

Synthesis of Aziridines and the Functionalisation of the Intact Ring

A Thesis Submitted by

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I declare that the work presented within this document is my own. Work of others or whereby help has been received, this has been appropriately acknowledged.

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Abstract

Aziridines continue to offer synthetic interest, whilst providing important intermediates in the preparation of a variety of biologically active targets. This thesis describes the preparation of novel functionalised aziridines that offer new complementary reactivity in aziridine functionalisation chemistry. The development of divergent stereospecific methodology to functionalise these aziridines will also be explored, keeping the ring intact during this process.

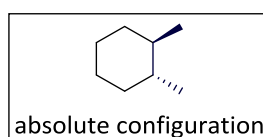
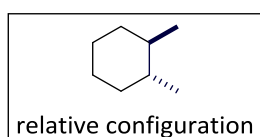
The first preparation of an iodo-aziridine is detailed, achieved via the use of LiCH_2I and imines in a diastereoselective addition-cyclisation protocol. Both aromatic and alkyl iodoaziridines can be accessed in good yields, exclusively as their *cis*-diastereoisomers.

These bench stable functionalised aziridines provide scaffolds for further derivatisation of the intact ring via formation of aziridinyl anions, aziridinyl radicals and aziridinyl metal species. Stereospecific lithiation of alkyl and aryl *N*-Ts iodoaziridines at low temperature generates an unstabilized aziridinyl lithium species which can be subsequently trapped with a range of carbon and heteroatom electrophiles allowing the exclusive formation of *cis*-substituted aziridines. Furthermore, aziridinyl radicals can be generated from the *N*-Ts iodoaziridine via single electron transfer in a radical substitution. The resulting aziridines are accessed predominately as their *trans*-diastereoisomer, with the reaction proceeding via a planar aziridinyl radical intermediate. The use of transition metal catalysis has also enabled the first cross-coupling of an iodoaziridine, with excellent diastereoselectivity observed in the coupling protocol. The stereochemical outcome at each stage of functionalisation will be fully discussed.

Stereochemical Notation

Relative configuration indicates where a compound has been prepared as a racemic mixture. This is represented by solid and broken lines.

Absolute configuration indicates a compound which has been prepared as a single enantiomer. This is depicted by lines which narrow at one terminus as shown below.



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b) Abbreviations

9-BBN	9-boracyclo[3.3.1]nonane
Ar	aromatic
atm	atmosphere(s)
aq.	aqueous
Bn	benzyl
Boc	<i>t</i> -butyloxycarbonyl
Bus	<i>tert</i> -butylsulfonyl
br	broad
Bu	butyl
Cbz	carbobenzyloxy
cod	1,5-cyclooctadiene
Cy	cyclohexyl
d	doublet, day(s)
D	deuterium
DABCO	1,4-diazabicyclo[2.2.2]octane
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DMA	dimethylacetamide
DMAP	4-dimethylaminopyridine
DMF	dimethylformamide
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone
DMSO	dimethylsulfoxide
DNA	deoxyribonucleic acid
dr	diastereomeric ratio
EDG	electron donating group
ee	enantiomeric excess
equiv	equivalent(s)
ESI	electrospray ionisation
Et	ethyl
EWG	electron withdrawing group
<i>gem</i>	geminal
h	hour(s)

HMBC	heteronuclear multiple bond coherence
HMPA	hexamethylphosphoramide
HMTA	hexamethylenetetramine
HRMS	high resolution mass spectrometry
HSQC	heteronuclear single quantum coherence
Hz	Hertz
<i>i</i>	iso
IR	infra-red
<i>J</i>	coupling constant
L	ligand
lit.	literature
LDA	lithium diisopropylamide
LG	leaving group
LiTMP	lithium-2,2,6,6-tetramethylpiperidide
M	molar
m	multiplet
<i>m</i> CPBA	<i>meta</i> -chloroperoxybenzoic acid
Me	methyl
min	minute(s)
mp	melting point
MS	mass spectrometry
<i>n</i>	neo
NMR	nuclear magnetic resonance
Ns	nosyl (<i>o</i> -nitrobenzenesulfonyl)
<i>p</i>	para
PEPPSI	Pyridine Enhanced Precatalyst Preparation Stabilisation Initiation
PG	protecting group
Ph	phenyl
Phth	phthaloyl
PMDETA	<i>N,N,N',N',N''</i> -pentamethyldiethylenetriamine
PMP	<i>para</i> -methoxyphenyl
ppm	part(s) per million
Pr	propyl
R	organic group

R_f	retention factor
rt	room temperature
s	singlet
sec	second(s)
T	temperature
<i>t</i> , <i>tert</i>	tertiary
t	time, triplet
taut.	tautomerisation
TBAF	tetra- <i>n</i> -butylammonium fluoride
TBS	<i>tert</i> -butyldimethylsilyl
THF	tetrahydrofuran
TLC	thin layer chromatography
TMEDA	tetramethylethylenediamine
Tol	tolyl
TMS	trimethylsilyl
Ts	tosyl (4-methylphenylsulfonyl)
W	watt(s)
X	halide

1: Introduction

1: Introduction

1.1: General Introduction

Aziridines, three membered saturated aza-heterocycles, have received widespread synthetic investigation since the first report by Gabriel (1888), when accessed via the cyclisation of 2-chloroethylamine.¹ Since this seminal report, a variety of approaches to substituted aziridines has been realised. The chemistry of aziridines is dominated by the release of significant ring strain present in the three membered ring upon reaction with suitable carbon and heteroatom nucleophiles, affording either functionalised ring opened or ring expanded products. As well as being key synthetic intermediates, this ring strain associated with aziridines has been shown to be essential to biological activity of aziridine containing natural products.

Although there has been significant interest in aziridine synthesis, recent attention has turned towards derivatisation of intact aziridines. The generation of aziridinyl anions at low temperature, via regioselective ring deprotonation, has been shown to be suitable to allow the construction of new carbon-carbon bonds keeping the ring intact during this process. This has also been recently extended to transition metal catalysed aziridinyl cross-coupling of functionalised aziridines with aryl and vinyl halides.

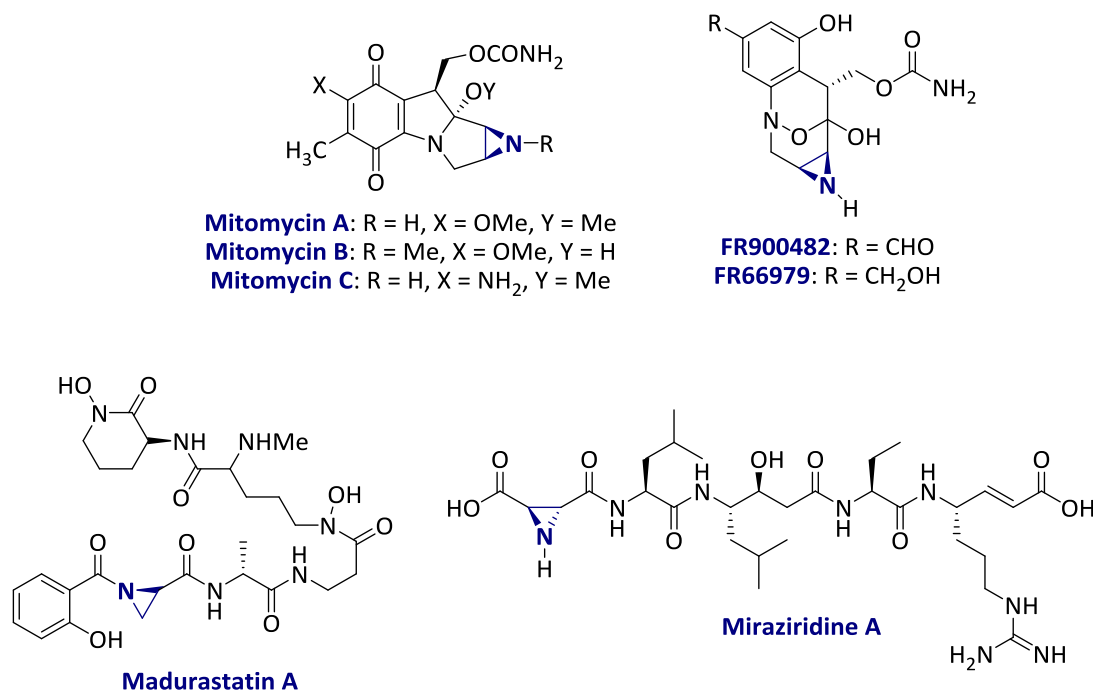
This thesis will aim to develop a stereocontrolled approach to novel functionalised aziridines using carbenoid reagents. Further derivatisation will also be demonstrated via the regioselective formation of aziridinyl anions, aziridinyl radicals and aziridinyl metal species, generating new carbon-carbon bonds and keeping the ring intact during this functionalisation process.

The following section of this thesis will aim to set this work into context, with particular focus placed on current aziridination methodology and intact aziridine functionalisation. Key literature reviews will be highlighted throughout this thesis where appropriate.

1.2: Aziridine Containing Natural Products

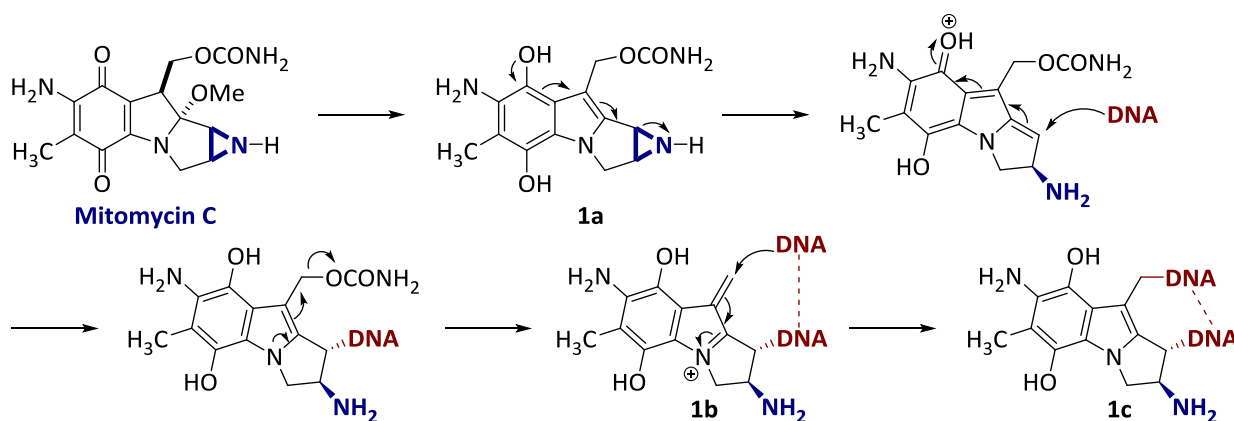
Aziridine containing natural products have been shown to be interesting synthetic targets with a wealth of biological activity associated with the reactivity of the aziridine ring. For a review on aziridine alkaloids acting as potential therapeutic agents, see Dembitsky (2007).² Important aziridine containing natural products are highlighted below (**Figure 1**).

Figure 1: Examples of aziridine containing natural products.



The Mitosanes are a family of aziridine containing natural products, with the first mitomycins (A and B) isolated from the plant *Streptomyces caespitosus* by Hata (1956).³ Mitomycin C, isolated by Wakaki (1958), displays significant anti-tumour activity due to the ability of the aziridine alkaloid to cross-link DNA.⁴ Due to this, it has been the attention of several synthetic approaches. For a detailed review on the studies towards the synthesis of the mitomycin family including mitomycin C, see Danishefsky (1995).⁵ Although Mitomycin C has been shown to be inert to nucleophiles at pH = 7,⁴ a reductive activation mechanism has been proposed to generate a reactive electrophilic mitomycin derivative in order to cross link DNA (**Scheme 1**).⁶ Reduction of mitomycin C generates indole **1a**, which undergoes aziridine ring opening, relieving the ring strain present,⁷ enabling it to act as a potent alkylating agent towards guanine residues in DNA.⁸ N-Assisted elimination of the primary carbamate generates a second electrophilic site on mitomycin derivative **1b**, allowing for a second covalent bond to DNA to be formed (guanine on complementary DNA strand, **1c**).⁹

Scheme 1: Mitomycin C crosslinking DNA.



FR900482 and FR66979 are structurally related to the mitosane family,¹⁰ and also display potent cytotoxic activity against various tumour cells *in vitro*. Similarly, activation via reduction of both FR900482 and FR66979 has shown to be required in order to form DNA interstrands, with the aziridine motif essential to biological activity. The generation of free radicals, via reduction of the weak N-O bond has also been attributed to potential biological activity.¹¹

Madurastatin A is a naturally occurring peptide isolated from a pathogenic *Actinomadura madurae* IFM 0745 strain.¹² The peptide consists of serine and salicylic acid moieties, and also contains an aziridine motif which is essential for its biological activity. Madurastatin A has also been shown to be a siderophore, with suitable co-ordination sites for ferric ions (hydroxamate and salicylate moieties).

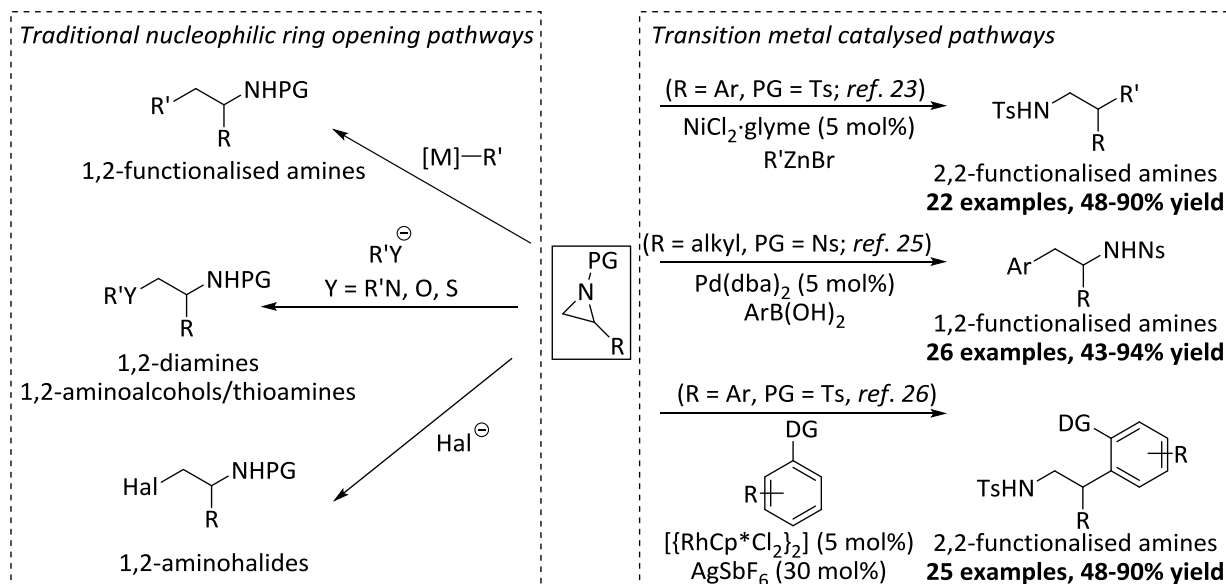
Miraziridine A was isolated from the marine sponge *Theonella mirabilis* in 2000, consisting of three main entities: an aziridine carboxylic acid, a statine and a vinylogous arginine.¹³ The aziridine containing natural product, first synthesised in 2000, has been shown to have biological activity as a cysteine inhibitor in alkylating pendant cysteine thiols via nucleophilic aziridine ring opening protocols.¹⁴

1.3: Aziridine Ring Strain - Ring Opening and Ring Expansion Reactions

Aziridine reactivity is mainly associated with the high ring strain present in the three membered ring system. For ethyleneimine (*N*-H aziridine), the bond angles (C-N-C and C-C-N) of 59.6° and 60.2° are heavily distorted from the optimal 109.5° found in common tetrahedral systems.¹⁵ The distorted C-N bonds required in the ring system result in an enhancement of their *p*-character. As a consequence of this distortion, the *s*-character of both the *N*-lone pair and *N*-H bond is increased, also leading to increased pyramidalisation around nitrogen.¹⁶ This is reflected in the basicity of the aziridine *N*-lone pair (aziridinium ion has $pK_A = 7.98$),¹⁷ with homologous larger saturated secondary cyclic amine ring

systems all exhibiting greater degrees of basicity. Due to this high ring strain present (Bäeyer strain estimated to be around 111 kJmol⁻¹ for ethyleneimine),¹⁷ aziridines are reactive to a wide range of carbon and heteroatom based nucleophiles affording 1,2-difunctionalised products in a regioselective and stereoselective fashion (**Figure 2**, left).¹⁸

Figure 2: Aziridines as common intermediates in organic synthesis.

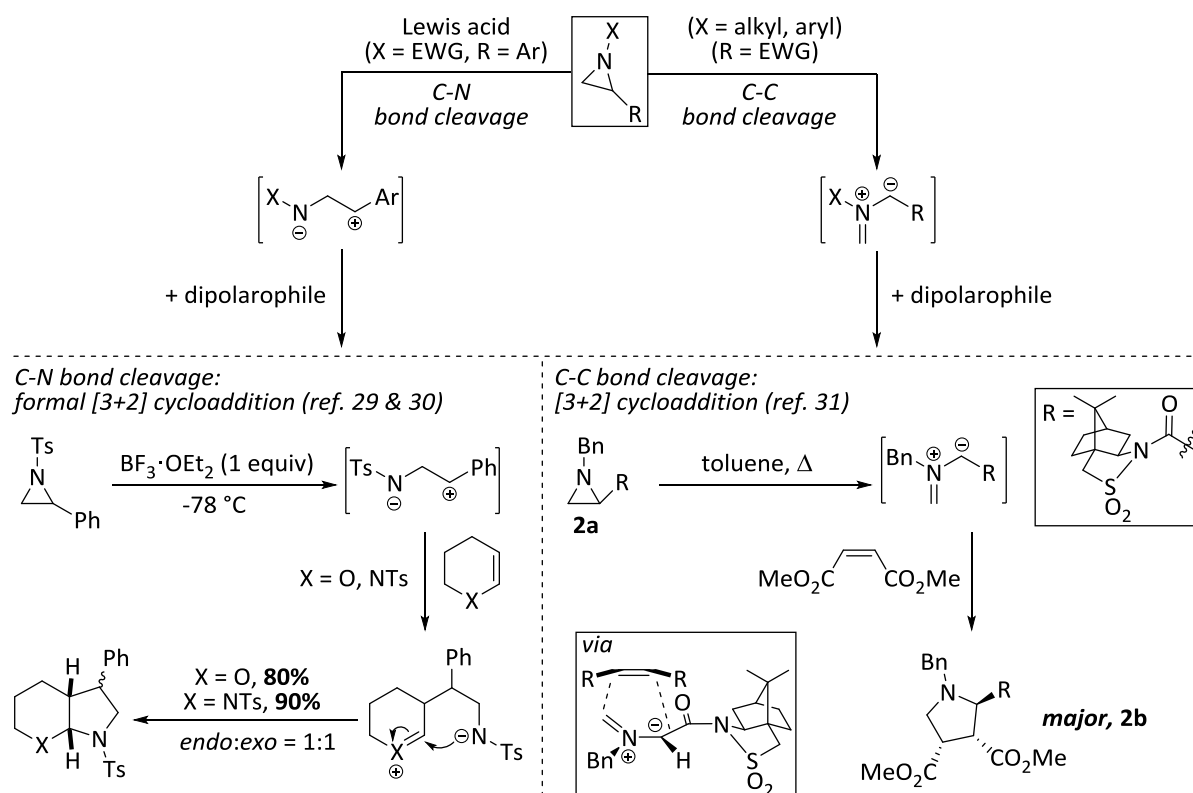


The nature of the *N*-substituent can have an effect on ring opening processes, with aziridines generally split up into two classes: activated and non-activated. These classifications are assigned whether or not typical nucleophilic ring opening reactions can occur without the need for further activation (*e.g.* protonation) at nitrogen. Commonly *N*-electron withdrawing groups, deemed as *N*-activating groups, are employed in aziridine synthesis allowing for both the polarisation of C-N bonds towards nucleophilic ring opening processes, and also giving further stabilisation to the resulting charged ring opened products. The reader is directed towards the following reviews for nucleophilic aziridine ring opening chemistry: Hu (2004),¹⁹ and Lu (2010).²⁰ A different mode of aziridine reactivity is observed upon reaction with transition metal catalysts, which has recently been reviewed by Doyle (2014).²¹ A brief selection of transformations will be presented here (**Figure 2**, right). In general, transition metal catalysis has enabled access to ring opened aziridine derivatives, via chemo-, regio- and stereoselective C-C bond formations. Since seminal reports by Hillhouse demonstrating the oxidative addition of Ni(0) complexes to aziridines,²² nickel catalysed cross-coupling of aziridines has been well explored. Doyle and co-workers employed a nickel catalysed Negishi cross-coupling of aryl substituted *N*-tosyl aziridines and functionalised organozinc reagents, affording a range of branched 2,2-functionalised amines.²³ C-C bond formation was shown to occur exclusively at the benzylic position via postulated radical intermediates, with the *N*-tosyl protecting

group deemed responsible for directing this bond formation. The protocol was extended to alkyl substituted aziridines via use of a modified sulfonyl protecting group, although with reduced regioselectivities (4:1, linear:branched).²⁴ Michael and co-workers established an improved protocol, employing a palladium catalysed Suzuki coupling of alkyl *N*-nosyl aziridines with aryl boronic acids.²⁵ This enabled the formation of new C-C bonds with increased levels of regioselectivity (>20:1 linear:branched). More recently, arene C-H activation pathways have been demonstrated in the coupling of *N*-sulfonyl aziridines with arenes under chelation assistance, employing a Ru catalyst.²⁶ 2-Phenylpyridine derivatives were shown to be suitable directing groups for the C-H activation pathway, generating a library of β -branched amines.

Aziridine ring strain has also enabled aziridines to be used as masked 1,3-dipoles, via cleavage of either the C-N or C-C bond under varying reaction conditions (**Figure 3**).

Figure 3: Aziridines as masked 1,3-dipoles via C-N or C-C bond cleavage.



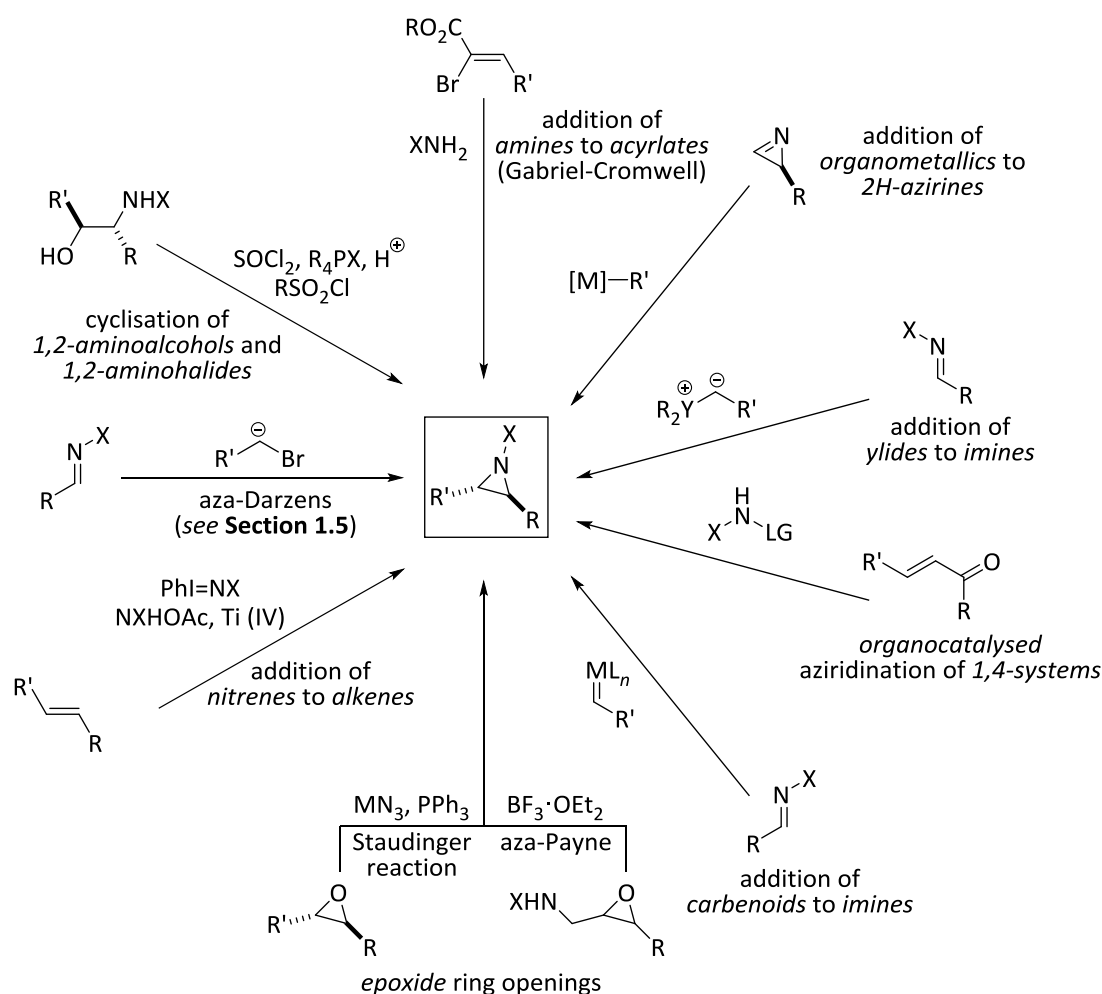
These 1,3-dipoles have been frequently employed in [3+2] cycloadditions to access five membered *N*-containing heterocycles, whereby an overall expansion of the aziridine ring has occurred. These transformations have been highlighted and reviewed extensively by both Dauban (2009),²⁷ and Pinho e Melo (2012).²⁸ Selected examples will be presented here.

Mann and co-workers demonstrated that subjection of phenyl *N*-tosyl aziridine to 1 equiv of $\text{BF}_3 \cdot \text{OEt}_2$, used as a Lewis acid, was sufficient to promote aziridine ring opening via C-N bond cleavage.^{29,30} Trapping of this 1,3-dipole with dihydropyran and *N*-Ts 1,2,3,4-tetrahydropyridine, afforded a charged intermediate which was shown to undergo an overall formal [3+2] cycloaddition to the corresponding bicyclic compounds in excellent yields, although with no facial selectivity. Nitriles and carbonyls have been also shown to be suitable dipolarophiles in formal [3+2] cycloadditions involving 1,3-dipoles originating from aziridines. Garner and co-workers established a stereocontrolled approach to the synthesis of a variety of chiral pyrrolidines using azomethine ylides, generated via a C-C aziridine bond cleavage.³¹ Thermolysis of aziridine carboxylate sultam **2a**, via a conrotatory electrocyclic aziridine ring opening generated an azomethine ylide. Trapping of this ylide with dimethyl maleate afforded pyrrolidine **2b** as the major diastereoisomer, arising from the preferred *endo-re* transition state depicted.

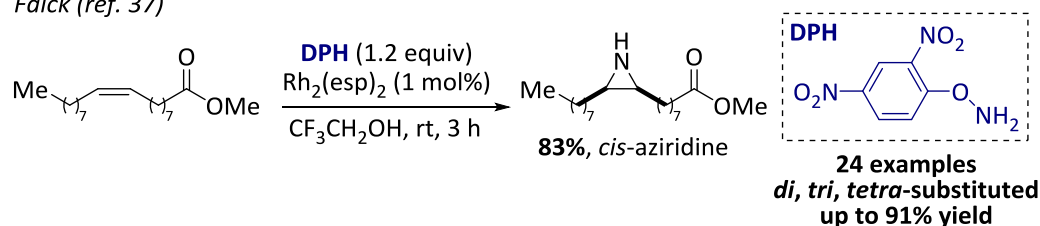
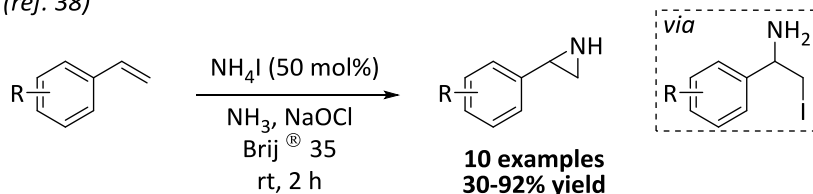
1.4: Common Approaches to the Synthesis of Aziridines

As previously demonstrated, the aziridine motif is a key intermediate in the synthesis of a wide range of amines and *N*-containing heterocycles. As a consequence, there is ongoing interest in more efficient and robust methodology to access aziridines from a variety of precursors in a stereocontrolled manner. A variety of approaches to aziridine derivatives have been developed with common protocols summarised below (**Figure 4**). This has been well documented by Sweeney (2002),¹⁷ Padwa (2006),³² Pellisier (2010),³³ (2014),³⁴ and Luisi (2014).³⁵ The reader is directed towards these highlighted reviews for in depth discussion surrounding general aziridine synthesis, although the aza-Darzens approach will be fully discussed in the following section (**Section 1.5**, page 19).

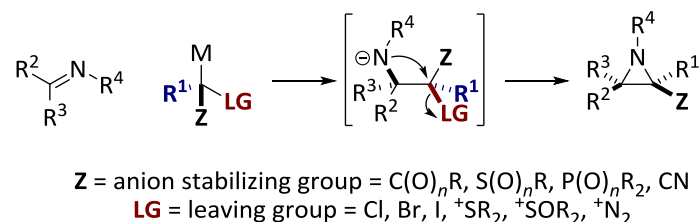
Figure 4: Common approaches to aziridine synthesis.



Recent aziridination methods have however focused on the development of protecting group free synthesis, primarily due to many synthetic nitrogen containing targets requiring the removal of this protecting group, which can involve the use of undesirable reaction conditions.³⁶ Falck and co-workers have developed a stereospecific synthesis of a range of substituted *N*-H aziridines, employing olefin derivatives and DPH (*O*-(2,4-dinitrophenyl)hydroxylamine), under Rh catalysis (**Scheme 2**).³⁷ Under mild reaction conditions, a range of substituted olefins underwent efficient *N*-H aziridination. The methodology offers tolerance of a wide range of common functional groups under the reaction conditions, including alcohols and epoxides which have previously been shown to be incompatible under common aziridination protocols. Computational studies indicated that the aziridination is likely to occur via a Rh nitrene species. De Vos and co-workers have also disclosed a catalytic synthesis of *N*-H aziridines from styrenes, using a micellar reaction system and ammonia as the nitrogen source.³⁸ It has been proposed that the use of iodide in combination with bleach affords an iodonium intermediate (via oxidation of iodide), which is subsequently ring opened by ammonia. Intramolecular cyclisation afforded aromatic substituted *N*-H aziridines in moderate to good yields.

Scheme 2: Direct synthesis of *N*-H aziridines from olefins.*Falck (ref. 37)**De Vos (ref. 38)***1.5: Aza-Darzens Reaction**

The aza-Darzens reaction can be considered a classical approach to the synthesis of functionalised aziridines. First reported by Deyrup (1969),³⁹ the protocol involves the nucleophilic addition of functionalised carbanions (bearing anion stabilizing groups) to imines, followed by subsequent 3-*exo-tet* cyclisation of the intermediate to afford the functionalised aziridine (**Scheme 3**).

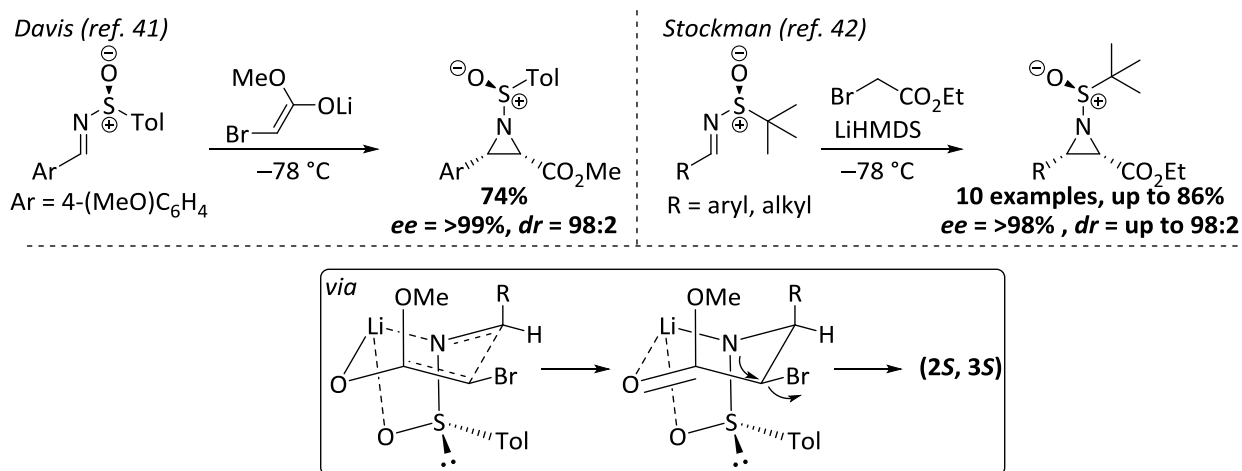
Scheme 3: General overview of aza-Darzens reaction.

