidine motif is present in a number of drug leads[4] and in natural products[5] (Figure 1).

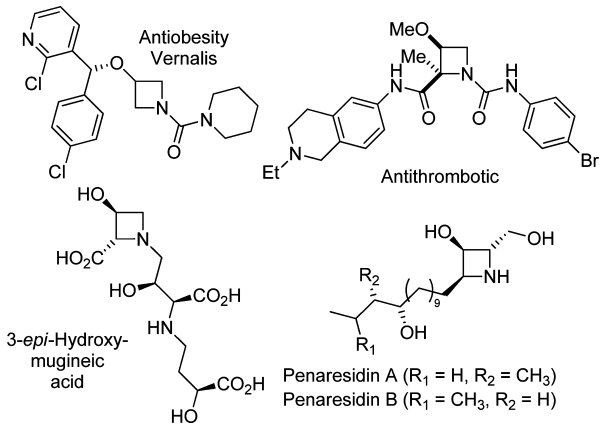
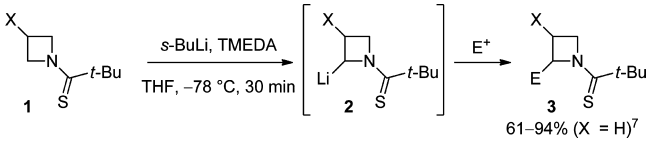


Figure 1. Examples of 3-oxygenated azetidine-containing drug leads[4] and natural products.[5]

In most strategies to substituted azetidines, the substituents are required to be present on a precursor or precursors, prior to ring formation.[1,6] We recently reported a method for α-electrophile incorporation on azetidine **1** (Scheme 1, X = H), in which the rarely studied *N*-thiopivaloyl group plays a crucial role.[7] The ready availability of the 3-hydroxyazetidine system (from epichlorohydrin and benzhydrylamine)[8] and its value in medicinal chemistry programs prompted the present investigations of the 3-oxygenated system **1** (Scheme 1, X = OR). Despite the potential issues of β-elimination from the α-lithiated intermediate **2** and controlling diastereoselectivity in the electrophile trapping, this work has resulted in a promising entry to 2,3-disubstituted azetidines **3** (X = OR).

Scheme 1. α-Deprotonation and Electrophile Trapping of *N*-Thiopivaloylazetidine



RESULTS AND DISCUSSION

We initially attempted lithiation–deuteration (as well as in situ silylation) of silyloxythioamide **7** (Scheme 2). Silyloxythioamide **7** was prepared in four steps from *N*-benzhydrylazetidin-3-ol (**4**), by silylation to give silyl ether **5** (quant), hydrogenolytic N-deprotection and N-pivaloylation to give silyloxyamide **6** (90% over two steps), and finally, amide thionation using P_2S_5 (93%). However, only starting thioamide **7** and/or azetine **9** (up to 98% yield) were obtained from the lithiation experiments. Azetine **9** is likely formed by rapid β-elimination of silyloxide from the transient α-lithiated intermediate **8**.[9]

With the aim of avoiding the undesired elimination pathway, we examined C,O-dilithiation of the unprotected azetidinol **12**.[10] This azetidinol **12** could be conveniently prepared in two steps from commercially available azetidin-3-ol hydrochloride

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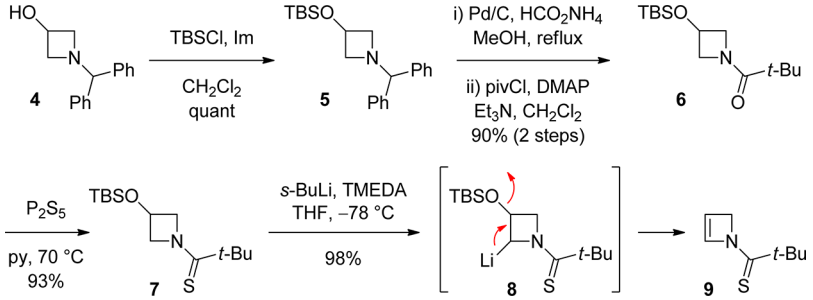
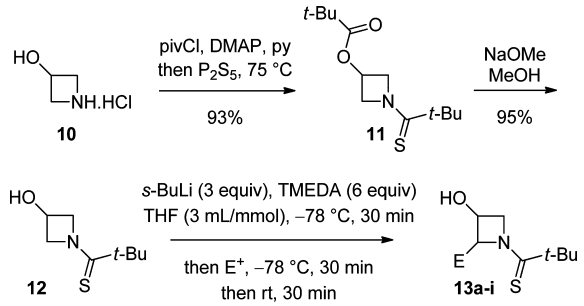
Scheme 2. Synthesis and Lithiation–Elimination of Silyloxythioamide 7



(**10**) (Scheme 3), by diacylation and amide thionation (93%), followed by de-esterification (95%) of the resulting thioamide ester **11**.

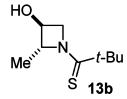
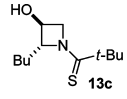
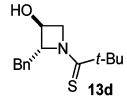
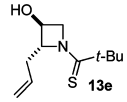
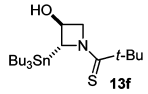
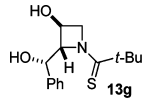
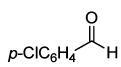
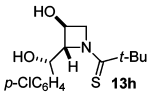
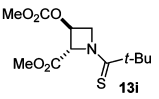
Scheme 3. Synthesis and Lithiation of Azetidinol 12



In the event, azetidinol **12** underwent partial lithiation–deuteration (92% recovery, 48% D, 90:10 dr) under the conditions originally used with azetidine **1** (X = H) but using twice the quantity of *s*-BuLi (2.4 equiv) to take account of the free hydroxyl. Further experimentation in THF established that complete deuterium incorporation to give **13a** (E = D) could be obtained by increasing the concentration (from 0.1 to 0.3 M), with the optimal yield (91%, 90:10 dr) being obtained using the conditions indicated in Scheme 3. Lithiation above −78 °C led to reduced dr values (73:26 at −46 °C), whereas no significant improvement was observed at −98 °C. Using no, or decreased equivalents, of TMEDA did give product but in slightly suppressed yields. Experiments carried out in Et_2O did not give higher than 33% deuterium incorporation, with poor solubility of the deprotonated species likely being a contributory factor. Application of the optimized conditions in THF to a range of other electrophiles gave the results shown in Table 1.

Alkylation (entries 1–4), including benzylation and allylation (entries 3 and 4), as well stannylation (entry 5), and reaction with aromatic aldehydes (entries 6 and 7) and with Mander's reagent (entry 8) all proceeded to give the corresponding 2,3-disubstituted azetidine **13** in good yield. Aside from methylation (entry 1),[11] high *trans*-2,3-diastereoselectivity was observed with the electrophiles in Table 1. With azetidine **1** (X = H), benzaldehyde and *para*-chlorobenzaldehyde had previously given the adduct alcohols as single diastereomers;[7] for azetidinol **12**, these prochiral electrophiles led to the same relative stereochemistry between C-2 and the side-chain carbinol but at a reduced level (entries 6 and 7). The reaction with methyl cyanoformate gave *C*- and *O*-methoxycarbonylated azetidine **13i** (entry 8), which provides potential access to azetidine amino acids and mugineic acid-type natural products

Table 1. Scope of Electrophile Incorporation into Azetidinol 12

entry	electrophile	2,3-disubstituted azetidine **13**	yield (%)
1	MeI	 **13b**	72[a]
2	BuI	 **13c**	68
3	BnBr	 **13d**	74
4		 **13e**	60
5	Bu_3SnCl	 **13f**	82
6		 **13g**	72[b]
7		 **13h**	81[b]
8		 **13i**	68[a]

[a]Ratio of *trans*/*cis* 69:31 (entry 1), 93:7 (entry 8); major diastereoisomer shown. [b]Ratio of 75:25 (entry 6) and 57:43 (entry 7) mixture of epimers at side-chain carbinol; major diastereoisomer shown.

(Figure 1). The above stereochemical assignments are based on X-ray crystallographic analysis of the minor epimer *epi*-**13g** (epimeric to **13g** at the side-chain benzylic position) derived from benzaldehyde[12] and proton coupling constant analysis.[13] The vicinal coupling constant between the ring protons at C-2 and C-3 was 3.3 Hz for both **13g** and *epi*-**13g** and was similar (2–4 Hz) for all other adducts in Table 1.[14] In contrast, ^3J for

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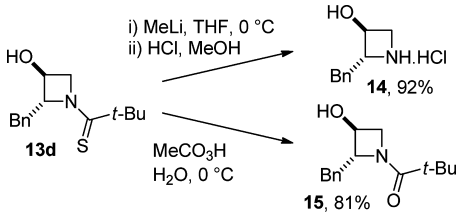
the corresponding minor *cis*-methylated diastereoisomer of **13b** was 6.6 Hz.

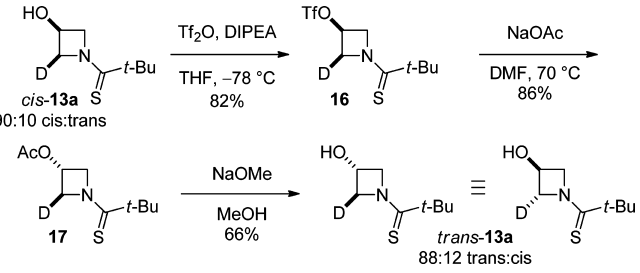
Effective deprotection of an α-substituted azetidinol **13** can be achieved using MeLi in THF with TMEDA at 0 °C (92% from **13d**, isolated as the hydrochloride salt **14**, Scheme 4). Conversion to the corresponding pivalamide **15**, in 81% yield from **13d**, was facilitated using $MeCO_3H$.

Scheme 4. Deprotection and Thioamide to Amide Conversion



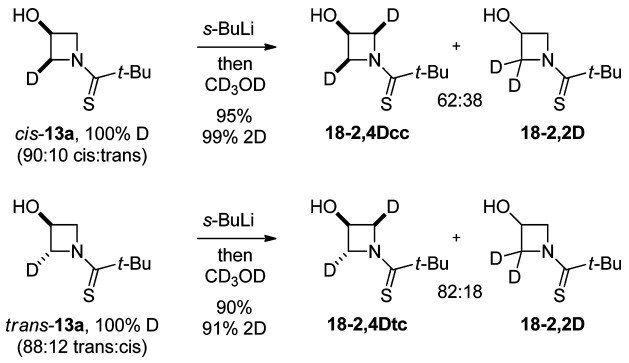
In contrast to the results shown in Table 1, deuterium trapping of lithiated azetidinol **12** occurs predominantly *cis* to the hydroxyl group (*cis*-**13a**, 90:10 *cis*/*trans*). This *cis* configuration was assigned from ^{1}H NMR analysis.[13] On deuteration, the appearance of the multiplet due to H-3 at the carbinol carbon changed from a triplet of triplets (^3J = 6.6 and 3.9 Hz) for **12** to a triplet of doublets (^3J = 6.6 and 3.9 Hz) for *cis*-**13a**, indicating the loss of a 3.9 Hz coupling, corresponding to loss of a proton *cis* to the alcohol. These observations prompted an investigation into the stereoselectivity of the lithiation and electrophile trapping steps,[15] using *cis*-**13a** and the inverted deuterium adduct *trans*-**13a**. The latter was synthesized by inversion of the alcohol in *cis*-**13a** through acetate displacement of the derived triflate **16** to give acetate **17**, followed by deacetylation (Scheme 5). In contrast to *cis*-**13a**, H-3 for the inverted deuterium adduct *trans*-**13a** appeared as a doublet of triplets (^3J = 6.6 and 3.9 Hz).