The initial addition of the stabilized carbanion to the imine is diastereodetermining and irreversible, with cyclisation of the resulting intermediate being stereospecific in nature. A variety of both anion stabilizing groups and leaving groups in the synthesis of substituted aziridines have been investigated. For comprehensive reviews in this area, see Sweeney (2009),⁴⁰ and Pellissier (2010),³³ (2014).³⁴

Asymmetric variants of the aza-Darzens reaction have increasingly been employed to access enantioenriched aziridines with high diastereoselectivities. The facial selectivity of the aza-Darzens reaction in the initial addition step can be influenced by reagent control in the imine component or through choice of nucleophile. Reagent control in aza-Darzens chemistry using the imine component is well established, with chiral *N*-sulfinyl protecting groups often employed due to ease of access

(condensation of aldehyde with sulfinamides). This has been well demonstrated by both Davis,⁴¹ and Stockman in the asymmetric synthesis of 2,3-disubstituted aziridines (**Scheme 4**).⁴²

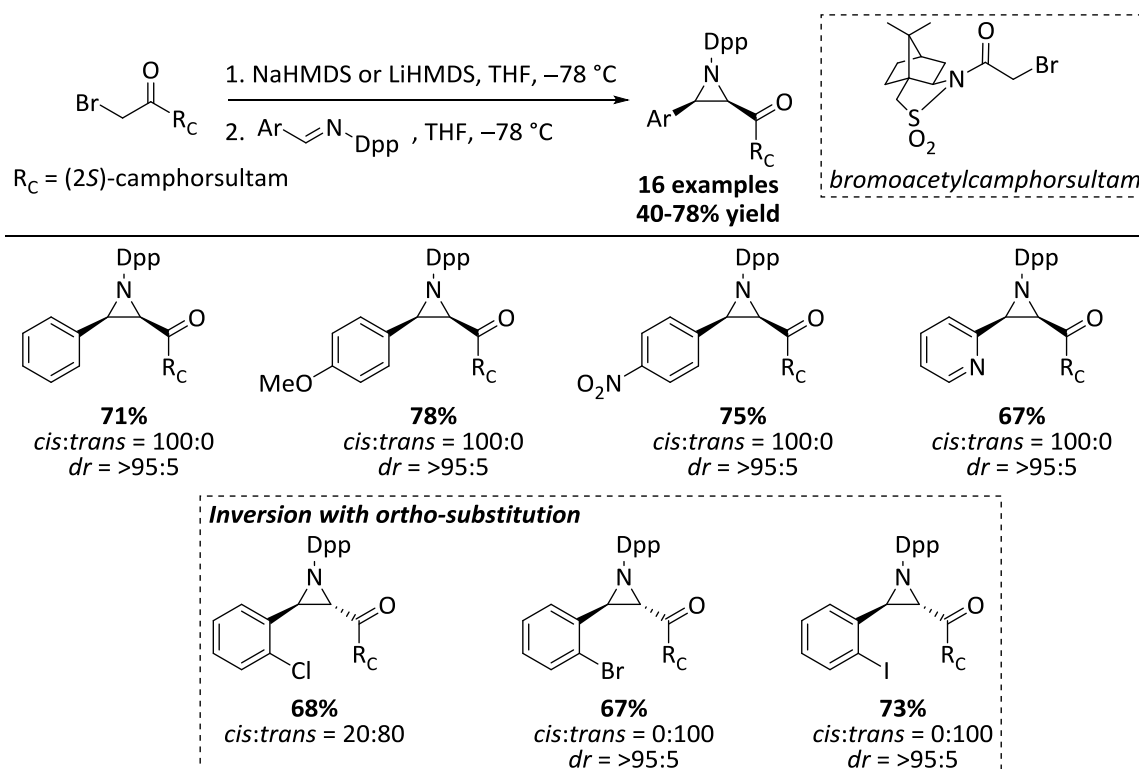
Scheme 4: Reagent control using imine component in aza-Darzens reaction.



Both chiral *tert*-butanesulfinyl and *p*-toluenesulfinyl *N*-protecting groups were successfully employed, allowing the preparation of aziridine carboxylates in high yields and diastereoselectivities. In both cases, the major products were assigned as the *cis*-aziridines, with the high levels of diastereocontrol observed arising from a closed 6-membered transition state, first proposed by Davis.⁴¹ Davis applied this methodology to the synthesis of 2*H*-azirine 2-carboxylate esters, via base assisted elimination of sulfenic acid (RSOH), by treating *N*-sulfinyl aziridine carboxylates with TMSCl and LDA at -95 °C,⁴³ or in the presence of LDA and iodomethane at -78 °C.⁴⁴ The azirine derivatives were further utilised towards the first asymmetric synthesis of marine cytotoxic antibiotics (*R*)-(-) and (*S*)-(+)-dysidazirine.

Reagent control using the anionic reaction component has also been well explored (**Scheme 5**). Notably, Sweeney and co-workers employed (2*S*)-camphorsultam as a chiral auxiliary in an asymmetric synthesis of chiral *N*-phosphinyl protected aziridines.^{45,46} Reaction of bromoacetylcamphorsultam in the presence of either LiHMDS or NaHMDS, afforded the corresponding chiral enolate. Subsequent reaction with a range of aryl substituted *N*-phosphinyl imines followed by 3-*exo-tet* cyclisation afforded *cis*-2,3-disubstituted aziridines in excellent yield and diastereoselectivities. However steric and electronic effects were shown to be crucial in the resulting stereochemistry of the aziridine products, with inversion of stereochemistry observed for many *ortho*-substituted aromatics.^{47,48} The inversion of stereochemistry has been proposed to arise from both unfavourable steric and dipole interactions between the *ortho*-aromatic substituent and the bromide, leading to an open transition state model.

Scheme 5: Reagent control using anionic component in aza-Darzens reaction.⁴⁵⁻⁴⁸



1.6: Aziridine Derivatisation, Keeping Ring Intact During Functionalisation

Recently, there has been significant interest in developing methodology in order to functionalise aziridines, keeping the ring intact during this process. This has mainly been achieved via two main methodologies:

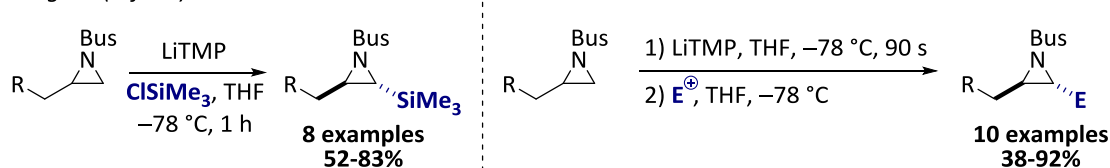
- aziridine ring deprotonation and subsequent trapping with suitable electrophiles;
- formation of aziridinyll metal species via suitable functional group exchange.

Most commonly, intact aziridine functionalisation has been achieved through the use of aziridinyll anions, trapping these highly reactive species with electrophiles. For a comprehensive review in this area, see Florio (2010).⁴⁹ An outline in their preparation and reactivity will be presented here.

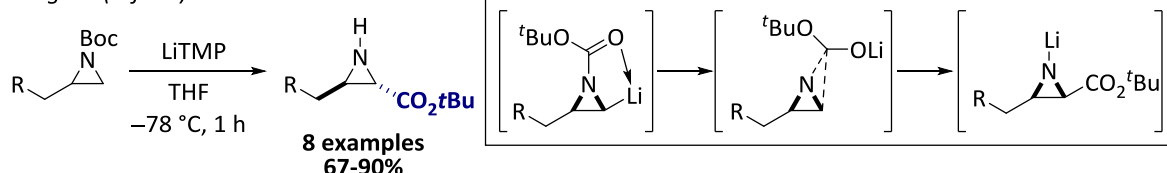
The generation of an aziridinyll anion can occur regio- and stereoselectively, but this is dependent on substituents already present on the ring (**Scheme 6**). Hodgson first reported the functionalisation of terminal *N*-Bus aziridines via generation of aziridinyll anions to afford a range of α,β -aziridinyllsilanes and disubstituted *N*-Bus aziridines in excellent yields.⁵⁰

Scheme 6: Regio- and stereoselective intact aziridine functionalisation.

Hodgson (ref. 50)



Hodgson (ref. 52)

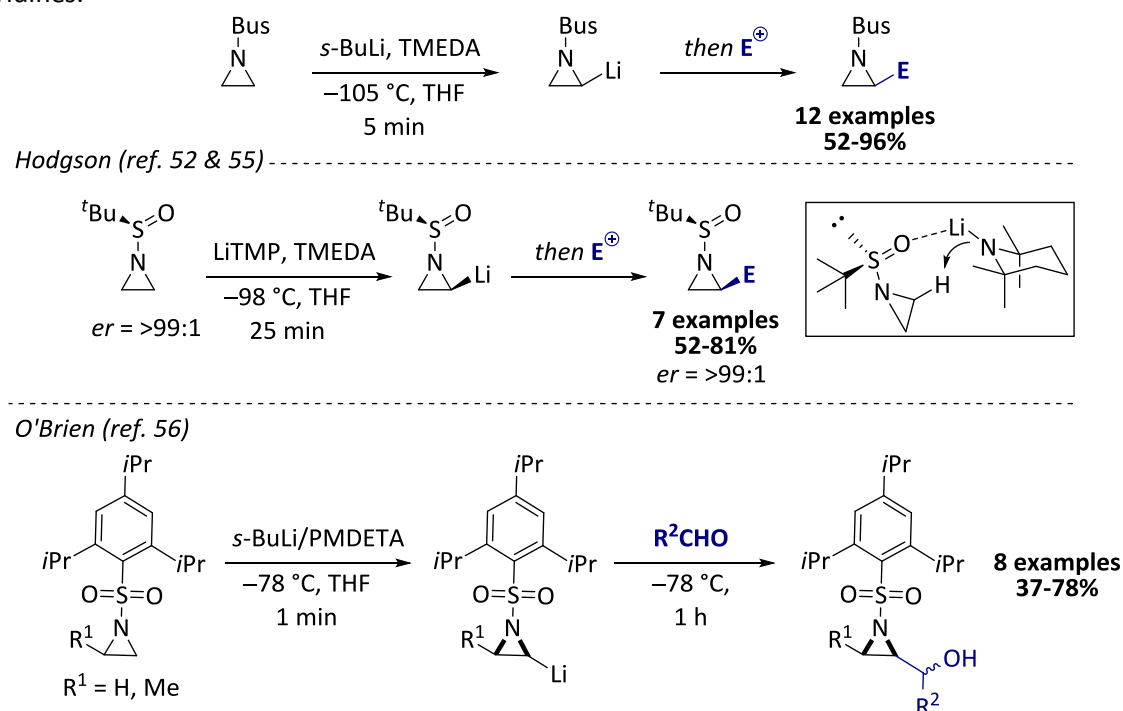


Regio- and stereoselective ring deprotonation occurs; at the least hindered position, *trans* to the alkyl group already present on the ring affording the *trans*-aziridinyl lithium. Subsequent *in situ* trapping with ClSiMe_3 or use of a two step protocol with other external electrophiles afforded a wide range of *trans*-1,2-disubstituted aziridines. However, this lithiation/trapping sequence was shown to be dependent on choice of *N*-protecting group, with strikingly different behaviour observed for aziridines bearing a Boc protecting group. First reported by Florio and co-workers on an enantioenriched *N*-Boc phenylaziridine,⁵¹ regio- and stereoselective lithiation afforded an aziridinyl lithium intermediate. An [1,2] aza-Wittig rearrangement followed by trapping with a proton source afforded the corresponding unprotected aziridinyl ester, whereby the Boc group had migrated from *N* to *C*. Hodgson further improved and extended the methodology using LiTMP in place of *s*-BuLi, with a range of *trans*-substituted aziridinyl esters and aziridinyl phosphonates obtained in good to excellent yields.⁵² However attempts at trapping the aziridinyl lithium intermediate with external electrophiles were unsuccessful due to the rapid nature of the [1,2] *N* to *C* migration at -78°C . Only *in situ* trapping of the aziridinyl lithium intermediate with ClSiMe_3 afforded desired silylated product, as previously shown by Beak.⁵³ Aggarwal has also cleverly demonstrated this *in situ* trapping methodology in a stereocontrolled synthesis of β -amino alcohols, using terminal *N*-Boc aziridines, boronic esters and LiTMP.⁵⁴

Hodgson revealed that an unsubstituted *N*-Bus aziridine could be itself taken and functionalised, without aziridine ring opening and the need for *in situ* trapping protocols (**Scheme 7**).⁵⁵ Deprotonation of *N*-Bus aziridine with a mixture of *s*-BuLi/TMEDA at -105°C (required for stability of aziridinyl lithium intermediate) and trapping with electrophiles afforded substituted *N*-Bus aziridines in excellent yields. Furthermore, the chiral *N*-*tert*-butylsulfinyl aziridine, prepared from Ellman's reagent can be employed in a highly diastereoselective lithiation protocol to access substituted aziridines as single enantiomers in analogous fashion. O'Brien, employing both unsubstituted and

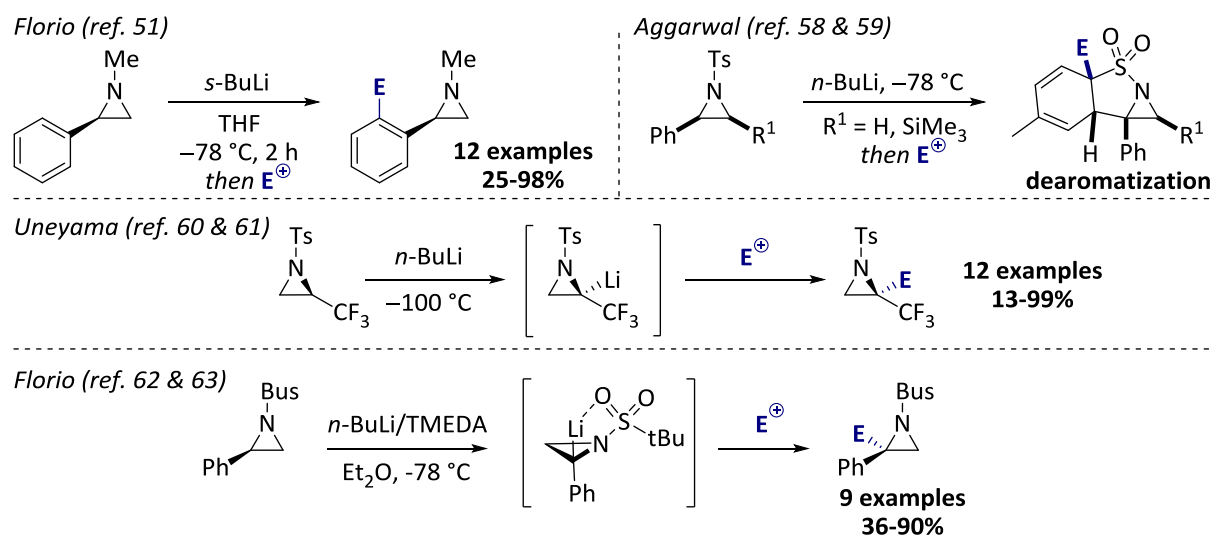
methyl *N*-2,4,6-triisopropylbenzenesulfonyl aziridines has also demonstrated a lithiation/trapping protocol to access α -hydroxy aziridines in moderate to good yields.⁵⁶ Contrasting to Hodgson's methodology, O'Brien successfully demonstrated an external lithiation/trapping protocol without the requirement for very low temperatures ($-100\text{ }^{\circ}\text{C}$), which has previously shown to be necessary to maintain both configurational and structural stability of the lithiated aziridinyl intermediate.

Scheme 7: Intact functionalisation of unsubstituted *N*-Bus, *N*-*tert*-butylsulfinyl and *N*-sulfonyl aziridines.



Aziridines bearing aromatic substituents behave differently under common lithiation conditions, again dependent on *N*-protecting group (**Scheme 8**). *N*-Alkyl phenylaziridines undergo directed *ortho* metalation, which are subsequently trapped with electrophiles affording *ortho*-substituted aromatic aziridines, keeping the ring intact during this functionalisation process.⁵¹ Successful trapping of *N*-sulfonyl aziridinyl lithium species have been shown to be problematic in the literature. Schaumann had identified that the presence of an *N*-tosyl protecting group led to dearomatisation of the tosyl group upon lithiation, due to 1,4-conjugate addition of the aziridinyl anion into the protecting group.⁵⁷ Also latter demonstrated by Aggarwal, after deprotonation of a *C*-silyl substituted *N*-Ts aziridine at the benzylic position, the resulting tricycles were trapped with a range of electrophiles.^{58,59}

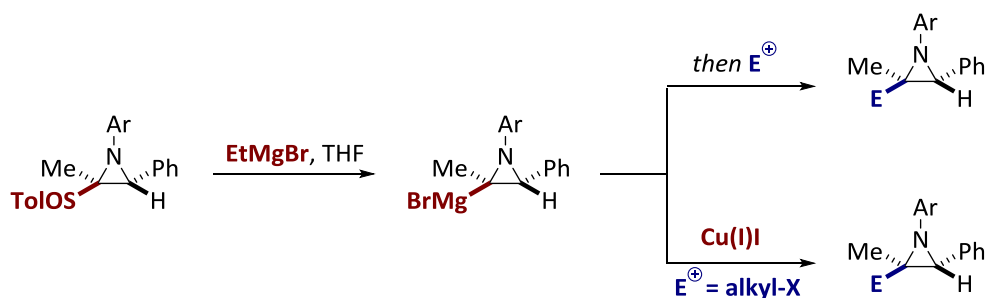
Scheme 8: Lithiation of *N*-protected phenylaziridines.



Uneyama and co-workers have however demonstrated that a lithiation/trapping sequence on *N*-Ts protected aziridines is possible, with the preparation of a range of trifluoromethyl substituted derivatives, via the generation of α -trifluoromethyl stabilized aziridinyl anions at $-100\text{ }^{\circ}\text{C}$.^{60,61} The aziridinyl anion was shown to be configurationally stable with retention of the configuration at the trifluoromethylated quaternary carbon centre observed in the final aziridine products. Florio and co-workers successfully demonstrated that *N*-Bus phenylaziridines could undergo a ring deprotonation/trapping sequence to afford functionalised aziridines.^{62,63} In this case, deprotonation occurs at the most acidic benzylic position, forming the most stabilized aziridinyl anion. Reaction with suitable electrophiles afforded exclusively 2,2-disubstituted *N*-Bus aziridines.

The generation of unstabilized aziridinyl metal species via functional group exchange is also a suitable approach to access aziridine derivatives. Complementary to aziridine ring deprotonation methodology, the generation of the aziridinyl anion species is site specific. Desulfinylation has proved a valuable synthetic method for the generation of aziridinyl anions (**Scheme 9**). Satoh demonstrated that stereospecific desulfinylation could be achieved on a range of *N*-aryl sulfinyl aziridines using EtMgBr or organolithiums, providing the corresponding aziridinyl metal species.^{64,65} The configurational stability of the aziridinyl magnesium species was exploited upon stereospecific reaction with electrophiles, affording an array of substituted aziridines, with retention of configuration at the reacting centre. Further transmetallation of the aziridinyl magnesium to an aziridinyl copper species was required to effect alkylation.⁶⁶

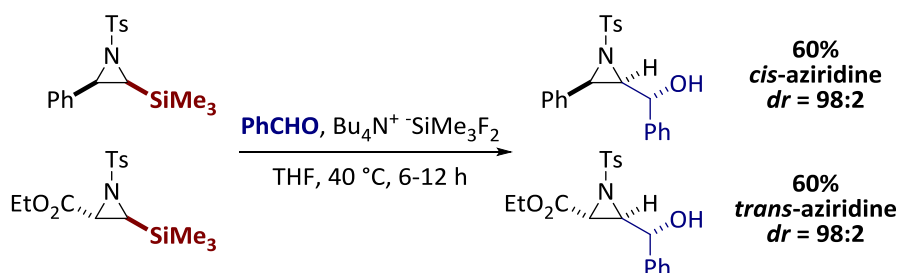
Scheme 9: Desulfinylation: functional group exchange to generate aziridinyll metal species.⁶⁴⁻⁶⁶



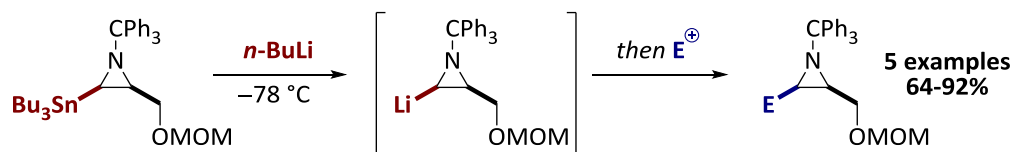
Aziridinyll anions have also been generated from C-silylaziridines (**Scheme 10**). Aggarwal and co-workers reported the stereoselective desilylation of *cis*-C-silylaziridines with tetrabutylammonium triphenyldifluorosilicate (TBAT), and trapping with a range of aldehydes, gave excellent retention of stereochemistry at the reacting centre with also high levels of stereocontrol in the newly formed stereocentre.^{58,59} *trans*-Substituted silylaziridines were also shown to react with retention of stereochemistry, affording the *trans*-substituted aziridinyll alcohol in good yield and high diastereoselectivity.

Scheme 10: Desilylation and destannylation of functionalised aziridines to form aziridinyll anions.

Aggarwal (ref. 58 & 59)



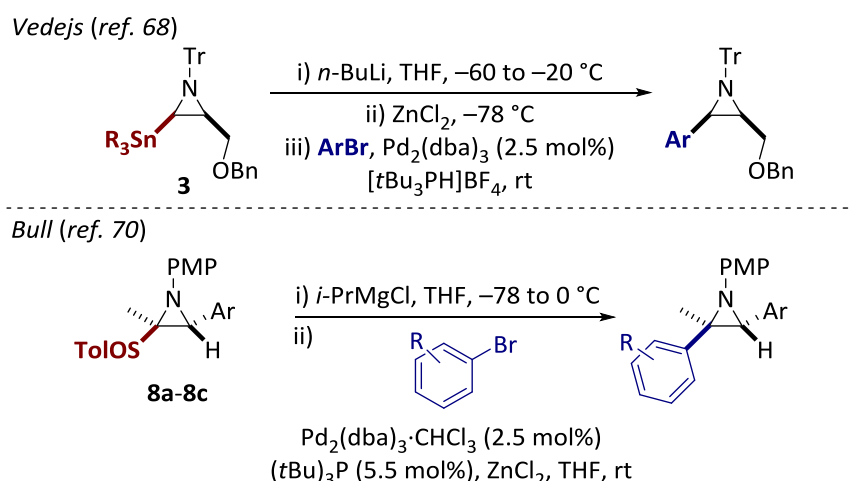
Vedejs (ref. 67)



Stannyl aziridines have also been employed as suitable precursors to aziridinyll anions. Vedejs and Moss reported the formation of aziridinyll anions after a $\text{Bu}_3\text{Sn-Li}$ exchange with $n\text{-BuLi}$ on *N*-trityl aziridines, generating a configurationally stable aziridinyll lithium at -78°C .⁶⁷ Stereospecific reaction with electrophiles afforded *cis*-2,3-disubstituted aziridines in good yields. Although the functional group methodology offers a good route into *cis*-substituted aziridines, the undesirable toxicity of the SnBu_4 by-product is a limitation of the protocol.

The use of highly reactive aziridinyl metal species in palladium-catalysed cross-coupling reactions with aryl and vinyl halides has recently been demonstrated. Vedejs has reported the seminal example of catalytic aziridinyl metal cross-coupling (**Scheme 11**), taking advantage of stannyl aziridines as stable metallated precursors.⁶⁸

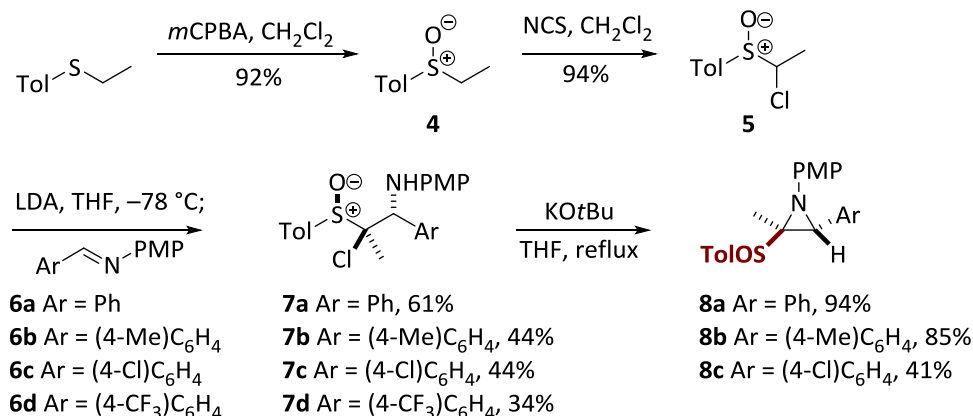
Scheme 11: Palladium-catalysed cross-coupling of metallated aziridines with aryl halides.



Stereospecific tin–lithium exchange was promoted with careful temperature control using *n*-BuLi. Transmetalation of the aziridinyl lithium to an aziridinyl zinc species and use in a palladium-catalysed Negishi cross-coupling protocol with a range of aryl bromides afforded aryl substituted aziridines in good yields, with retention of stereochemistry at the reacting centre. The OBn group may have a role in stabilizing the aziridinyl metal intermediates. Further studies by Vedejs revealed that modification of stannyl aziridine **3** to an aziridinyl stannatrane, enabled efficient aziridinyl metal cross-coupling in a modified Stille coupling in the presence of only a copper source and palladium(0).⁶⁹ Bull and co-workers have developed catalytic aziridinyl metal cross-coupling methodology,⁷⁰ utilising the Satoh sulfoxide–magnesium exchange. A range of sulfinyl aziridines (**8a-8c**) were accessed from ethyl tolyl sulfide in 4 steps (**Scheme 12**).⁶⁴⁻⁶⁶ *m*CPBA oxidation of ethyl tolyl sulfide to sulfoxide **4**, and subsequent α -chlorination with NCS afforded α -chlorosulfoxide **5** in excellent yield. Deprotonation of α -chlorosulfoxide **5** with LDA and addition into various aryl substituted *N*-PMP imines (**6a-6d**) afforded the corresponding β -chloroamines **7a-7d** with >95:5 diastereoselectivity, efficiently installing all 3 new stereocentres in one step. Base promoted cyclisation with KO*t*Bu generated sulfinyl aziridines **8a-8c** in moderate to excellent yields. Sulfoxide–magnesium exchange with *i*-PrMgCl afforded the corresponding aziridinyl magnesium species. Transmetalation to an aziridinyl zinc species and use in a palladium catalysed Negishi cross-coupling protocol, with both aryl and vinyl bromides afforded highly substituted *N*-PMP aziridines in

excellent yields, providing a less toxic aziridinyl cross-coupling protocol to that previously reported by Vedejs.

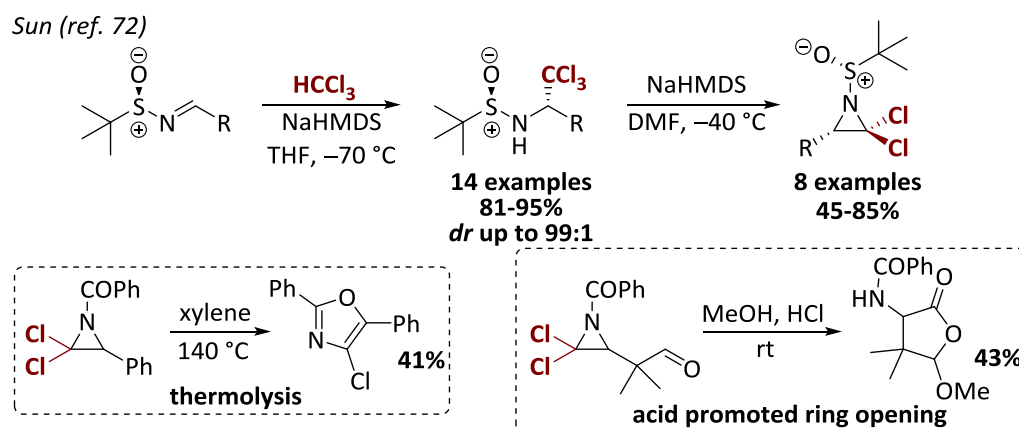
Scheme 12: Synthesis of sulfinyl aziridines from ethyl tolyl sulfide.



1.7: Synthesis and Reactivity of C-Halogenated Aziridines

The synthesis and reactivity of C-heteroatom substituted aziridines was comprehensively reviewed by De Kimpe (2007).⁷¹ Particular focus will be placed on the synthesis of C-halogen substituted aziridines, and the influence of halogen substitution on the further reactivity of the aziridine. Most commonly, *gem*-dichloroaziridines have been reported in the literature due to their ease in preparation, via the addition of a dichlorocarbene to imines (**Scheme 13**).

Scheme 13: Access to *gem*-dichlorinated aziridines and their further reactivity.

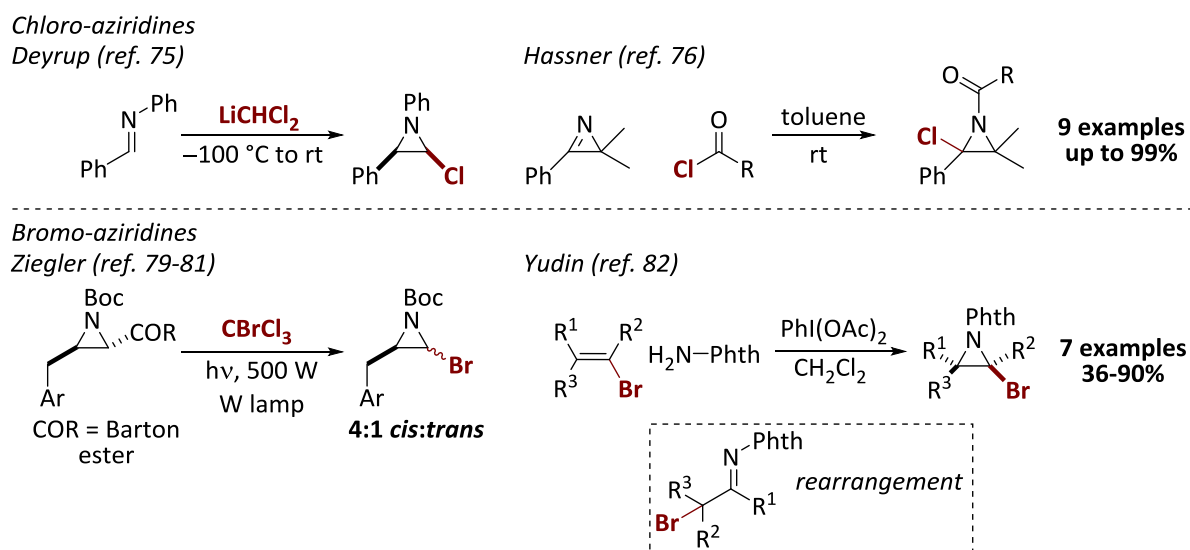


This has recently been demonstrated by Sun and co-workers in an asymmetric fashion.⁷² Stereoselective trichloromethylation of *N*-(*tert*-butylsulfinyl)aldimines with chloroform, gave rise to α -trichloromethyl amines in high diastereoselectivities, with base induced cyclisation giving rise to enantioenriched *gem*-dichloroaziridines in good yield. The use of bromoform in place of chloroform has also been explored in similar fashion to excellent effect, with methodology to access a range of

enantioenriched *gem*-dibromoaziridines also developed.⁷³ Due to the high reactivity of *gem*-dichloroaziridines towards ring opening and ring expansion, they have been used as precursors in the synthesis of other heterocycles,⁷¹ including thermolysis reactions and acid promoted ring expansions.⁷⁴

Monohalogenated aziridines have proven to be more difficult to access (**Scheme 14**). Pioneering work was carried out by Deyrup and co-workers in the formation of monochloroaziridines.⁷⁵ Dichloromethyl lithium was formed via a chlorine–lithium exchange reaction between CHCl_3 and *n*-BuLi at -100°C . Warming and reaction of the lithium carbenoid with *N*-benzylideneaniline afforded exclusively the corresponding *cis*-substituted chloroaziridine.

Scheme 14: Synthesis of monohalogenated aziridines.



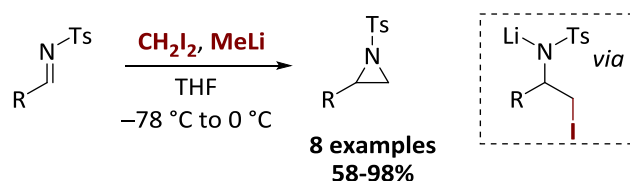
Since this innovative approach to chloroaziridines, Hassner detailed the addition of acyl chlorides across substituted azirines to give tetrasubstituted chloroaziridines.⁷⁶ Under mild reaction conditions, a range of acyl chlorides were employed to give the corresponding chloroaziridines in excellent yield. Other approaches involving the trapping of aziridinyll metal intermediates with C_2Cl_6 ,⁶⁷ and the addition of nitrenes across chloroalkenes have also been reported.⁷⁷ In terms of reactivity, it has been shown that the chloride on the aziridine ring itself can be displaced by a variety of nucleophiles, including organolithiums, thiolates and cyanide with inversion of stereochemistry at the reacting centre.⁷⁸ Ziegler first reported the preparation of bromoaziridines in an elegant Barton decarboxylation–bromination sequence from an aziridine carboxylate, affording a mixture of *cis*- and *trans*-bromoaziridines in 69% yield.^{79,80,81} The bromoaziridines were further utilised towards the synthesis of mitomycin-like antitumor agents in a reductive cyclisation sequence, with the regeneration of an aziridine radical species using HSnBu_3 and 1,1'-

azobis(cyclohexene-1-carbonitrile) (ACCN). Yudin and co-workers have successfully adopted an *N*-transfer approach to the synthesis of bromoaziridines, using *N*-aminophthalamide, (diacetoxyiodo)benzene and a range of substituted bromoalkenes.⁸² Advantageously, the nitrenoid species could be formed under mild transition-metal free conditions, giving access to substituted bromoaziridines in good yields. However, many of the bromoaziridines were shown to be thermally labile, under mild heating to give the corresponding α -bromohydrazones. The preparation of monofluoroaziridines has also recently been reported by De Kimpe, via the electrophilic fluorination of imines using NFSI (*N*-fluorobenzenesulfinimide), and then subsequent bromination, imine borohydride reduction and intramolecular cyclisation.⁸³ Iodo-substituted aziridines were unknown in the literature at the outset of this project.