Scheme 5. Synthesis of *trans*-13a



The preference for proton removal (*cis* or *trans* to OLi under the reaction conditions) was examined by lithiation−deuteration of *cis*-**13a** and of *trans*-**13a**, which gave dideuterated adducts **18** (Scheme 6). 2,4-Dideuterated adduct is present in a greater proportion from *trans*-**13a** (2,4-:2,2-, 82:18) than from *cis*-**13a** (2,4-:2,2-, 62:38), indicating a preference for *trans*-deprotonation, which in the case of *trans*-**13a** is blocked at C-2 by the presence of the *trans*-deuterium (primary kinetic isotope effect). While less preferable to *trans*-deprotonation, *cis*-deprotonation does occur competitively, as evidenced by the formation of the 2,2-dideuterated adduct **18-2,2D** from *trans*-**13a** and the unequal ratio of dideuterated adducts from *cis*-**13a** (assuming no significant secondary kinetic isotope effect). The presence of ∼10% of *trans*-**13a** in *cis*-**13a** and visa versa (which

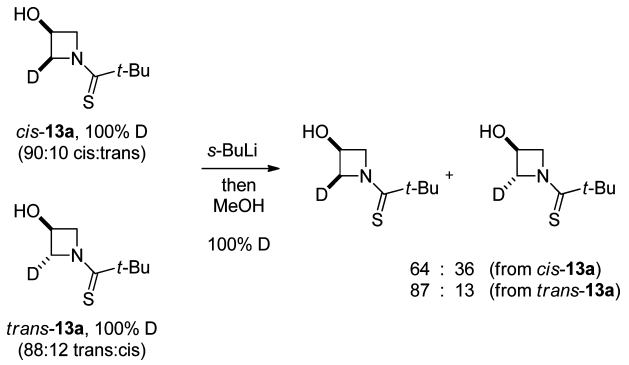
Scheme 6. Lithiation−Deuteration of *cis*-13a and of *trans*-13a



should lead to small amounts **18-2,4Dtc** and **18-2,4Dcc**, respectively—although not detectable/analyzable by NMR) does not negate these conclusions.

Lithiation−protonation of *cis*-**13a** and of *trans*-**13a** resulted in a *cis*/*trans* dr change from 90:10 to 64:36 (quant) and no change in dr (86% yield), respectively (Scheme 7).[13] These

Scheme 7. Lithiation−Protonation of *cis*-13a and of *trans*-13a



results can be rationalized as follows. The earlier dideuteration results with *cis*-**13a** and *trans*-**13a** (Scheme 6) indicate that the regioselectivity of the deprotonation between the 4- and 2-positions is ∼6:4 and 8:2, respectively, in favor of the 4-position. On lithiation−protonation of *cis*-**13a** (Scheme 7), the 4-lithiated intermediate (comprising ∼60% of the total lithiated azetidinol) will regenerate *cis*-**13a**, whereas the 2-lithiated species (∼40%) will give *trans*-**13a**. However, for lithiation−protonation of *trans*-**13a**, both the 4-lithiated *and* the 2-lithiated species regenerate *trans*-**13a**. These results therefore suggest that there is a strong bias for *cis*-protonation (deuteration), regardless of whether a *cis* or *trans* proton is originally removed.

Lithiation−benzylation of *cis*-**13a** and of *trans*-**13a** both result in a mixture of the two possible regioisomers: the *cis*- and *trans*-2-deuterated 4-benzylated derivatives (**19-2D$_c$-4Bn$_t$** and **19-2D$_t$-4Bn$_t$**) and the 2,2-derivative (**19-2D$_c$-2Bn$_t$**) (Scheme 8). The *cis*- and *trans*-2,4-derivatives (where *cis* and *trans* refer to stereochemistry relative to the alcohol) likely derive directly from 4-lithiation of the major and minor diastereoisomeric azetidinols which comprise the starting material, as the ratios match. Both stereoisomers can be observed in these cases, as the position of the deuterium can now be established relative to the newly installed benzyl group. 2-Lithiation−benzylation from either *cis*-**13a** or *trans*-**13a** gave only the *trans*-2-

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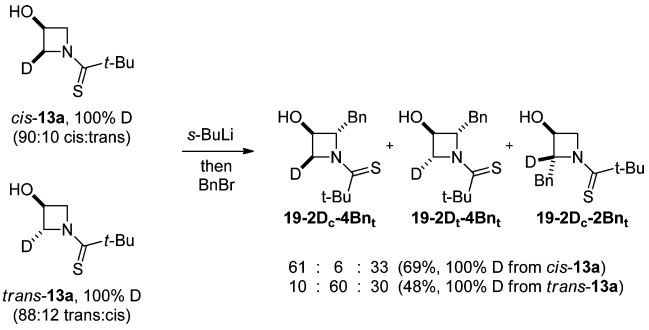
Scheme 8. Lithiation−Benzylation of *cis*-13a and of *trans*-13a



benzylated adduct **19-2D$_c$-2Bn$_t$**.[16] These observations indicate that there is a strong bias for electrophile trapping (apart from protonation/deuteration) to occur *trans* to the C-3 lithium alkoxide, regardless of whether a *cis* or *trans* proton is initially removed at C-2. However, further conclusions concerning configurational (in)stability of the intermediate organolithiums and whether the electrophile trapping step occurs with retention/inversion/SET pathways cannot be made from the results obtained.

CONCLUSIONS

In summary, readily available *N*-thiopivaloylazetidin-3-ol (**12**) has been shown to undergo α-lithiation−electrophile trapping with a range of electrophiles, providing 2-substituted 2-hydroxyazetidines **13**. Deuterium labeling studies indicate that the α-deprotonation step is preferentially, but not exclusively, *trans*-stereoselective. Nevertheless, high *trans*-diastereoselectivity is observed on incorporation of most electrophiles. A notable exception is protonation, where the alkoxide may be involved in directing the protonation *cis* to itself.[17] Our work indicates that the stereochemical outcome of the lithiated azetidinol trapping depends on the electrophile used but is independent of which α-proton (*cis* or *trans* to the hydroxyl group) is initially removed. These studies demonstrate that electrophile incorporation with high levels of diastereocontrol is possible on a simple azetidine and suggest that further opportunities exist for azetidine diversity generation using this strategy.

EXPERIMENTAL SECTION

3-((*tert*-Butyldimethylsilyl)oxy)-1-(diphenylmethyl)azetidine (5). To a stirred solution of *N*-benzhydrylazetidin-3-ol (**4**) (3.60 g, 15.0 mmol) and TBSCl (2.73 g, 18.1 mmol) in CH_2Cl_2 (30 mL) at rt was added imidazole (1.23 g, 18.1 mmol). After 30 min, the reaction mixture was filtered, and the filter cake washed with CH_2Cl_2 (10 mL). The filtrate was concentrated to dryness under reduced pressure. Purification (Si gel, pet ether/Et_2O 1:0→9:1) gave silyl ether **5**[18] as an off-white solid (5.30 g, quant): R_f 0.83 (pet ether/EtOAc 3:2); mp 45−47 °C; IR (neat/cm^{-1}) 2929 w, 2854 w, 2832 w, 1451 w, 1307 w, 1204 m, 1204 m, 1182 m, 1160 w, 880 m, 836 m, 780 m, 703 m; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42−7.18 (10H, m, Ar), 4.47 (1H, quint, J = 6.1 Hz, CHO), 4.37 (1H, s, C$\underline{H}$Ph$_2$), 3.55 (1H, dd, J = 6.1, 2.0 Hz, NC$\underline{H}$H), 3.53 (1H, dd, J = 6.1, 2.0 Hz, NC$\underline{H}$H), 2.84 (1H, dd, J = 6.3, 2.0 Hz, NCH$\underline{H}$), 2.82 (1H, dd, J = 6.3, 2.0 Hz, NCH$\underline{H}$), 0.87 (9H, s, Si(CH$_3$)$_2$C(C$\underline{H}_3$)$_3$), 0.03 (6H, s, Si(C$\underline{H}_3$)$_2$C(CH$_3$)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.3 (Ar), 128.4 (Ar), 127.4 (Ar), 127.0 (Ar), 78.6 (N$\underline{C}$HPh$_2$), 63.8 (NCH$_2$), 61.8 (CHO), 25.8 (Si(CH$_3$)$_2$C($\underline{C}$H$_3$)$_3$), 18.0 (Si(CH$_3$)$_2\underline{C}$(CH$_3$)$_3$), −5.0 (Si($\underline{C}$H$_3$)$_2$C(CH$_3$)$_3$); LRMS (ESI$^+$) 354.20 ([M + H]$^+$, 80%); HRMS (ESI$^+$) calcd for $C_{22}H_{32}NOSi$ 354.2248, found 354.2236.

1-(3-((*tert*-Butyldimethylsilyl)oxy)azetidin-1-yl)-2,2-dimethylpropan-1-one (6). To a stirred solution of silyl ether **5** (5.30 g, 15.0 mmol) in MeOH (100 mL) at rt were added ammonium formate (4.73 g, 75.0 mmol) and 10 wt % Pd/C (530 mg) under nitrogen. The reaction mixture was heated to reflux, and after 2 h, upon cooling to rt, the reaction mixture was filtered through a pad of Celite, then concentrated to dryness under reduced pressure. The crude residue was dissolved in CH_2Cl_2 (75 mL). To the resulting solution were added DMAP (670 mg, 5.5 mmol) and Et_3N (4.2 mL, 30.1 mmol). The reaction mixture was cooled to 0 °C, and pivCl (2.2 mL, 17.9 mmol) was added dropwise over 5 min. The reaction mixture was warmed slowly to rt and stirred overnight. After quenching with aq HCl (1 M, 75 mL) the aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layers were washed with H_2O (75 mL) then brine (75 mL), dried (Na_2SO_4), and concentrated to dryness under reduced pressure. Purification (Si gel, pet ether/EtOAc 19:1→4:1) gave silyloxyamide **6** as a white solid (3.65 g, 90%): R_f 0.36 (pet ether/Et_2O 3:2); mp 32−34 °C; IR (neat/cm^{-1}) 2956 m, 2931 m, 2858 w, 1628 s, 1415 m, 1131 m, 988 m, 836 m, 777 m; ^{1}H NMR (500 MHz, T = 363 K, toluene-d_8) δ 4.21 (1H, m, CHO), 4.05 (2H, dd, J = 9.1, 6.9 Hz, NC$\underline{H}$H), 3.84 (2H, dd, J = 9.1, 4.1 Hz, NCH$\underline{H}$), 1.08 (9H, s, C(O)C(CH$_3$)$_3$), 0.84 (9H, s, Si(CH$_3$)$_2$C(C$\underline{H}_3$)$_3$), −0.07 (6H, s, Si(C$\underline{H}_3$)$_2$C(CH$_3$)$_3$); ^{13}C NMR (125 MHz, T = 363 K, toluene-d_8) δ 177.1 (C═O), 62.7 (CHO), 61.4 (N−CH$_2$), 38.9 (C(O)$\underline{C}$(CH$_3$)$_3$), 27.7 (C($\underline{C}$H$_3$)$_3$), 26.0 (C($\underline{C}$H$_3$)$_3$), 18.2 (Si(CH$_3$)$_2\underline{C}$-(CH$_3$)$_3$), −4.8 (Si($\underline{C}$H$_3$)$_2$C(CH$_3$)$_3$); LRMS (ESI$^+$) 272.2 ([M + H]$^+$, 100%); HRMS (ESI$^+$) calcd for $C_{14}H_{30}NO_2Si$ 272.2040, found 272.2039.

1-(3-(*tert*-Butyldimethylsilyloxy)azetidin-1-yl)-2,2-dimethylpropane-1-thione (7). To a stirred solution of silyloxyamide **6** (3.65 g, 13.4 mmol) in pyridine (40 mL) at rt was added P_2S_5 (3.70 g, 16.6 mmol). The reaction mixture was heated to 75 °C for 2 h, then after cooling to rt was concentrated under reduced pressure to ∼20 mL. The partially concentrated reaction mixture was poured onto aq HCl (1 M, 100 mL) and stirred vigorously for 10 min. The aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with aq HCl (1 M, 100 mL), H_2O (100 mL), then brine (100 mL), dried (Na_2SO_4), and concentrated to dryness under reduced pressure. Purification (Si gel, pet ether/Et_2O 1:0→9:1) gave silyloxythioamide **7** as a white solid (3.60 g, 93%): R_f 0.57 (pet ether/Et_2O 9:1); mp 56−58 °C; IR (neat/cm^{-1}) 2960 m, 2929 m, 2858 m, 1487 m, 1470 m, 1128 s, 841 s, 775 m; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.67 (1H, ddd, J = 10.6, 6.6, 2.0, Hz, NC$\underline{H}$H), 4.58 (1H, tt, J = 6.6, 4.3 Hz, OC$\underline{H}$), 4.48 (1H, ddd, J = 12.4, 6.6, 2.0 Hz, NC$\underline{H}$H), 4.24 (1H, ddd, J = 10.6, 4.3, 2.0 Hz, NCH$\underline{H}$), 4.07 (1H, ddd, J = 12.4, 4.3, 2.0 Hz, NCH$\underline{H}$), 1.34 (9H, s, C(S)C(C$\underline{H}_3$)$_3$), 0.89 (9H, s, Si(CH$_3$)$_2$C-(C$\underline{H}_3$)$_3$), 0.07 (3H, s, Si(C$\underline{H}_3$)$_2$C(CH$_3$)$_3$), 0.07 (3H, s, Si(C$\underline{H}_3$)$_2$C-(CH$_3$)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.9 (C═S), 66.2 (NCH$_2$), 66.0 (NCH$_2$), 60.3 (CHO), 43.2 (C(S)$\underline{C}$(CH$_3$)$_3$), 29.7 (C($\underline{C}$H$_3$)$_3$), 25.6 (C($\underline{C}$H$_3$)$_3$), 17.9 (Si(CH$_3$)$_2\underline{C}$(CH$_3$)$_3$), −5.0 (Si-($\underline{C}$H$_3$)$_2$C(CH$_3$)$_3$), −5.1 (Si($\underline{C}$H$_3$)$_2$C(CH$_3$)$_3$); LRMS (FI$^+$) 287.17 ([M]$^+$, 100%); HRMS (FI$^+$) calcd for $C_{14}H_{29}NOSSi$ 287.1739, found 287.1737.