1.8: Diiodomethyl-metal Reagents

Concellón has demonstrated that iodomethyl lithium, formed via iodine–lithium exchange between CH_2I_2 and MeLi, could be utilised in an aza-Darzens protocol with *N*-Ts imines forming terminal aziridines in excellent yields (**Scheme 15**).^{84,85}

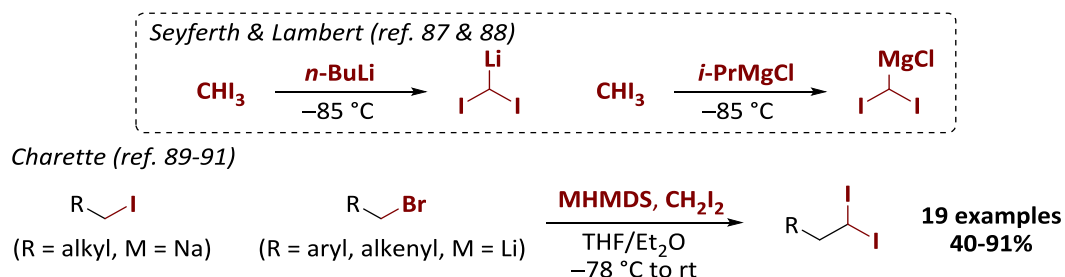
Scheme 15: Concellón formation of terminal aziridines using iodomethyl lithium.



The preparation and reactivity of lithium carbenoids of the LiCH_2X type, and their ongoing applications in synthesis has recently been well documented by Capriati and Florio.⁸⁶ The following section will mostly discuss the chemistry of MCH_2 reagents. Seyferth and Lambert described the synthesis of both ClMgCH_2 ,⁸⁷ and LiCH_2 ,⁸⁸ via metal–halogen exchange reactions from iodoform and *i*-PrMgCl/*n*-BuLi respectively at $-85\text{ }^\circ\text{C}$ in THF. The resulting carbenoids were then trapped with a variety of simple heteroatom based electrophiles generating functionalised *gem*-diiodides. Since these seminal investigations, the application of MCH_2 in organic synthesis has been rather limited, possibly due to a combination of two factors: i) the low temperatures required for the stability of the carbenoid reagent (prone to α -elimination upon warming); ii) incomplete conversion of primary alkyl halides to desired diiodide, with purification being problematic. However, Charette and co-workers recently illustrated an improved synthesis of MCH_2 (**Scheme 16**). Formation of diiodomethane anions (LiCH_2 or NaCH_2) can either occur via deprotonation of diiodomethane with either LiHMDS or NaHMDS at $-78\text{ }^\circ\text{C}$, in a mixed solvent system of THF:Et₂O.⁸⁹ Increased equivalents of MCH_2 were also found to be advantageous in increasing conversion. Both primary alkyl iodides and benzyl

bromides containing moderate functionality were subjected to these improved reaction conditions, with the corresponding diiodides isolated cleanly in good to excellent yields.

Scheme 16: Improved protocol for the formation of MCHI_2 from diiodomethane.

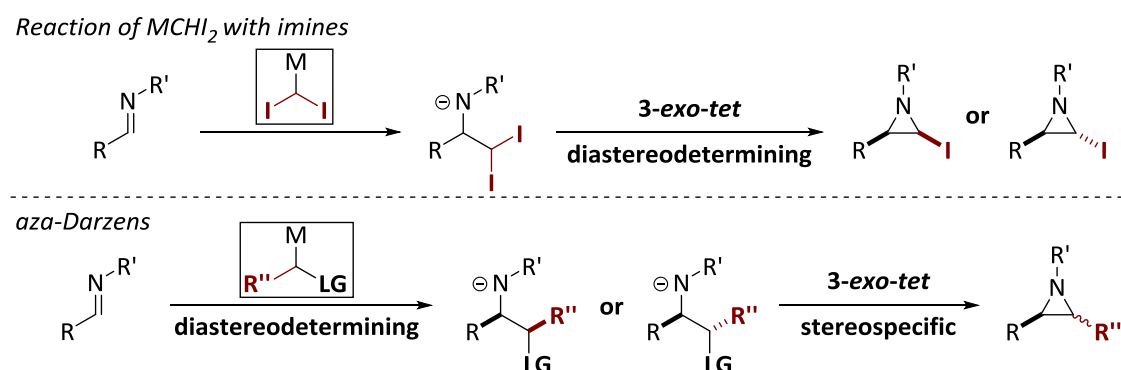


Aromatic substituted vinyl iodides could also be accessed stereoselectively from their corresponding benzyl bromides. Initial homologation followed by stereoselective elimination of iodide gave (*E*)- β -aryl vinyl iodides in excellent yields.^{90,91} The methodology was later utilised to access a range of functionalised *gem*-diiodoalkanes via nucleophilic displacement of primary iodides, generating substrates for intramolecular Simmons-Smith cyclopropanations.⁹² More recently, Pace employed LiCHI_2 in the homologation of isocyanates giving a variety of substituted *gem*-dihaloamides.⁹³

1.9.1: Project Aims, Concept & Preliminary Studies

This thesis examines the synthesis and functionalisation of iodoaziridines. Chloro-, bromo- and fluoroaziridines had been reported in the literature (*vide supra*), but iodo-aziridine derivatives were unknown. The synthesis of iodoaziridines would allow the study of this new functional group, in terms of intrinsic stability as well as reactivity. The possible synthesis of an iodoaziridine was envisaged via the reaction of diiodomethyl anions and imines. The addition of MCHI_2 to an imine may afford an amino *gem*-diiodide intermediate, which may be cyclised to the iodoaziridine either *in situ* or in a separate step (**Figure 5**).

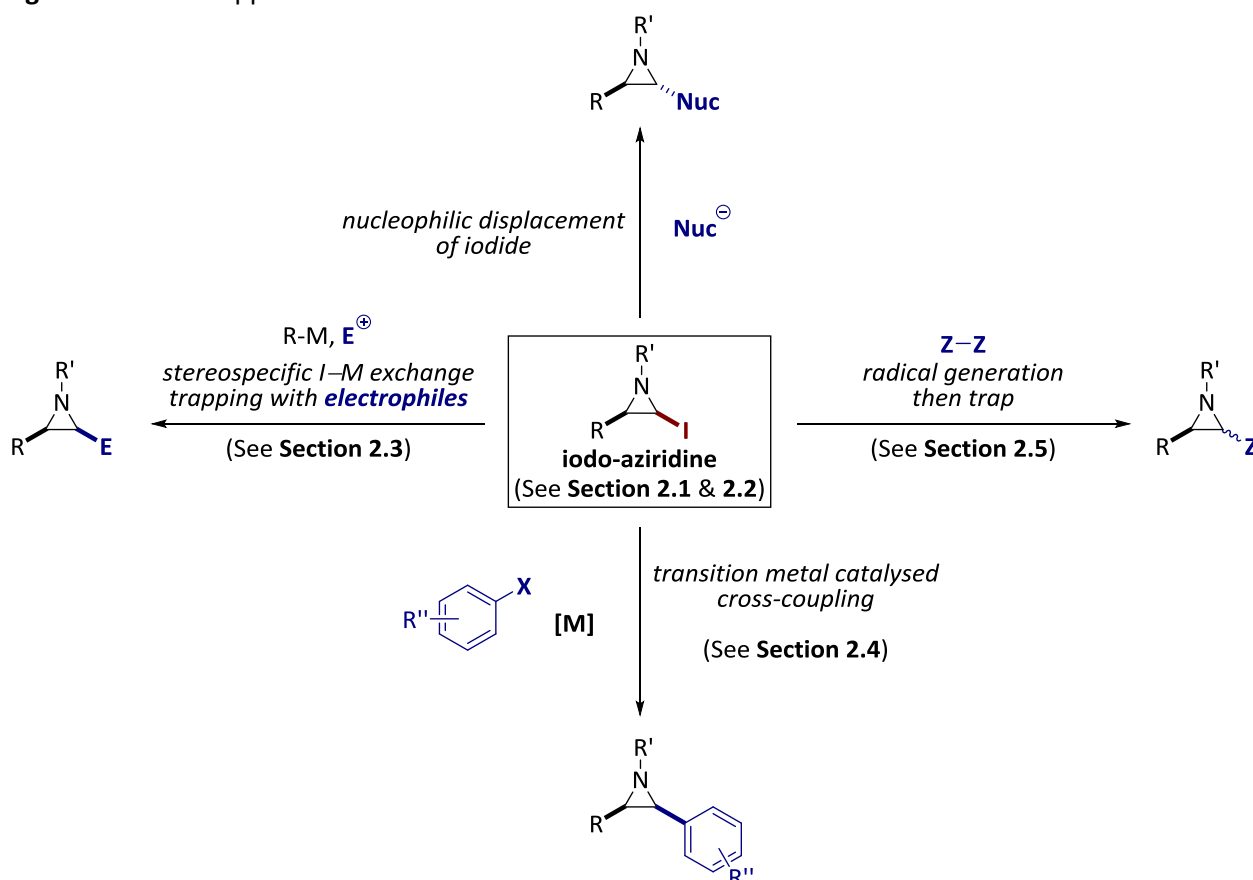
Figure 5: Addition of MCHI_2 to imines to access *cis*- or *trans*-iodoaziridines; comparison between classical aza-Darzens methodology.



In comparison with the classical aza-Darzens reaction (see **Section 1.5**, page 19), the diastereochemistry of the final aziridine products would be determined upon cyclisation of the intermediate, rather than the initial addition of the nucleophile, due to the symmetrical nature of MCHl_2 .

If iodoaziridines could be efficiently prepared, they may provide a suitable precursor for functionalisation of aziridines, keeping the ring intact during this process. Several transformations could be envisaged which would take advantage of the C–I bond (**Figure 6**):

Figure 6: Possible approaches to the functionalisation of intact aziridines from iodoaziridines.



The following transformations may be possible, to provide new or functionalised aziridine derivatives:

- (i) generation of aziridinyl anions via stereospecific I–M exchange, trapping with suitable electrophiles;
- (ii) direct displacement of the iodide on the ring with nucleophiles;
- (iii) employing the iodoaziridine in aziridine cross-coupling protocols with suitable transition metal catalysts;
- (iv) formation of aziridinyl radicals and reaction with suitable carbon or heteroatom radical traps.

The stereochemical outcome of these reactions, if viable, was difficult to predict and posed an interesting question. Stereoselective or stereospecific processes would be desirable.

The aims of this work were therefore as follows:

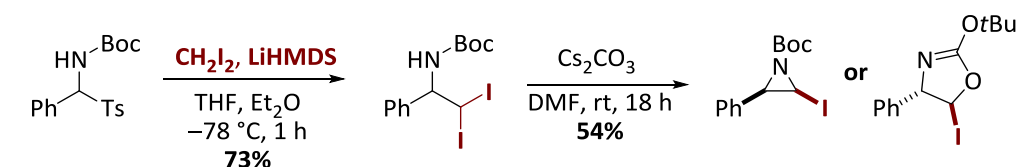
- (i) to develop a robust, high yielding and scalable synthesis of iodoaziridines with a wide reaction scope;
- (ii) to develop methodology to functionalise iodoaziridines, allowing for new carbon-carbon bond forming reactions to occur, keeping the ring intact during this functionalisation process.

1.9.2: Preliminary Studies

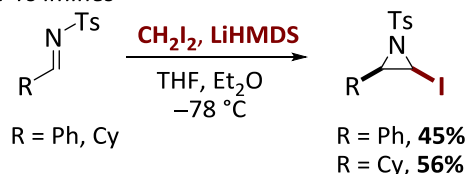
In preliminary studies, Bull and co-workers established the addition of LiCHI_2 to Ph *N*-Boc imine- HSO_2Tol adduct to generate the corresponding amino *gem*-diiodide (**Scheme 17**).⁹⁴

Scheme 17: Preliminary studies involving reactivity of LiCHI_2 with imines.

*Addition of LiCHI_2 to *N*-Boc imines*



*Addition of LiCHI_2 to *N*-Ts imines*



It was established after optimisation of reagent equivalents, solvent conditions, reaction additives, time and temperature that the amino *gem*-diiodide could be successfully isolated in 73% yield, and was stable to conventional silica gel chromatography (optimum conditions: 2.6 equiv CH_2I_2 , 3.0 equiv LiHMDS , THF/ Et_2O (2.2:1, 0.15 M), -78°C). Efforts were then focused towards a base induced diastereoselective cyclisation to afford an iodoaziridine. A variety of conditions were evaluated for the diastereoselective cyclisation, with Cs_2CO_3 in DMF proving most efficient affording a major product as a single diastereoisomer in 54% yield. The identity of this product had not been fully investigated, with two potential products considered: a *cis*-iodo-aziridine, and a *trans*-iodo-oxazoline.

Addition of LiCHI_2 to alkyl and aromatic *N*-Ts imines had also been established using similar reaction conditions affording the corresponding *cis*-*N*-Ts iodoaziridines, with diastereoselective cyclisation

occurring at $-78\text{ }^{\circ}\text{C}$. Both alkyl and aryl iodoaziridines had been successfully isolated in a one-pot procedure in moderate yields.

Building upon this previous work within the Bull Group on the formation and addition of diiodomethyl lithium to imines, the immediate aims on starting the project were as follows:

- (i) to identify the product arising from diastereoselective cyclisation of the amino *gem*-diiodide;
- (ii) to develop improved methodology to the diastereoselective access of iodoaziridines using carbenoid reagents.

2: Results and Discussion

2.1.1: *N*-Boc Iodoaziridines

This chapter will detail the formation of *N*-Boc iodoaziridines from LiCHI_2 and *N*-Boc imines. The optimisation of the reaction protocol will be explored, then scope of the reaction will be examined, varying both *N*-Boc imine substitution and *N*-carbamate protecting group. The effect of this substitution on the diastereoselectivity of the cyclisation will also be assessed. Mixed dihalocarbenoid systems of the form LiCHXY (where $X \neq Y$) will be discussed, in order to examine the diastereoselectivity of the carbenoid addition at -78°C and the subsequent cyclisation.

A concise account detailing aspects of this work can be found in *Chemical Communications*.⁹⁵

2.1.2: Reaction Optimisation

Work began on replicating conditions for the formation of the amino *gem*-diiodide, previously employed by Bull and co-workers (**Table 1**).⁹⁴ *N*-Boc imine- HSO_2Tol adducts were chosen as suitable starting materials due to their facile synthesis and ease of handling, compared to *N*-Boc imines which readily hydrolyse. The desired *N*-Boc imines were formed *in situ* via deprotonation with excess base (or diiodomethylithium), which has recently been well documented by Petrini.⁹⁶ LiCHI_2 was formed by deprotonation of CH_2I_2 by LiHMDS for 20 min at -78°C prior to the addition of the substrate. An electron withdrawing group on nitrogen was deemed necessary to stabilize any build up of negative charge in the transition state, aid the initial nucleophilic addition of LiCHI_2 and help to stabilize the iodoaziridine towards undesired *N*-assisted iodide elimination.

Table 1: Optimisation for the formation of *cis*-N-Boc iodoaziridines.

$\text{9a} \xrightarrow[\text{THF, Et}_2\text{O, } -78^\circ\text{C (time) to } T_2 (^\circ\text{C})]{\text{CH}_2\text{I}_2, \text{LiHMDS}} \text{10a, 11a, 12a}$

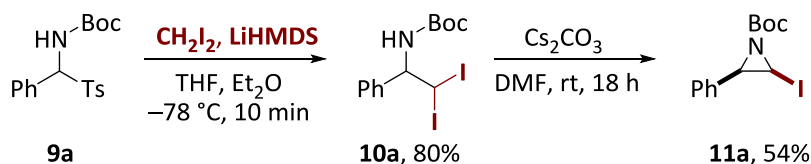
entry ^a	time at -78°C (min) ^b	T_2 ($^\circ\text{C}$)	time at T_2 $^\circ\text{C}$ (min)	product ratio ^c 10a : 11a : 12a	yield (%) ^d
1	60	$-^e$	–	10a only	
2	10	$-^e$	–	10a only	10a, 80%
3	30	-30	90	2 : 1 : –	
4	30	-20	60	9 : 3 : 1	
5	30	0	90	– : 5 : 1	
6	30	rt	60	– : 7 : 1	
7	30	rt	90	– : 18 : 1	
8	30	rt	90	– : 9 : 1	11a, 83%
9	–	rt (water bath)	5	5 : 48 : 1	
10	30	rt (water bath)	90	– : 32 : 1	11a, 76%
11	30	rt (water bath)	90	– : 50 : 1	11a, 82%
12	10	30	10	11a only	11a, 83%

^a Reaction conditions: imine- HSO_2Tol adduct **9a** (0.60 mmol), LiHMDS (1.56 mmol, 1.0 M in THF), CH_2I_2 (1.80 mmol), THF:Et₂O (0.15 M at deprotonation), -78°C to T_2 $^\circ\text{C}$. ^b Time following the addition of **9a**. ^c Ratio obtained from crude ^1H NMR spectrum. ^d Isolated yield. ^e Reaction quenched at -78°C .

The 1,2-addition of LiCHI_2 to the imine occurs rapidly at -78°C , and after 60 min at -78°C , only diiodide **10a** is observed by ^1H NMR spectroscopy (**Table 1**, entry 1). 2.6 equiv of LiCHI_2 was deemed optimal from previous work,⁹⁴ with 1.0 equiv of LiCHI_2 required for the formation of the corresponding *N*-Boc imine. A slight excess of diiodomethane was employed in all cases, with respect to LiHMDS (3.0 equiv vs. 2.6 equiv). A shorter reaction time was investigated at -78°C (entry 2) providing an excellent 80% yield for diiodide **10a**. In the absence of diiodomethane, the addition of LiHMDS also occurs rapidly at -78°C affording the corresponding aminor within 5 min. However this aminor was not stable to silica gel chromatography and was not isolated due to degradation upon several purification attempts. To probe the stability of diiodide **10a** under the reaction conditions, a deuterium labelling study with D_2O was carried out. Quenching the reaction at -78°C led to the formation of the expected diiodide with partial incorporation of deuterium at *N* (30% D

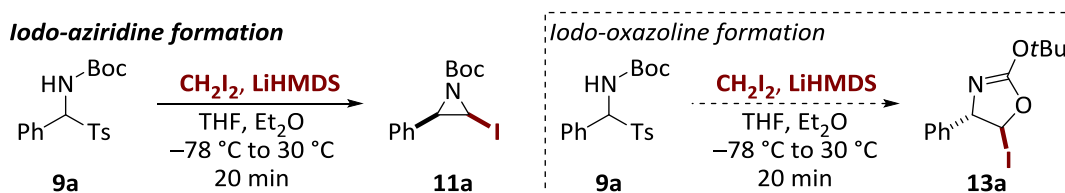
incorporation),ⁱ with no incorporation at the CHI₂ position. This indicated that the relatively acidic CHI₂ group was not being deprotonated under the reaction conditions by the LiCHI₂ carbenoid. Using conditions previously developed in the Bull Group, base-induced cyclisation of diiodide **10a**, using 2.0 equiv Cs₂CO₃ in DMF, afforded iodoaziridine **11a**, in 54% yield exclusively as the *cis*-diastereoisomer (**Scheme 18**).

Scheme 18: Optimised 2-step formation of *cis*-iodoaziridine **11a**.



The identity of the cyclised product was quickly established as *cis*-iodoaziridine **11a** by stereochemical and spectroscopic properties (**Figure 7**).

Figure 7: Varying structural assignments, *cis*-iodoaziridine **11a** vs. *trans*-iodo-oxazoline **13a**.



(i) **spectroscopic evidence:** assigned as **11a** via IR stretching frequency (C=O; 1724 cm⁻¹). Due to *N* lone pair being sp³ hybridised in the aziridine, less conjugation into π*_(C=O) orbital results in higher stretching frequency (typical 2-alkoxy oxazoline C=N stretching frequency = 1660–1680 cm⁻¹)^{97,98};

(ii) **structural identity:** either an iodine–magnesium or iodine–lithium exchange reaction with **11a**, forming an aziridinyl metal species and quenching with a proton source would afford a known terminal aziridine. Exchange with *t*-BuLi at –78 °C and quench with MeOH after 30 min led to decomposition, whereas changing organometallic to *i*-PrMgCl led to no conversion of starting iodoaziridine. However, employing *n*-BuLi in the exchange protocol led to the formation of the expected terminal aziridine, with all observed data consistent with that reported in the literature.⁹⁹ Interestingly, no products arising from *N* to C [1,2] Boc migration were observed in the crude ¹H NMR spectrum as a result of aziridinyl lithium formation, as previously reported by both Florio,⁵¹ and Hodgson,⁵² for the lithiation of phenyl *N*-Boc aziridine.

i) 30% D incorporation may be attributed due to rapid H/D exchange at *N*.

(iii) ***cis*-stereochemistry**: $^3J_{\text{HH}} = 5.4$ Hz for **11a** ring protons, which is consistent with other *cis*-halogenated aziridines in the literature (cf. *cis*-*N*-Boc bromoaziridines reported by Ziegler and co-workers, $^3J_{\text{HH}} = 4.9$ Hz for aziridine ring protons; *trans*-bromoaziridine, $^3J_{\text{HH}} = 1.9$ Hz).⁷⁹⁻⁸¹

A one-pot strategy to access *cis*-iodoaziridines became a key goal, in order to rapidly gain access to iodoaziridines and facilitate investigation into further functionalisation of the intact aziridine. Pleasingly, cyclisation of diiodide **10a** under the reaction conditions could be promoted by simple warming of the reaction mixture. Upon warming to -20 °C (**Table 1**, entries 3-4, page 36), the formation of 3 products was evident, by characteristic ^1H NMR signals: amino *gem*-diiodide **10a**, characterised by broad singlets at δ 5.46, 5.37 and 4.90 ppm (CHI_2 , NH and CHPh); *cis*-iodoaziridine **11a**, characterised by doublets at δ 4.72 and 3.59 ppm (CHI and CHPh); and vinyl iodide **12a**, arising from elimination of iodide from the diiodide intermediate, characterised by a singlet at δ 5.78 ppm (C=CHI). Although cyclisation was proving to be slow at -20 °C, this process could be accelerated by further warming of the reaction mixture after the initial addition of diiodomethyl lithium. At 0 °C, full cyclisation from diiodide **10a** was observed (entry 5) affording a 5:1 mixture of *cis*-iodoaziridine **11a** and vinyl iodide **12a**. Lifting the reaction vessel out of the -78 °C bath, and warming to rt further improved the ratio of *cis*-iodoaziridine **11a** to vinyl iodide **12a** (entries 6-8). Reducing the equivalents of LiHMDS in order to minimise formation of **12a** led to reduced carbenoid formation and ultimately less conversion to the desired iodoaziridine **11a**. The use of LDA in place of LiHMDS was also pursued at this stage with little success, with a mixture of all three products evident after the slow warming protocol. After investigating the effect of reaction time on the product distribution, it became evident that subtle control of the rate of warming was crucial in preventing undesired elimination to vinyl iodide **12a**. Rapid warming from -78 °C to rt with the use of a water bath at rt (entries 9-11), ensured minimal side product formation. However, it became critical to completely avoid the formation of **12a** as it was found to be co-eluting with iodoaziridine **11a** upon silica gel chromatography. The rate of warming from -78 °C towards the temperature required for cyclisation was assessed again, and was shown to be crucial in avoiding elimination. Warming to 30 °C in a pre-warmed water bath enabled a reproducible cyclisation protocol and hence avoiding the formation of the undesired elimination product, enabling the exclusive formation of *cis*-iodoaziridine **11a** in 83% yield. It is likely that the rate of warming from -78 °C is crucial in decomposing excess LiCHI_2 to non-basic species, therefore avoiding any potential elimination pathways to vinyl iodide **12a**.

With *cis*-*N*-Boc iodoaziridine **11a** in hand, it became important to assess its stability before studying its further derivatisation. A previous observation after cleanly isolating **11a** by silica gel chromatography was that it is prone to rapid degradation upon concentration. This is presumably due to either *N*-assisted iodide elimination forming a highly reactive aziridinium species, or light induced radical cleavage of the weak C-I bond. Stability studies were carried out with clean iodoaziridine **11a**, with a range of storage conditions assessed to prevent this undesired decomposition and determine a practical operating window (**Table 2**).

Table 2: Assessing stability of *cis*-*N*-Boc iodoaziridine **11a**.

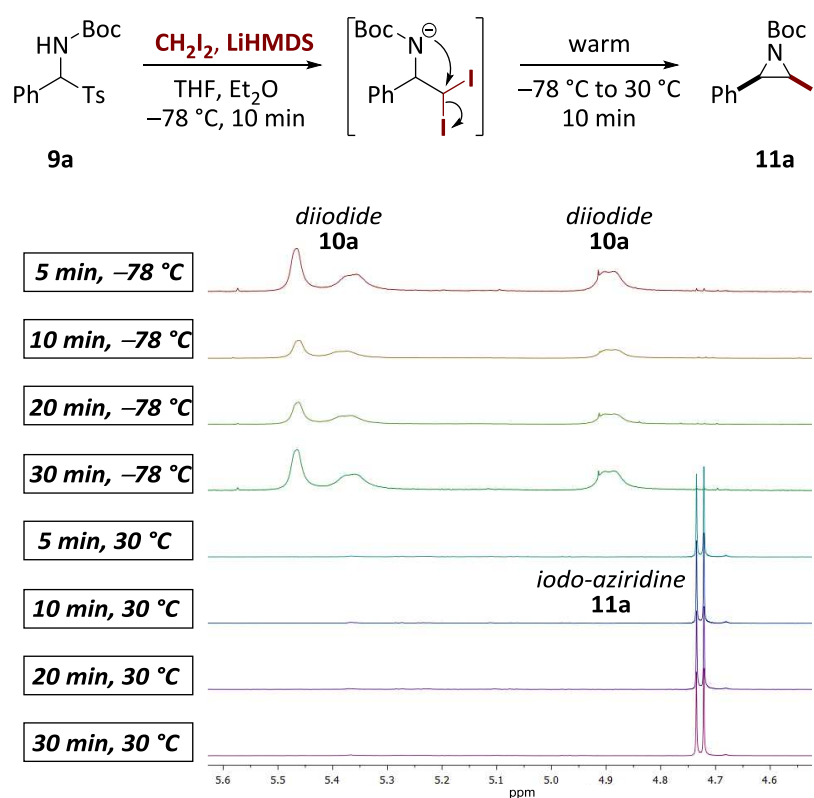
entry	solvent	temperature (°C)	additive	time	¹ H NMR analysis of 11a
1		rt		2 min	decomposition
2		rt	10 mg Cu powder	24 h	decomposition
3		−20 °C		24 h	decomposition
4		−20 °C	10 mg Cu powder	24 h	stable
5	CH ₂ Cl ₂	−20 °C		7 days	stable
6	dry CH ₂ Cl ₂	−20 °C		>10 days	stable
7	CDCl ₃	−20 °C		>10 days	stable

After removing the solvent under reduced pressure after conventional silica gel column chromatography, neat iodoaziridine **11a** was obtained, but the material rapidly decomposed in light, which was observable by an instant darkening of the product flask (**Table 2**, entry 1). This was also confirmed by ¹H NMR spectroscopy, with no characteristic aziridine or aziridine decomposition product signals observed. A small amount of Cu powder was then added to act as a potential stabilizer (entry 2), but after a prolonged period at rt, decomposition was again observed. Performing the same experiments at −20 °C (entries 3-4) was shown to have a major effect on the stability of iodoaziridine **11a**, with it now being stable on the addition of 10 mg Cu powder after 24 h. However, further purification would have to be carried out in order to remove the Cu prior to use. Therefore a different approach was taken: stock solutions (entries 5-7) of known amounts of iodoaziridine **11a** in both CH₂Cl₂ and CDCl₃ were generated, which were shown to be stable for over a week at −20 °C in the dark without significant decomposition (by ¹H NMR spectroscopy). Aliquots could then be taken from the stock solution, stripped of solvent and the iodoaziridine dissolved in the solvent of choice prior to further manipulation.

2.1.3: Mechanism and Rationale for Observed Diastereochemistry

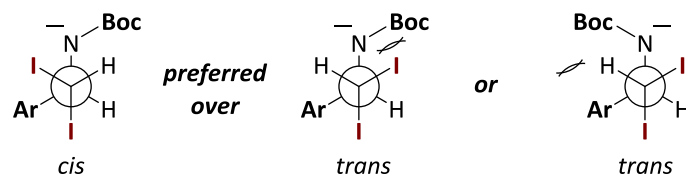
Mechanistically, the reaction proceeds by an addition–cyclisation protocol as shown below (**Figure 8**). Formation of Ph *N*-Boc imine via elimination of HSO₂Tol and subsequent addition of LiCHl₂ affords the corresponding anionic diiodide intermediate at low temperatures. Rapid warming of the reaction mixture induces a highly diastereoselective 3-*exo-tet* cyclisation to form *cis*-iodoaziridine **11a**. This mechanistic hypothesis is supported by a ¹H NMR reaction sampling study. This study, in which reaction aliquots were taken at regular intervals at –78 °C and 30 °C, quenched and analysed by ¹H NMR spectroscopy, indicated the exclusive formation of diiodide **10a** at –78 °C and then clean conversion to *cis*-iodoaziridine **11a** upon warming the reaction mixture to 30 °C.

Figure 8: Mechanistic proposal of addition–cyclisation protocol and sampling/¹H NMR spectroscopy study evidencing addition–cyclisation mechanistic hypothesis.



The proposal for the observed diastereoselectivity of the reaction is based upon subtle steric factors. As the LiCHl₂ reagent is symmetrical in nature, the initial nucleophilic addition of the carbenoid cannot determine the stereochemical outcome of the reaction meaning the cyclisation step is diastereodetermining (*vide supra* for discussion on the mechanistically analogous aza-Darzens reaction, **Section 1.5**, page 19). Possible transition states for cyclisation are depicted below (**Figure 9**).

Figure 9: Newman projections of possible transition states and rationale for observed diastereoselectivity in cyclisation step.

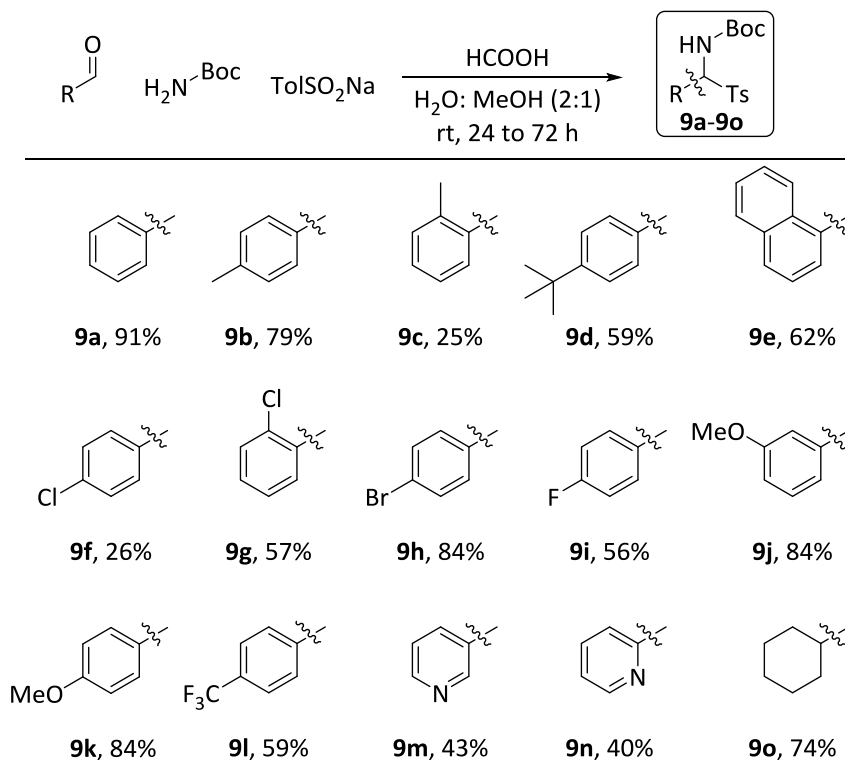


For cyclisation to occur, *N* and I must be arranged antiperiplanar as required for nucleophilic attack. With the large aryl and *N*-Boc protecting group likely to adopt an *anti* conformation, this leaves two possible transition states for cyclisation. It is proposed that the non-displaced iodide preferentially sits *gauche* to the aryl group, minimising the unfavourable steric clash between itself and the Boc group, leading to the formation of the *cis*-diastereoisomer.

2.1.4: Reaction Scope

The scope of the reaction was initially explored by varying substitution on the *N*-Boc imine- HSO_2Tol adduct. The various imine- HSO_2Tol adducts were prepared according to the method of Jacobsen and co-workers in an acid catalysed multi-component reaction (**Scheme 19**), in low to excellent yields.¹⁰⁰

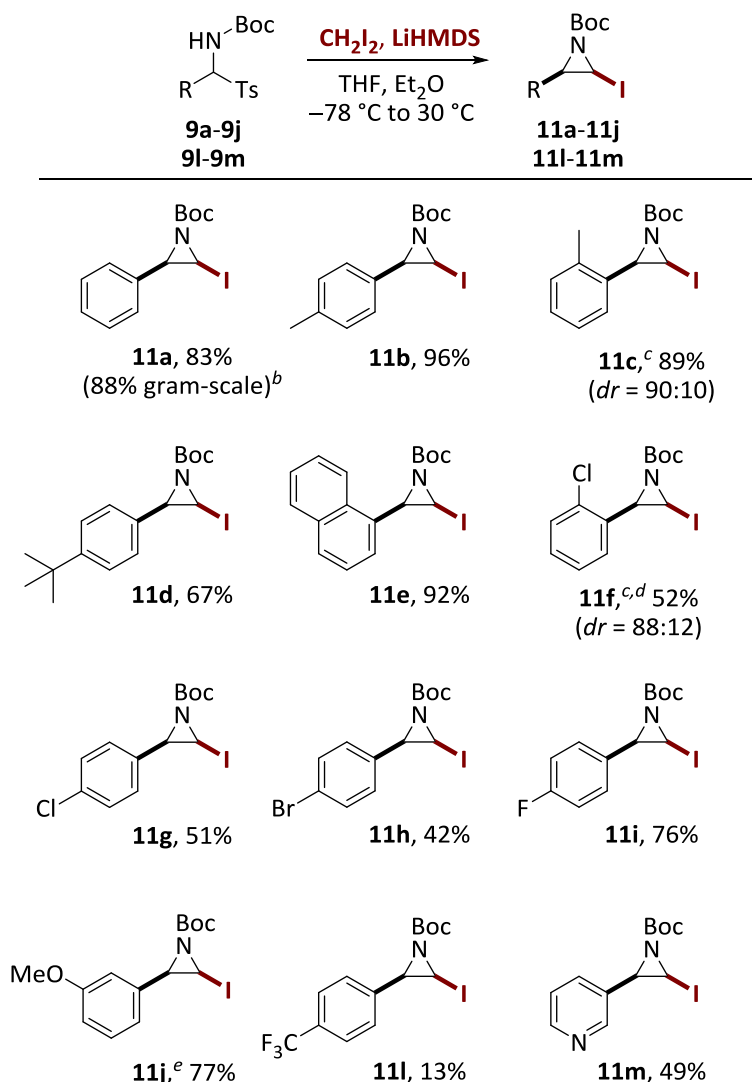
Scheme 19: Synthesis of *N*-Boc imine- HSO_2Tol adducts.^a



^a Reaction conditions: aldehyde (1.5 equiv), *tert*-butyl carbamate (1.0 equiv), *p*-toluenesulfonate (2.0 equiv), $\text{H}_2\text{O}:\text{MeOH}$ (2:1), rt, 24 h to 72 h.

Variation in aromatic substitution on the imine-HSO₂Tol adduct generally led to the successful isolation of the corresponding *N*-Boc iodoaziridines in good to excellent yields, exclusively as their *cis*-diastereoisomers under the standard reaction conditions (**Scheme 20**).

Scheme 20: Scope for formation of *cis*-*N*-Boc iodoaziridines, using diiodomethylithium and *in situ* formed *N*-Boc imines.^a



^a Reaction conditions: imine-HSO₂Tol adduct (0.60 mmol), LiHMDS (1.56 mmol, 1 M in THF), CH₂I₂ (1.80 mmol), THF:Et₂O (0.15 M at deprotonation), -78 °C to 30 °C. All examples >95:5 *cis:trans*, only the *cis*-diastereoisomer could be observed by ¹H NMR spectroscopy unless stated in parenthesis. ^b Reaction performed on 3 mmol scale. ^c Warmed to 30 °C for 30 min to induce cyclisation of intermediate diiodide. ^d Diiodide also isolated in 5% yield. ^e Purification on neutral alumina to prevent decomposition on silica gel.

Under the standard conditions, Ph substituted imine-HSO₂Tol adduct **9a** returned the corresponding *cis*-*N*-Boc iodoaziridine **11a** in an excellent yield of 83%. The reaction was also performed on a gram-scale (3 mmol), giving **11a** in 88% yield. The synthesis was also attempted on a 5 mmol scale, but

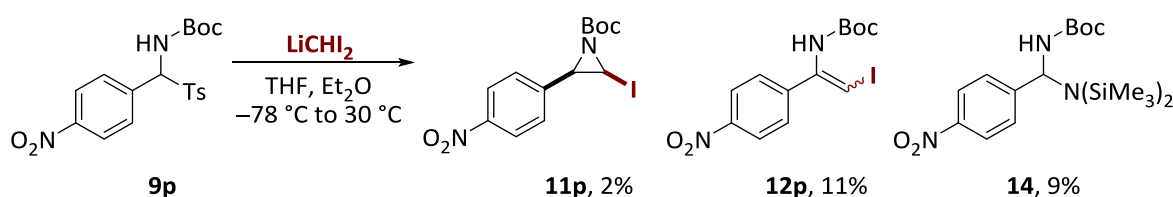
problems with undesired decomposition to benzaldehyde (from unreacted starting material) and elimination to vinyl iodide **12a** occurred. This was attributed to difficulties in rapidly and uniformly cooling/warming the reaction mixture under the optimised protocol on the increased reaction scale.

Incorporation of alkyl substituents on the aromatic moiety and use of a naphthyl derivative (**9b-9e**), gave the corresponding iodoaziridines (**11b-11e**) in excellent yields as their *cis*-diastereoisomers, although an amended protocol had to be adopted for the *ortho*-tolyl substrate. Under the standard reaction conditions, it was evident for the *ortho*-tolyl substrate **11c** that incomplete cyclisation to the iodoaziridine from the amino *gem*-diiodide was occurring (1.4:1 **11c:10c**). An alternative protocol which involved a longer period at the cyclisation temperature (30 min), ensured full cyclisation from the amino *gem*-diiodide intermediate, affording iodoaziridine **11c** as a 90:10 mixture of *cis:trans* diastereoisomers. This reduction in diastereoselectivity is believed to be due to eclipsing steric interactions, raising the energy of the cyclisation transition state that leads to the *cis*-diastereoisomer, and resulting in some minor formation of the *trans*-substituted iodoaziridine. A corresponding benefit from formation of the minor *trans*-product was to give us assurance that the assignment of the major diastereoisomer as *cis* was rational. Halogenated aromatics were next examined, with the *ortho*-chlorophenyl iodoaziridine **11f**, displaying similar difficulties in the cyclisation step. Under the newly developed protocol for *ortho*-substituted aromatics, *ortho*-chlorophenyl iodoaziridine **11f** was prepared as a mixture of *cis:trans* iodoaziridines (87:13) in 52% yield. Full cyclisation was not observed in this instance, with the corresponding amino *gem*-diiodide **10f** also isolated in 5% yield. The significant reduction in rate of cyclisation and diastereoselectivity can possibly be explained by co-ordination of the Cl lone pairs with the lithium cation in the pre-cyclisation reaction intermediate. 4-Chlorophenyl, 4-bromophenyl and 4-fluorophenyl substituted iodoaziridines (**11g-11i**) were all accessed in good yields, exclusively as their *cis*-diastereoisomers under the standard conditions. Electron rich aromatics were also tolerated under these reaction conditions. The 3-methoxyphenyl bearing iodoaziridine **11j** was successfully isolated after purification on neutral alumina (77%, *cis*-diastereoisomer), due to significant degradation to 3-methoxybenzaldehyde upon conventional silica gel chromatography. More electron deficient *N*-Boc imine- HSO_2Tol adducts were next examined under the standard reaction conditions (**11l-11m**). Although the initial addition of diiodomethyl lithium proved to be a success, the increased acidity of the proton at the benzylic proton led to undesired side reactions upon warming of the mixture, including elimination and rearrangement of the amino *gem*-diiodide intermediate. This led to lower isolated yields for 4-trifluoromethyl substituted *cis*-iodoaziridine **11l** and also for 3-pyridyl heteroaromatic substitution in product **11m**.

2.1.5: Highly EWG, EDG & Alkyl Substitution Under Standard Conditions.

Lower yields were observed with highly electron withdrawing aromatic groups under the standard reaction conditions. For the 4-nitrophenyl substituted *N*-Boc imine- HSO_2Tol adduct **9p** (Scheme 21),ⁱⁱ amination **14** was isolated in 10% yield. This can be attributed to the nitro group acting as a competing electrophile for the carbenoid, ultimately leading to decomposition.

Scheme 21: Product distribution with 4-nitrophenyl substituted *N*-Boc imine- HSO_2Tol adduct **9p**.



In spite of this increased competition, desired addition of diiodomethyl lithium to the imine was observed, with 2% of *cis*-iodoaziridine **11p** and 11% of vinyl iodide **12p** also isolated. Decomposition of the carbenoid and competing reactivity was also evident with 2-pyridyl imine- HSO_2Tol adduct **9n**, with poor recovery and significant 2-pyridinecarboxaldehyde observed in the crude ^1H NMR spectrum. Submission of a 4-cyano substituted *N*-Boc imine- HSO_2Tol adduct under the standard reaction conditions led to decomposition, with only 4-cyanobenzaldehyde observed in the ^1H NMR spectrum of the crude product.

Several attempts were made at isolating the 4-methoxyphenyl *cis*-*N*-Boc iodoaziridine **11k** (arising from the addition of LiCH_2I to *N*-Boc imine- HSO_2Tol adduct **9k**), which was successfully formed under the standard reaction conditions (as observed via crude ^1H NMR spectra). A ^1H NMR spectroscopy sampling study again indicated rapid formation of the amino *gem*-diiodide intermediate at -78°C (stable after 30 min of reaction sampling, aliquot taken every 10 min). Warming of the reaction mixture induced full cyclisation of this intermediate exclusively to the corresponding *cis*-*N*-Boc iodoaziridine, with the iodoaziridine showing signs of decomposition under the reaction conditions after 20 min at 30°C . Initial attempts at purification via silica gel chromatography led to decomposition to 4-methoxybenzaldehyde. The stability of the crude reaction mixture to slurries of various stationary phases (including a control containing 10% EtOAc /hexane) was therefore examined to find an alternative stationary phase for purification (Table 3). The sensitivity of the crude reaction mixture to purification was illustrated, with the control experiment causing decomposition over 30 minutes stirring at rt (Table 3, entry 1),

ii) 4-nitrophenyl substituted *N*-Boc imine- HSO_2Tol adduct **9p**, synthesised by D. T. Sbircea.

presumably due to light induced homolytic cleavage of the weak C-I bond. As predicted from prior purification efforts, decomposition occurred on silica gel (entry 2). However, other stationary phases examined (entries 3-6) conferred stability to iodoaziridine **11k** as determined by re-analysis of the crude reaction mixture via ^1H NMR spectroscopy. From this stability study, neutral alumina was chosen as a suitable stationary phase for the purification of the crude reaction mixture.

Table 3: Stationary phase screen with crude 4-methoxyphenyl *cis*-*N*-Boc iodoaziridine **11k** – ^1H NMR spectroscopy study.

entry ^a	stationary phase	observation via ^1H NMR
1	control ^b	decomposition
2	silica gel	decomposition
3	silica gel + 1% Et ₃ N	iodoaziridine stable
4	florisil	iodoaziridine stable
5	neutral alumina	iodoaziridine stable
6	basic alumina	iodoaziridine stable

^a Crude **11k** submitted to slurries containing relevant stationary phase in 10% EtOAc/hexane. ^b Sample of crude **11k** stirred in 10% EtOAc/hexane.

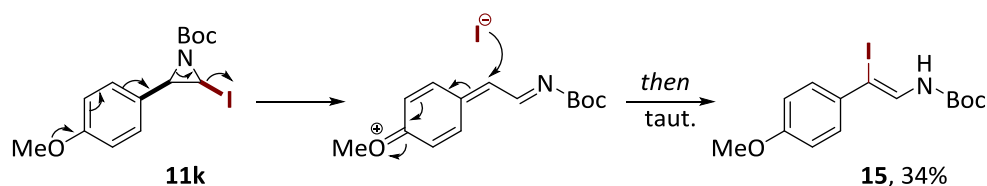
Initially, purification via column chromatography on neutral alumina resulted in co-elution of diiodomethane with iodoaziridine **11k** (Table 4, entry 1).

Table 4: Attempted purification of 4-methoxyphenyl *cis*-*N*-Boc iodoaziridine **11k**.

entry	stationary phase / conditions	eluant	outcome (^1H NMR analysis)
1	neutral alumina	10% EtOAc/hexane	co-elution of CH ₂ I ₂ and 11k
2	neutral alumina	0-5% EtOAc/hexane	15 only
3	neutral alumina	0-10% EtOAc/hexane	15 only (34% isolated yield)
4	basic alumina	10% EtOAc/hexane	co-elution of CH ₂ I ₂ and 11k
5	pad neutral alumina <i>then</i> reduced pressure to remove CH ₂ I ₂	10% EtOAc/hexane	decomposition

The undesired rearrangement of **11k** to vinyl iodide **15** was also evident which was believed to be occurring via aziridine ring opening and elimination of iodide, aided by the electron rich aromatic system (Figure 10). Re-combination of iodide and tautomerisation affords vinyl iodide **15**.

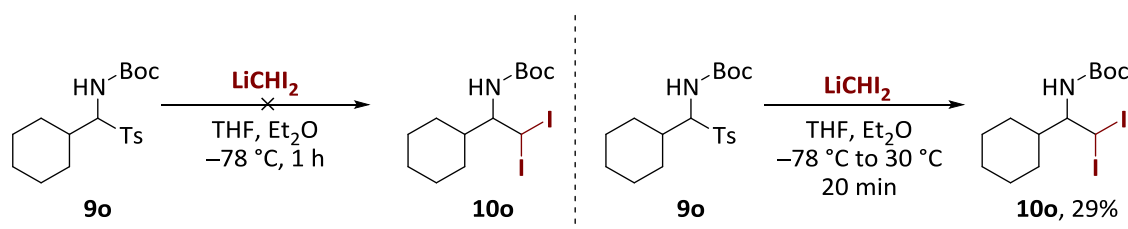
Figure 10: Undesired rearrangement of iodoaziridine **11k** to vinyl iodide **15** upon purification.



The use of a less polar eluant system in order to improve separation from diiodomethane, caused a significant increase in the degree of rearrangement and possibly further decomposition (entries 2-3), leading to the isolation of vinyl iodide **15** in 34% yield. Changing stationary phase in order to change the potential interactions of the silicate with the substrate had no beneficial effect (**Table 4**, entry 4). Finally, the removal of HMDS followed by diiodomethane was considered (entry 5). Passing the crude reaction mixture through a pad of neutral alumina to remove excess HMDS was shown to be successful via ^1H NMR spectroscopy. However, removal of diiodomethane under reduced pressure caused instant degradation, indicated by an instant darkening of the crude iodoaziridine mixture. Although the addition of LiCHI_2 to **9k** was shown to be a success, the resulting purification and isolation of *cis*-iodoaziridine **11k** could not be established under a variety of methods due to either undesired rearrangement or decomposition.

Previous work within the Bull Group had established that the addition of LiCHI_2 to Cy imine- HSO_2Tol adduct **9o** at -78°C did not lead to successful formation of the desired amino *gem*-diiodide.ⁱⁱⁱ However, submission of **9o** to the one-pot iodoaziridination protocol did not yield the iodoaziridine as predicted, but the corresponding diiodide **10o** cleanly in a 29% yield (**Scheme 22**).

Scheme 22: Varying reaction conditions to access alkyl substituted diiodide **10o**.



Although the Cy *N*-Boc imine can be considered more electrophilic,^{iv} the low yield for diiodide could be attributed to competing α -deprotonation by LiCHI_2 over desired nucleophilic addition. As the carbenoid addition is known to occur at above -78°C (due to previous work at -78°C leading to no

iii) Crude product mixture contained multiple products by TLC and ^1H NMR spectroscopy, of which none were assigned to the corresponding amino *gem*-diiodide.

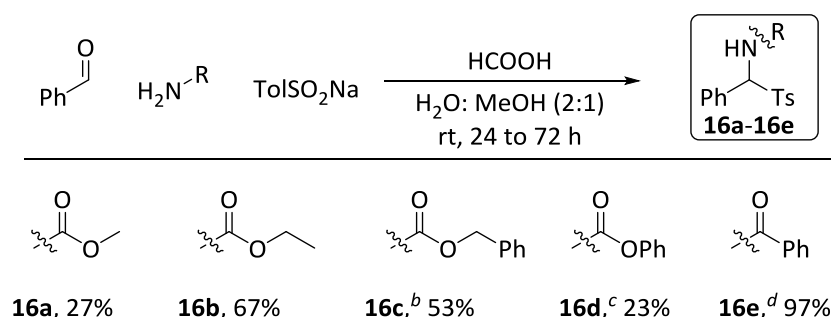
iv) Relative electrophilicity of alkyl and aryl *N*-Boc imines estimated via ^{13}C NMR chemical shift for C=N carbon. *e.g.* imine derived from **9o**, δ 178.2 ppm (C=N); imine derived from **9a**, δ 169.6 ppm (C=N). See Wulff (*ref.* 205).

desired product observed by ^1H NMR),ⁱⁱⁱ degradation of the carbenoid prior to addition to the imine could potentially account for loss of material, with the rest of the imine being hydrolysed upon workup.

2.1.6: Variation of *N*-Protecting Group

Variation of *N*-protecting group was carried out in order to probe the effect of both sterics and electronics on the diastereoselectivity and overall success of the iodoaziridination protocol. A range of suitable imine- HSO_2Tol adducts were prepared, varying the size of carbamate and also including the use of an amide to probe electronic effects (**Scheme 23**).

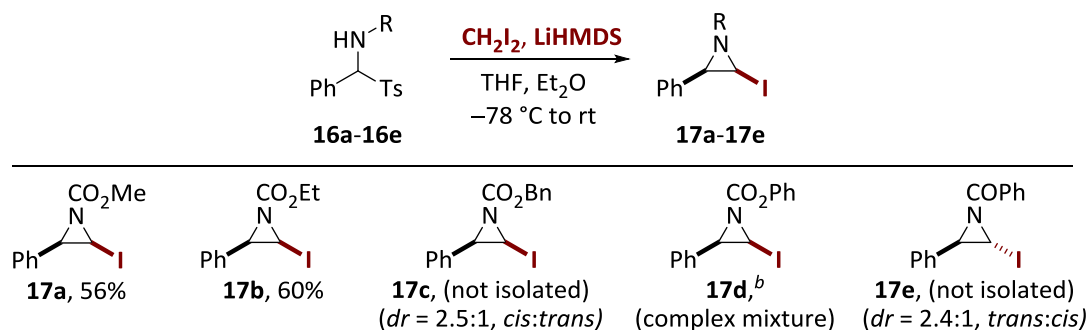
Scheme 23: Synthesis of varying *N*-protected imine- HSO_2Tol adducts.^a



^a Reaction conditions: aldehyde (1.5 equiv), NH_2R (1.0 equiv), *p*-toluenesulfonate (2.0 equiv), $\text{H}_2\text{O}:\text{MeOH}$ (2:1), rt, 24 h to 72 h. ^b Synthesised by D-T. Sbircea. ^c Synthesised by N. Aristidou. ^d Synthesised by T. A. Taylor, accessed via use of TMSCl/MeCN instead of $\text{HCOOH}/\text{H}_2\text{O}/\text{MeOH}$.

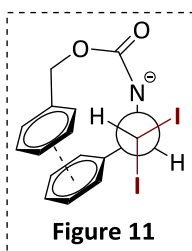
The effect of varying the carbamate *N*-protecting group effect on the yield and diastereoselectivity of the reaction was investigated using the following conditions: 1.0 equiv imine- HSO_2Tol adduct, 2.4 equiv CH_2I_2 , 2.6 equiv LiHMDS , $\text{THF}/\text{Et}_2\text{O}$, -78°C to rt (**Scheme 24**).

Scheme 24: Variation of *N*-protecting group in iodoaziridination protocol.^a



^a Reaction conditions: imine- HSO_2Tol adduct (0.60 mmol), LiHMDS (1.56 mmol, 1.0 M in THF), CH_2I_2 (1.80 mmol), $\text{THF}:\text{Et}_2\text{O}$ (0.15 M at deprotonation), -78°C to rt. All examples $>95:5$ *cis:trans*, only the *cis*-diastereoisomer could be observed by ^1H NMR unless stated in parenthesis. ^b Reaction carried out by M. Schlegel.

Variation of carbamate protecting group from CO₂tBu to CO₂Me and CO₂Et, resulted in the successful formation of iodoaziridines **17a** and **17b**, exclusively as their *cis*-diastereoisomers in good yields. The



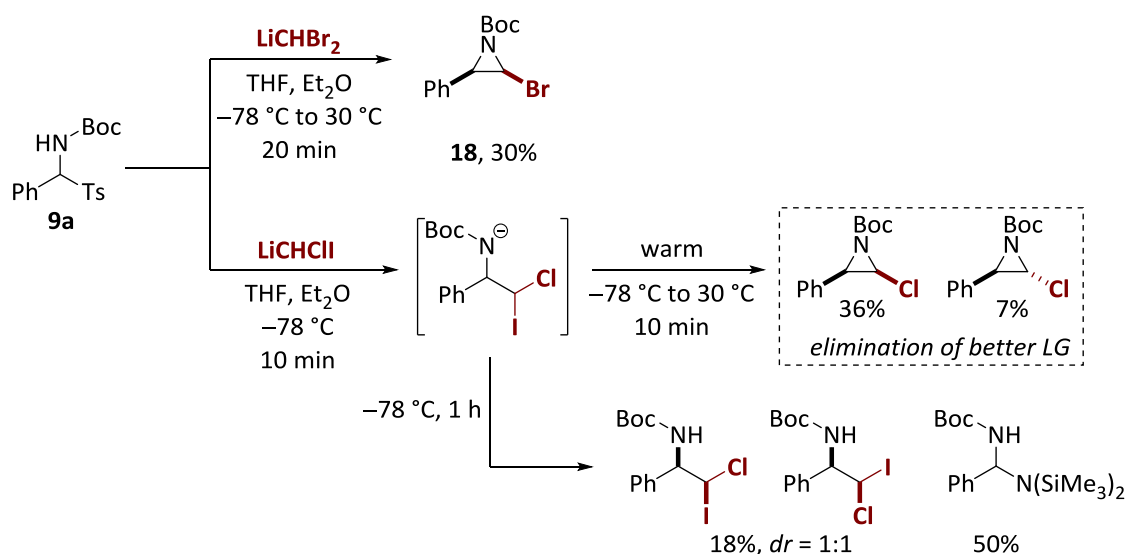
cis-diastereochemistry and the aziridine products were assigned by characteristic ³J_{HH} coupling constants and doublets in the crude ¹H NMR spectra for both **17a** and **17b** (CHI and CHPh, *J* = 5.4 Hz). Rapid warming from –78 °C to ambient temperatures was required to minimise the formation of unwanted side products and to ensure full cyclisation of the amino *gem*-diiodide intermediate. However, the benzyl carbamate protected imine–HSO₂Tol adduct **16c** afforded a complicated

mixture of products under the reaction conditions. Elimination to the corresponding vinyl iodide, after the initial addition of diiodomethyl lithium to **16c** was the major product observed by ¹H NMR spectroscopy. Benzyl carbamate protected iodoaziridine **17c** was observed by ¹H NMR spectroscopy in the crude reaction mixture, although this was as a mixture of diastereoisomers (*cis:trans*, 2.5:1) and it proved difficult to cleanly isolate with the mixture of diastereoisomers co-eluting with the vinyl iodide. A possible explanation for this erosion of stereocontrol is that potential π-π stacking interactions between the Cbz protecting group and the Ph group could lower the energy of the transition state leading to the minor isomer (**Figure 11**). Employing phenyl carbamate **16d** under the optimised reaction conditions led to a complex mixture of products observed in the crude ¹H NMR mixture, with no resolution achieved after column chromatography. The complex mixture obtained could be attributed to attack of LiCHl₂ at the carbonyl, leading to elimination of phenoxide. Reaction with amide **16e** also yielded a mixture of *trans*- and *cis*-iodoaziridine (*trans:cis*, 2.4:1), with *trans*-iodoaziridine **17e** now the major product. This was also observed in the crude ¹H NMR spectrum, but again isolation proved problematic, with decomposition observed on a variety of stationary phases and the compound not cleanly isolated.

2.1.7: Other Carbenoid Systems

We were keen to investigate the possibility of using the standard reaction conditions to investigate the reactivity of other dihalocarbenoid systems. Dibromomethyl lithium (LiCHBr₂), generated via the deprotonation of dibromomethane with LDA, has previously been utilised by Concellón in the synthesis of bromocyclopropanes.¹⁰¹ The 1,4-addition of LiCHBr₂ to enantiomerically pure chromium alkenyl[(((–)-8-phenylmenthyl)oxy)]carbene complexes, followed by cyclisation of the dibromide intermediate afforded chiral bromocyclopropanes with high diastereoselectivities and in excellent yields. In an analogous fashion, we were keen to explore the reactivity of LiCHBr₂ under the standard reaction conditions. Employing LiCHBr₂ in place of LiCHl₂ and reaction with imine–HSO₂Tol adduct **9a**, afforded *cis*-*N*-Boc bromoaziridine **18** in an unoptimised yield of 30% (**Scheme 25**).

Scheme 25: Use of different dihalocarbenoids under the optimised reaction conditions.



The *cis*-diastereochemistry of the resulting aziridine ring protons ($J = 5.1$ Hz) is in agreement with that reported by Ziegler and co-workers for *cis*-*N*-Boc bromoaziridines.⁷⁹⁻⁸¹ Mixed dihalocarbenoid systems of the form LiCHXY ($X \neq Y$) were also investigated, posing interesting questions about the reactivity of the proposed intermediate and the observed diastereoselectivity in the reaction. Chloriodomethane was chosen as a suitable carbenoid precursor, due to cost and availability. Due to the unsymmetrical nature of the carbenoid, the initial nucleophilic addition of LiCHClI could now become diastereodetermining, rather than the intramolecular cyclisation. Preference for *cis*-conformation in the aziridine products would give a mixture of *cis*-chloro and *cis*-iodoaziridines, whereas preference for the elimination of the better leaving group from the dihalogenated intermediate would give exclusively chloroaziridines (*cis*- and *trans*-substituted). Deprotonation using LiHMDS under the standard reaction conditions and reaction with imine-HSO₂Tol adduct **9a** gave exclusively a mixture of chloroaziridines. Both *cis*- and *trans*-substituted chloroaziridines were observed, indicating the preference for the system to eliminate the better leaving group. Quenching the reaction at -78 °C prior to warming, the diastereoselectivity of the addition of LiCHClI to **9a** could be assessed. The two diastereoisomers resulting from carbenoid addition were isolated as a 1:1 mixture in poor yield at -78 °C. Interestingly however, 50% of the corresponding amination resulting from direct addition of the base was observed. This potentially indicates the reduced nucleophilicity of LiCHClI in comparison to LiCH₂I or incomplete deprotonation of CH₂ClI by LiHMDS. Considering the 1:1 *dr* observed at -78 °C, and the higher yield for the *cis*-chloroaziridine obtained, this either suggests that the cyclisation to the *cis*-product remains a lower energy pathway or the *trans*-product decomposes more readily.

2.1.8: Conclusions

Addition of LiCHI_2 , formed via the deprotonation of diiodomethane with LiHMDS, to phenyl *N*-Boc imine- HSO_2Tol adduct **9a** at $-78\text{ }^\circ\text{C}$ has been shown to exclusively afford the corresponding amino *gem*-diiodide **10a**. Reaction with Cs_2CO_3 in DMF induced a highly diastereoselective intramolecular cyclisation to *N*-Boc iodoaziridine **11a**, exclusively as the *cis*-diastereoisomer. Stability studies have highlighted that the *cis*-*N*-Boc iodoaziridine is both structurally and configurationally stable in solution. The observed diastereoselectivity has been attributed to subtle steric interactions in the cyclisation transition state between the non-displaced iodide and *N*-protecting group, leading to the formation of exclusively the *cis*-diastereoisomer. Subsequent optimisation of the reaction protocol and a mechanistic study revealed a desirable one-pot addition/cyclisation protocol via rapid warming of the reaction mixture to $30\text{ }^\circ\text{C}$, after addition of LiCHI_2 at low temperatures. The methodology was successfully extended to a range of aryl substituted *N*-Boc imine- HSO_2Tol adducts (**9a-9n**), affording the corresponding iodoaziridines in good to excellent yields (**11a-11n**), with high levels of diastereocontrol in the cyclisation step. Cyclohexyl substituted imine- HSO_2Tol adduct **9o** afforded the corresponding amino *gem*-diiodide **10o** under the standard reaction conditions. Variation of *N*-carbamate protecting group and use of LiCHBr_2 was also shown to be effective.

2.2.1: *N*-Ts Iodoaziridines

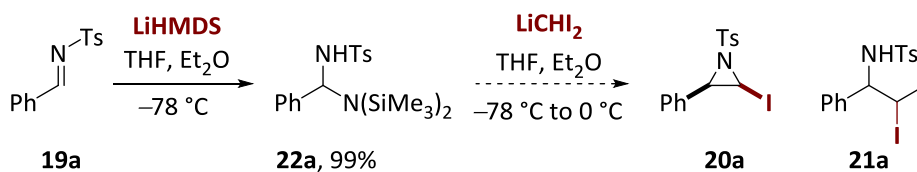
After the successful isolation of a range of aryl substituted *cis*-*N*-Boc iodoaziridines, alternative protecting groups were considered to extend the reaction scope to alkyl substituted iodoaziridines. A toluenesulfonyl (Ts) group was chosen to be suitable due to it being electron withdrawing in nature,¹⁰² stabilizing the amino *gem*-diiodide intermediate formed. In this section, the encouraging early optimisation results will be developed (see **Section 1.9.2**, page 32), by defining a set of optimised reaction conditions and expanding the reaction scope. Stereoselective reactions between LiCHI_2 and optically pure *N*-sulfinyl imines will also be explored allowing access to enantioenriched iodoaziridines.

Concise accounts detailing this work can be found in *The Journal of Organic Chemistry*,¹⁰³ and *The Journal of Visualized Experiments*.¹⁰⁴

2.2.2: Reaction Optimisation

Following earlier studies, the 1,2-addition of LiCHI_2 to Ph *N*-Ts imine at -78°C proved productive, with three major products observed by ^1H NMR: *cis*-iodoaziridine **20a**; amino *gem*-diiodide **21a** and aminal **22a** resulting from competing direct addition of the base to the imine. In contrast to the analogous *N*-Boc substrate, diastereoselective cyclisation was occurring at -78°C and did not require warming of the reaction mixture to induce cyclisation. The undesired formation of aminal **22a** under the reaction conditions was of immediate concern, as this implied that CH_2I_2 was not being fully deprotonated under the reaction conditions. This was later confirmed by deuteration studies,^v whereby after a standard deprotonation protocol, the mixture was quenched with d_4 -MeOD indicating only 30% D incorporation. As a result, LiHMDS remained in solution and reacted with imine **19a** before diiodomethyl lithium. It was shown that this reaction affording aminal **22a** was irreversible under the reaction conditions (**Scheme 26**).

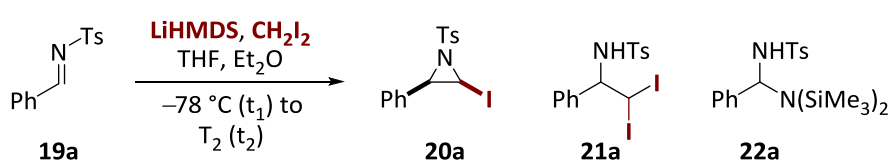
Scheme 26: Formation of aminal **22a** shown to be irreversible under reaction conditions.



v) Deuteration studies carried out by D. P. Affron.

Treatment of imine **19a** with LiHMDS at -78°C afforded aminor **22a** in quantitative yield. However submission of aminor **22a** to the reaction conditions only returned starting material (**Scheme 26**). During the optimisation, it therefore became imperative to minimise the formation of the undesired aminor and aim to optimise for the combined yield of iodoaziridine **20a** and diiodide **21a**. Due to the irreversible nature of this reaction, variation of the reaction time at -78°C had no major impact on the yield of aminor **22a**. Longer deprotonation times were also evaluated, but this led to a decreased combined yield for **20a** + **21a**, presumably due to degradation of the carbenoid under the prolonged reaction conditions.