1-(2-Azetinyl)-2,2-dimethylpropane-1-thione (9). To a stirred solution of silyloxythioamide **7** (100 mg, 0.35 mmol) in THF (1 mL) at −78 °C was added TMEDA (315 μL, 2.10 mmol). *s*-BuLi (777 μL, 1.35 M in cyclohexane/hexane (92/8), 1.05 mmol) was added dropwise to the reaction mixture over 5 min, resulting in a characteristic deep yellow color. After 30 min, MeOH (71 μL, 1.75 mmol) was added, and the reaction mixture was stirred for 10 min. The cooling bath was removed, and the reaction mixture was stirred for another 10 min, quenched with aq HCl (1 M, 5 mL), and extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with H_2O (5 mL) then brine (5 mL), dried (Na_2SO_4), and concentrated to dryness under reduced pressure. Purification (Si gel, pet ether/Et_2O 9:1) gave azetine **9** as a yellow syrup (53 mg, 98%): R_f 0.30 (pet ether/Et_2O 9:1); IR (neat/cm^{-1}) 2968 w, 1456 s, 1364 w, 1137 m, 935 m, 689 m; ^{1}H NMR (400 MHz, $CDCl_3$, 3:1 mixture of rotamers) (major rotamer) δ 6.98 (1H, s, NCH), 6.04 (1H, s, NCH═C$\underline{H}$), 4.67 (2H, s, NCH$_2$), 1.38 (9H, s, C(CH$_3$)$_3$); (minor rotamer) δ

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7.35 (1H, s, NCH), 6.14 (1H, s, NCH=CH), 4.86 (2H, s, NCH_2), 1.42 (3H, s, $C(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$) (major rotamer) δ 203.8 (C=S), 139.4 (NCH), 118.0 (NCH=CH), 62.0 (NCH_2), 43.0 ($C(CH_3)_3$), 30.3 ($C(CH_3)_3$); (minor rotamer) δ 203.8 (C=S), 141.7 (NCH), 118.7 (NCH=CH), 63.9 (NCH_2), 43.0 ($C(CH_3)_3$), 31.0 ($C(CH_3)_3$); LRMS (FI^+) 155.08 ($[M]^+$,100%); HRMS (FI^+) calcd for $C_8H_{13}NS$ 155.0769, found 155.0767.

1-(2,2-Dimethylpropanethioyl)azetidin-3-yl pivalate (11). A suspension of azetidin-3-ol hydrochloride (**10**) (8.0 g, 73 mmol) in py (80 mL) was heated to 50 °C for 5 min, then cooled to rt. DMAP (1.8 g, 15 mmol) and pivCl (22 mL, 179 mmol) were added, and after 1 h, P_2S_5 (19 g, 85 mmol) and py (50 mL) were added and the reaction mixture was heated to 75 °C. After 1 h, the reaction mixture was cooled, concentrated to half volume under reduced pressure, diluted with EtOAc (200 mL), and washed with aq HCl (2 M, 500 mL). The organic layer was washed successively with H_2O (200 mL) and brine (200 mL), dried (Na_2SO_4), filtered, and concentrated to dryness under reduced pressure. Purification (Si gel, heptane/EtOAc 1:0→4:1) gave thioamide ester **11** as a colorless syrup which solidified on standing (17.4 g, 93%): R_f 0.45 (heptane/EtOAc 4:1); mp 50−52 °C; IR (neat/cm^{-1}) 2965 w, 2872 w, 1781 s, 1484 m, 1465 m, 1321 m, 1139 s, 1004 w, 890 m; ^1H NMR (400 MHz, $CDCl_3$) δ 5.12 (1H, tt, J = 6.8, 4.2 Hz, CHO), 4.80 (1H, ddd, J = 11.6, 6.8, 2.1 Hz, NCHH), 4.54 (1H, ddd, J = 13.3, 6.8, 2.1 Hz, NCHH), 4.27 (1H, ddd, J = 11.6, 4.2, 2.1 Hz, NCHH), 4.19 (1H, ddd, J = 13.3, 4.2, 2.1 Hz, NCHH), 1.33 (9H, s, $C(CH_3)_3$), 1.21 (9H, s, $C(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.6 (C=S), 178.0 (C(O)), 63.3 (NCH_2), 62.0 (CHO), 61.9 (NCH_2), 43.2 ($C(S)C(CH_3)_3$), 38.5 ($C(O)C(CH_3)_3$), 29.7 ($C(S)C(CH_3)_3$), 26.9 ($C(O)C(CH_3)_3$); LRMS (ESI^+) 280.12 ($[M + Na]^+$ 100%); HRMS (ESI^+) calcd for $C_{13}H_{23}NNaO_2S$ 280.1342, found 280.1339.

1-(3-Hydroxyazetidin-1-yl)-2,2-dimethylpropane-1-thione (12). To a solution of thioamide ester **11** (15.0 g, 58 mmol) in MeOH (20 mL) was added NaOMe (26 mL, 25 wt % in MeOH, 117 mmol). After 1 h, the reaction mixture was concentrated to dryness under reduced pressure and the crude reaction mixture purified (Si gel, heptane/EtOAc 1:0→2:3) to give azetidinol **12** as a colorless syrup which solidified on standing (9.6 g, 95%): R_f 0.27 (pet ether/EtOAc 3:2); mp 54−56 °C; IR (neat/cm^{-1}) 3363 br, 2968 w, 1471 s, 1447 s, 1137 m, 1007 m, 730 s; ^1H NMR (400 MHz, $CDCl_3$) δ 4.69 (1H, ddd, J = 11.0, 6.6, 2.0 Hz, NCHH), 4.63 (1H, tt, J = 6.6, 3.9 Hz, CHOH), 4.47 (1H, ddd, J = 13.1, 6.6, 2.3 Hz, NCHH), 4.31 (1H, ddd, J = 11.0, 3.9, 2.3 Hz, NCHH), 4.09 (1H, ddd, J = 13.1, 3.9, 2.0 Hz, NCHH), 3.26 (1H, br, OH), 1.32 (9H, s, $C(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.0 ($C(S)C(CH_3)_3$), 65.8 (NCH_2), 65.5 (NCH_2), 59.9 (CHOH), 43.2 ($C(CH_3)_3$), 29.6 ($C(CH_3)_3$); LRMS (FI^+) 173.09 ($[M]^+$, 100%); HRMS (FI^+) calcd for $C_8H_{15}NOS$ 173.0874, found 173.0879.

General Procedure A: α-Deprotonation/Electrophile Trapping of Azetidinol 12. To a stirred solution of azetidinol **12** (100 mg, 0.58 mmol) in THF (2 mL) at −78 °C under argon was added TMEDA (519 μL, 3.46 mmol). *s*-BuLi (1.24 mL 1.40 M in cyclohexane/hexane (92:8), 1.73 mmol) was added dropwise to the reaction mixture over 5 min, resulting in a characteristic deep yellow color. After 30 min, the electrophile was added and the reaction mixture stirred for 30 min. The cooling bath was removed, and the reaction mixture was stirred for another 30 min, quenched with aq HCl (1 M, 5 mL), and extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with H_2O (5 mL) then brine (5 mL), dried (Na_2SO_4), and concentrated to dryness under reduced pressure.

1-(2-Deutero-3-(hydroxy)-azetidin-1-yl)-2,2-dimethylpropane-1-thione (*cis*-13a). CD_3OD (70 μL, 1.7 mmol) was used following General Procedure A. Purification (Si gel, pet ether/EtOAc 3:2) gave the deuterated azetidinol **13a** as a colorless syrup which solidified on standing (92 mg, 91%, 100% D, 90:10 *cis*/*trans*,[13] dr determined by integration at δ_H 4.67 + 4.42 and 4.28 + 4.04): R_f 0.27 (pet ether/EtOAc 3:2); mp 54−56 °C; IR (neat/cm^{-1}) 3361 br, 2966 m, 1467 s, 1395 w, 1134 s, 1006 m; ^1H NMR (400 MHz, $CDCl_3$) δ 4.67 (0.95H, dd, J = 11.0, 6.6 Hz, $NCH_{cis}H_{trans}$), 4.59 (1H, td, J = 6.6, 3.9 Hz, CHOH), 4.42 (0.95H, dd, J = 13.1, 6.6 Hz, $NCH_{cis}H_{trans}$), 4.28 (0.53H, ddd, J = 11.0, 3.9, 2.3 Hz, $NCH_{cis}H_{trans}$), 4.04 (0.57H, ddd, J = 13.1, 3.9, 2.3 Hz, $NCH_{cis}H_{trans}$), 3.75 (1H, br, OH), 1.29 (9H, s, $C(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.9 (C=S), 65.8 (NCH_2), 65.5 (t, J = 23 Hz, NCHD), 65.4 (NCH_2), 65.1 (t, J = 23 Hz, NCHD), 59.6 (CHOH), 59.6 (t, J = 7 Hz, CHOH), 43.1 ($C(CH_3)_3$), 29.5 ($C(CH_3)_3$); LRMS (ESI^+) 175.11 ($[M + H]^+$, 85%); HRMS (ESI^+) calcd for $C_8H_{15}DNOS$ 175.1010, found 175.1011.

1-(3-Hydroxy-2-methyl-azetidin-1-yl)-2,2-dimethylpropane-1-thione (13b). MeI (180 μL, 2.9 mmol) was used following General Procedure A, but on half the scale. Purification (Si gel, pet ether/EtOAc 4:1) gave methylated azetidinol **13b** as a pale yellow syrup (39 mg, 72%, 69:31 *trans*/*cis*,[13] dr determined by integration at δ_H 1.32 and 1.30): R_f 0.38 (pet ether/EtOAc 3:2); IR (neat/cm^{-1}) 3364 br, 2965 w, 2929 w, 1461 s, 1434 s, 1364 w, 1135 m; LRMS (ESI^+) 188.12 ($[M + H]^+$, 40%); HRMS (ESI^+) calcd for $C_9H_{18}NOS$ 188.1104, found 188.1105. **Major diastereoisomer**: ^1H NMR (400 MHz, $CDCl_3$) δ 4.74 (1H, ddd, J = 11.4, 6.1, 2.4 Hz, $NCH_{cis}H_{trans}$), 4.59 (1H, qdd, J = 6.6, 3.0, 2.4 Hz, NCH), 4.23 (1H, dd, J = 11.4, 3.0 Hz, $NCH_{cis}H_{trans}$), 4.14 (1H, dt, J = 6.1, 3.0 Hz, CHOH), 3.18 (1H, br, OH), 1.56 (3H, d, J = 6.6 Hz, CH_3), 1.32 (9H, s, $C(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.2 (C=S), 74.0 (NCH), 67.9 (CHOH), 64.6 (NCH_2), 43.5 ($C(CH_3)_3$), 29.6 ($C(CH_3)_3$), 16.0 ($CHCH_3$). **Minor diastereoisomer**: ^1H NMR (400 MHz, $CDCl_3$) δ 4.97 (1H, qd, J = 6.6, 6.6 Hz, NCH), 4.74 (1H, m, CHOH), 4.67 (1H, ddd, J = 10.9, 7.3, 1.0 Hz, $NCH_{cis}H_{trans}$), 4.33 (1H, ddd, J = 10.9, 5.3, 2.0 Hz, $NCH_{cis}H_{trans}$), 2.82 (1H, br, OH), 1.55 (3H, d, J = 6.6 Hz, CH_3), 1.30 (9H, s, $C(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.3 (C=S), 70.6 (NCH), 64.6 (NCH_2), 61.7 (CHOH), 43.3 ($C(CH_3)_3$), 29.5 ($C(CH_3)_3$), 10.3 ($CHCH_3$).