Table 4: Optimisation of the reaction protocol.



entry ^a	LiHMDS (equiv)	CH_2I_2 (equiv)	conc. [M] ^b	t_1 (min)	T_2 ($^{\circ}\text{C}$)	t_2 (min)	additive ^c	yield ^d		
								20a	21a	22a
1	2.2	2.5	0.06	60				20	17	15
2	2.5	10	0.06	60				16	55	15
3	2.2	2.5	0.06	60			DMPU	19	55	8
4	2.2	2.5	0.06	60			HMPA	3	8	12
5	2.2	2.5	0.06	60			TMEDA	48	1	19
6	2.0	2.3	0.15	60				31	8	8
7	3.0	3.4	0.15	60				55	15	5
8	4.0	4.0	0.15	60				63	19	7
9	3.0	3.4	0.16	30	0	15		64	0	14
10	3.0	3.0	0.16	– ^e	0	15		81 (75) ^f	0	14

^a Reaction conditions: imine **19a** (0.50 mmol), CH_2I_2 , LiHMDS, THF: Et_2O . Entries 1–5 carried out by J. A. Bull. ^b Concentration of LiCH_2I prior to imine addition. ^c 1.0 equiv of additive used. ^d Yield determined by ^1H NMR spectroscopy with reference to an internal standard (1,3,5-trimethoxybenzene). ^e Reaction warmed to 0°C instantly after addition of imine. ^f Isolated yield in parenthesis.

Optimisation began by evaluating similar conditions to those successfully utilised for *N*-Boc imines, including solvent ratios, concentration and reaction time (**Table 4**).^{vi} Employing the conditions developed for *N*-Boc imines only afforded a unsatisfactory combined yield for **20a** + **21a**, although

vi) Initial reaction optimisation carried out by J. A. Bull.

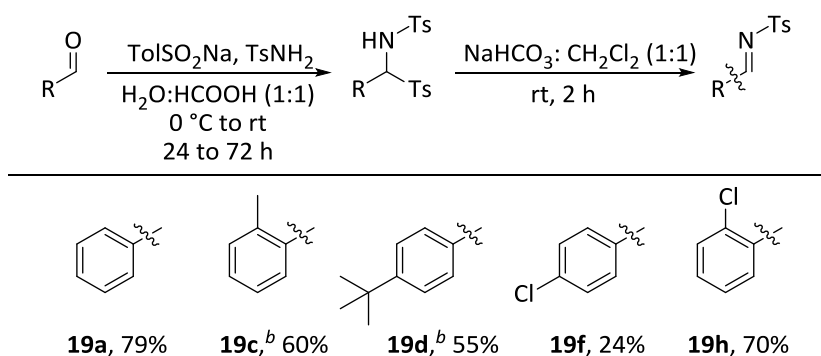
increasing the excess of diiodomethane to 10 equiv led to a much improved yield (entries 1-2). It however became important to minimise the excess of diiodomethane due to the toxic nature of the reagent and to ease purification of the reaction mixture. A variety of Lewis basic additives were therefore screened (entries 3-5). DMPU was found to be the best additive, affording the highest combined yield for **20a** + **21a**.^{vii} HMPA was found to be detrimental to the reaction, whilst TMEDA interestingly promoted cyclisation of amino *gem*-diiodide **21a** to iodoaziridine **20a** under the reaction conditions. After further exploration using DMPU as an additive, no significant increase in the yield for **20a** + **21a** was achieved. Both the equivalents of CH₂I₂ and LiHMDS used were found to be crucial in product distribution (entries 6-8). Increasing the equivalents of both CH₂I₂ and LiHMDS (up to 4 equiv) returned the best yield for **20a** + **21a** due to the increased concentration of LiCHI₂ in solution. After extensive experimentation, it became apparent that the addition of LiCHI₂ to the imine was occurring rapidly under the reaction conditions and prolonged reaction times were causing degradation of the desired product. Continuing with 3.0 equiv of LiHMDS, in a similar fashion to the *N*-Boc iodoaziridines, full cyclisation from amino *gem*-diiodide **21a** to iodoaziridine **20a** could be achieved by rapid warming of the reaction mixture. This was found to be most effective when warming the reaction mixture from -78 °C to 0 °C which prevented unwanted degradation of the iodoaziridine at elevated temperatures under the reaction conditions (entry 9). Finally, conditions were developed to maximise the yield of iodoaziridine **20a** by immediately warming the reaction mixture to 0 °C after the addition of the imine (entry 10). Other ratios of THF/Et₂O were explored at this stage, including those use previously for *N*-Boc iodoaziridines, however a ratio of THF/Et₂O = 2.5:1 remained optimal. This resulted in an 81% yield as measured by ¹H NMR spectroscopy, corresponding to a 75% isolated yield of iodoaziridine **20a**. These conditions were then used as the standard conditions to explore the scope of the iodoaziridination protocol.

2.2.3: Reaction Scope

The scope of the reaction was firstly explored by preparing a range of aryl substituted *N*-Ts imines (**Scheme 27**). These imines were prepared mostly according to the method of Chemla and co-workers,¹⁰⁵ via their corresponding imine-HSO₂Tol adducts.

vii) Study on the effect of reaction additives carried out by J. A. Bull.

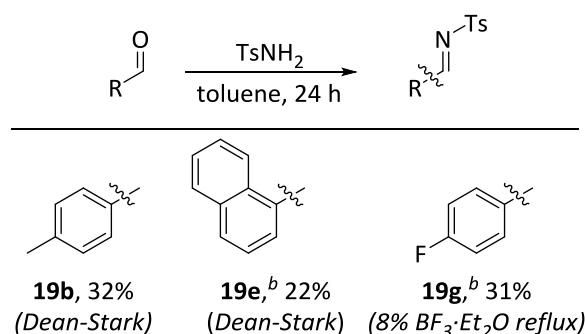
Scheme 27: Preparation of *N*-Ts imines via method of Chemla and co-workers.^a



^a Reaction conditions: aldehyde (1.5 equiv), TsNH₂ (1.0 equiv), *p*-toluenesulfonate (1.2 equiv), H₂O:HCOOH (1:1), rt, 24 h to 72 h, *then* NaHCO₃:CH₂Cl₂, rt, 2 h. ^b Synthesised by D. P. Affron.

More challenging aromatic substituted *N*-Ts imines were prepared via a direct condensation between the relevant aldehyde and *p*-toluenesulfonamide using either Dean-Stark methodology or through Lewis acid catalysis (**Scheme 28**).

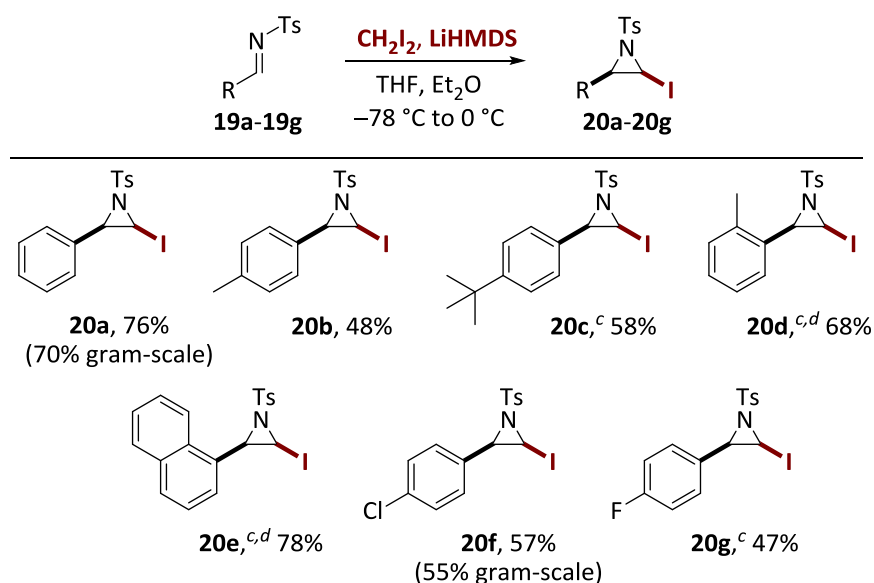
Scheme 28: Condensation between *p*-toluenesulfonamide and aryl substituted aldehydes.^a



^a Reaction conditions: aldehyde (1.2 equiv), TsNH₂ (1.0 equiv), toluene, reflux, 24 h. ^b Synthesised by D. P. Affron.

The aryl substituted imines were then subjected to the standard reaction conditions, returning good to excellent yields of exclusively the corresponding *cis*-iodoaziridines, with purification of the iodoaziridines carried out on deactivated basic alumina (activity IV) (*vide infra*) (**Scheme 29**). An alternative procedure was also developed to account for *ortho*-substitution, whereby the reaction was warmed to rt instead of 0 °C (Method B). This was to ensure full cyclisation from the amino *gem*-diiodide intermediate, due to reduced rates of cyclisation at 0 °C.

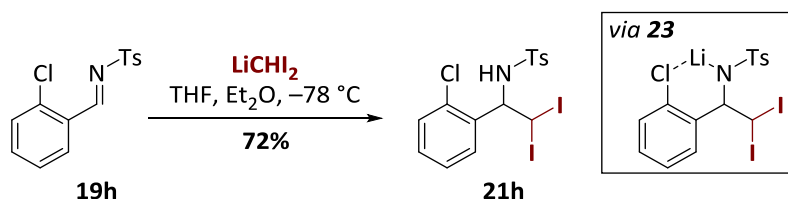
Scheme 29: Scope for iodoaziridination protocol for aryl substituted *N*-Ts imines.^{a,b}



^a Reaction conditions: *Method A*: imine (0.50 mmol), *n*-BuLi (1.50 mmol), HMDS (1.50 mmol), CH_2I_2 (1.70 mmol), THF: Et_2O (0.16 M at deprotonation), $-78\text{ }^\circ\text{C}$ to $0\text{ }^\circ\text{C}$. ^b All examples >95:5 *cis:trans*, only the *cis*-diastereoisomer could be observed by ^1H NMR spectroscopy. ^c Examples synthesised by D. P. Affron. ^d *Method B*: identical to *Method A* but reaction warmed to rt for 20 min after addition of imine.

The protocol was successfully scaled up to 3 mmol (gram-scale), to yield Ph substituted *N*-Ts iodoaziridine **20a** in 70% yield. Electron donating groups were tolerated under the reaction conditions, affording iodoaziridines **20b-20c**, although in reduced yields. Basic alumina (activity IV) was required for the successful isolation of these iodoaziridines due to rearrangement chemistry and degradation dominating their reactivity on silica gel (for discussion *vide infra*). *ortho*-Substitution required the use of a modified reaction procedure (*Method B*, warming to rt instead of $0\text{ }^\circ\text{C}$) to ensure full cyclisation from the diiodide intermediate. Under the standard reaction conditions *ortho*-tolyl imine **19d** gave a 9:5 mixture of iodoaziridine **20d**: amino *gem*-diiodide **21d**. This was dramatically improved by employing *Method B* (>19:1 iodoaziridine: amino *gem*-diiodide), allowing the isolation of iodoaziridine **20d** in good yield and high purity. *Method B* was also successfully employed to afford 1-naphthyl substituted iodoaziridine **20e** in excellent yield. 4-Chlorophenyl and 4-fluorophenyl substituted imines were both tolerated under the reaction conditions to afford the halogen substituted aromatic iodoaziridines **20f-20g**, with iodoaziridine **20f** also accessed on a 3 mmol scale in good yield. Under the standard reaction conditions, *ortho*-chloro substituted imine **19h** only yielded the corresponding amino *gem*-diiodide **21h** (**Scheme 30**). This was eventually subjected to the reaction conditions at $-78\text{ }^\circ\text{C}$ to yield diiodide **21h** in 72% yield. The lack of cyclisation is attributed to potential coordination of the chlorine lone pairs with the lithiated intermediate **23**.

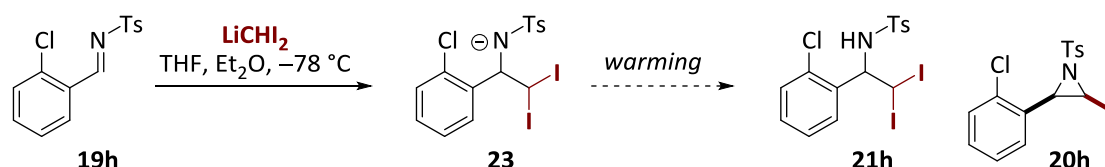
Scheme 30: Minimal cyclisation observed with *ortho*-chlorophenyl imine **19h** under standard conditions.^a



^a Reaction conditions: *Method A*: imine (0.50 mmol), *n*-BuLi (1.50 mmol), HMDS (1.50 mmol), CH_2I_2 (1.70 mmol), THF: Et_2O (0.16 M at deprotonation), -78°C , 10 min.

In comparison with the *N*-Boc example **11f**, cyclisation from diiodide **21h** to iodoaziridine **20h** could also be achieved upon increased reaction time at the cyclisation temperature. Iodoaziridine **20h** was evident upon analysis of characteristic ^1H NMR aziridine signals: *cis*-iodoaziridine **20h**, characterised by doublets at 4.89 ppm (CHI) and 4.06 ppm (CHAR), $^3J_{\text{HH}} = 6.2$ Hz. A reaction sampling study (Table 5) indicated that although this diastereoselective cyclisation could be achieved, the rate of cyclisation was reduced compared to the *N*-Boc example. Warming the reaction mixture by 10°C and taking reaction aliquots every 10 minutes yielded more of the desired *cis*-iodoaziridine, but overall led to a loss in recovery, presumably due to degradation of the diiodide/iodoaziridine under the more forcing cyclisation conditions. Cyclisation conditions previously developed for *N*-Boc iodoaziridines (Cs_2CO_3 , DMF), also led to decomposition of amino *gem*-diiodide **21h**.

Table 5: ^1H NMR spectroscopy cyclisation study for *ortho*-chlorophenyl imine **19h**.

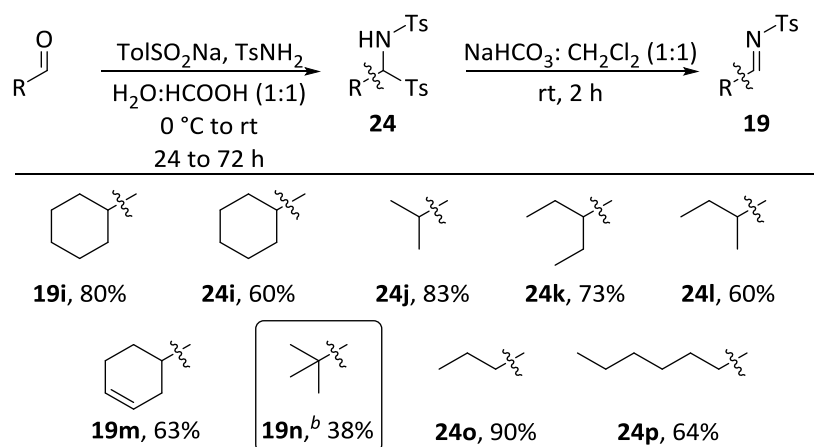


entry	temperature ($^\circ\text{C}$)	total reaction time (min)	yield ^a	
			21h	20h
1	-78	10	95	–
2	0	20	86	8
3	20	30	72	14
4	30	40	45	36
5	40	50	11	46
6	50	60	2	19

^a Yield determined by ^1H NMR spectroscopy with reference to an internal standard (1,3,5-trimethoxybenzene) present in reaction mixture.

Alkyl substitution was evaluated next, with a range of primary and secondary alkyl *N*-Ts imines prepared according to the method of Chemla and co-workers (**Scheme 31**).¹⁰⁵ Many of the alkyl imines were retained as their imine–HSO₂Tol adducts due to their increased stability to hydrolysis and concerns around enamine formation. *tert*-Butyl substituted imine **19n** was prepared via a Lewis acid catalysed direct condensation between pivaldehyde and *p*-toluenesulfonamide, due to incompatibility with the method described by Chemla.

Scheme 31: Preparation of alkyl *N*-Ts imines and alkyl *N*-Ts imine–HSO₂Tol adducts via method of Chemla and co-workers.^a

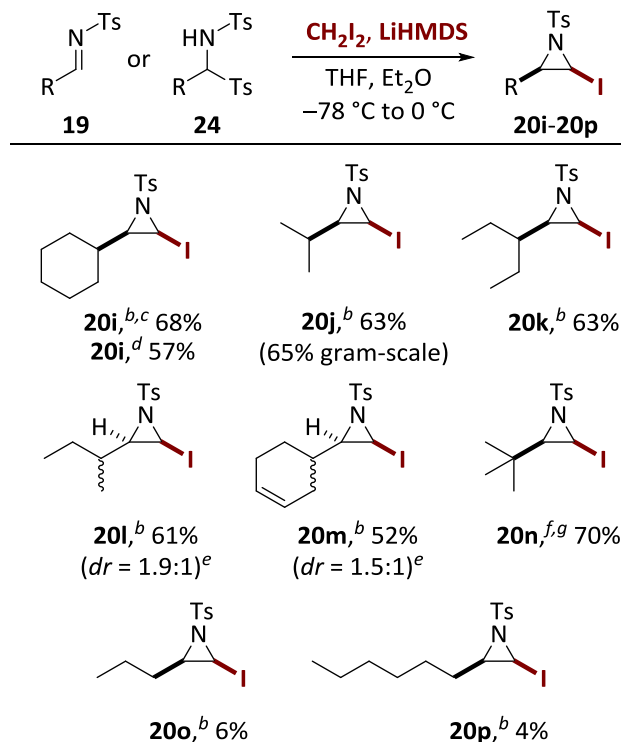


^a Reaction conditions: aldehyde (1.5 equiv), TsNH₂ (1.0 equiv), *p*-toluenesulfonate (1.2 equiv), H₂O:HCOOH (1:1), rt, 24 h to 72 h, then NaHCO₃:CH₂Cl₂, rt, 2 h. ^b Reaction conditions: pivaldehyde (1.05 equiv), TsNH₂ (1.0 equiv), BF₃·Et₂O (8 mol%), toluene, reflux.

A third protocol was developed for the use of imine–HSO₂Tol adducts, whereby an extra equivalent of both diiodomethane and LiHMDS was employed in order to generate the relevant imine *in situ* via base assisted elimination of HSO₂Tol (Method C). In the previous work with *N*-Boc imines, alkyl substitution was not tolerated. However, installation of the *N*-Ts protecting group allowed access to a range of alkyl substituted *N*-Ts iodoaziridines, exclusively as their *cis*-diastereoisomers (**Scheme 32**). Cyclohexyl substituted iodoaziridine **20i** was accessed from both imine **19i** (Method A) and imine–HSO₂Tol adduct **24i** (Method C) in comparable yields. Varying branched alkyl substitution led to the generation of iodoaziridines **20j–20l** exclusively as their *cis*-diastereoisomers. Low facial selectivity was observed in iodoaziridine **20l** during the addition step, leading to a *dr* of 1.9:1, but with excellent diastereoselectivity upon cyclisation. Similarly, the imine derived from 3-cyclohexenecarboxaldehyde also delivered minor facial selectivity in the corresponding iodoaziridine **20m**, 1.5:1) in good yield. *tert*-Butyl substituted imine **19n** was submitted under the *ortho*-substituted reaction conditions (Method B), due to concerns of the *tert*-butyl group reducing the rate of cyclisation in the cyclisation transition state. However, *tert*-butyl substituted iodoaziridine

20n was accessed exclusively as its *cis*-diastereoisomer in an excellent 70% yield, despite significant steric clashes between the *tert*-butyl and iodide group in the product.

Scheme 32: Alkyl substituted *N*-Ts imines and imine- HSO_2Tol adducts under standard reaction conditions.^a



^a All examples >95:5 *cis:trans*, only the *cis*-diastereoisomer could be observed by ^1H NMR. ^b Reaction conditions: *Method A*: imine (0.50 mmol), *n*-BuLi (1.50 mmol), HMDS (1.50 mmol), CH_2I_2 (1.70 mmol), THF: Et_2O (0.16 M at deprotonation), $-78\text{ }^\circ\text{C}$ to $0\text{ }^\circ\text{C}$. ^c Example synthesised by A. D. Trowbridge. ^d *Method C*: imine- HSO_2Tol adduct (0.50 mmol), *n*-BuLi (2.00 mmol), HMDS (2.00 mmol), CH_2I_2 (2.20 mmol), THF: Et_2O (0.16 M at deprotonation), $-78\text{ }^\circ\text{C}$ to $0\text{ }^\circ\text{C}$. ^e Relative configurations not determined. ^f *Method B*: identical to *Method A* but reaction warmed to rt for 20 min after addition of imine. ^g Example synthesised by D. P. Affron.

Primary substituted *N*-Ts imine- HSO_2Tol adducts did not perform well under the reaction conditions with LiHMDS acting as a competing nucleophile. Due to the steric bulk of LiHMDS, the rate of addition into α -branched *N*-Ts imines was significantly reduced allowing the desired addition of LiCHI_2 . However, with no α -branching, LiHMDS was a far superior nucleophile to LiCHI_2 , which has previously shown to be irreversible under the reaction conditions. Employing primary substituted imine- HSO_2Tol adducts **24o-24p** returned poor yields of corresponding iodoaziridines **20o-20p**. Attempts at increasing both the equivalents of LiHMDS and CH_2I_2 (up to 10 equiv) led to no increased formation of the desired primary iodoaziridines. The undesired addition of LiHMDS over LiCHI_2 was confirmed for the case of $\text{R} = \text{H}$, whereby only the corresponding aminal was observed by ^1H NMR spectroscopy, which decomposed upon purification due to hydrolysis.

2.2.4: Stability Study Protocol

Whereas the majority of the *N*-Boc iodoaziridines were stable to silica gel chromatography, it was evident that some of the product *N*-Ts iodoaziridines were decomposing on silica gel. Although the yield for tolyl iodoaziridine **20b** closely resembled that observed by ^1H NMR spectroscopy (use of 1,3,5-trimethoxybenzene as an internal standard), the recovery of the same iodoaziridine after purification using silica gel was less than 50%. As previously described for *N*-Boc iodoaziridine **11k** (*vide supra*, Section 2.1.5, page 44), a screen of a range stationary phases was carried out, in order to assess the effect of the stationary phase on the stability of iodoaziridine **20b** and to prevent the degradation observed during a conventional silica gel column. Due to the problems encountered with recovery of *N*-Ts iodoaziridines **20b-20c** after silica gel chromatography, it was decided that a similar strategy would be employed, but with quantitative assessment of the recovery and degradation through the use of an internal standard. It was believed that this would enable a judicious choice of stationary phase for the purification of *N*-Ts iodoaziridines **20a-20p**. This was achieved by adding a known amount of internal standard (1,3,5-trimethoxybenzene) to the crude reaction mixture. The crude reaction mixture was then dissolved in CH_2Cl_2 and split up into 8 equal aliquots, one of which was processed so that a ^1H NMR yield was obtained for the reaction. The remaining aliquots were then tested against a range of stationary phases, modeling the experience of a compound during a conventional chromatographic procedure, including choice of eluant and length of the chromatographic procedure (around 30 min). The aliquots were submitted to a slurry containing the relevant stationary phase in the typical eluant system (5-10% EtOAc/hexane), including a 'control phase' whereby the reaction aliquot was tested against the choice of eluant. The slurries were then filtered under reduced pressure, washed through with CH_2Cl_2 , and the filtrate analysed by ^1H NMR spectroscopy whereby the levels of degradation were assessed by comparison to the ^1H NMR yield obtained for the crude. For one of the more challenging examples to purify, iodoaziridine **20b**, the stability study protocol enabled the identification of the most suitable stationary phase for purification and aided in the isolation of the iodoaziridine with high recovery (compared to the ^1H NMR yield) and purity (Table 6). The study also highlighted the formation of a rearranged product when submitted to slurries containing silica gel and florisil – iodo-aldehyde **25** (Table 6 and Figure 11).

Table 6: The effect of various stationary phases on the stability of iodoaziridine **20b**.

19b $\xrightarrow[\text{THF, Et}_2\text{O, } -78^\circ\text{C to } 0^\circ\text{C}]{\text{LiCHI}_2}$ **20b** **25**

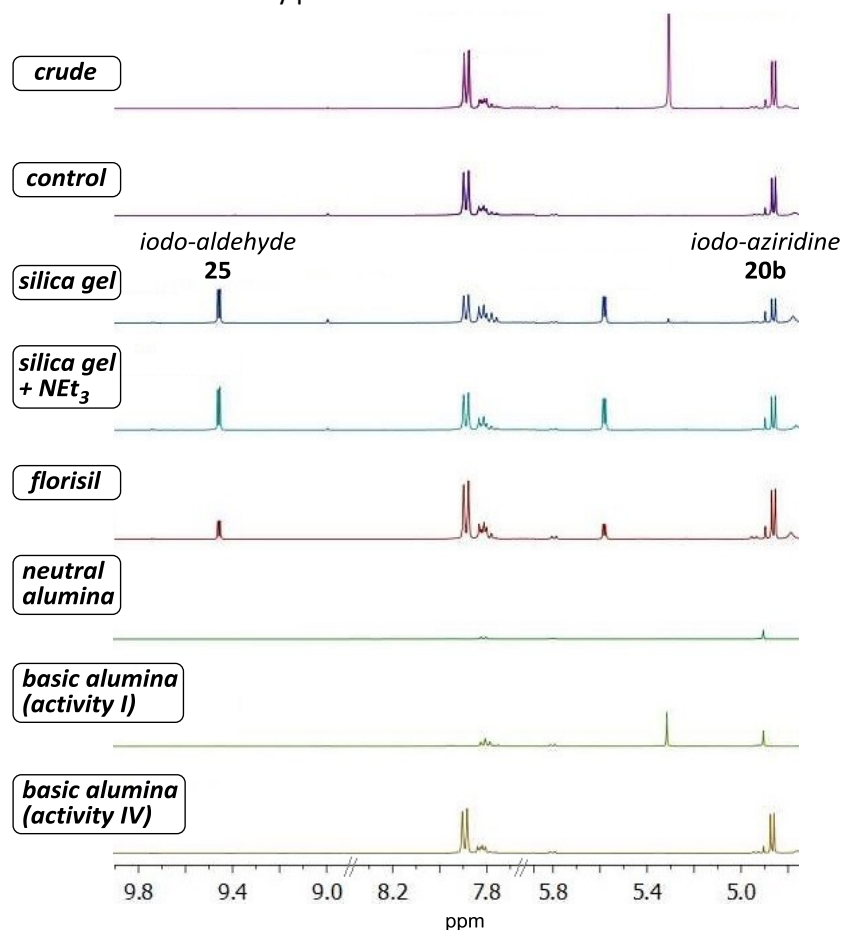
entry	stationary phase	recovery of 20b (%) ^a	yield of 25 (%) ^a
1	crude	59	0
2	control ^b	59	0
3	silica gel	25	32
4	silica gel + 1% Et ₃ N	26	30
5	florisil	41	15
6	neutral alumina	0	0
7	basic alumina (activity I) ^c	1	0
8	basic alumina (activity IV) ^d	53	0

^a Yield determined by ¹H NMR spectroscopy with reference to an internal standard (1,3,5-trimethoxybenzene). ^b Sample of crude **20b** stirred in 5% EtOAc/hexane. ^c Basic alumina (activity I) oven-dried for 24 h, and cooled under reduced pressure prior to use. ^d Basic alumina (activity IV) prepared by addition of water (10% w/v) to basic alumina (activity I).

The recovery of iodoaziridine **20b** was dramatically affected on changing stationary phase (**Table 6**). Treatment of an aliquot of crude iodoaziridine **20b** with both a slurry of bench silica (**Table 6**, entry 3) and base-doped silica gel (1% NEt₃, entry 4) caused a significant loss in recovery of the iodoaziridine product and rearrangement to aldehyde **25**. This was evident for florisil, a magnesium based silicate, with minor degradation observed to iodo-aldehyde **25**. No recovery was observed with either neutral alumina or basic alumina (activity I), with both appearing to trap iodoaziridine **20b**. The activity of alumina has shown to be dependent on the water content, with increasing amounts of water leading to a lower activity grade alumina. The degree of activity has been expressed in terms of an activity scale, described by Brockmann and co-workers.^{106,107} This is primarily due to water occupying the most energetic sites on the alumina, which in turn is not transported by the much less polar and immiscible eluant system.¹⁰⁸ This enables an overall reduced interaction between the alumina and the compound being purified. Deactivating basic alumina (activity I) to basic alumina (activity IV) by addition of water (10% w/v), the stability of iodoaziridine **20b** was greatly enhanced on the support, with the ¹H NMR yield for basic alumina (activity IV) closely resembling that of the crude mixture (53% ¹H NMR yield, *cf.* 58% crude ¹H NMR yield). Repeating the reaction with purification of the crude **20b** on deactivated basic alumina (activity IV) led to an isolated yield of 48%, and without observation of iodo-aldehyde **25** as predicted by the

stability study. Validation of this method to accurately and rapidly compare the effect of various stationary phases was ensured with the isolated yield for iodoaziridine **20b** closely resembling that predicted (48% isolated yield, cf. 53% ^1H NMR yield when using deactivated basic alumina (activity IV)).

Figure 11: Stability study – ^1H NMR cross-section highlighting degradation of iodoaziridine **20b** to iodo-aldehyde **25** on various stationary phases.



The stationary phase stability protocol was also repeated for iodoaziridine **20a** with nearly every stationary phase returning almost quantitative recovery (**Table 7**). However, both neutral alumina and basic alumina (activity I) (**Table 7**, entries 6-7) showed a loss in recovery of iodoaziridine **20a**, with the iodoaziridine also getting trapped on these stationary phases. The degradation products observed when treating iodoaziridine **20a** with silica gel and base doped silica gel (entries 3-4) were also assigned as the corresponding iodo-aldehyde. Only a small drop off in recovery was observed with basic alumina (activity IV), so therefore the rest of the examples prepared were purified using deactivated alumina due to the enhanced stability this conferred. The methodology developed during this project has been successfully applied to a range of examples, and could potentially have use across organic synthesis for determining the optimum stationary phase when a compound shows instability towards silica gel chromatography.

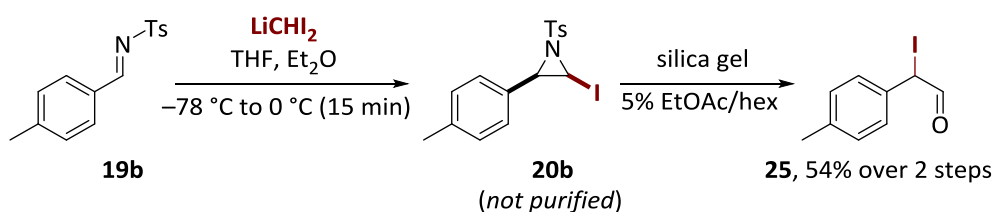
Table 7: Stationary phase stability study protocol for iodoaziridine **20a**.

entry	stationary phase	yield of 20a (%) ^a
1	crude	80
2	control ^b	80
3	silica gel	78
4	silica gel + 1% Et ₃ N	77
5	florisil	79
6	neutral alumina	4
7	basic alumina (activity I) ^c	0
8	basic alumina (activity IV) ^d	79

^a Yield determined by ¹H NMR spectroscopy with reference to an internal standard (1,3,5-trimethoxybenzene). ^b Sample of crude **20a** stirred in 5% EtOAc/hexane. ^c Basic alumina (activity I) oven-dried for 24 h, and cooled under reduced pressure prior to use. ^d Basic alumina (activity IV) prepared by addition of water (10% w/v) to basic alumina (activity I).

2.2.5: Iodoaziridine Rearrangement

As noted in the stability study protocol, it became apparent that the more electron rich aromatic substituted iodoaziridine **20b** was prone to rearrangement when treated with acidic stationary phases to give iodo-aldehyde **25**. Full conversion from iodoaziridine **20b** to iodo-aldehyde **25** was achieved by treating a crude sample of **20b** with silica gel in the air, giving **25** in 54% yield over 2 steps (**Scheme 33**). Concellón and co-workers have also reported a similar rearrangement of iodo-epoxides, forming α -iodo-aldehydes.¹⁰⁹

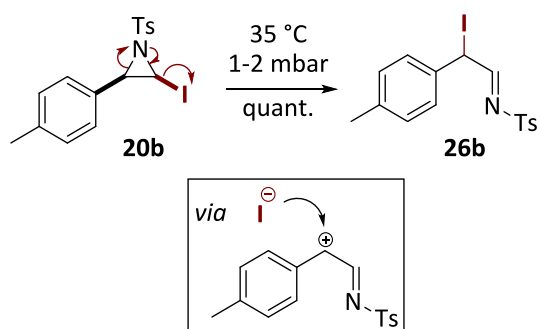
Scheme 33: Formation of iodo-aldehyde **25** via treatment of crude mixture with silica.^a

^a Reaction conditions: *Method A*: imine (0.50 mmol), *n*-BuLi (1.50 mmol), HMDS (1.50 mmol), CH_2I_2 (1.70 mmol), THF: Et_2O (0.16 M at deprotonation), -78°C to 0°C , then silica gel, EtOAc/hexane, 2 h.

Although this rearrangement to iodo-aldehyde **25** was prevented by shrewd choice of stationary phase, it became apparent that the neat iodoaziridine itself was also subject to quantitative rearrangement with mild heating under reduced pressure to iodo-imine **26b**. Heating under reduced pressure was shown to be necessary to afford clean rearrangement, with the presence of air causing undesired degradation of either the iodoaziridine or iodo-imine product. Mechanistically, this is

proposed to occur via a unimolecular ring opening, eliminating iodide, forming a benzylic cation, which is subsequently trapped with iodide (**Scheme 34**). Similar rearrangements have been highlighted in the literature by Yudin and co-workers, successfully demonstrating the rearrangement of substituted bromoaziridines to α -bromohydrazone.⁸² This rearrangement was also observed with *tert*-butylphenyl substituted iodoaziridine **20c**, even at room temperature. However due to the rate of rearrangement and instability of the imine product, isolation proved problematic.

Scheme 34: Rearrangement of iodoaziridine **20b** to iodo-imine **26b** under reduced pressure.