1-(3-Hydroxy-2-butyl-azetidin-1-yl)-2,2-dimethylpropane-1-thione (13c). BuI (986 μL, 8.66 mmol) was used following General Procedure A, but on five times the scale. Purification (Si gel, pet ether/EtOAc 19:1→4:1) gave butylated azetidinol **13c** as a pale yellow syrup (451 mg, 68%): R_f 0.64 (pet ether/EtOAc 3:2); IR (neat/cm^{-1}) 3372 br, 2958 w, 2923 m, 2854 m, 1461 s, 1435 m, 1363 w, 1134 m, 737 m; ^1H NMR (400 MHz, $CDCl_3$) δ 4.68 (1H, ddd, J = 12.6, 7.5, 1.8 Hz, $NCH_{cis}H_{trans}$), 4.52 (1H, m, NCH), 4.24−4.19 (2H, m, CHOH and $NCH_{cis}H_{trans}$), 2.90 (1H, br s, OH), 2.41−2.33 (1H, m, $CHHCH_2CH_2CH_3$), 1.67 (1H, ddt, J = 14.7, 7.3, 7.1 Hz, $CHHCH_2CH_2CH_3$), 1.38−1.24 (4H, m, $CH_2CH_2CH_2CH_3$), 1.33 (9H, s, $C(CH_3)_3$), 0.91 (3H, t, J = 7.1 Hz, $CH_2CH_2CH_2CH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.3 (C=S), 78.0 (NCH), 66.6 (CHOH), 64.9 (NCH_2), 43.5 ($C(CH_3)_3$), 29.7 ($C(CH_3)_3$), 28.3 ($CH_2CH_2CH_2CH_3$), 25.9 ($CH_2CH_2CH_2CH_3$), 22.5 ($CH_2CH_2CH_2CH_3$), 14.0 ($CH_2CH_2CH_2CH_3$); LRMS (ESI^+) 230.17 ($[M + H]^+$, 55%); HRMS (ESI^+) calcd for $C_{12}H_{24}NOS$ 230.1573, found 230.1569.

1-(3-Hydroxy-2-benzyl-azetidin-1-yl)-2,2-dimethylpropane-1-thione (13d). BnBr (1.03 mL, 8.66 mmol) was used following General Procedure A, but on five times the scale. Purification (Si gel, heptane/EtOAc 9:1→8:2) gave benzylated azetidinol **13d** as a pale yellow syrup (559 mg, 74%): R_f 0.64 (pet ether/EtOAc 3:2); IR (neat/cm^{-1}) 3365 br, 2966 w, 2930 w, 1455 s, 1432 s, 1125 m, 995 m, 702 s; ^1H NMR (400 MHz, $CDCl_3$) δ 7.32−7.22 (5H, m, Ar), 4.83 (1H, dddd, J = 7.8, 3.3, 3.0, 2.0 Hz, NCH), 4.28 (1H, dt, J = 6.1, 3.0 Hz, CHOH), 4.22 (1H, ddd, J = 11.1, 6.1, 2.0 Hz, $NCH_{cis}H_{trans}$), 4.10 (1H, dd, J = 11.1, 3.0 Hz, $NCH_{cis}H_{trans}$), 3.46 (1H, dd, J = 13.9, 3.3 Hz, CHHPh), 3.36 (1H, dd, J = 13.9, 7.8 Hz, CHHPh), 1.86 (1H, br, OH), 1.33 (9H, s, $C(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.6 (C=S), 136.4 (Ar), 129.7 (Ar), 128.4 (Ar), 126.7 (Ar), 77.5 (NCH), 65.2 (CHOH), 64.7 (NCH_2), 43.6 ($C(CH_3)_3$), 33.8 (CH_2Ph), 29.6 ($C(CH_3)_3$); LRMS (ESI^+) 286.14 ($[M + Na]^+$, 100%); HRMS (ESI^+) calcd for $C_{15}H_{22}NOS$ 264.1417, found 264.1414.

1-(2-Allyl-3-hydroxyazetidin-1-yl)-2,2-dimethylpropane-1-thione (13e). Allyl bromide (75 μL, 0.87 mmol) was used following General Procedure A, but on half the scale. Purification (Si gel, pet ether/EtOAc 9:1→1:1) gave allylated azetidinol **13e** as a yellow syrup (37 mg, 60%): R_f 0.23 (pet ether/EtOAc 4:1); IR (neat/cm^{-1}) 3369 br, 2966 w, 2872 w, 1460 s, 1395 w, 1135 m, 1001 s, 918 m, 796 w,

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732 w; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.74 (1H, ddt, J = 17.2, 10.1, 7.1 Hz, CH_2CH=$CH_{cis}H_{trans}$), 5.18 (1H, d J = 17.2 Hz, CH_2CH=$CH_{cis}H_{trans}$), 5.16 (1H, d, J = 10.1 Hz, CH_2CH=$CH_{cis}H_{trans}$), 4.65–4.61 (2H, m, NCH and $NCH_{cis}H_{trans}$), 4.27 (1H, dt, J = 6.5, 3.0 Hz, CHOH), 4.22 (1H, dd, J = 11.0, 3.2 Hz, $NCH_{cis}H_{trans}$), 2.92 (1H, ddd, J = 14.5, 7.5, 2.5 Hz, $CHHCH$=CH_2), 2.76 (1H, ddd, J = 14.5, 7.5, 7.0 Hz, $CHHCH$=CH_2), 2.66 (1H, br, OH), 1.33 (9H, s, $C(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.6 (C=S), 131.9 (CH=CH_2), 119.0 (CH=CH_2), 76.4 (NCH), 65.4 (CHOH), 64.9 (NCH_2), 43.6 ($C(CH_3)_3$), 32.6 (CH_2CH=CH_2), 29.7 ($C(CH_3)_3$); LRMS (ESI$^+$) 214.13 ([M + H]$^+$, 85%); HRMS (ESI$^+$) calcd for $C_{11}H_{19}NNaOS$ 236.1080, found 236.1082.

1-(3-Hydroxy-2-(tributylstannyl)azetidin-1-yl)-2,2-dimethylpropane-1-thione (13f). Bu_3SnCl (2.3 mL, 8.48 mmol) was used following General Procedure A, but on five times the scale. Purification (Si gel, pet ether/EtOAc 39:1→4:1) gave stannylated azetidinol **13f** as a colorless syrup (1.1 g, 82%): R_f 0.33 (pet ether/EtOAc 9:1); IR (neat/cm^{-1}) 3361 br, 2923 w, 2854 w, 1465 s, 1364 w, 1124 w, 910 m, 732 s; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.72 (1H, ddd, J = 11.6, 5.8, 2.5 Hz, $NCH_{cis}H_{trans}$), 4.58 (1H, ddt, J = 6.3, 5.8, 3.3 Hz, CHOH), 4.40–4.38 (1H, m, NCH), 4.36 (1H, dd, J = 11.6, 3.3. Hz, $NCH_{cis}H_{trans}$), 2.30 (1H d, J = 6.3 Hz, CHOH), 1.65–1.42 (6H, m, $CH_2CH_2CH_2CH_3$), 1.35 (9H, s, $C(CH_3)_3$), 1.36–1.26 (6H, m, $CH_2CH_2CH_2CH_3$), 0.97–0.92 (6H, m, $CH_2CH_2CH_2CH_3$), 0.90 (9H, t, J = 7.3 Hz, $CH_2CH_2CH_2CH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.5 (C=S), 71.6 (NCH), 66.0 (NCH_2), 64.9 (CHOH), 42.7 ($C(CH_3)_3$), 30.0 ($CH_2CH_2CH_2CH_3$), 29.0 ($CH_2CH_2CH_2CH_3$), 27.5 ($C(CH_3)_3$), 13.7 ($CH_2CH_2CH_2CH_3$), 11.5 ($CH_2CH_2CH_2CH_3$); LRMS (ESI$^+$) 464.20 ([M + H]$^+$, 68%); HRMS (ESI$^+$) calcd for $C_{20}H_{41}NOSSn$ 464.2005, found 464.1991.

1-(3-Hydroxy-2-(hydroxy(phenyl)methyl)azetidin-1-yl)-2,2-dimethylpropane-1-thione (13g). Benzaldehyde (352 μL, 3.46 mmol) was used following General Procedure A, but on twice the scale. By TLC, both diastereoisomers appeared to have the same R_f, with residual starting azetidinol **12** also falling at the same R_f. Purification (Si gel, heptane/EtOAc 4:1) was achieved using UV trace of eluting products. By TLC analysis of fractions, no difference could be determined between the products. However, UV analysis of the product-containing fractions showed two distinct products and traces of starting material, collected individually, to give both benzaldehyde azetidinol diastereoisomers: *epi*-**13g** as a clear crystalline solid (60 mg, 19%) and **13g** as a pale yellow syrup (171 mg, 53%). A crystal of *epi*-**13g** for X-ray crystallographic analysis was obtained by slow evaporation from $CDCl_3$. **Minor diastereoisomer** (*epi*-**13g**): R_f 0.45 (pet ether/EtOAc 3:2); mp 145–148 °C; IR (neat/cm^{-1}) 3444 w, 2964 w, 2928 w, 1486 s, 1362 w, 1180 w, 1106 m, 1008 m, 703 m; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45–7.28 (5H, m, Ar), 5.76 (1H, d, J = 1.8 Hz, PhCH(OH)), 4.95 (1H, ddd, J = 3.3, 1.9, 1.8 Hz, NCH), 4.44 (1H, dt, J = 6.6, 3.3 Hz, CHOH), 4.29 (1H, ddd, J = 11.0, 6.6, 1.8 Hz, $NCH_{cis}H_{trans}$), 4.09 (1H, dd, J = 11.0, 3.3 Hz, $NCH_{cis}H_{trans}$), 3.48 (1H, s, OH), 1.34 (9H, s, $C(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.8 (C=S), 139.3 (Ar), 128.5 Ar), 127.8 (Ar), 126.3 (Ar), 82.5 (NCH), 70.8 (PhCH(OH)), 64.9 (NCH_2), 62.4 (CHOH), 43.7 ($C(CH_3)_3$), 29.7 ($C(CH_3)_3$); LRMS (ESI$^+$) 302.10 ([M + Na]$^+$ 85%); HRMS (ESI$^+$) calcd for $C_{15}H_{21}NNaO_2S$ 302.1185, found 302.1181; for X-ray data, see Supporting Information. **Major diastereoisomer** (**13g**): R_f 0.45 (pet ether/EtOAc 3:2); IR (neat/cm^{-1}) 3354 br, 2966 w, 2924 wm 1455 s, 1433 m, 1364 w, 1244 w, 1130 w, 1041 w, 704 m; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.35–7.26 (5H, m, Ar), 5.80 (1H, d, J = 5.8 Hz, CHOH), 5.73 (1H, d, J = 4.3 Hz, PhCH(OH)), 5.72 (1H, dd, J = 4.9, 4.3 Hz, PhCH(OH), 4.62 (1H, ddd, J = 4.9, 2.6, 2.0 Hz, NCH), 4.03 (1H, ddt, J = 6.3, 5.8, 2.6 Hz, CHOH), 3.84 (1H, dd, J = 11.3, 2.6 Hz, $NCH_{cis}H_{trans}$), 3.36 (1H, ddd, J = 11.3, 6.3, 2.0 Hz, $NCH_{cis}H_{trans}$), 1.15 (9H, s, $(C(CH_3)_3$); ^{13}C NMR (100 MHz, DMSO-d_6) δ 209.6 (C=S), 140.8 (Ar), 127.5 (Ar), 127.1 (Ar), 126.3 (Ar), 80.0 (NCH), 65.5 (NCH_2), 65.2 (PhCH(OH), 60.8 (CHOH), 42.7 ($C(CH_3)_3$), 29.2 ($C(CH_3)_3$); LRMS (ESI$^+$) 302.10 ([M + Na)$^+$] 70%); HRMS (ESI$^+$) calcd for $C_{15}H_{21}NNaO_2S$ 302.1185, found 302.1186.