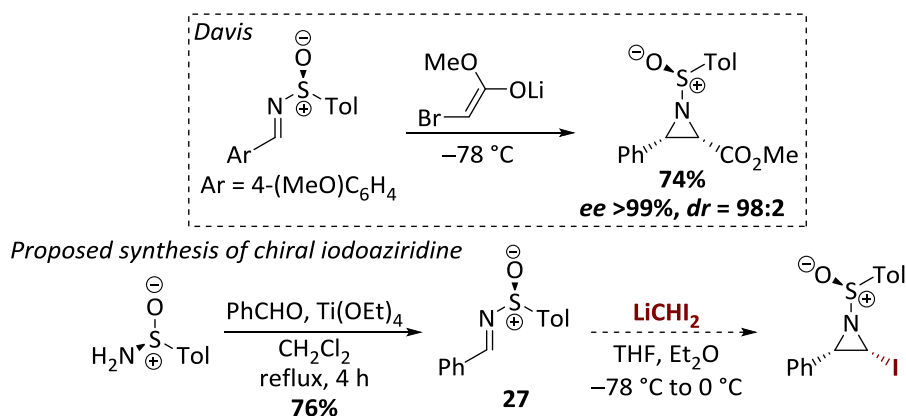


2.2.6: Preparation of Enantioenriched Iodoaziridines

The use of a chiral *N*-protecting group would allow facial selectivity upon addition of diiodomethylithium, allowing a stereoselective approach to *cis*-iodoaziridines. The use of Ellman's chiral auxiliary in stereoselective aziridine synthesis has been widespread in recent years via aza-Darzens methodology. The stereochemical outcome of reactions involving chiral *N*-toluenesulfinyl and *N-tert*-butanesulfinyl protecting groups with nucleophiles has been comprehensively reviewed in the literature; see Stockman (2006),¹¹⁰ Chemla (2009),¹¹¹ and most recently Ellman (2010).¹¹²

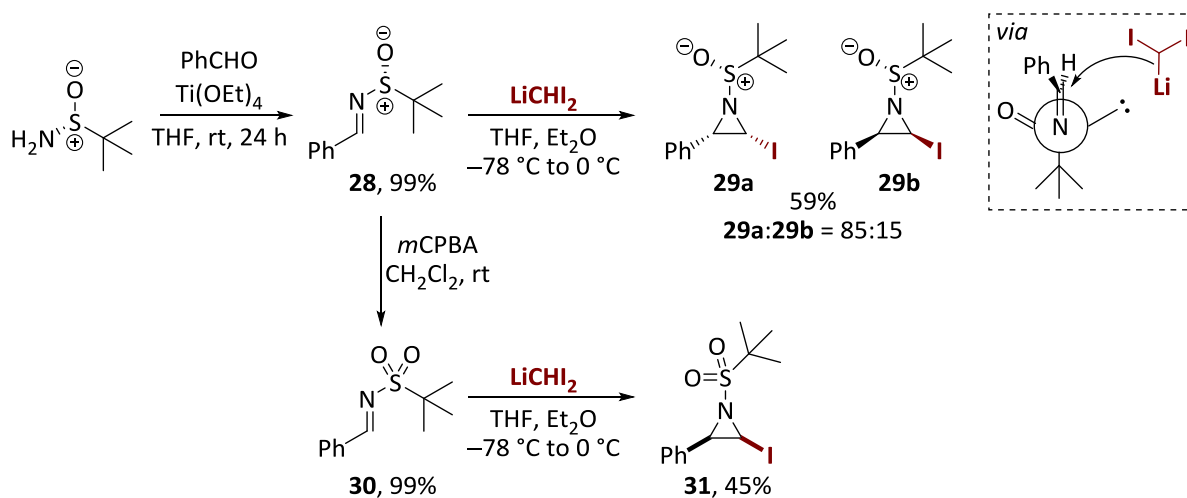
Seminal investigations by Davis had demonstrated the efficiency of addition of organometallic reagents to chiral *N*-toluenesulfinyl imines.⁴¹ Excellent facial selectivity arising from 1,2-addition was observed with a variety of α -bromo-enolates, leading to highly diastereoselective intramolecular cyclisation affording enantioenriched aziridines (up to >99% *ee*) (**Scheme 35**). Using this as a starting point, *N*-sulfinyl imine **27** was prepared from commercially available (*S*)-sulfinamide by condensing with benzaldehyde in the presence of Ti(OEt)₄. Submission of **27** under the standard reaction conditions led to a complex crude mixture of products as shown by both ¹H NMR spectroscopy and TLC, with only trace *cis*-iodoaziridine present, with the carbenoid likely to have preferentially attacked directly at sulfur rather than the desired 1,2-pathway.¹¹³

Scheme 35: *p*-Toluenesulfinyl as chiral protecting group in stereoselective aziridine synthesis.



N-*tert*-Butyl sulfinyl was therefore chosen as a suitable protecting group to explore (previously shown to have stabilizing interactions in lithiation chemistry, *vide supra*, **Section 1.6**, page 23),⁵⁵ with the sterically demanding *tert*-butyl group protecting sulfur from nucleophilic attack by diiodomethylithium. In analogous fashion, the *N*-*tert*-butanesulfinyl imine was prepared from (*R*)-*N*-*tert*-butanesulfonamide and benzaldehyde, affording sulfinyl imine **28** in quantitative yield (**Scheme 36**).

Scheme 36: Synthesis of *N*-sulfinyl and *N*-Bus protected iodoaziridines.^a



^a Work carried out by D. P. Affron. Basic alumina (activity V) prepared by addition of water (15% w/v) to basic alumina (activity I).

Pleasingly, addition of diiodomethylithium under the standard conditions was now productive, affording exclusively *cis*-aziridines **29a** and **29b** (*dr* = 85:15, **29a:29b**).^{viii} The major and minor diastereoisomers could be predicted, based on previous non-chelation control models in the literature with attack of diiodomethylithium over the least hindered face of the imine in the open

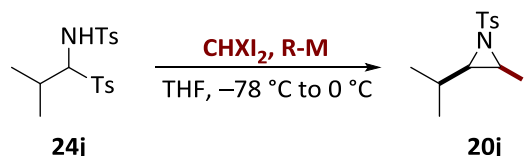
viii) Enantioenriched *N*-sulfinyl iodoaziridines **29a** and **29b** accessed by D. P. Affron.

transition state.¹¹⁴ Further oxidation of sulfinyl imine **28** with *m*CPBA afforded the corresponding *tert*-butyl sulfonyl (*N*-Bus) imine **30**. Submission of **30** to the standard conditions gave *cis*-iodoaziridine **31** in 45% yield. Both *N*-sulfinyl and *N*-Bus protected iodoaziridines were purified on deactivated basic alumina (activity V) after stability studies revealed major degradation on other stationary phases.

2.2.7: ClMgCHI₂, an Alternative Protocol

We believed that generating diiodomethyl lithium via other approaches, could have a positive effect on both the yield and ease of purification of iodoaziridines. Comparable yields were observed for **20j**, generating diiodomethyl lithium via iodine–lithium exchange between iodoform and *n*-BuLi at –78 °C (Table 8, entries 1-2). Significantly due to the absence of LiHMDS, no undesired amination was observed and also purification could now be achieved efficiently on silica gel.^{ix}

Table 8: Optimisation of improved procedure for *N*-Ts iodoaziridine formation varying diiodomethyl-metal reagents.



entry ^a	CHXI ₂ (equiv)	R-M (equiv)	yield 20j (%) ^c
1 ^b	X = H, CH ₂ I ₂ (4.4)	LiHMDS (4.0)	63
2	X = I, CHI ₃ (4.0)	<i>n</i> -BuLi (4.0)	65 ^d
3	X = I, CHI ₃ (4.0)	MeLi (4.0)	0 ^d
4	X = I, CHI ₃ (4.0)	<i>i</i> -PrMgCl (4.0)	(98) ^d 75
5	X = I, CHI ₃ (2.2)	<i>i</i> -PrMgCl (2.2)	74 ^d
6	X = I, CHI ₃ (4.0)	EtMgCl (4.0)	87
7	X = I, CHI ₃ (3.0)	EtMgCl (3.0)	85

^a Reaction conditions: imine–HO₂STol adduct (0.50 mmol), CHXI₂ (equiv), R-M (equiv), THF (0.26 M at exchange), –78 °C to 0 °C. ^b Reaction conditions: imine–HO₂STol adduct (0.50 mmol), *n*-BuLi (2.00 mmol), HMDS (2.00 mmol), CH₂I₂ (2.20 mmol), THF:Et₂O (0.16 M at deprotonation), –78 °C to 0 °C. ^c Isolated yield. ^d Yield determined by ¹H NMR spectroscopy with reference to an internal standard (1,3,5-trimethoxybenzene).

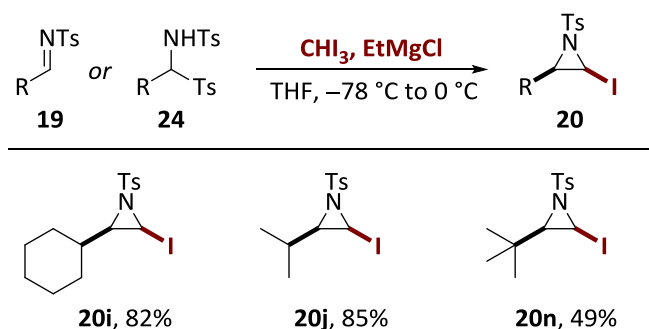
It was found that employing MeLi in a similar I–Li exchange at –78 °C led to no iodoaziridine formation. Diiodomethyl lithium formed *in situ* was subsequently trapped with the iodomethane

ix) Decomposition of amination generated by undesired LiHMDS addition to benzaldehyde led to co-elution of benzaldehyde and iodoaziridine.

generated in the exchange protocol forming 1,1-diiodoethane. As a consequence of this, we returned to the literature and examined the possibility of using diiodomethylmagnesium reagents in the iodoaziridination protocol, generated via magnesium–iodine exchange.

Magnesium carbenoids have previously been shown to have similar reactivity to analogous lithium carbenoids, tolerating a wide range of functional groups in the process.¹¹⁵ Advantageously, they can be generated under milder reaction conditions and have been shown to have increased thermal and configurational stability.¹¹⁶ The generation and reactivity of magnesium carbenoids via sulfoxide–magnesium exchange has recently been reviewed by Satoh (2012).¹¹⁷ To further probe into the synthesis of iodoaziridine **20j**, we were interested in the formation of diiodomethylmagnesium chloride, first reported by Seyferth and Lambert.⁸⁷ This methodology has recently been adopted by Schmidt and co-workers, employing ClMgCHI₂ in the synthesis of iodinated alcohols,¹¹⁸ and cyclopropanes,¹¹⁹ via Mg–I exchange between iodoform and *i*-PrMgCl at –78 °C. Applying Schmidt’s conditions to the formation of iodoaziridine **20j** initially proved very promising. Formation of ClMgCHI₂ using 4.0 equiv of both *i*-PrMgCl and CHI₃, followed by an addition/cyclisation protocol (10 min, –78 °C then 15 min, 0 °C) resulted in formation of *cis*-iodoaziridine **20j** in excellent yield (entry 4). Advantageously, no dual solvent system was required for the formation and stability of the magnesium carbenoid, simplifying the protocol. However, isolated yields were not corresponding to ¹H NMR yields (98% ¹H NMR yield vs. 75% isolated yield). This was initially believed to be a purification problem, with the exchange product causing decomposition of iodoaziridine **20j** upon purification. A reduction in the quantities of both *i*-PrMgCl and CHI₃ to 2.2 equivalents in order to reduce the amount of exchange product, unfortunately led to a reduced yield of iodoaziridine (entry 5). It was found that a significant increase in yield could be achieved when employing EtMgCl under identical reaction conditions (entry 6). Finally, we were able to reduce the equivalents of both iodoform and EtMgCl (entry 7), leading to an 85% yield of iodoaziridine **20j**. The final optimised conditions developed were applied to other alkyl *N*-Ts imines enabling the preparation of gram-quantities of iodoaziridines in high yield and purity, exclusively as their *cis*-diastereoisomers (**Scheme 37**) (e.g. for iodoaziridine **20j**, 3 mmol reaction scale led to 930 mg **20j**, 85% yield).

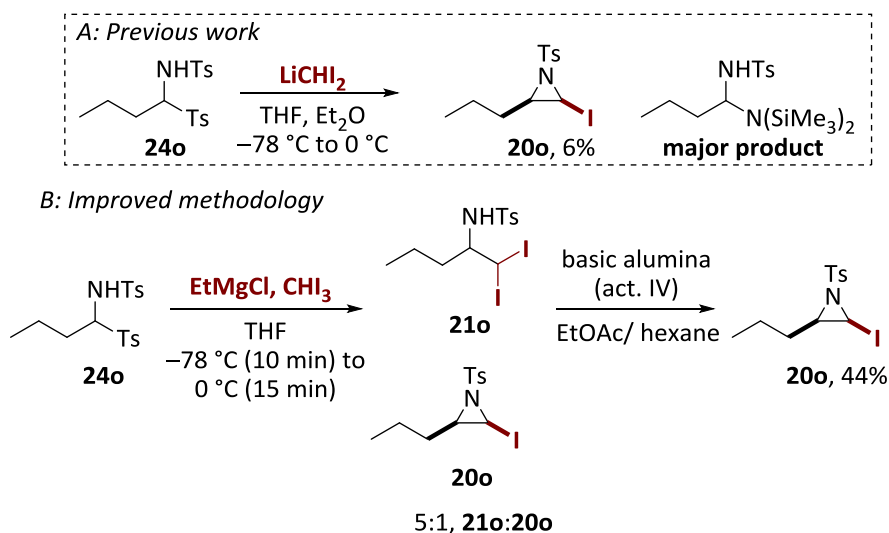
Scheme 37: Scope of secondary alkyl substituted iodoaziridines utilising Mg-carbenoids.^a



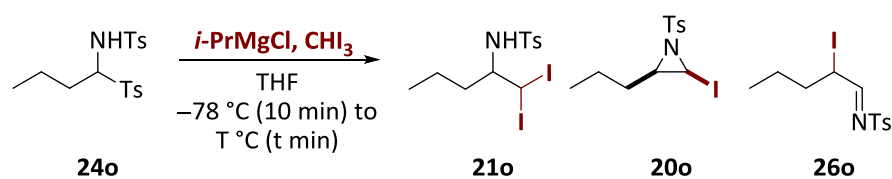
^a Reaction conditions: imine- HO_2STol adduct/imine (3.00 mmol), CHI_3 (9.00 mmol), EtMgCl (9.00 mmol), THF (0.26 M at exchange), -78°C to 0°C .

To further probe the reactivity of ClMgCHI_2 in the iodoaziridination protocol, the reaction with imine- HSO_2Tol adduct **24o** was examined (Scheme 38).

Scheme 38: Comparison of methodologies to access iodoaziridine **20o**.



Previously, poor yields were obtained for primary substituted imine- HSO_2Tol adducts under the LiCHI_2 conditions due to competing irreversible addition of LiHMDS (6% for iodoaziridine **20o**). Generating LiCHI_2 via I-Li exchange between $n\text{-BuLi}/\text{CHI}_3$ only led to a slight improvement in yield for **20o** (13% yield by ^1H NMR spectroscopy). Gratifyingly under the alternative optimised reaction conditions, the addition of ClMgCHI_2 was shown to be productive affording a 5:1 mixture of amino *gem*-diiodide **21o**: *cis*-iodoaziridine **20o** in the crude ^1H NMR mixture. Surprisingly purification upon deactivated basic alumina (activity IV), diiodide **21o** exclusively cyclised to iodoaziridine **20o**, resulting in a 45% isolated yield of **20o**. Although, the overall yield for iodoaziridine **20o** had dramatically improved, we were keen to establish whether full conversion could be achieved by varying the reaction conditions (Table 9).

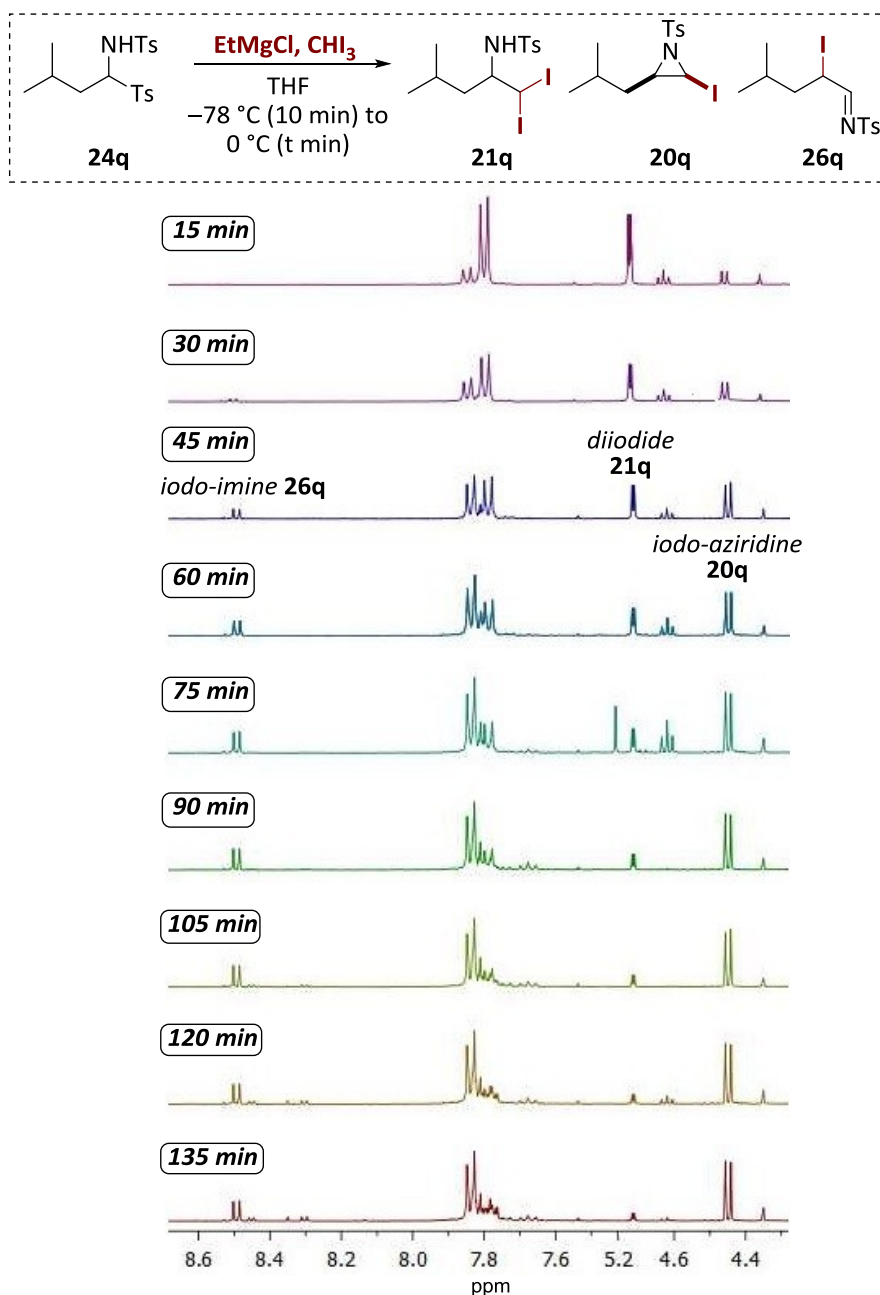
Table 9: Varying reaction conditions to control rate of cyclisation and rearrangement.

entry ^a	T (°C)	time (min)	yield (%) ^b		
			21o	20o	26o
1	0	15	81	16	0
2	0	30	77	22	0
3	0	45	69	31	0
4	0	45	52	40	0
5	15	15	41	18	5
6	30	15	15	7	10

^a Reaction conditions: imine-HO₂STol adduct (0.50 mmol), CHI₃ (4.0 equiv), *i*-PrMgCl (4.0 equiv), THF (0.26 M at exchange). ^b Yield determined by ¹H NMR spectroscopy with reference to an internal standard (1,3,5-trimethoxybenzene).

Reduced conversions to diiodide **21o** and iodoaziridine **20o** were observed employing EtMgCl in place of *i*-PrMgCl, therefore the latter was used for the exchange protocol. Both the reaction time and the cyclisation temperature were next evaluated. Prolonged time at the cyclisation temperature (0 °C), led to more cyclised iodoaziridine **20o** with excellent recovery of both **20o** and diiodide **21o** (entries 1-4). Warming the reaction from -78 °C to 15 °C (water bath) gave no further improvement on the ratio of **21o**:**20o** (entry 5). As a consequence of this increased cyclisation temperature, rearrangement of iodoaziridine **20o** to iodo-imine **26o** was observed. This had previously been demonstrated for more electron rich aryl substituted iodoaziridines when heated under reduced pressure. A similar ring opening, elimination of iodide and trapping of the cation with iodide has been postulated as a possible mechanism for the formation of **26o**. As predicted, increased cyclisation temperatures led to increased formation of the undesired iodo-imine **26o**, with overall mass recovery significantly reduced. In both cases, the loss in recovery of material can be apportioned to the instability of the alkyl iodo-imine formed after the rearrangement of iodoaziridine **20o**. A sampling study was carried out using primary substituted imine-HSO₂Tol adduct **24q**, aiming to find improved cyclisation conditions at 0 °C (**Figure 12**).

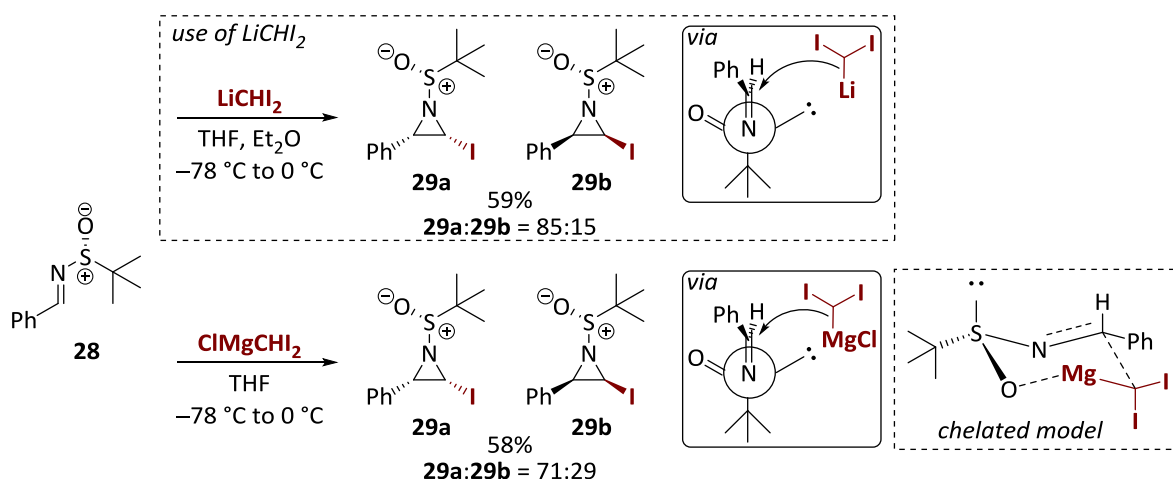
Figure 12: Sampling study using **24q** under CIMgCHI_2 conditions.



Similarly to the reaction of CIMgCHI_2 with imine- HSO_2Tol adduct **24o**, a mixture of iodoaziridine **20q** and diiodide **21q** was present after 30 minutes at 0°C , with **21q** being the major component of the reaction mixture. Prolonged reaction times at 0°C led to increased conversion to iodoaziridine **20q**, but the iodoaziridine was prone to rearrangement during this period. Since modification of the conditions was shown to give rearrangement, short reaction times were implemented to afford a mixture of diiodide **21q** and iodoaziridine **20q**, with purification upon deactivated basic alumina (activity IV) leading to cyclisation of **21q** and clean isolation of **20q**. These novel conditions developed were shown to give a vast improvement in both yield and conversion for primary iodoaziridines, with iodoaziridines **20o** and **20q** isolated in high purity.

Due to the success observed with the improved protocol, it became of interest to investigate the reactivity of ClMgCHI_2 with other classes of substrate previously examined, especially chiral *N*-sulfinyl imines. Addition of LiCHI_2 under the standard conditions for *N*-Ts iodoaziridines, afforded exclusively *cis*-aziridines **29a** and **29b** in a modest *dr* of 85:15 (**29a:29b**). The addition was predicted to occur via an open transition state, giving the major diastereoisomer **29a**. Changing the nature of the MCHI_2 reagent and the solvent system employed would potentially offer a different stereochemical outcome to the reaction. Chelating transition states have been shown to be favoured by the use of Grignard reagents in non-coordinating solvents, whereas typically open transition states are favoured by organolithiums in co-ordinating solvents.¹¹² The reaction conditions developed for the use of ClMgCHI_2 were applied to sulfinyl imine **28** (Scheme 39).

Scheme 39: Use of ClMgCHI_2 with chiral sulfinyl imine **28**.

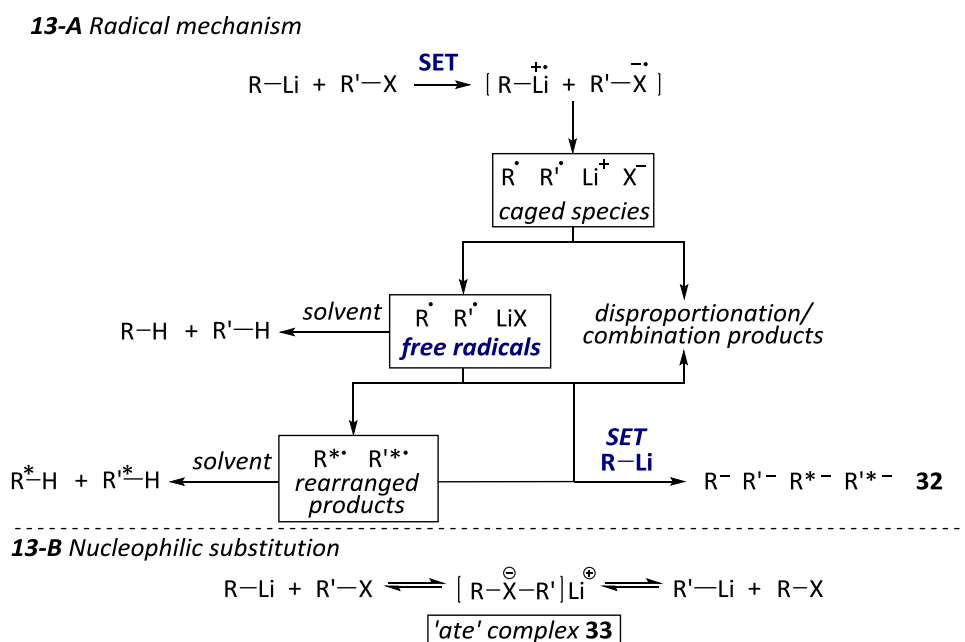


Reaction of ClMgCHI_2 with sulfinyl imine **28** afforded the expected chiral *cis*-*N*-sulfinyl iodoaziridines in 58% yield, albeit in a reduced diastereoselectivity (**29a:29b** = 71:29) compared when utilising LiCHI_2 . The major diastereoisomer was assigned based on previous assignments when employing LiCHI_2 . The observed diastereoselectivity is consistent with that based on an open transition state. This is most likely due to the competitive co-ordination of THF over the sulfinyl oxygen with Mg in the 6-membered transition state, resulting in a loss of stereocontrol. Ellman has shown that such 1,2-additions into chiral *N*-sulfinyl imines proceed with a high degree of stereocontrol when non-polar solvents are employed, due to the minimisation of this coordination effect.¹²⁰ However due to the requirement for ethereal solvents for the stability of the carbenoid reagent, the exploration of other solvent systems has not yet been explored.

2.3.1: Iodine–Lithium Exchange and Trapping with Electrophiles

Having established suitable methodology for the synthesis of aryl and alkyl iodoaziridines (**Section 2.1** and **Section 2.2**),^{95,103,104} it was envisaged that these functionalised aziridines would provide ideal scaffolds for derivatisation of the intact ring. Iodine–lithium exchange has been demonstrated to be a highly efficient process for the generation of organolithium species,¹²¹ with protocols utilising low reaction temperatures to avoid undesired side reactions. However, these protocols are generally rapid in nature as they are driven by pK_A considerations, with the exchange equilibrium shifted in favour of the organic group which can best stabilize a partial negative charge.¹²² Several mechanisms have been proposed for the iodine–lithium exchange protocol, with evidence suggesting that three main mechanistic pathways could be in operation. For a detailed review on mechanistic understanding of halogen–lithium exchange, see Bailey (1988).¹²¹ It has been suggested that the exchange protocol could occur via a free radical mechanism or a nucleophilic substitution mechanism (through an ‘ate’ complex) (**Figure 13**). It must be noted, that the proposed mechanisms are based on a monomer organolithium species. Typically, the behaviour of organolithium species in solution can be challenging to predict due to the presence of organolithium aggregations which are dependent on the structure of the carbanion, solvent polarity and donor ligands present.¹²³

Figure 13: Proposed mechanistic pathways for halogen–lithium exchange.



Studies by both Bryce-Smith,¹²⁴ and Ashby have shown that radical pathways could be responsible for halogen–lithium exchange processes (**Figure 13-A**).^{125,126} Radical clock experiments by Ashby demonstrated that alkyl bromides gave the cyclisation products expected in a radical mechanism (resulting from 5-*exo-trig* cyclisation in norbornene derivatives), whereas the corresponding iodides failed to yield the same product. Ashby concluded that two different mechanisms were in operation – a radical based mechanism (for bromides) and a heterolytic mechanism (for iodides). The proposed radical mechanism occurs via a single electron transfer (SET) from the organolithium to the halide, generating short-lived solvent caged radical anion and cation species. Two pathways can occur, dependent on the lifetime of these species – either disproportionation or the formation of carbon centred ‘free radical’ species. Skeletal rearrangements can possibly occur, generating rearranged radical species. Both sets of radicals can be quenched as a consequence of hydrogen abstraction, or subsequently further reduced by another SET protocol generating nucleophilic carbanion species **32**. Reaction with electrophiles allows the formation of functionalised derivatives. Alternative nucleophilic substitution pathways have also been proposed for halogen–lithium exchange. Gilman initially proposed the attack of the halide by the organolithium, with a carbanion as a leaving group.¹²⁷ It was later suggested by Wittig that ‘ate’ complex **33** could be a viable intermediate in this process.¹²⁸ (**Figure 13-B**). Since this proposal, many reports have demonstrated that the proposed equilibrium is a measure of relative carbanion stability.¹²⁹ Farnham has also supported the postulated ‘ate’ complex intermediate, isolating a hypervalent iodine structure from an iodine–lithium exchange reaction, which showed further nucleophilic behaviour.¹³⁰

Due to experimental evidence, the following has been proposed:

- (i) Aryl iodides/bromides undergo the nucleophilic ‘ate’ complex mechanism;
- (ii) Primary alkyl iodides undergo the nucleophilic ‘ate’ complex mechanism;
- (iii) Secondary alkyl iodides undergo the nucleophilic ‘ate’ complex mechanism with competition from radical pathways;
- (iv) Alkyl bromides undergo radical based mechanisms.

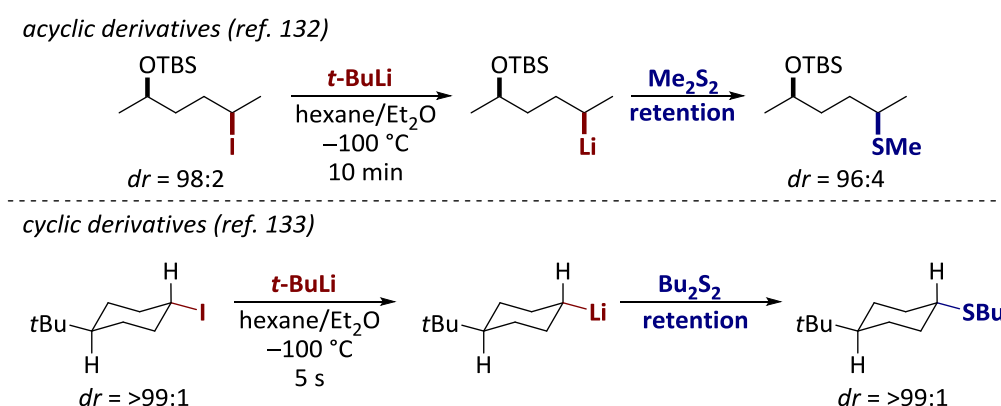
In this section, the reactivity of *N*-Ts iodoaziridines towards organolithiums will be fully explored, aiming to trap an intermediate *N*-Ts aziridinyl lithium species with electrophiles, affording a novel library of *N*-Ts aziridines. The stereochemistry of the aziridine products would also give insight to the configurational stability of the lithiated aziridine and the mechanism of iodine–lithium exchange.

A concise account detailing this work can be found in *Organic Letters*.¹³¹

2.3.2: Recent Methodology and Applicability to Iodoaziridines

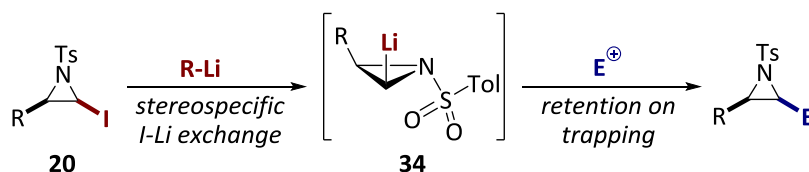
Recently, Knochel has demonstrated the stereospecific preparation of acyclic and cyclic alkylolithiums at low temperature, from their corresponding alkyl iodides.^{132,133} This enabled the preparation of a wide range of stereodefined alkyl and cycloalkyl derivatives by reaction with a range of electrophiles, with retention of stereochemistry at the reacting centre (**Scheme 40**). This has also been recently extended to secondary alkyl iodides which are further functionalised at the 3-position, forming 1,3-difunctionalised derivatives with excellent diastereoselectivities.¹³⁴

Scheme 40: Knochel's preparation of stereodefined alkyl derivatives, generated via stereospecific iodine–lithium exchange and trapping with electrophiles.



The remarkable configurational stability of these unstabilized organolithiums at low temperature, generated via iodine–lithium exchange, became of immediate interest due to the unexplored reactivity of the iodoaziridine towards organolithiums. Employing *N*-Ts iodoaziridines (due to ease of availability and synthesis) in the reaction protocol (**Scheme 41**), stereospecific iodine–lithium exchange would afford an aziridinyl lithium species **34**, and owing to the potential configurational stability at low temperature, trapping with suitable electrophiles would allow access to *cis*-substituted aziridines.

Scheme 41: Stereospecific iodine–lithium exchange and trapping with electrophiles to afford *cis*-substituted aziridines.



This approach would potentially offer a complementary stereochemical outcome to intact aziridine functionalisation approaches via other deprotonation/electrophilic trapping methodology (*vide*

supra, **Section 1.6**, page 21). The nature of the *N*-protecting group or other ring substituents would also become inconsequential on the outcome of a lithiation/trapping sequence, with the generation of the aziridinyl lithium species being site specific.

This strategy to intact iodoaziridine functionalisation would also be reliant on other factors. Aforementioned, the configurational stability of the aziridinyl lithium species after iodine–lithium exchange would be critical in the stereochemical outcome in the reaction, but due to the unstabilized nature of the aziridinyl lithium species, the structural stability at low temperature would be key in avoiding any undesired degradation. The *trans* relationship of the *N*-tosyl protecting group and the C-Li bond in intermediate **34** would also be crucial, preventing undesired addition of the C-Li bond into the tosyl group as previously reported in the literature, affording a tricyclic species (*vide supra*, **Scheme 8**, page 24).^{135,136} The *trans* relationship is however the most likely preferred conformation, due to the potential unfavourable steric interactions between the R group present on the ring and the *N*-protecting group.

2.3.3: Optimisation of Iodine–Lithium Exchange Protocol

The iodine–lithium exchange was first examined using iodoaziridine **20j** with *n*-BuLi and 3-pentanone as the electrophile of choice, due to reaction with the aziridinyl lithium generating no extra stereocentre, simplifying analysis of the ¹H NMR spectrum of the crude product. After significant experimentation (**Table 10**), in an attempt to overcome the limitations working at –100 °C, a reproducible method was established for the stereospecific iodine–lithium exchange and reaction with 3-pentanone, exclusively affording the corresponding *cis*-aziridine alcohol in an excellent yield of 83% (measured by ¹H NMR spectroscopy against an internal standard) (**Table 10**, entry 1). The protocol developed involved the addition of a solution of iodoaziridine **20j** in THF to a pre-cooled solution of *n*-BuLi in THF (pre-cooled to –102 °C for 5 min prior to iodoaziridine addition – external reaction temperature). Initially, incomplete lithiation was a major issue due to overcooling of the reaction mixture ultimately leading to the reaction mixture freezing.^x This was mainly due to concerns of the reaction mixture significantly warming upon the addition of the iodoaziridine solution. However, this was overcome by maintaining the external reaction temperature at –102 °C by carefully adding the iodoaziridine solution dropwise down the side of the flask over 30 s. After 5 s at –100 °C, the exchange was complete affording the aziridinyl lithium intermediate and an excess of 3-pentanone was added, resulting in the formation of the *cis*-aziridine alcohol **35a** and also the formation of unsubstituted aziridine **36** in small amounts. No reactivity of the aziridinyl lithium

x) THF freezing point = –108 °C

intermediate with *n*-butyl iodide (the by-product arising from the iodine–lithium exchange with *n*-butyllithium) was observed. The *cis*-diastereochemistry of the aziridine was assigned based on $^3J_{\text{H-H}}$ coupling constants in the ^1H NMR spectrum of the crude product, with values observed consistent with that reported in the literature for *cis*-aziridines (e.g. for *cis*-aziridine **35a**, $\text{CH}(\text{CHEt}_2\text{OH})$, $\delta = 2.88$ ppm, $^3J_{\text{H-H}} = 7.2$ Hz, $^3J_{\text{H-H}}$ for *trans*-aziridine typically = 4–5 Hz).⁵⁰

Table 10: Optimisation of the iodine–lithium exchange protocol, trapping with 3-pentanone.

Reaction scheme: **20j** $\xrightarrow[\text{THF, } -100\text{ }^\circ\text{C, 5 s}]{n\text{-BuLi (1.5 equiv)}}$ $\xrightarrow[\text{THF, } -100\text{ }^\circ\text{C, 5 min}]{\text{3-pentanone (3.0 equiv)}}$ **35a** + **36**

"standard conditions"

entry ^a	deviation from "standard conditions"	yield (%) ^b		
		35a	36	20j^c
1	none	83 (81) ^d	17	0
2	<i>n</i> -BuLi (1.2 equiv)	61	22	14
3	<i>n</i> -BuLi (1.2 equiv)/ 15 s lithiation	67	23	10
4	<i>n</i> -BuLi (1.2 equiv)/ 30 s lithiation	76	15	0
5	reaction run at $-78\text{ }^\circ\text{C}$	11	36	4
6	hexane/ Et_2O (3:2), ¹³² instead of THF	10	23	54
7	hexane/THF (3:2), instead of THF	46	29	17
8	THF/ Et_2O (3:2), instead of THF	73	17	0
9	Et_2O , instead of THF	48	27	5
10	2-Me THF, instead of THF	27	44	16
11	no 3-pentanone	0	90 (86) ^d	0
12	concentration = 0.065 M ^e	84 (81) ^d	11	0

^a Reaction conditions: *n*-BuLi (1.5 equiv), THF (0.13 M), $-100\text{ }^\circ\text{C}$; then addition of aziridine **20j** (0.27 mmol) in THF, 5 s; then 3-pentanone (3.0 equiv), THF, $-100\text{ }^\circ\text{C}$, 5 min. ^b Yield determined by ^1H NMR spectroscopy with reference to an internal standard (1,3,5-trimethoxybenzene). ^c Unreacted iodoaziridine **20j**. ^d Isolated yield. ^e *n*-BuLi concentration before aziridine addition.

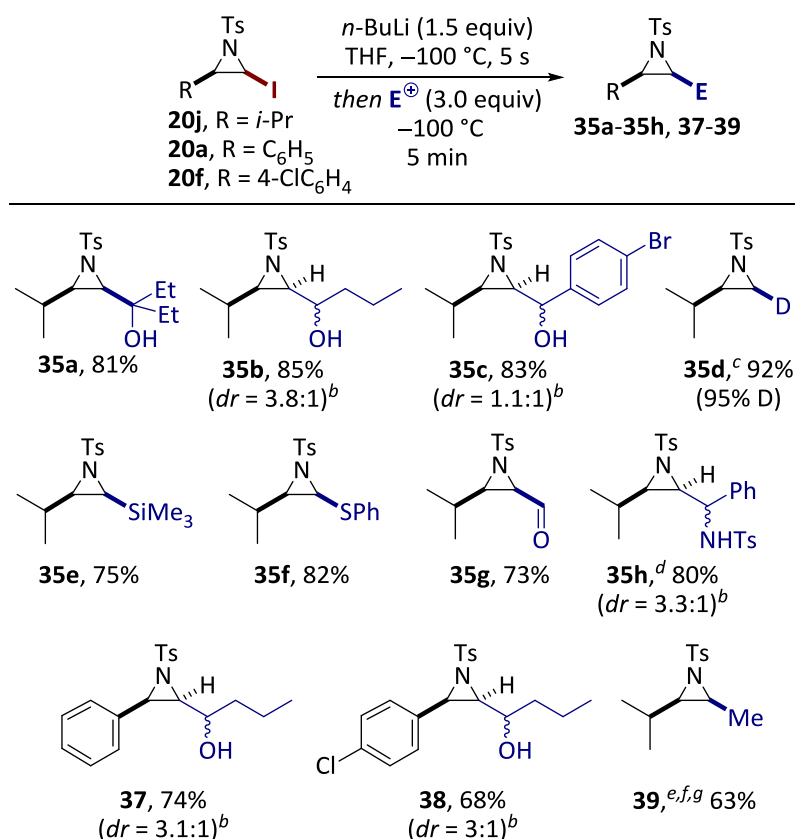
The reaction parameters were systematically varied during the reaction optimisation. Reducing the equivalents of *n*-BuLi (**Table 10**, entries 2–4) led to incomplete lithiation. This could be improved by increasing the reaction time for lithiation (up to 30 s) without significant decomposition of the aziridinyl lithium intermediate. The iodine–lithium exchange was attempted at elevated temperatures (entry 4), with little success and a loss in recovery of aziridine was observed presumably due to the degradation of the aziridinyl lithium intermediate. This degradation was

observed in the ^1H NMR spectrum of the crude reaction mixture, due to the presence of *p*-toluenesulfonamide, a prominent degradation product. This degradation also emphasised the requirement for the low temperature in order to maintain the structural stability of the unstabilized aziridinyllithium species. A range of solvents were then examined (entries 5-10). Solvent combinations utilised for the formation/trapping of unstabilized aziridinyllithium species, successfully demonstrated by Knochel and co-workers,¹³² were detrimental to the protocol due to the limited solubility of iodoaziridine **20j** under the reaction conditions (entries 6-7). More polar solvent combinations enhanced the solubility of iodoaziridine **20j** (entry 8), although THF alone was still found to be far superior. This was also evident with Et₂O (entry 9) and 2-Me THF (entry 10). In the absence of the electrophile under the standard reaction conditions (entry 11), it was demonstrated that unsubstituted aziridine **36** was formed in high yield. This again indicated the structural and configurational stability of the aziridinyllithium intermediate, with no addition into the *N*-tosyl protecting group observed. The concentration of the reaction (concentration of *n*-BuLi in THF prior to iodoaziridine addition) was also examined, with a reduction in concentration having no major effect on the yield of *cis*-aziridine **35a**. Ultimately, it was decided that these latter dilute reaction conditions would be utilised to examine the reaction scope, in order to aid temperature control on addition of various electrophiles.

2.3.4: Exploring Reaction Scope and Reactivity of Aziridinyllithium

The scope of the stereospecific iodine–lithium exchange was explored by varying both the substitution on the iodoaziridine (alkyl and aromatic), and choice of electrophile (**Scheme 42**). Aliphatic and aromatic substituted aldehydes were both tolerated affording *cis*-aziridine alcohols **35b** and **35c** respectively, with modest *dr* observed at the newly formed stereocentre. Deuteration of the lithiated aziridine was possible at –100 °C with 5 equiv *d*₄-MeOD, affording deuterio-aziridine **35d**, with 95% D-incorporation. Reaction with ClSiMe₃ and S₂Ph₂ afforded the *cis*-heteroatom substituted aziridines **35e–35f** in excellent yield. In the latter case, *n*-butyl phenyl sulfide was observed in the ^1H NMR spectrum of the crude product, arising from the reaction of *n*-butyl iodide generated in the iodine–lithium exchange and the thiolate leaving group. This may act to protect the newly formed *cis*-aziridine from nucleophilic ring opening by the thiolate leaving group. Reaction with DMF furnished the corresponding aziridine aldehyde **35g** in excellent yield of 73%.

Scheme 42: Scope for iodine-lithium exchange and trapping with electrophiles on *cis*-*N*-Ts iodoaziridines.

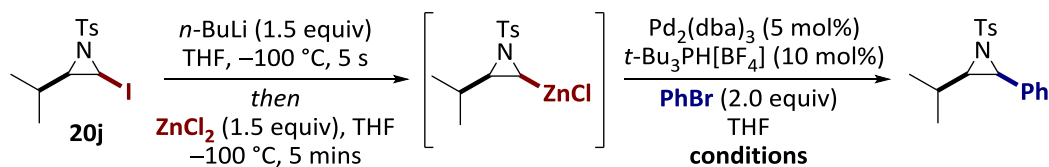


^a Reaction conditions: *n*-BuLi (1.5 equiv), THF (0.065 M), $-100\text{ }^{\circ}\text{C}$, addition of aziridine (0.27 mmol) in THF, 5 s; then electrophile (3.0 equiv), THF, $-100\text{ }^{\circ}\text{C}$, 5 min. ^b *dr* observed by ^1H NMR spectroscopy in crude reaction mixture. ^c 5.0 equiv MeOD used. ^d 1.0 equiv imine **19a** used. ^e Reaction mixture warmed to $-90\text{ }^{\circ}\text{C}$. ^f Contained **36** as an inseparable impurity (13% yield). Yield for **39** calculated based on desired product only. ^g 5.0 equiv MeI used.

Employing phenyl *N*-Ts imine **19a** in the iodine–lithium exchange/electrophilic trapping sequence required a minor modification of the reaction conditions. Hydrolysis of excess electrophile led to formation of *p*-toluenesulfonamide upon work-up, which co-eluted with desired *cis*-aziridine **35h** during silica gel column chromatography. Successful trapping/purification was achieved by reducing the equivalents of imine **19a** from 3 equiv to 1 equiv, providing a mixture of *cis*-aziridine amines **35h** in excellent yield, again with a modest *dr* at the newly formed stereocentre. This represented the first example, to our knowledge, of the reaction of an aziridinyl lithium with an imine. Aromatic substituted iodoaziridines **20a** and **20f** were successfully submitted to the standard reaction conditions, trapping with butyraldehyde to exclusively afford *cis*-aziridine alcohols **37** and **38** respectively. *cis*-Aziridine alcohols, arising from iodine–lithium exchange/electrophilic trapping were exclusively observed over a potential competing benzylic deprotonation/trapping sequence in both cases.

Attempted Negishi couplings of the aziridinyl lithium intermediate **34** with PhBr proved unsuccessful, (Table 11), using aziridine cross-coupling conditions previously outlined by Vedejs,¹³⁷ and more recently adopted by Hodgson in azetine cross-coupling.¹³⁸

Table 11: Attempted Negishi cross-couplings of aziridinyl lithium intermediate.



entry ^a	conditions	outcome
1	warm to -78 °C then to 0 °C, then [Pd], 0 °C to rt, 16 h	decomposition to <i>p</i> -toluenesulfonamide
2	addition of [Pd] at -100 °C, then slow warm to rt, 16 h	decomposition to <i>p</i> -toluenesulfonamide

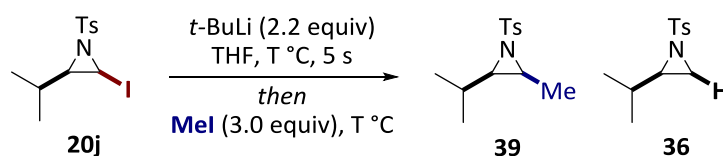
^a Reaction conditions: *n*-BuLi (1.5 equiv), THF (0.065 M), -100 °C, addition of aziridine **20j** (0.27 mmol) in THF, 5 s; then ZnCl₂ (1.5 equiv), THF, -100 °C, 5 min; then Pd₂dba₃ (5 mol%), *t*-Bu₃PH[BF₄] (10 mol%), PhBr (2.0 equiv), THF, conditions.

Formation of the aziridinyl zinc species after iodine–lithium exchange was evident due to rapid change in colour of the reaction mixture after the addition of ZnCl₂. However it was deemed that the stability of the unstabilized metallated intermediate at increased reaction temperatures was not sufficient to perform the transmetallation to Pd, hence decomposition to *p*-toluenesulfonamide.

2.3.5: Alkylation of Aziridinyl Lithium

Initial studies into the alkylation of the aziridinyl lithium species with iodomethane began by performing the iodine–lithium exchange with *t*-BuLi and using an excess of electrophile to trap the intermediate (Table 12). This was initially considered due to the *n*-BuLi, generated after iodine–lithium exchange with *n*-BuLi, potentially acting as a competing electrophile with iodomethane. Addition of an aziridine solution in THF to pre-cooled *t*-BuLi in THF, followed by rapid addition of iodomethane was found to be the most reproducible reaction protocol, to ensure complete iodine–lithium exchange.

Table 12: Optimisation of iodine–lithium exchange with *t*-BuLi, followed by alkylation with iodomethane.



entry ^a	T (°C)	time (min)	yield (%) ^b			recovery (%) ^b
			39	36	20j ^c	
1	−100	5	0	98	1	99
2	−78	5	26	20	2	48
3	−90	5	8	38	4	50
4	−100 to −90	5	68	26	1	95
5	−100 to −90	10	61	18	1	79

^a Reaction conditions: *t*-BuLi (2.2 equiv), THF (0.13 M); then addition of aziridine **20j** (0.27 mmol) in THF, 5 s; then iodomethane (3.0 equiv), THF. ^b Yield determined by ¹H NMR spectroscopy with reference to an internal standard (1,3,5-trimethoxybenzene). ^c Unreacted iodoaziridine **20j**.

Alkylation was not observed at −100 °C with 2.2 equiv *t*-BuLi (**Table 12**, entry 1), although quantitative iodine–lithium exchange was apparent due to the formation of unsubstituted aziridine **36**. It was postulated that the aziridinyl lithium intermediate was not reactive enough at −100 °C to undergo alkylation with iodomethane. A change in electrophile to benzyl bromide also afforded the identical outcome. An examination of the temperature profile of the exchange/alkylation proved critical. Performing the exchange/alkylation at elevated temperatures (−90 °C and −78 °C) afforded the desired alkylated *cis*-aziridine (entries 2–3). However a loss in aziridine recovery was observed, presumably due to degradation of the aziridinyl lithium intermediate. Performing the iodine–lithium exchange at −100 °C, then slowly warming the reaction mixture to −90 °C after addition of iodomethane returned excellent yields of the desired *cis*-aziridine **39** after 5 min. A prolonged reaction time at −90 °C had no major impact on the yield of *cis*-aziridine **39**. *In situ* formation of MeLi was also investigated, using MeLi for the iodine–lithium exchange at −78 °C. However, only 9% of the desired methylated aziridine was observed by ¹H NMR spectroscopy with the major products attributed as being both unsubstituted aziridine **36** and general degradation.

With the iodine–lithium exchange protocol having been optimised for the use of *t*-BuLi, it was decided that the conditions outlined previously (*vide supra*, **Scheme 42**), using *n*-BuLi (1.5 equiv) in place of *t*-BuLi, were more desirable and practical from the perspective of safety and cost. As previously demonstrated, the exchange is also rapid with this organolithium, and under the modified

reaction conditions, alkylation of the aziridinyl lithium affording *cis*-aziridine **39** was possible, without competing alkylation from 1-iodobutane (**Table 13**).

Table 13: Optimisation of iodine–lithium exchange with *n*-BuLi, followed by alkylation with iodomethane.

entry ^a	MeI equiv	desiccant	ratio ^b		yield (%)
			39	36	
1	3.0	-	1.7	1	-
2	3.0 ^c	Na ₂ SO ₄	2.8	1	-
3	5.0	Na ₂ SO ₄	4.5	1	63 ^d

^a Reaction conditions: *n*-BuLi (1.5 equiv), THF (0.065 M) –100 °C, addition of aziridine **20j** (0.27 mmol) in THF, 5 s; then MeI (equiv), THF, –100 °C to –90 °C, 5 min. ^b Ratio calculated by comparison of integrals in crude ¹H NMR spectrum. ^c MeI dried over Na₂SO₄ prior to use. ^d Contained **36** as an inseparable impurity (13% yield). Yield for **39** calculated based on desired product only.

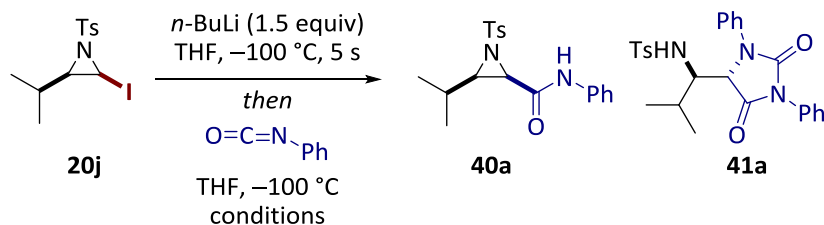
However, competing dehalogenation affording unsubstituted aziridine **36** was problematic at this elevated temperature (**Table 13**, entry 1). The use of Na₂SO₄ as a desiccant for the iodomethane prior to use, provided an increase in the desired alkylated *cis*-aziridine, (entry 2) which was further improved by increasing the equivalents used to 5.0 equiv (entry 3). These variations in the reaction protocol led to the successful alkylation of the aziridinyl lithium species to afford *cis*-aziridine **39** in an excellent yield of 63%. Attempted alkylation with allyl iodide under the modified reaction conditions returned starting *cis*-iodoaziridine, presumably due to reaction of the aziridinyl lithium with iodine. Reaction with allyl bromide generated unsubstituted aziridine **36**, characteristic of a successful iodine–lithium exchange, but unsuccessful electrophilic trapping. Raising the reaction temperature after the addition of electrophile at –100 °C to 0 °C to encourage alkylation was also unsuccessful, with only unsubstituted aziridine **36** present in the crude ¹H NMR spectrum.

2.3.6: Using Isocyanates as Electrophiles

Initial attempts to trap the aziridinyl lithium intermediate with phenyl isocyanate showed interesting and unexpected further reactivity at –100 °C. Under the optimised reaction conditions, the expected aziridine carboxamide **40a** was observed, exclusively as the *cis*-diastereoisomer, along with the formation of 1,3,5-trisubstituted hydantoin **41a** as a single diastereoisomer. The reaction was then

optimised for the formation of hydantoin **41a**, with the temperature profile of the reaction again proving critical to product distribution (**Table 14**).

Table 14: Selective formation of 1,3,5-trisubstituted hydantoins.

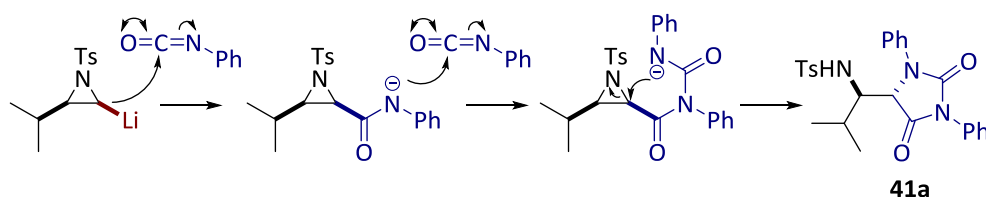


entry ^a	conditions	40a : 41a ^b	yield (%) ^c
1	-100 °C, 5 min	6.8:1	40a , 65
2	-100 °C, 10 min	2.4:1	-
3	warm to -90 °C, 5 min	3.8:1	-
4	warm to -78 °C, 5 min	1.5:1	-
5	warm to 0 °C, 5 min	41a only	41a , 85

^a Reaction conditions: *n*-BuLi (1.5 equiv), THF (0.065 M), -100 °C; then addition of aziridine **20j** (0.27 mmol) in THF, 5 s; then phenyl isocyanate (3.0 equiv), THF, conditions. ^b Ratio calculated by comparison of integrals in crude ¹H NMR spectrum, (CHCO) vs. (CHNPh). ^c Isolated yield.

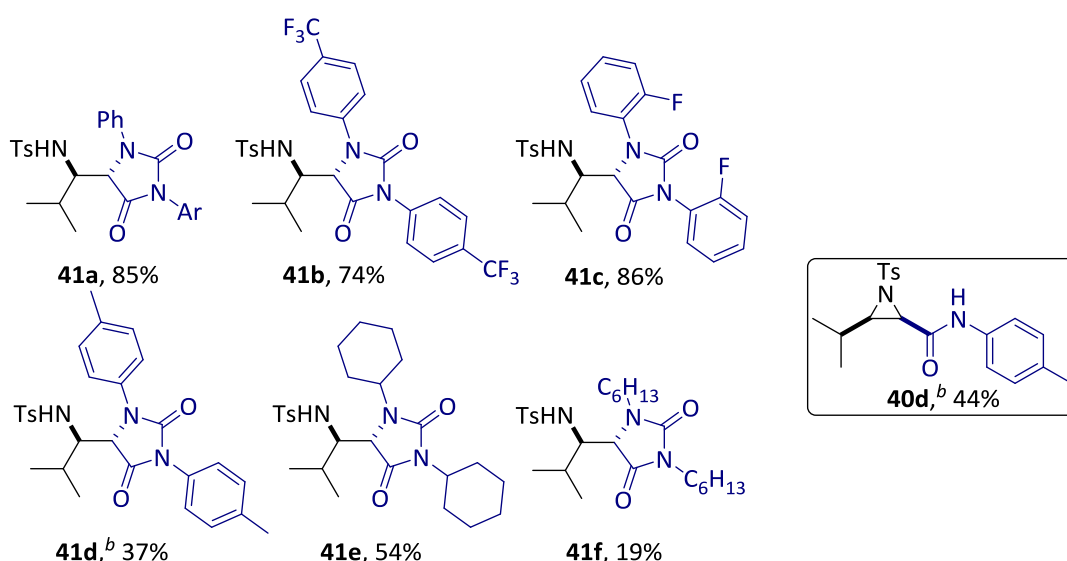
Under the previously optimised reaction conditions (**Table 14**, entry 1), the anticipated *cis*-aziridine aziridine carboxamide **40a** was formed along with minor amounts of hydantoin **41a**, leading to a 65% isolated yield of **40a**. At this stage, reduced equivalents of phenyl isocyanate (1.2 equiv and 1.5 equiv) were investigated to prevent the undesired further reactivity to hydantoin **41a** after the initial trapping. However a mixture of **40a**, **41a** and unsubstituted aziridine **36** were observed in both cases, indicating that the aziridine amide anion is potentially more reactive than the initial aziridinyl anion. Prolonged reaction times led to increased cyclisation to hydantoin **41a** at -100 °C (entry 2). However, warming the reaction mixture after the initial addition of 3.0 equiv phenyl isocyanate led to increased amounts of hydantoin **41a** (entries 3-4). Full cyclisation to **41a** was achieved by rapidly warming the reaction mixture from -100 °C to 0 °C after the initial addition of phenyl isocyanate, leading to an 85% isolated yield as a single diastereoisomer. Mechanistically, it is proposed that after the initial iodine–lithium exchange, the aziridinyl lithium reacts with 1.0 equiv of phenyl isocyanate to form an aziridinyl amide anion (**Figure 14**). Reaction with excess phenyl isocyanate, followed by 5-*exo-tet* aziridine ring opening afforded 1,3,5-trisubstituted hydantoin **41a** as a single diastereoisomer.

Figure 14: Formation of 1,3,5-trisubstituted hydantoins using phenyl isocyanate as an electrophile



The scope of the hydantoin formation was then explored, varying the isocyanate employed in the reaction (**Figure 15**).

Figure 15: Scope of 1,3,5-trisubstituted hydantoin formation varying isocyanate.^a



^a Reaction conditions: *n*-BuLi (1.5 equiv), THF (0.065 M), $-100\text{ }^{\circ}\text{C}$; then addition of aziridine **20j** (0.27 mmol) in THF, 5 s; then isocyanate (3.0 equiv), THF, $-100\text{ }^{\circ}\text{C}$ to $0\text{ }^{\circ}\text{C}$. ^b Aziridine carboxamide **40d** also isolated in 44% yield.

Variation of aryl isocyanate, including electron deficient and electron rich aromatics led to the successful formation of a range of 1,3,5-trisubstituted hydantoins (**41a-41f**). The use of more electron rich aromatic substituted isocyanates (*e.g.* *p*-tolyl isocyanate), led to incomplete cyclisation to hydantoin **41d** in 37% yield, with *cis*-aziridine carboxamide **40d** also isolated in a modest yield of 44%. 2-Methoxyphenyl isocyanate was also submitted under the reaction conditions to examine the reactivity of more electron rich isocyanates, with similar behaviour observed (1.1:1, aziridine carboxamide: hydantoin in ^1H NMR spectrum of the crude reaction mixture). This product ratio was still observed on raising the equivalents of electrophile from 3.0 equiv to 5.0 equiv. The conclusions were that electron rich aromatic isocyanates suffered in the second trapping step, due to the reduced electrophilicity of the isocyanate, making this step significantly slower. Secondary and primary alkyl substituted isocyanates were also tolerated, affording alkyl substituted hydantoins **41e**

and **41f**. The reduced yield when employing the primary substituted isocyanate may be attributed to the increased acidity of the protons α - to the isocyanate moiety, forming unsubstituted aziridine **36** over the desired aziridinyl amide anion.

2.3.7: Conclusions

Iodine–lithium exchange has been successfully employed on *N*-Ts iodoaziridines for the first time, generating highly reactive aziridinyl lithium species at low temperature. Reaction with a range of electrophiles has afforded a novel library of *N*-Ts aziridines, exclusively as their *cis*-diastereoisomers. The generation of the aziridinyl lithium species has shown to be site specific for both alkyl and aromatic substituted iodoaziridines, providing a complementary stereochemical approach to current protocols for aziridinyl anion generation/trapping with electrophiles. The *cis*-diastereochemistry of the resulting aziridines has shown that the mechanism of iodine–lithium exchange is likely to occur without the involvement of radical intermediates.¹²⁴⁻¹²⁶ The formation of an aziridinyl radical species, due to iodine–lithium exchange, would be expected to lead to epimerisation at the reacting centre. However this protocol has been shown to be stereospecific, with the *cis*-stereochemistry of the starting iodoaziridine retained in the functionalised products. Use of isocyanates under the optimised reaction conditions led to interesting further reactivity, with careful temperature control enabling the synthesis of an aziridinyl amide or a 1,3,5-trisubstituted hydantoin. The formation of the 1,3,5-trisubstituted hydantoin, as a single diastereoisomer, occurs via a double electrophile trapping followed by 5-*exo-tet* aziridine ring opening.

2.4: Transition Metal Catalysed Iodoaziridine Cross-Coupling

The use of alkyl halides in transition metal catalysed cross-coupling has received particular recent attention,¹³⁹ with novel strategies developed to form both sp^3-sp^2 and sp^3-sp^3 carbon-carbon bonds. The following sections will present the investigation into the cross-coupling of an *N*-Ts iodoaziridine, employing the iodoaziridine as an electrophilic cross-coupling partner. Both transition metal and organometallic cross-coupling partner will be varied, aiming to form new carbon-carbon bonds keeping the aziridine ring intact during this functionalisation process. Relevant reaction conditions previously reported in the literature will be examined and applied to the cross-coupling of the iodoaziridine. A brief overview of each transition metal investigated will be presented. Relevant reviews will be highlighted for further discussion concerning recent advances in transition metal catalysed cross-coupling reactions.

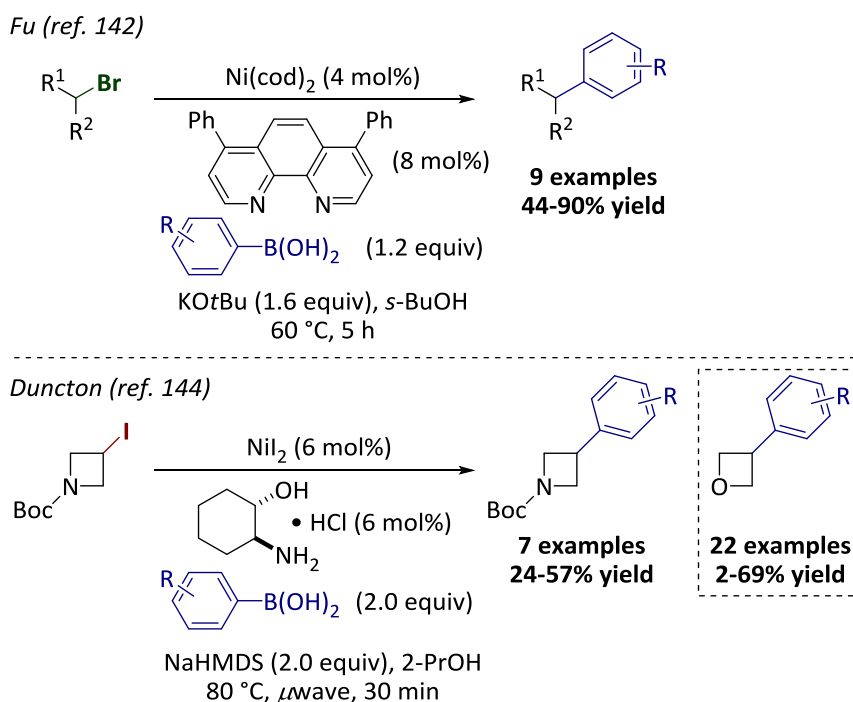
2.4.1.1: Nickel Catalysed Iodoaziridine Cross-Coupling

Nickel catalysis has emerged as an important alternative to palladium cross-coupling in recent years, in terms of both cost and applicability. Contemporary methodology has focused on Suzuki-Miyaura cross-coupling reactions between boron derivatives and a wide range of electrophiles, due to mild reaction conditions and broad functional group tolerance observed with these transformations. Various alkyl electrophiles have been shown to be successfully cross-coupled under Ni catalysis, which had previously been problematic under palladium catalysis due to undesired competing reaction pathways. The reader is directed towards reviews by Han (2013),¹⁴⁰ and Jamison (2014)¹⁴¹ for significant further discussion on recent literature in this area.