1-(2-((4-Chlorophenyl)(hydroxy)methyl)-3-hydroxyazetidin-1-yl)-2,2-dimethylpropane-1-thione (13h). *p*-Chlorobenzaldehyde (122 mg, 0.87 mmol) was used following General Procedure A, but on half the scale. Purification (Si gel, pet ether/EtOAc 9:1→4:1) gave both aldehyde azetidinol diastereoisomers: *epi*-**13h** as a pale yellow syrup (31 mg, 34%) and **13h** as a pale yellow syrup (43 mg, 47%). **Minor diastereoisomer** (*epi*-**13h**): R_f 0.54 (pet ether/EtOAc 3:2); IR (neat/cm^{-1}) 3254 br, 2969 w, 1470 s, 1244 w, 1127 m, 1090 m, 1007 m, 911 m, 854 w, 730 s; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37–7.32 (4H, m, Ar), 5.65 (1H, s, *p*-ClPhCH(OH)), 4.91 (1H, dt, J = 3.2, 2.0 Hz, NCH), 4.35 (1H, dt, J = 6.5, 3.2 Hz, CHOH), 4.26 (1H, ddd, J = 11.0, 6.5, 2.0 Hz, $NCH_{cis}H_{trans}$), 4.09 (1H, dd, J = 11.0, 3.2 Hz, $NCH_{cis}H_{Trans}$), 1.32 (9H, s, $C(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.9 (C=S), 137.7 (Ar), 133.6 (Ar), 128.6 (Ar), 127.8 (Ar), 82.2 (NCH), 70.5 (*p*-ClPhCH(OH)), 64.9 (NCH_2), 62.3 (CHOH), 43.7 ($C(CH_3)_3$), 29.6 ($C(CH_3)_3$); LRMS (ESI$^+$) 336.10 ([M + Na]$^+$, 100%); HRMS (ESI$^+$) calcd for $C_{15}H_{20}ClNNaO_2S$ 336.0795, found 336.0800. **Major diastereoisomer** (**13h**): R_f 0.37 (pet ether/EtOAc 3:2); IR (neat/cm^{-1}) 3363 br, 2972 w, 1459 s, 1365 w, 1131 m, 1091 m, 906 s, 791 m, 727 s; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (4H, s, Ar), 5.47 (1H, d, J = 6.8 Hz, *p*-ClPhCH(OH), 4.87 (1H, dd, J = 6.8, 1.8 Hz, NCH), 4.14–4.06 (3H, m, CHOH and $NCH_{cis}H_{trans}$), 1.30 (9H, s, $C(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 213.5 (C=S), 137.6 (Ar), 134.0 (Ar), 128.6 (Ar), 128.3 (Ar), 81.5 (NCH), 71.0 (*p*-ClPhCH(OH)), 64.4 (NCH_2), 62.4 (CHOH), 43.8 ($C(CH_3)_3$), 29.7 ($C(CH_3)_3$); LRMS (ESI$^+$) 336.10 ([M + Na]$^+$, 82%); HRMS (ESI$^+$) calcd for $C_{15}H_{20}ClNNaO_2S$ 336.0795, found 336.0800.

Methyl 1-(2,2-dimethylpropanethioyl)-3-[(methoxycarbonyl)oxy]azetidine-2-carboxylate (13i). Methyl cyanoformate (276 μL, 3.46 mmol) was used following General Procedure A. Purification (Si gel, pet ether/EtOAc 9:1→4:1) gave azetidine diester **13i** as a pale yellow syrup which solidified on standing (115 mg, 68% 93:7 *trans*/*cis*,[13] dr determined by integration of δ_H 5.01 and 4.56): R_f 0.70 (pet ether/EtOAc 3:2); mp 85–87 °C; IR (neat/cm^{-1}) 2960 w, 1739 s, 1430 s, 1295 m, 1272 m, 1199 m, 1158 m, 992 m, 931 m, 790 m; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.01 (1H, dt, J = 6.7, 3.4 Hz, CHO), 4.96 (1H, m, NCH), 4.89 (1H, ddd, J = 11.1, 6.7, 1.9 Hz, $NCH_{cis}H_{trans}$), 4.44 (1H, dd, J = 11.1, 3.4 Hz, $NCH_{cis}H_{trans}$), 3.83 (3H, s, OCH_3), 3.78 (3H, s, OCH_3), 1.34 (9H, s, $C(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.3 (C=S), 167.0 (NCHC(O)), 154.3 (CHOC(O)), 72.0, (NCH), 66.5 (CHO), 61.9 (NCH_2), 55.5 (OCH_3), 52.6 (OCH_3), 43.2 ($C(CH_3)_3$), 29.5 ($C(CH_3)_3$); LRMS (ESI$^+$) 312.1 ([M + Na]$^+$, 100%); HRMS (ESI$^+$) calcd for $C_{12}H_{19}NNaO_5S$ 312.0876, found 312.0868.

2-Benzylazetidin-3-ol hydrochloride (14). To a solution of benzylated azetidinol **13d** (69 mg, 0.26 mmol) in THF at 0 °C were added TMEDA (196 μL, 1.31 mmol) and MeLi (873 μL, 1.50 M in Et_2O, 1.31 mmol). After 4 h, the reaction mixture was quenched with MeOH (few drops) and concentrated to dryness under reduced pressure. The crude reaction mixture was dissolved in a minimum of MeOH and loaded onto a SCX-2 ion exchange column. The column was washed through with CH_2Cl_2 (20 mL) and collected. The amine product was released with NH_3 (10 mL, 7 M in MeOH) followed by CH_2Cl_2 (20 mL) and collected. The basic fractions were concentrated to dryness under reduced pressure, redissolved in MeOH (2 mL), and treated with HCl (2 M in Et_2O, 2 mL), followed by concentrating to dryness under reduced pressure to isolate the crude hydrochloride salt. The crude product was suspended in acetone (2 mL) and decanted to remove organic impurities, giving azetidine hydrochloride salt **14** as a pale yellow solid (48 mg, 92%): mp 127–131 °C; IR (neat/cm^{-1}) 3306 br, 2956 w, 2938 w, 2458 m, 2184 br, 1454 w, 1173 m, 1117 m, 1031 w, 977 w, 747 m, 702 s; ^{1}H NMR (400 MHz, CD_3OD) δ 7.38–7.25 (5H, m, Ar), 4.53 (1H, q, J = 7.4 Hz, CHOH), 4.40 (1H, ddd, J = 8.9, 7.4, 6.8 Hz, NCH), 4.07 (1H, dd, J = 10.5, 7.4 Hz, NCHH), 3.74 (1H, dd, J = 10.5, 7.4 Hz, NCHH), 3.24 (1H, dd, J = 14.4, 6.8 Hz, CHHPh), 3.17 (1H, dd, J = 14.4 8.9 Hz, CHHPh); ^{13}C NMR (100 MHz, CD_3OD) δ 136.5 (Ar), 130.2 (Ar), 130.1 (Ar), 128.5 (Ar), 73.0 (NCH), 68.4 (CHOH), 53.1, (NCH_2), 38.1 (CH_2Ph); LRMS (ESI$^+$) 164.09 ([M − HCl + H)]$^+$, 40%); HRMS (ESI$^+$) calcd for $C_{10}H_{14}NO$ 164.1070, found 164.1070.

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1-(2-Benzyl-3-hydroxyazetidin-1-yl)-2,2-dimethylpropan-1-one (15). To an ice-cold stirred solution of AcOH (3 mL) and H_2O_2 (4 mL, 35% in H_2O) was added benzylated azetidinol **13d** (59 mg, 0.24 mmol) in CH_2Cl_2 (1 mL). After 4 h at 0 °C, the reaction mixture was poured onto saturated aq $NaHCO_3$ (30 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with saturated aq $NaHCO_3$ (10 mL), H_2O (10 mL), then brine (10 mL), dried (Na_2SO_4), filtered, and concentrated to dryness under reduced pressure to give pivalamide **15** as a colorless syrup (45 mg, 81%): R_f 0.23 (pet ether/EtOAc 3:2); IR (neat/cm^{-1}) 2359 br, 2963 w, 1595 s, 1412 m, 1364 w, 1232 w, 1129 w, 736 w, 702 m; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32−7.20 (5H, m, Ar), 4.44 (1H, ddd, J = 7.8, 3.7, 3.3 Hz, NCH), 4.18 (1H, dt, J = 6.8, 3.7 Hz, CHOH), 4.10 (1H ddd, J = 9.3, 6.8, 1.0 Hz, $NCH_{cis}H_{trans}$), 3.95 (1H, dd, J = 9.3, 3.7 Hz, $NCH_{cis}H_{trans}$), 3.20, (1H, dd, J = 13.9, 3.3 Hz, CHHPh), 3.02 (1H, dd, J = 13.9, 7.8 Hz, CHHPh), 1.15 (9H, s, $C(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.1 (C(O)), 136.7 (Ar), 129.6 (Ar), 128.3 (Ar), 126.4 (Ar), 71.7 (NCH), 65.7 (CHOH), 60.1 (NCH_2), 38.7 ($C(CH_3)_3$), 36.7 (CH_2Ph), 27.0 ($C(CH_3)_3$); LRMS (ESI$^+$) 270.12 ([M + Na]$^+$, 78%); HRMS (ESI$^+$) calcd for $C_{15}H_{21}NNaO_2$ 270.1465, found 270.1466.

2-Deutero-1-(2,2-dimethylpropanethioyl)-azetidin-3-yl trifluoromethanesulfonate (16). To a stirred solution of deuterated adduct *cis*-**13a** (417 mg, 2.39 mmol) in CH_2Cl_2 (10 mL) at −78 °C was added DIPEA (538 μL, 3.11 mmol) followed by dropwise addition of Tf_2O (482 μL, 2.87 mmol). After 30 min, MeOH (1 mL) was added and the reaction mixture concentrated to dryness under reduced pressure. Purification (Si gel, pet ether/EtOAc 19:5→9:1) gave triflate **16** as a pale yellow syrup which solidified on standing (601 mg, 82%): R_f 0.27 (pet ether/EtOAc 3:2); mp 55−57 °C; IR (neat/cm^{-1}) 2981 w, 2907 w, 1470 m, 1441 m, 1353 s, 1218 m, 1171 m, 986 m, 914 m, 849 m; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.49 (1H, td, J = 6.4, 3.8 Hz, CHO), 4.91 (0.95 H, dd, J = 11.9, 6.9 Hz, $NCH_{cis}H_{trans}$), 4.73−4.62 (1.51H, m, $NCH_{cis}H_{trans}$), 4.46 (0.58H, ddd, J = 13.8, 3.8, 2.1 Hz, $NCH_{cis}H_{trans}$), 1.36 (9H, s, $C(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.7 (C═S), 118.3 (Q, J = 320 Hz, CF_3), 72.9 (CHO), 72.9 (t, J = 5 Hz, CHO), 62.7 (NCH_2), 62.4 (T, J = 23 Hz, NCHD), 61.7 (NCH_2), 61.4 (T, J = 23 Hz, NCHD), 43.6 ($C(CH_3)_3$), 29.7 ($C(CH_3)_3$); δ_F (377 MHz, $CDCl_3$) −74.7 (CF_3); LRMS (FI$^+$) 306.04 ([M]$^+$, 100%); HRMS (FI$^+$) calcd for $C_9H_{13}DF_3NO_3S_2$ 306.0430, found 306.0432.

2-Deutero-1-(2,2-dimethylpropanethioyl)azetidin-3-yl acetate (17). To a stirred solution of triflate **16** (586 mg, 1.91 mmol) in DMF (10 mL) was added NaOAc (5.3 g, 65 mmol), and the reaction mixture was heated to 70 °C. After 16 h, the reaction mixture was cooled to rt, washed with H_2O (10 mL), and extracted with EtOAc (3 × 10 mL), and the combined organic layers were dried (Na_2SO_4), filtered, and concentrated to dryness under reduced pressure. Purification (Si gel, pet ether/EtOAc 9:1→4:1) gave acetate **17** as a colorless syrup (355 mg, 86%): R_f 0.41 (pet ether/EtOAc 4:1); IR (neat/cm^{-1}) 2968 w, 1741 s, 1462 m, 1437 m, 1364 w, 1225 s, 1143 m, 731 m; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.15 (1H, dt, J = 6.8, 3.8 Hz, CHO), 4.81 (0.59H, ddd, J = 11.4, 6.8, 1.3 Hz, $NCH_{cis}H_{trans}$), 4.55 (0.60H, ddd, J = 13.4, 6.8, 1.3 Hz, $NCH_{cis}H_{trans}$), 4.35 (0.93H, dd, J = 11.4, 3.8 Hz, $NCH_{cis}H_{trans}$), 4.23 (0.91H, dd, J = 13.4, 3.8 Hz, $NCH_{cis}H_{trans}$), 2.12 (3H, s, $OC(O)CH_3$), 1.34 (9H, s, $C(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.6 (C═S), 170.4 (C(O)), 63.3 (NCH_2), 63.0 (T, J = 23 Hz, NCHD), 62.0 (CHO), 62.0 (t, J = 9 Hz, CHO), 61.8 (NCH_2), 61.6 (T, J = 23 Hz, NCHD), 43.3 ($C(CH_3)_3$), 29.7 ($C(CH_3)_3$), 20.6 (CH_3); LRMS (ESI$^+$) 217.1 ([M + H]$^+$, 100%); HRMS (ESI$^+$) calcd for $C_{10}H_{16}DNNaO_2S$ 239.0935, found 239.0928.

1-(2-Deutero-3-(hydroxy)-azetidin-1-yl)-2,2-dimethylpropane-1-thione (*trans*-13a). To a stirred solution of acetate **17** (350 mg, 1.62 mmol) in MeOH (10 mL) was added NaOMe (15 drops, 30% in MeOH). After 10 min, the reaction mixture was concentrated to dryness under reduced pressure. The residue was washed with aq HCl (1 M, 10 mL) and extracted with EtOAc (20 mL), and the organic layer was washed with H_2O (10 mL), then brine (10 mL), dried (Na_2SO_4), filtered, and concentrated to dryness under reduced pressure. Purification (Si gel, pet ether/EtOAc 3:2→2:3) gave azetidin-3-ol *trans*-**13a** as a colorless syrup which solidified on standing (186 mg, 66%, 100% D, 88:12 *trans*/*cis*,[13] dr determined by integration of δ_H 4.70 + 4.48 and 4.32 + 4.10): R_f 0.27 (pet ether/EtOAc 3:2); mp 54−56 °C; IR (neat/cm^{-1}) 3359 br, 2968 w, 1469 s, 1364 w, 1255 w, 1138, 1005 m, 951 w, 730 s; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.70 (0.56 H, ddd, J = 11.1, 6.6, 1.5 Hz, $NCH_{cis}H_{trans}$), 4.65 (1H, dt, J = 6.6, 3.9 Hz, CHOH), 4.48 (0.56H, ddd, J = 12.9, 6.6, 1.5 Hz, $NCH_{cis}H_{trans}$), 4.32 (0.94H, dd, J = 11.1, 3.9 Hz, $NCH_{cis}H_{trans}$), 4.10 (0.94H, dd, J = 12.9, 3.9 Hz, $NCH_{cis}H_{trans}$), 3.14 (1H, br, OH), 1.33 (9H, s, $C(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.0 (C═S), 65.8 (NCH_2), 65.5 (T, J = 23 Hz, NCHD), 65.5 (NCH_2), 65.2 (T, J = 23 Hz, NCHD), 59.8 (CHOH), 59.8 (t, J = 10 Hz, CHOH), 43.2 ($C(CH_3)_3$), 29.6 ($C(CH_3)_3$); LRMS (ESI$^+$) 175.2 ([M + H]$^+$, 100%); HRMS (ESI$^+$) calcd for $C_8H_{14}DNNaOS$ 197.0829, found 197.0825.

Lithiation−Deuteration of *cis*-13a: 1-(2,4-Dideutero-3-hydroxyazetidin-1-yl)-2,2-dimethylpropane-1-thione (18-2,4Dcc) and 1-(2,2-Dideutero-3-hydroxyazetidin-1-yl)-2,2-dimethylpropane-1-thione (18-2,2D). To a stirred solution of azetidinol *cis*-**13a** (50 mg, 0.29 mmol) in THF (1 mL) at −78 °C under argon was added TMEDA (261 μL, 1.74 mmol). *s*-BuLi (614 μL, 1.40 M in cyclohexane/hexane (92/8), 0.86 mmol) was added very slowly dropwise to the reaction mixture over 5 min. After 30 min, CD_3OD (52 μL, 1.45 mmol) was added, and the reaction mixture was stirred for 10 min. The cold bath was removed, and the reaction mixture was stirred for another 10 min, quenched with aq HCl (1 M, 5 mL), and extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with H_2O (5 mL) then brine (5 mL), dried (Na_2SO_4), and concentrated to dryness under reduced pressure to give azetidinol **18** as a pale yellow syrup (50 mg, 95%, 99% 2D, 62:38 2,4-:2,2-,[13] dr determined by integration of δ_H 4.66 + 4.42 and 4.29 + 4.04 in comparison to *cis*-**13a**):[13] IR (neat/cm^{-1}) 3365 br, 2967 w, 2932 w, 1465 s, 1364 w, 1134 s, 1007 m, 913 m, 730 s; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.66 (0.76H, dd, J = 11.1, 6.6 Hz, $NCH_{cis}H_{trans}$), 4.59 (1H, t, J = 6.6 Hz, CHOH), 4.42 (0.76H, dd, J = 12.9, 6.6 Hz, $NCH_{cis}H_{trans}$), 4.29 (0.23H, dd, J = 11.1, 3.5 Hz, $NCH_{cis}H_{trans}$), 4.04 (0.26H, dd, J = 12.9, 3.5 Hz, $NCH_{cis}H_{trans}$), 3.76 (1H, br s, OH), 1.29 (9H, s, $C(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.9 (C═S), 65.8 (NCH_2), 65.5 (T, J = 23 Hz, NCHD), 65.4 (NCH_2), 65.1 (T, J = 23 Hz, NCHD), 59.5 (CHOH), 59.5 (t, J = 8 Hz, CHOH), 43.1 ($C(CH_3)_3$), 29.5 ($C(CH_3)_3$); LRMS (ESI$^+$) 198.08 ([M + Na]$^+$, 93%); HRMS (FI$^+$) calcd for $C_8H_{13}D_2NOS$ 175.1000, found 175.1001.

Lithiation−Deuteration of *trans*-13a: 1-(2,4-Dideutero-3-hydroxyazetidin-1-yl)-2,2-dimethylpropane-1-thione (18-2,4Dtc) and 1-(2,2-Dideutero-3-hydroxyazetidin-1-yl)-2,2-dimethylpropane-1-thione (18-2,2D). To a stirred solution of azetidinol *trans*-**13a** (50 mg, 0.29 mmol) in THF (1 mL) at −78 °C under argon was added TMEDA (261 μL, 1.74 mmol). *s*-BuLi (614 μL, 1.40 M in cyclohexane/hexane (92/8), 0.86 mmol) was added very slowly dropwise to the reaction mixture over 5 min. After 30 min, CD_3OD (52 μL, 1.45 mmol) was added and the reaction mixture stirred for 10 min. The cold bath was removed, and the reaction mixture was stirred for another 10 min, quenched with aq HCl (1 M, 5 mL), and extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with H_2O (5 mL) then brine (5 mL), dried (Na_2SO_4), and concentrated to dryness under reduced pressure to give azetidinol **18** as a pale yellow syrup (45 mg, 90%, 91% 2D, 82:18 2,4-:2,2-,[13] dr determined by integration of δ_H 4.69 + 4.46 and 4.31 + 4.08 in comparison to *trans*-**13a**):[13] IR (neat/cm^{-1}) 2251 br, 2968 w, 1467 s, 1364 w, 1139 m, 1112 m, 1007 w, 912 w, 730 s; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.69 (0.47H, dd, J = 11.1, 6.6 Hz, $NCH_{cis}H_{trans}$), 4.64−4.60 (1H, m, CHOH), 4.46 (0.49H, dd, J = 12.9, 6.6 Hz, $NCH_{cis}H_{trans}$), 4.31 (0.56H, dd, 11.1, 3.9 Hz, $NCH_{cis}H_{trans}$), 4.08 (0.57H, dd, J = 12.9, 3.9 Hz, $NCH_{cis}H_{trans}$), 3.46 (1H, br, OH), 1.32 (9H, s, $C(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.0 (C═S), 65.8 (NCH_2), 65.5 (T, J = 23 Hz, NCHD), 65.5 (T, J = 23 Hz, NCHD), 65.5 (NCH_2), 65.2 (T, J = 23 Hz, NCHD), 65.1 (T, J = 23 Hz, NCHD), 59.7 (CHOH), 59.7 (t, J = 8 Hz, CHOH), 59.7 (t, J = 8 Hz, CHOH), 43.2 ($C(CH_3)_3$), 29.6 ($C(CH_3)_3$); LRMS (ESI$^+$) 198.1

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([M + Na]$^+$, 100%); HRMS (ESI$^+$) calcd for $C_8H_{13}D_2NNaOS$ 198.0892, found 198.0893.

Lithiation−Protonation of *cis*-13a: 1-(2-Deutero-3-hydroxyazetidin-1-yl)-2,2-dimethylpropane-1-thione (13a). To a stirred solution of azetidinol *cis*-**13a** (50 mg, 0.29 mmol) in THF (1 mL) at −78 °C under argon was added TMEDA (261 μL, 1.74 mmol). *s*-BuLi (614 μL, 1.40 M in cyclohexane/hexane (92/8), 0.86 mmol) was added very slowly dropwise to the reaction mixture over 5 min. After 30 min, MeOH (58 μL, 1.43 mmol) was added and the reaction mixture stirred for 10 min. The cold bath was removed, and the reaction mixture was stirred for another 10 min, quenched with aq HCl (1 M, 5 mL), and extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with H_2O (5 mL) then brine (5 mL), dried (Na_2SO_4), and concentrated to dryness under reduced pressure to give azetidinol **13a** as a pale yellow syrup (50 mg, quant, 100% D, 64:36 *cis*/*trans*,[13] dr determined by integration of δ_H 4.67 + 4.42 and 4.28 + 4.04). Characterization data are the same as that of *cis*-**13a**, with the exception of two additional peaks in the ^{13}C NMR spectrum: 65.5 (T, *J* = 23 Hz, NCHD), 65.2 (T, *J* = 23 Hz, NCHD).

Lithiation−Protonation of *trans*-13a: 1-(2-Deutero-3-hydroxyazetidin-1-yl)-2,2-dimethylpropane-1-thione (*trans*-13a). To a stirred solution of azetidinol *trans*-**13a** (50 mg, 0.29 mmol) in THF (1 mL) at −78 °C under argon was added TMEDA (261 μL, 1.74 mmol). *s*-BuLi (614 μL, 1.40 M in cyclohexane/hexane (92/8), 0.86 mmol) was added very slowly dropwise to the reaction mixture over 5 min. After 30 min, MeOH (52 μL, 1.45 mmol) was added and the reaction mixture stirred for 10 min. The cold bath was removed, and the reaction mixture was stirred for another 10 min, quenched with aq HCl (1 M, 5 mL), and extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with H_2O (5 mL) then brine (5 mL), dried (Na_2SO_4), and concentrated to dryness under reduced pressure to give azetidinol *trans*-**13a** as a pale yellow syrup (43 mg, 86%, 100% D, 87:13 *trans*/*cis*,[13] dr determined by integration of δ_H 4.70 + 4.48 and 4.32 + 4.10). Characterization data are the same as that of *trans*-**13a**.

Lithiation−Benzylation of *cis*-13a: 1-(4-Deutero-3-hydroxy-2-phenylazetidin-1-yl)-2,2-dimethylpropane-1-thione (19-2D$_c$-4Bn$_t$, 19-2D$_t$-4Bn$_t$) and 1-(4-Deutero-3-hydroxy-2-phenylazetidin-1-yl)-2,2-dimethylpropane-1-thione (19-2D$_c$-2Bn$_t$). To a stirred solution of azetidinol *cis*-**13a** (50 mg, 0.29 mmol) in THF (1 mL) at −78 °C under argon was added TMEDA (261 μL, 1.74 mmol). *s*-BuLi (614 μL, 1.4 M in cyclohexane/hexane (92/8), 0.86 mmol) was added very slowly dropwise to the reaction mixture over 5 min. After 30 min, BnBr (102 μL, 0.86 mmol) was added and the reaction mixture stirred for 30 min. The reaction mixture was warmed to room temperature and stirred for another 30 min, quenched with aq HCl (1 M, 5 mL), and extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with H_2O (5 mL) and brine (5 mL), dried (Na_2SO_4), and concentrated to dryness under reduced pressure. Purification (Si gel, heptane/EtOAc 1:0→2:3) gave azetidinol **19** as a pale yellow syrup (52 mg, 69%, 100% D, 61:6:33 **2D$_c$-4Bn$_t$/2D$_t$-4Bn$_t$/2D$_c$-2Bn$_t$**[13] dr determined by integration of δ_H 4.80, 4.18 and 4.08): R_f 0.64 (pet ether/EtOAc 3:2); IR (neat/cm^{-1}) 3364 br, 3027 w, 2967 w, 1454 s, 1434 m, 1395 w, 1135 m, 1096 m, 910 m, 730 s, 702 m; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32−7.22 (5H, m, Ar), 4.80 (0.67H, ddd, *J* = 7.6, 3.5, 2.9 Hz, NCH) 4.24 (1H, dd, *J* = 6.3, 2.9 Hz, C<u>H</u>OH), 4.18 (0.94H, dd, *J* = 11.1, 6.3 Hz, NCH$_{Cis}$<u>H</u>$_{Trans}$), 4.08 (0.38H, dd, *J* = 11.1, 2.9 Hz, NC<u>H</u>$_{Cis}$H$_{Trans}$), 3.43 (1H, dd, *J* = 13.9, 3.5 Hz, C<u>H</u>HPh), 3.35 (0.3H, d, J = 13.9 Hz, CDC<u>H</u>HPh), 3.36 (0.7H, dd, *J* = 13.9, 7.6 Hz, CH<u>H</u>Ph), 2.63 (1H, br, OH), 1.31 (9H, s, C(CH$_3$)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.8 (C(S)), 136.5 (Ar), 129.7 (Ar), 128.4 (Ar), 126.7 (Ar), 77.5 (NCH), 65.3 (CHOH), 64.7 (NCH$_2$), 64.4 (T, *J* = 23 Hz, NCDH), 43.6 (<u>C</u>(CH$_3$)$_3$), 33.9 (<u>C</u>H$_2$Ph), 29.7 (C(<u>C</u>H$_3$)$_3$); LRMS (ESI$^+$) 287.12 ([M + Na]$^+$, 100%); HRMS (ESI$^+$) calcd for $C_{15}H_{20}DNNaOS$ 287.1299, found 287.1296.

Lithiation−Benzylation of *trans*-13a: 1-(4-Deutero-3-hydroxy-2-phenylazetidin-1-yl)-2,2-dimethylpropane-1-thione (19-2D$_t$-4Bn$_t$, 19-2D$_c$-4Bn$_t$) and 1-(2-Deutero-3-hydroxy-2-phenylazetidin-1-yl)-2,2-dimethylpropane-1-thione (19-2D$_c$-2Bn$_t$). To a stirred solution of azetidinol *trans*-**13a** (26 mg, 0.15 mmol) in THF (0.5 mL) at −78 °C under argon was added TMEDA (135 μL, 0.90 mmol). *s*-BuLi (333 μL, 0.45 mmol, 1.35 M in cyclohexane/hexane (92/8)) was added very slowly dropwise to the reaction mixture over 5 min. After 30 min, BnBr (54 μL, 0.45 mmol) was added and the reaction mixture stirred for 30 min. The reaction mixture was warmed to room temperature and stirred for another 30 min, quenched with aq HCl (1 M, 5 mL), and extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with H_2O (5 mL) and brine (5 mL), dried (Na_2SO_4), and concentrated to dryness under reduced pressure. Purification (Si gel, pet ether/EtOAc 4:1→2:3) gave azetidinol **19** as a pale yellow syrup (19 mg, 48%, 100% D, 60:10:30 **2D$_t$-4Bn$_t$/2D$_c$-4-Bn$_t$/2D$_c$-2Bn$_t$**[13] dr determined by integration of δ_H 4.81, 4.19 and 4.09): R_f 0.64 (pet ether/EtOAc 3:2); IR (neat/cm^{-1}) 3373 br, 2967 w, 1454 s, 1435 m, 1129 m, 1091 m, 997 m, 910 m, 730 s, 702 m; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32−7.23 (5H, m, Ar), 4.81 (0.70H, dt, *J* = 6.6, 2.8 Hz, NCH), 4.25 (1H, m, C<u>H</u>OH), 4.19 (0.40H, dd, *J* = 11.1, 6.8 Hz, NCH$_{Cis}$<u>H</u>$_{Trans}$), 4.09 (0.90H, dd, *J* = 11.1, 2.8 Hz, NC<u>H</u>$_{Cis}$H$_{Trans}$), 3.43 (1H, dd, *J* = 13.9, 3.5 Hz, C<u>H</u>HPh), 3.35 (0.3H, d, J = 13.9 Hz, CDC<u>H</u>HPh), 3.36 (0.7H, dd, *J* = 13.9, 7.6 Hz, CH<u>H</u>Ph), 2.52 (1H, br, OH), 1.32 (9H, s, C(CH$_3$)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.7 (C(S)), 136.5 (Ar), 129.7 (Ar), 128.4 (Ar), 126.8 (Ar), 77.5 (NCH), 65.3 (CHOH), 64.7 (NCH$_2$), 64.4 (T, *J* = 23 Hz, NCDH), 43.6 (<u>C</u>(CH$_3$)$_3$), 33.9 (<u>C</u>H$_2$)Ph), 29.7 (C(<u>C</u>H$_3$)$_3$); LRMS (ESI$^+$) 265.1 ([M + H]$^+$, 100%); HRMS (ESI$^+$) calcd for $C_{15}H_{20}DNNaOS$ 287.1299, found 287.1290.

2-Benzyl-1-(2,2-dimethylpropanethioyl)azetidin-3-yl acetate (20). To a stirred solution of benzyl adduct **13d** (412 mg, 1.56 mmol) in CH_2Cl_2 (5 mL) at −78 °C was added DIPEA (351 μL, 2.02 mmol) followed by dropwise addition of Tf_2O (289 μL, 1.72 mmol). After 30 min, MeOH (1 mL) was added and the reaction mixture concentrated to dryness under reduced pressure. The crude triflate was dissolved in DMF (5 mL) and to it was added NaOAc (1.28 g, 16 mmol) and the reaction mixture was heated to 70 °C. After 2 h, the reaction mixture was cooled to rt, washed with H_2O (10 mL), and extracted with EtOAc (3 × 10 mL), and the combined organic layers were dried (Na_2SO_4), filtered, and concentrated to dryness under reduced pressure. Purification (Si gel, pet ether/EtOAc 39:1→9:1) gave inverted acetate **20** as a colorless syrup (245 mg, 51%): R_f 0.44 (pet ether/EtOAc 9:1); IR (neat/cm^{-1}) 2968 w, 2872 w, 1742 s, 1455 m, 1431 m, 1364 w, 1224 s, 1155 w, 1111 m, 1007 w, 910 m, 729 s, 700 m; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36−7.19 (5H, m, Ar), 5.36−5.28 (2H, m, NCH and C<u>H</u>OH), 4.75 (1H, ddd, *J* = 10.9, 7.3, 1.0 Hz, NC<u>H</u>$_{trans}$H$_{cis}$), 4.20 (1H, ddd, *J* = 10.9, 5.3, 1.5 Hz, NCH$_{trans}$<u>H</u>$_{cis}$), 3.78 (1H, dd, *J* = 13.8, 1.6 Hz, C<u>H</u>HPh), 3.30 (1H, dd, *J* = 13.8, 9.2 Hz, CH<u>H</u>Ph), 2.09 (3H, s, CH$_3$), 1.32 (9H, s, C(CH$_3$)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.7 (C═S), 170.0 (C═O), 137.3 (Ar), 129.5 (Ar), 128.1 (Ar), 126.4 (Ar), 72.4 (NCH), 63.6 (CHOH), 63.3 (NCH$_2$), 43.6 (<u>C</u>(CH$_3$)$_3$), 30.4 (N<u>C</u>H$_2$Ph), 29.6 (C(<u>C</u>H$_3$)$_3$), 20.6 (CH$_3$); LRMS (ESI$^+$) 306.2 ([M + H]$^+$, 100%); HRMS (ESI$^+$) calcd for $C_{17}H_{23}NNaO_2S$ 328.1342, found 328.1337.

1-(2-Benzyl-3-hydroxyazetidin-1-yl)-2,2-dimethylpropane-1-thione (*cis*-13d). To a stirred solution of inverted acetate **20** (245 mg, 0.80 mmol) in MeOH (3 mL) was added NaOMe (10 drops, 30% in MeOH). After 1 h, the reaction mixture was concentrated to dryness under reduced pressure. The residue was washed with aq HCl (1 M, 10 mL) and extracted with CH_2Cl_2 (10 mL), and the organic layer was washed brine (10 mL), dried (Na_2SO_4), filtered, and concentrated to dryness under reduced pressure gave *cis*-benzyl adduct *cis*-**13d** as a pale orange syrup which solidified on standing (184 mg, 87%); diastereoselectivity determined by ^{1}H NMR coupling constant analysis: R_f 0.47 (pet ether/EtOAc 4:1); mp 101−103 °C; IR (neat/cm^{-1}) 3368 br, 2996 w, 2964 w, 2929 w, 1468 s, 1435 s, 1357 w, 1253 w, 1149 m, 1109 m, 1037 w, 984 w, 829 w, 746 m, 702 m; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42−7.21 (5H, m, Ar), 5.17 (1H, dddd, *J* = 10.4, 7.3, 2.4, 2.0 Hz, NCH), 4.77 (1H, td, *J* = 7.3, 5.6 Hz, C<u>H</u>OH), 4.65 (1H, dd, *J* = 10.8, 7.3 Hz, NC<u>H</u>$_{trans}$H$_{cis}$), 4.23 (1H, ddd, *J* = 10.8, 5.6, 2.0 Hz, NCH$_{trans}$<u>H</u>$_{cis}$), 3.83 (1H, dd, *J* = 13.7, 2.4 Hz, C<u>H</u>HPh), 3.31 (1H, dd, *J* = 13.4, 10.4 Hz, CH<u>H</u>Ph), 2.03 (1H, br, OH), 1.34 (9H, s, C(CH$_3$)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.2 (C═S), 138.2 (Ar), 129.4 (Ar), 128.5 (Ar), 126.4 (Ar), 74.5 (NCH), 64.7 (NCH$_2$), 62.5 (CHOH), 43.5 (<u>C</u>(CH$_3$)$_3$), 29.6 (C(<u>C</u>H$_3$)$_3$); LRMS

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(ESI+) 286.2 ([M + Na]+, 100%); HRMS (ESI+) calcd for $C_{15}H_{21}NNaOS$ 286.1236, found 286.1244.

■ ASSOCIATED CONTENT

Supporting Information

^1H and ^{13}C NMR spectra for all compounds, ^1H analysis of deuterated adducts and X-ray data for *epi*-**13g**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(16) By ^1H NMR comparison with **13d** and *cis*-**13d**, the latter being available from **13d** through the corresponding inverted acetate **20** by an identical alcohol inversion sequence to that used for *trans*-**10a** (see Experimental Section).

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Generation and Electrophile Trapping of *N*-Boc-2-lithio-2-azetine: Synthesis of 2-Substituted 2-Azetines

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Supporting Information

ABSTRACT: *s*-BuLi-induced α-lithiation−elimination of LiOMe from *N*-Boc-3-methoxyazetidine and further in situ α-lithiation generates *N*-Boc-2-lithio-2-azetine which can be trapped with electrophiles, either directly (carbonyl or heteroatom electrophiles) or after transmetalation to copper (allowing allylations and propargylations), providing a concise access to 2-substituted 2-azetines.

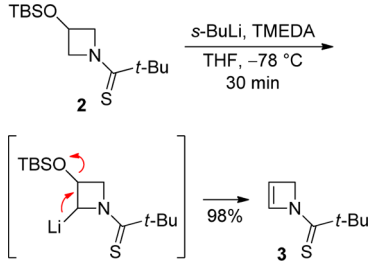
2-Azetidinones (β-lactams) and azetidines are well-studied four-membered azacyclic systems with important biological activities.[1] In contrast, the unsaturated and more strained 2-azetine (1,2-dihydroazete) system **1** (Figure 1) is comparatively less explored, which partly reflects issues of ease of access and stability (notably the propensity to undergo 4e electrocyclic ring-opening to 1-azabutadienes), although electron-withdrawing groups on the nitrogen are known to reduce instability.[2,3]

1

Figure 1. 2-Azetine **1**.

As part of a program with the aim of providing flexible and divergent routes to substituted 4-membered azacycles involving substituent incorporation onto a pre-existing and straightforwardly accessed azetidine core, we recently reported α-lithiation−electrophile trapping of *N*-thiopivaloylazetidine[4] and -azetidin-3-ol[5] in enantio- and diastereocontrolled processes, respectively. During the development of the latter work, we found that the unprotected 3-hydroxyl group was essential, as protection (e.g., as the TBS ether **2**) only led to efficient elimination on attempted α-lithiation−electrophile trapping, to generate the corresponding stable 2-azetine **3** (98%) (Scheme 1).[5] This observation led us to consider the possibility of α-electrophile incorporation using *N*-protected 2-azetine, in which the unsaturation retained in the adducts could provide a site for further synthetic manipulation. Here we communicate our promising preliminary results in this area.

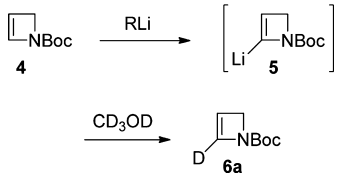
Scheme 1. Lithiation−Elimination of Silyloxythioamide 2[5]



2 **3**

While *N*-protection/activation with the thiopivaloyl group had been found to be uniquely successful in enabling α-lithiation−electrophile trapping of azetidine and 3-hydroxyazetidine,[4,5] with 2-azetine **3** only modest isolated yields of trapped products (~15% using either MeI or BnBr) could be obtained despite extensive experimental investigations.[6] We therefore turned our attention to alternative nitrogen protection. Following pioneering studies by Beak and co-workers, Boc protection now is well-established for facilitating α-lithiation−electrophile trapping of normal-sized azacycles[7] (including Csp^2 α-lithiation of 1,2,3,4-tetrahydropyridine[8]), although simple *N*-Boc aziridines undergo rapid N→C Boc migration following α-lithiation.[9] In the present case, we were pleased to find that the known *N*-Boc-2-azetine (**4**)[10] underwent regioselective lithiation at the α-sp^2 position[11] followed by deuteration to give 2-D-2-azetine **6a** (54% yield, 100% D, Scheme 2) under conditions typically used with *N*-Boc heterocycles [*s*-BuLi (1.2 equiv), TMEDA (1.2 equiv), THF, −78 °C, 1 h]. Further experimentation established that *n*-BuLi was similarly effective (56%); the absence of TMEDA did not affect the yield (54%), and LiTMP (1.4 equiv, THF, −78 °C, 45 min) also delivered sp^2 α-lithiation−trapping (70%).

Scheme 2. Lithiation−Deuteration of *N*-Boc-azetine (4)



4 **5** **6a**

Despite the above encouraging preliminary results, yield variability in duplicate lithiation−deuteration experiments,

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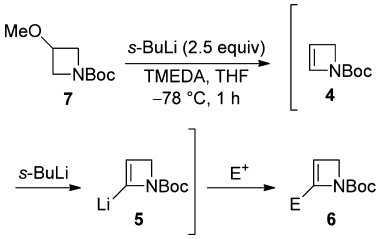
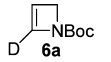
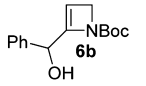
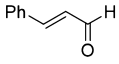
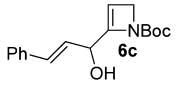
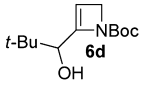
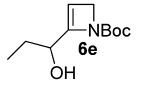
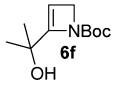
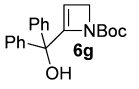
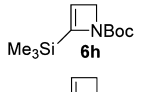
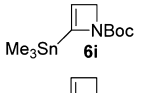
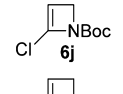
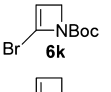
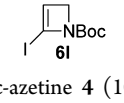
Table 1. Scope of Carbonyl and Heteroatom Electrophiles with Li-azetine 5



entry	electrophile	azetine **6**	yield of **6**
1	CD_3OD	 **6a**	88% (100% D)
2		 **6b**	97%
3		 **6c**	78%
4		 **6d**	84%
5		 **6e**	82%
6		 **6f**	44%
7		 **6g**	51%[a]
8	Me_3SiCl	 **6h**	74%
9	Me_3SnCl	 **6i**	76%
10	Cl_3CCCl_3	 **6j**	63%
11	$BrCl_2CCBrCl_2$	 **6k**	71%
12	I_2	 **6l**	60%

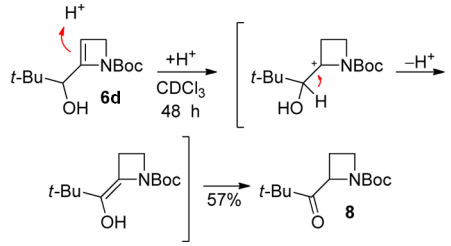
[a]Yield corrected for inseparable *N*-Boc-azetine **4** (10% by ^{1}H NMR analysis).[12]

together with modest yields in the synthesis of *N*-Boc-azetine (**4**) [previously prepared (46%) by *t*-BuOK-induced elimination from the corresponding 3-tosylate;[10] in our hands, elimination (66%) by way of the 3-chloride was preferred[12]] and the instability/tendency of unsubstituted *N*-Boc-azetine (**4**) to polymerize when left at rt and slowly during storage at −20 °C, led us to consider a modified strategy[7b,8] where the unsubstituted *N*-Boc-2-azetine (**4**) was generated and lithiated in situ. This approach resulted in an efficient and reproducible method to 2-D **6a** (88% yield, 100% D) when *N*-Boc-3-methoxyazetidine (**7**), available commercially or readily prepared by methylation (NaH, MeI, quant)[12] of widely available *N*-Boc-azetidin-3-ol, was reacted with 2.5 equiv of *s*-BuLi.[13] The scope of the reaction with respect to electrophile variation was investigated following these conditions (Table 1).

Aldehydes (Table 1, entries 2−5) and ketones (entries 6 and 7), including an enal (entry 3) and potentially enolizable substrates (entries 5 and 6), provided the corresponding secondary and tertiary alcohols **6b−g** in generally good yields. Using carbonyl-based electrophiles at a higher oxidation level (BzCl, ethyl chloroformate, Mander's reagent) or alkylating agents (MeI, BuI, BnBr, allyl bromide) did not prove viable, only resulting in the isolation of *N*-Boc azetine **4** or decomposition of starting materials. However, heteroatom incorporation could be achieved, generating the corresponding silylated (entry 8), stannylated (entry 9), and halogenated 2-azetines (entries 10−12), although in these latter cases reversed-phase chromatography[14] was necessary for satisfactory product isolation.

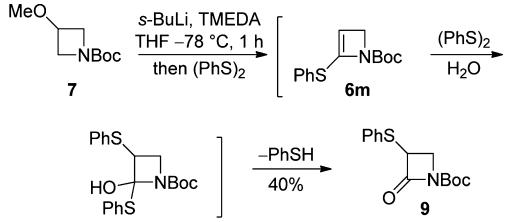
Observations with two electrophiles (pivalaldehyde and diphenyl disulfide) show further reactivity following electrophile trapping. While the hindered alcohol **6d** derived from pivalaldehyde could be isolated in good yield as indicated (84%, Table 1, entry 4), exposure to $CDCl_3$ which had not been passed through alumina prior to use resulted in prototropy[15] driven by relief of strain, to the corresponding saturated ketone **8** (57%, Scheme 3); other aldehyde-derived adducts did not undergo analogous isomerizations.

Scheme 3. Isomerization of Alcohol 6d to Ketone 8



Reaction with diphenyl disulfide (2.5 equiv) led, unusually, to *N*-Boc-α-phenylthio-β-lactam (**9**) (40%, Scheme 4). The

Scheme 4. β-Lactam 9 from 3-Methoxyazetidine 7



formation of β-lactam **9** may proceed through initial electrophile trapping where the resulting electron-rich azetine **6m** undergoes further reaction with the electrophile, followed by hydrolysis (Scheme 4); reduction in the quantity of $(PhS)_2$ used (to 0.9 or 1.0 equiv) did not result in recovery of any identifiable products.

While direct allylation of lithiated azetine **5** had proven problematic, transmetalation to the organocopper[16] allowed C−C bond formation by nucleophilic substitution to give allylated and propargylated azetines **10** (Table 2).

Simple allylation and methallylation proceeded satisfactorily (Table 2, entries 1 and 2). With unsymmetrical allylic bromides

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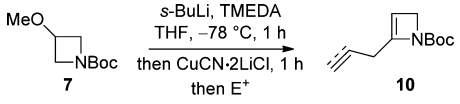
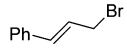
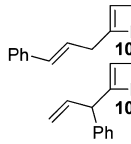
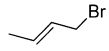
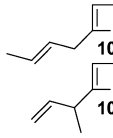
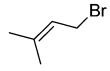
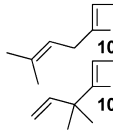
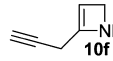
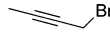
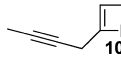
Table 2. Scope of Copper-Mediated Allylation and Propargylation



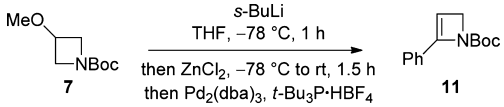
entry	electrophile	azetine **10**	yield of **10**
1		 **10a**	60%
2		 **10b**	55%
3		 **10c** / **10c′**	50% **10c:10c′** 100:0[a]
4		 **10d** / **10d′**	78% **10d:10d′** 47:53[a]
5		 **10e** / **10e′**	64% **10e:10e′** 61:39[a]
6		 **10f**	37%
7		 **10g**	46%

[a]Isolated ratio after chromatography.

(cinnamyl, crotyl, and prenyl), mixtures of S_N2- and S_N2'-derived azetines were observed [S_N2:S_N2' by crude ^{1}H NMR analysis, 91:9 (entry 3), 47:53 (entry 4), 66:33 (entry 5)], while propargylation proceeded by S_N2 (entries 6 and 7). The latter contrasts with S_N2' regioselectivity giving allenes seen with *N*-Boc-α-aminoalkylcuprates.[17]

While attempted Suzuki cross-couplings with bromide **6k** did not prove viable, Negishi coupling[18,19] gave 2-phenylated azetine **11** in 27% yield (Scheme 5).

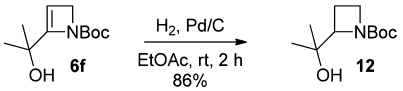
Scheme 5. Phenylated Azetine 11 by Negishi Cross-Coupling



Hydrogenation[3b] of a carbonyl-derived azetinol **6f** provided straightforward access to the corresponding saturated azetidine alcohol **12** (86%, Scheme 6); as noted previously, such adducts are not available by α-lithiation−electrophile trapping of *N*-Boc-azetidine, although *N*-thiopivaloylazetidine is a viable substrate.[4]

In summary, commercially available *N*-Boc-3-methoxyazetidine (**7**) has been shown to undergo α-lithiation−elimination to form *N*-Boc-azetine (**4**) in situ, which can be further α-lithiated regioselectively at the sp^2 center[8,11] and trapped with a range of electrophiles, including allylic and propargylic halides

Scheme 6. Hydrogenation of a 2-Substituted Azetine



by way of transmetalation to copper, providing a direct entry to 2-substituted *N*-Boc azetines. 2-Azetine stability depends significantly on the electron-withdrawing ability of the *N* substituent (aryl, sulfonyl, acyl, alkoxy carbonyl); our work demonstrates that the comparatively modestly electron-withdrawing Boc group is sufficient to allow isolation of 2-substituted 2-azetines, provided they are handled, and in many cases stored, under basic conditions. These studies indicate that electrophile incorporation can be achieved on simple monocyclic azetines and suggest that further opportunities exist for azetine diversity generation using this strategy, with potential to access substituted azetidines through double bond manipulation.

■ ASSOCIATED CONTENT

Supporting Information

Full experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(6) Chromatographic purification of these substituted thioamide azetines proved challenging, usually resulting in significant loss of material, and with products typically eluting with nonpolar byproducts.

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(12) See the Supporting Information for details.
(13) *s*-BuLi without TMEDA gave 2-D-2-azetine **6a** (74% 100% D). LiTMP (2.5 equiv, THF −78 °C) gave 2-D-2-azetine **6a** (62%, 100% D) after 5 h (48%, 100% D after 30 min).
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(19) No 2-phenylated azetine **11** was isolated if TMEDA was present; see also ref 18c.

■ NOTE ADDED AFTER ASAP PUBLICATION

Title and numbering in Scheme 3 were incorrect in the version published ASAP on January 10, 2014; the correct version reposted on January 13, 2014.