Fu and co-workers recently established the first Suzuki coupling of unactivated secondary alkyl halides with boronic acids using Ni catalysis (**Scheme 43**).¹⁴² Employing $Ni(cod)_2$ in combination with the bidentate bathophenanthroline ligand, a range of alkyl bromides were successfully cross-coupled with aryl boronic acids with varying electronic properties, in good yields. A more versatile catalytic system was later reported by Fu and co-workers in 2006, employing $Ni(II)$ salts and amino alcohol ligands.¹⁴³ Two different catalytic systems were described, allowing for the seminal cross-coupling of less reactive alkyl chlorides with boronic acids and improved scope for alkyl bromides and iodides. In a slight modification to this latter work by Fu, Duncton and co-workers successfully demonstrated that Ni catalysis could be employed in the synthesis of aryl-azetidines and aryl-oxetanes from their corresponding iodides in moderate yields.¹⁴⁴ Although moderate yielding, a variety of cross-coupled saturated heterocyclic derivatives were accessed, keeping the ring intact during this

functionalisation process. Asymmetric variants have also been developed by Fu, employing NiBr_2 -diglyme and various (*R,R*)-DMPEDA derivatives,¹⁴⁵ with specified conditions outlined to successfully cross-couple certain alkyl halides with borane reagents.

Scheme 43: Examples of Ni catalysed Suzuki cross-coupling of secondary alkyl halides in the literature.

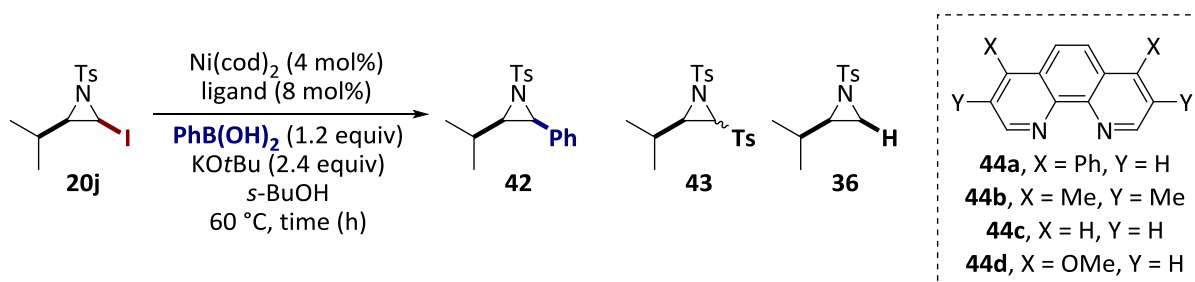


Due to the ready availability of aryl boronic acids and their inherent stability,¹⁴⁶ it was decided that this could be a suitable approach to the functionalisation of *N*-Ts iodoaziridines, keeping the ring intact during this process. In the following section, the reactivity of *N*-Ts iodoaziridines towards a range of literature nickel-catalysed Suzuki reactions will be assessed, attempting to cross-couple with phenyl boronic acid. The stereochemistry of the resulting aziridine products would also give insight into the reaction mechanism associated with Ni catalysed processes.

2.4.1.2: Assessment of Literature Conditions

Fu's Suzuki-Miyaura cross-coupling conditions were first evaluated, using bromocyclohexane as a model substrate. The desired cross-coupled phenylcyclohexane was successfully observed in the ^1H NMR spectrum of the crude reaction mixture in 78% ^1H NMR yield (*cf.* 91% yield obtained by Fu).¹⁴² With Fu's conditions having been successfully replicated, attentions turned towards the cross-coupling of iodoaziridine **20j** with phenyl boronic acid (**Table 15**).

Table 15: Attempted Ni catalysed Suzuki cross-coupling of iodoaziridine **20j** and phenyl boronic acid.



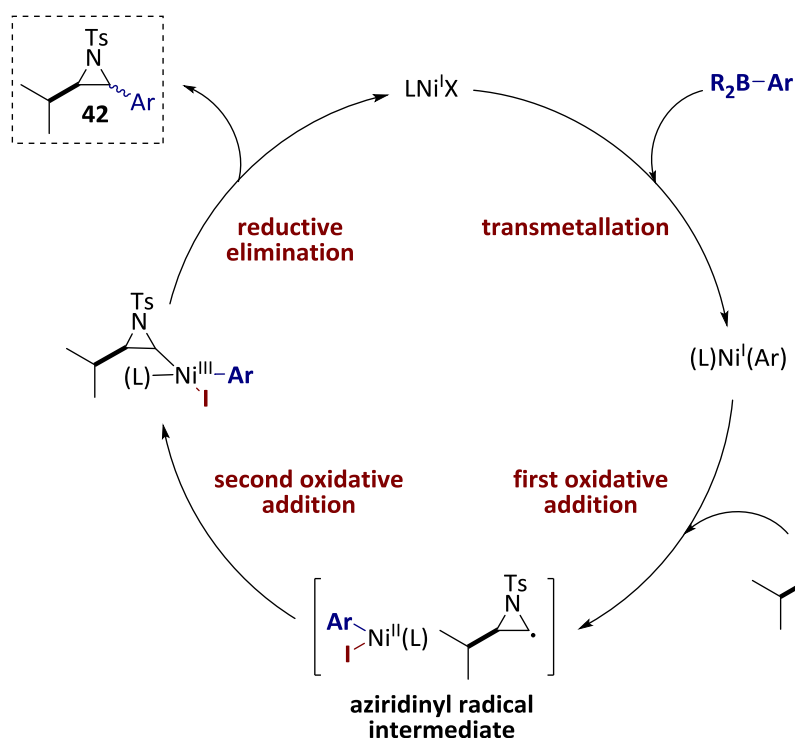
entry	ligand	time (h)	yield (%) ^a			
			42	43	36	20j ^b
1	44a	2	2	8 (<i>dr</i> = 3.0:1 <i>cis:trans</i>)	7	0
2	44b	2	1	15 (<i>dr</i> = 1.5:1 <i>cis:trans</i>)	4	0
3	44c	2	2	14 (<i>dr</i> = 1.3:1 <i>cis:trans</i>)	5	0
4	44d	2	2	14 (<i>dr</i> = 1.3:1 <i>cis:trans</i>)	5	0
5	44a	0.5	1	14 (<i>dr</i> = 1.8:1 <i>cis:trans</i>)	7	3
6 ^c	44a	2	1	4 (<i>dr</i> = 1.8:1 <i>trans:cis</i>)	6	28
7 ^d	44a	2	4	13 (<i>dr</i> = 1.8:1 <i>trans:cis</i>)	5	13
8 ^d	44a	5	5	15 (<i>dr</i> = 1.8:1 <i>trans:cis</i>)	8	9

^a Yield determined by ^1H NMR spectroscopy with reference to an internal standard (1,3,5-trimethoxybenzene). ^b Unreacted iodoaziridine **20j**. ^c Reaction run at $25\text{ }^\circ\text{C}$. ^d 1.6 equiv KOtBu used.

Reactions were cooled, filtered through a plug of silica to remove inorganics and the resulting crude reaction mixture analysed by ^1H NMR spectroscopy. Upon examination of Fu's optimised reaction conditions (albeit reducing reaction time to aid stability of starting material and potential product), a complex mixture of products was observed by ^1H NMR spectroscopy (**Table 15**, entry 1). Attempts at resolving components of the reaction mixture by column chromatography were unsuccessful. However, the desired cross-coupled aziridine **42** was observed, as the *cis*-diastereoisomer in a ^1H NMR yield of 2%. Other products identified from the reaction mixture were tosyl *N*-Ts aziridine mixture **43** (after successful isolation),¹⁴⁷ and dehalogenated aziridine **36**. In an attempt to rationalise the formation of tosyl *N*-Ts aziridine mixture **43**, examination of the literature suggested that activation of secondary alkyl halides with Ni complexes occurred via radical pathways.¹⁴⁸ This was also demonstrated by Fu in the coupling of *endo*- and *exo*-2-bromonorbornane with phenyl boronic acid.¹⁴² Both coupling reactions gave rise to identical products, arising from the *exo*-

norbornane which suggested a non-planar carbon centred radical intermediate. Several experimental and theoretical mechanistic studies since Fu's report have also reinforced radical based pathways for Ni catalysed cross-coupling of alkyl halides with boron derivatives.^{149,150} Applying these findings to iodoaziridine **20j**, a catalytic cycle is proposed below (**Figure 16**). A Ni(I)/Ni(III) catalytic cycle has been proposed, with transmetallation between the boron reagent and Ni giving a Ni(I) complex. A radical oxidative addition of the iodoaziridine would afford a Ni(II) complex and the aziridinyl radical intermediate. A second oxidative addition to give a Ni(III) complex, followed by reductive elimination would afford cross-coupled aziridine **42**, in turn regenerating the active catalytic species.

Figure 16: Ni catalysed cross-coupling of iodoaziridine **20j**.



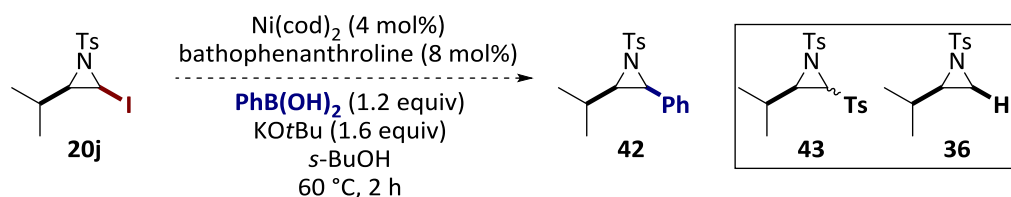
As shown above, activation of iodoaziridine **20j** via radical pathways would lead to the formation of an aziridinyl radical species. It was therefore postulated that an intermolecular transfer of a tosyl group was occurring, via attack of the aziridinyl radical species at sulfur of another iodoaziridine, rather than the desired second oxidative addition step. The complex mixture of products observed in the crude 1H NMR mixture was also apportioned to the uncontrollable high reactivity of the aziridinyl radical species.^{xi} In attempt to tune the reactivity of the Ni complex and prevent the degradation of

xi) Change of work up to an aqueous based protocol led to no improvement in yield for cross-coupled aziridine **42**, with similar degradation and complex mixture of products observed by 1H NMR.

the aziridiny radical intermediate, phenanthroline ligands with varying substitution were examined (entries 1-4). This however had no impact on the desired cross-coupling. Other reaction variables were also examined at this stage, employing bathophenanthroline **44a** as ligand of choice, again with limited success (entries 5-8). Two main deductions were however made at this point:

- (i) iodoaziridine **20j** was more stable under reaction conditions at lower reaction temperatures.
- (ii) fewer equivalents of KOtBu led to less consumption of starting iodoaziridine **20j**.

Keen to explore the effect of different Ni catalytic systems, Fu's modified reaction conditions employing Ni(II) halide salts were evaluated and successfully replicated (55% ¹H NMR yield for coupling of iodocyclohexane with 4-methoxyphenylboronic acid, *cf.* 77% yield obtained by Fu).¹⁴³ These conditions were then applied to iodoaziridine **20j**, using phenyl boronic acid as the cross-coupling partner. Changing [Ni] to NiI₂ and NiBr₂·glyme in combination with a range of amine/amino alcohol ligands appeared to have no effect on the desired cross-coupling reaction. Variation of base to NaHMDS also promoted the formation of tosyl *N*-Ts aziridine **43** and aziridine decomposition, with this rearrangement dominating the reactivity of the system. This was presumed to be due to the incompatibility of alkoxides with the iodoaziridine. With similar degradation patterns observed upon changing both Ni source and ligand type, control reactions were carried out on the initial Ni(cod)₂/bathophenanthroline system,¹⁴² to establish the cause of iodoaziridine degradation under the reaction conditions (**Table 16**).

Table 16: Control reactions establishing effect of reaction components on iodoaziridine **20j**.

entry	conditions	yield (%) ^a			
		42	43	36	20j ^b
1	conditions as above	4	14 (<i>dr</i> = 3.7:1 <i>trans</i> : <i>cis</i>)	5	18
2	no Ni(cod)_2	0	18 (<i>dr</i> = 3.5:1 <i>trans</i> : <i>cis</i>)	1	18
4	only KOtBu + solvent	0	13 (<i>dr</i> = 3.3:1 <i>trans</i> : <i>cis</i>)	5	5
5	no base	0	0	0	95

^a Yield determined by ¹H NMR spectroscopy with reference to an internal standard (1,3,5-trimethoxybenzene). ^b Unreacted iodoaziridine **20j**.

Under Fu's optimised conditions for the cross-coupling of secondary alkyl halides with boronic acids, noticeable formation of the tosyl *N*-Ts aziridine mixture **43** was evident (**Table 16**, entry 1), as previously described. Removal of Ni(cod)_2 from the system also interestingly led to formation of **43**, demonstrating that [Ni] was not responsible for the formation of the aziridinyl radical species. Surprisingly, submission of iodoaziridine **20j** to only KOtBu and 2-PrOH at 60 °C was found to generate the tosyl *N*-Ts aziridine mixture **43** (entry 3), suggesting that an alkoxide species was responsible for the aziridinyl radical formation. This was reinforced by performing the reaction in the absence of KOtBu (entry 4), whereby 95% starting iodoaziridine **20j** was recovered after 2 h at 60 °C. After examination of the literature, it became evident that KOtBu was acting as a single electron transfer reagent, first disclosed by Itami in 2008,¹⁵¹ causing the generation of an aziridinyl radical species. This was further confirmed on trapping the reactive intermediate with diphenyl diselenide, giving a mixture of *trans*- and *cis*-seleno-aziridines (*dr* = 8:1, *trans*:*cis*). For further discussion on the formation of aziridinyl radical species using KOtBu and formation of selenium substituted aziridines, see **Section 2.5**.

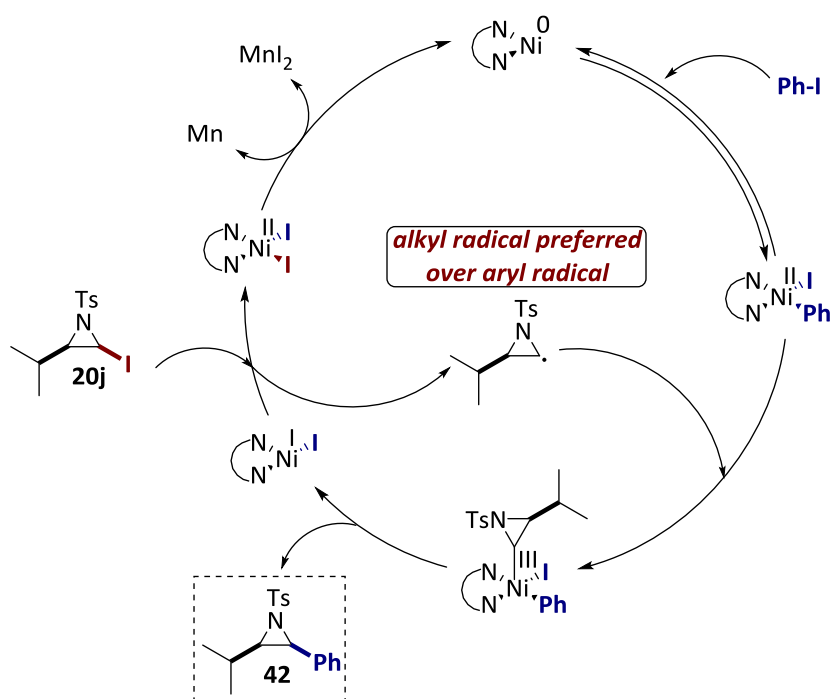
Other Ni catalysed Suzuki cross-coupling protocols by Fu involving a range of alkyl halides,^{152,153,154} were also evaluated. However the incompatibility of alkoxides with iodoaziridine **20j** due to aziridinyl radical formation was of concern. Other modes of activating phenyl boronic acid prior to cross-coupling with iodoaziridine (in the absence of alkoxide), were therefore considered. Sources of fluoride were evaluated with little success, employing the fluoride source in place of KOtBu under

the reaction conditions. Use of 1.6 equiv CsF quantitatively returned starting iodoaziridine **20j**, whereas use of TBAF led to decomposition of the reaction mixture. Both NaOAc and K₂CO₃ were also evaluated as alternative bases in the protocol, but in both instances only starting iodoaziridine **20j** was evident in the crude ¹H NMR spectrum.

2.4.1.3: Reductive Cross-Coupling

Reductive cross-coupling protocols involving iodoaziridine **20j** were also envisaged. This has recently been comprehensively reviewed by Weix (2014),¹⁵⁵ involving discussion of the principles of reactivity and selectivity in the Ni catalysed protocol. Weix has shown the advantageous nature of direct cross-coupling of two electrophiles (alkyl/aryl or alkyl/alkyl halide combinations), avoiding the necessity for using activated organometallic nucleophilic species, which can be difficult to generate and subsequently handle. The reductive cross-coupling protocol can occur solely in the presence of a Ni salt and suitable reductants,^{156,157} with cross-coupling selectivity governed by the differing reactivity of the alkyl halide and aryl halide under the reaction conditions. A general proposed mechanism for the potential cross-coupling of iodoaziridine **20j** with aryl iodides is shown below (**Figure 17**).

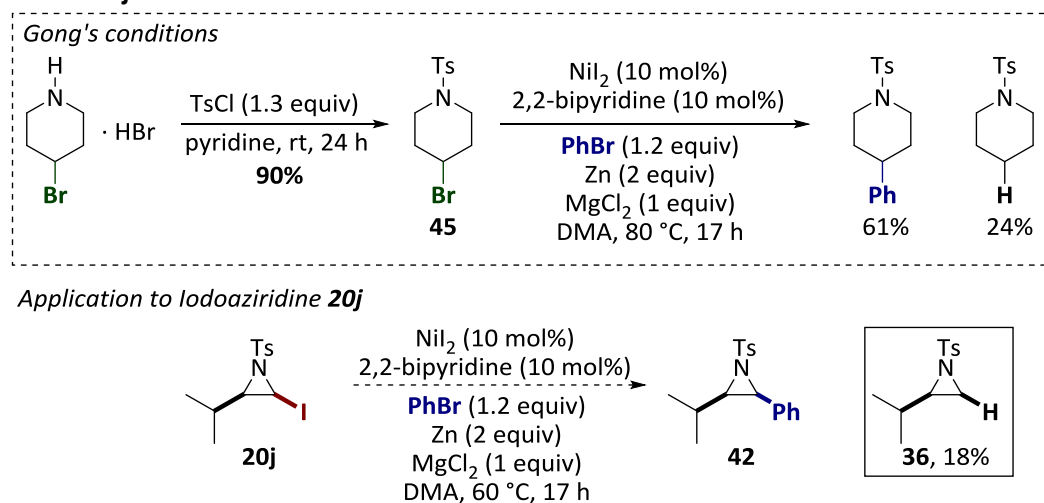
Figure 17: General proposed mechanism for cross-coupling of aryl iodides with iodoaziridine **20j**.



Selective oxidative addition of the aryl iodide to a Ni(0) species affords a Ni(II) complex, and reacts with an aziridinyl radical to form the diorganonickel(III) intermediate. Reductive elimination of the cross-coupled iodoaziridine generates a reactive Ni(I) iodide complex that can react with iodoaziridine **20j**, to regenerate the aziridinyl radical species. The Ni(II) diiodide is then reduced back

to the active Ni(0) species upon reaction with a suitable reductant. Due to the radical nature of the proposed mechanism, and formation of the aziridiny radical species from the iodoaziridine previously observed, reductive cross-coupling conditions were applied to iodoaziridine **20j**. Initially conditions by Gong and co-workers were evaluated,¹⁵⁸ focusing on the reductive cross-coupling between bromobenzene and 4-bromo-1-tosylpiperidine **45**. The optimisation substrate used by Gong, 4-bromo-1-tosylpiperidine **45**, was prepared via tosylation of the commercially available 4-bromopiperidine hydrobromide salt (**Scheme 44**).¹⁴³

Scheme 44: Evaluation of literature reductive cross-coupling protocol and application to iodoaziridine **20j**.



Due to the optimal ligand (4,4'-di-*tert*-butyl-2,2'-bipyridine) not being available, the reaction was investigated using 2,2'-bipyridine, a ligand explored during reaction optimisation. It became evident that heating with less electron rich bipyridine systems was required to promote arylation, and upon heating to 80 °C, 61% of the desired arylated piperidine was observed by ¹H NMR, matching that observed by Gong. Interesting to note is the difference in temperature required for the two catalytic systems. Under the optimised conditions with 4,4'-di-*tert*-butyl-2,2'-bipyridine as ligand, the reaction can be effectively run at rt, whereas heating was required to promote arylation with 2,2'-bipyridine. After replicating these conditions, we evaluated these conditions on iodoaziridine **20j**, albeit slightly reducing the reaction temperature to 60 °C due to known degradation of the iodoaziridine to sulfonamide at high temperatures. However, due to the highly reducing conditions, decomposition of iodoaziridine **20j** was shown to occur, with only 18% of dehalogenated aziridine **36** observable by ¹H NMR spectroscopy. Running the reaction at rt led to similar degradation, with 27% **20j** and 13% **36** observed by ¹H NMR. Further work in this area would evaluate Gong's conditions with electron rich bipyridine ligand systems, allowing a reduction in reaction temperature. Other potential coupling partners and reductants are yet to be explored.¹⁵⁹

2.4.1.4: Conclusions: Ni Catalysis

In conclusion, Ni catalysis was examined under a variety of common Ni catalysed Suzuki cross-coupling conditions that have recently been described in the literature.¹⁴³⁻¹⁵⁹ The generation of an aziridiny radical species was shown to occur under the alkoxide reaction conditions, which caused mainly degradation of the reaction mixture. Intermolecular tosyl transfer, via attack of the aziridiny radical at sulfur of another aziridine species is likely to be responsible for this degradation pathway. A variety of ligands and Ni sources were evaluated with similar behaviour observed. Reductive cross-coupling protocols were also examined, involving the cross-coupling of two electrophilic species. Under the strongly reductive reaction conditions, dehalogenation to give unsubstituted aziridine **36** and decomposition to *p*-toluenesulfonamide was observed.

2.4.2.1: Palladium Catalysed Iodoaziridine Cross-Coupling

The importance of the Suzuki-Miyaura reaction was recognised in 2010 with the joint award of the Nobel Prize in Chemistry for palladium catalysed cross-coupling reactions.¹⁶⁰ Although the construction of biaryl motifs is well established using Pd catalysis, the coupling of alkyl halides had been slower to develop due to competing β -hydride elimination pathways preventing desired coupling pathways occurring. Since the seminal sp^3 - sp^3 coupling by Suzuki (1992),¹⁶¹ utilising iodoalkanes and alkyl-9-BBN reagents in the presence of catalytic $Pd(PPh_3)_4$, several protocols have however been established using bulky and electron rich phosphine ligands, which has recently been outlined by Sigman (2011).¹⁶² These ligand properties have allowed Pd complexes to become sufficiently electron rich to undergo oxidative addition into sp^3 C-X bonds, and significantly sterically demanding in order to prevent β -hydride elimination pathways, whilst increasing the rate of reductive elimination. Although the catalytic cycle for the palladium catalysed Suzuki-Miyaura reaction is well established in the literature (oxidative addition, transmetallation, reductive elimination – Pd(0)/Pd(II) catalytic cycle),¹⁶⁰ there still remains a lack of mechanistic understanding concerning transmetallation and the precise role of the base during this step.^{163,164,165}

This section will consider the Pd catalysed Suzuki-Miyaura cross-coupling of an *N*-Ts iodoaziridine, using phenyl boronic acid as the coupling partner. A range of literature conditions will be assessed aiming to form new carbon-carbon bonds onto the intact aziridine. Key to the success of the reaction will be oxidative addition into the C-I bond, rather than the also relatively weak C-N aziridine bond which has previously been demonstrated in the literature (*vide supra*, **Section 1.3**, page 15) affording ring opened cross-coupled products.

2.4.2.2: Assessment of Literature Conditions

Initially, use of KOH as a base was investigated under Pd catalysed Suzuki cross-coupling conditions developed by Organ and co-workers using a PEPPSI catalyst (PEPPSI – Pyridine Enhanced Precatalyst Preparation Stabilisation Initiation).¹⁶⁶ The PEPPSI–IPr catalytic system has been shown to be both electron rich (due to the NHC ligand) and significantly bulky to aid reductive elimination. The active Pd(0) species can be generated *in situ* via reduction of the stable Pd(II) complex. Similar Ni catalysed conditions were also evaluated, with both reactions mainly leading to formation of tosyl *N*-Ts aziridine **43**, which is believed to be indicative of an aziridiny radical species formed under the reaction conditions (Table 17).

Table 17: Use of KOH in Suzuki-Miyaura cross-coupling.

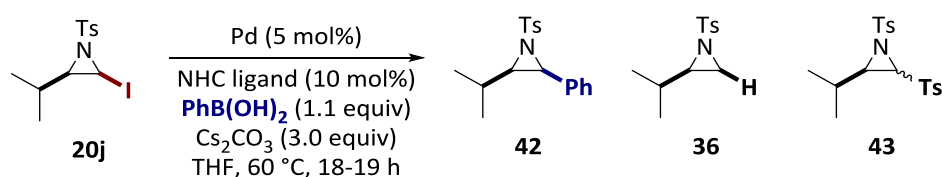
entry ^a	Pd source	ligand	yield ^b			20j ^c	recovery
			42	36	43		
1	PEPPSI TM –IPr (10 mol%)	-	3	10	20 ^d	37	70
2	Ni(cod) ₂ (4 mol%)	bathophen (8 mol%)	3	29	25 ^e	1	58

^a Reaction conditions: aziridine **20j** (0.14 mmol), M (mol%), ligand (mol%), PhB(OH)₂ (1.1 equiv), KOH (3.0 equiv), THF (0.07 M), 60 °C, 18-19 h. ^b Yield determined by ¹H NMR spectroscopy with reference to an internal standard (1,3,5-trimethoxybenzene). ^c Unreacted iodoaziridine **20j**. ^d *dr* of mixture approximately 2:1 *trans:cis*. ^e *dr* of mixture approximately 3:2 *cis:trans*.

Concerned with the generation of alkoxides and aziridine radicals under basic conditions, a variety of common bases employed in Pd cross-coupling were examined (2 equiv base with respect to iodoaziridine **20j**), heating in THF at 60 °C, with the resulting mixtures analyzed by ¹H NMR. As expected, use of KOtBu resulted in iodoaziridine degradation, whereas a loss in recovery was also observed with DBU (82% by ¹H NMR), AgNO₃ (80% by ¹H NMR) and K₃PO₄ (94% by ¹H NMR). Potassium carbonate was chosen as a suitable base to explore further PEPPSI catalysis (5% PEPPSI–IPr). However examination of solvent and temperature profiles led to minimal product conversion (< 5% by ¹H NMR). Use of temperatures in excess of 60 °C and use of biphasic solvent systems (commonly employed in Suzuki reactions) generally led to decomposition of iodoaziridine **20j** to *p*-tolylsulfonamide. Disappointingly, an increase in Pd loading to 10% also led to no major increase in desired arylated aziridine. As a result of this, the electronics of the NHC system were

investigated. Using the PEPPSI-IPr system as a control reaction, the generation of Pd-NHC complexes in situ from NHC salts, using both PdCl₂ and Pd(OAc)₂ were evaluated, based on work by Nolan (**Table 18**).¹⁶⁷ Employing Cs₂CO₃ and varying both imadazolium salt and Pd(II) source, enabled generation of a variety of Pd(0)-NHC complexes. No desired increase in cross-coupled aziridine **42** was observed under these modified reaction conditions. Significant degradation to the corresponding tosyl *N*-Ts aziridine **43** was observed under the reaction conditions, indicative of the formation of an aziridiny radical species.

Table 18: Variation of Pd/NHC ligand system in Pd catalysed Suzuki cross-coupling.



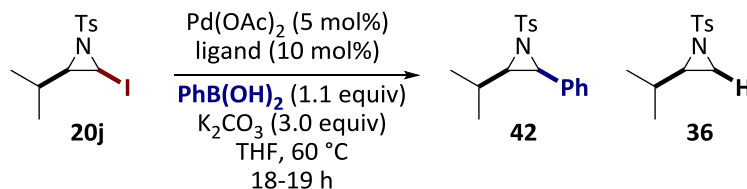
entry ^a	Pd source	NHC ligand	yield ^b				recovery
			42	36	43^c	20j^d	
1 ^e	-	PEPPSI TM -IPr	4	-	-	93	97
2	Pd(OAc) ₂	ItBu-HBF ₄	4	10	24	19	57
3	Pd(OAc) ₂	IPr-HCl	2	15	8	54	79
4	Pd(OAc) ₂	ICy-HBF ₄	3	18	11	50	82
5	Pd(OAc) ₂	IMes-HCl	1	7	8	66	85
6	PdCl ₂	ItBu-HBF ₄	6	4	18	40	68
7	PdCl ₂	ICy-HBF ₄	5	2	6	70	84

^a Reaction conditions: aziridine **20j** (0.14 mmol), Pd(OAc)₂ (5 mol%), NHC ligand (10 mol%), PhB(OH)₂ (1.1 equiv), Cs₂CO₃ (3.0 equiv), THF (0.07 M), 60 °C, 18-19 h. ^b Yield determined by ¹H NMR spectroscopy with reference to an internal standard (1,3,5-trimethoxybenzene). ^c *dr* of mixture approximately 2:1 *trans:cis*. ^d Unreacted iodoaziridine **20j**. ^e Control reaction: PEPPSITM-IPr (10 mol%), PhB(OH)₂ (1.1 equiv), K₂CO₃ (3.0 equiv), THF, 60 °C, 18 h.

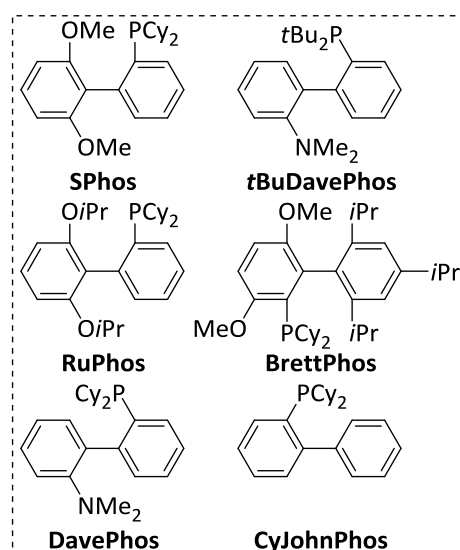
Catalytic systems comprising monophosphine ligands and Pd salts were next explored. Employing a Pd/PCy₃ catalytic system in combination with KF (used as a mild base) reported by Fu (2000),¹⁶⁸ led to no reactivity of iodoaziridine **20j** under the reaction conditions. Variation of both Pd source (Pd(OAc)₂ and Pd(dbp)₃) and base (KF, CsF, Cs₂CO₃, AgOAc, K₃PO₄) under Fu's optimised conditions led to no desired cross-coupled product by ¹H NMR spectroscopy. Buchwald has recently demonstrated that biaryl monophosphine ligand systems can be effective in the coupling of challenging substrates, including hindered aryl boronic acids and unreactive aryl chlorides under

mild reaction conditions.¹⁶⁹ Keen to explore the effect of different ligand systems, a range of Buchwald ligands displaying varying electronics were screened (**Table 19**).

Table 19: Variation of Buchwald ligands in Suzuki cross-coupling of iodoaziridine **20j**.



entry ^a	ligand	yield (%) ^b			recovery
		42	36	20j ^c	
1	SPhos	1	-	85	86
2 ^d	SPhos	2	-	87	89
3	RuPhos	-	-	87	87
4	DavePhos	-	-	69	69
5	<i>t</i> -BuDavePhos	-	-	96	96
6	BrettPhos	-	4	88	88
7	CyJohnPhos	1	3	56	60



^a Reaction conditions: aziridine **20j** (0.14 mmol), Pd(OAc)_2 (5 mol%), ligand (10 mol%), PhB(OH)_2 (1.1 equiv), K_2CO_3 (3.0 equiv), THF (0.07 M), 60 °C. ^b Yield determined by ^1H NMR spectroscopy with reference to an internal standard (1,3,5-trimethoxybenzene). ^c Unreacted iodoaziridine **20j**. ^d Dioxane:H₂O (4:1) used instead of THF.

SPhos was first employed, with iodoaziridine **20j** displaying minimal reactivity under the reaction conditions (**Table 19**, entry 1). Conditions used within the Bull Group for the Suzuki coupling of 4-chlorobenzene sulfonyl oxetanes with phenyl boronic acid were also evaluated (entry 2),¹⁷⁰ with no major improvement in the yield of cross-coupled aziridine **42**. Use of RuPhos, DavePhos and *t*-BuDavePhos (entries 3-5) furnished no desired cross-coupled aziridine **42**, with decomposition of the reaction mixture to *p*-tolylsulfonamide evident upon analysis of the crude ^1H NMR spectra, leading to a loss in aziridine recovery. Similar reactivity was observed upon employing BrettPhos and CyJohnPhos (entries 6-7).

Due to lack of reactivity under these conditions, cross-couplings of analogous cyclopropanes were examined. Charette had previously disclosed the first Suzuki cross-coupling of iodocyclopropanes with both boronate esters and boronic acids.^{171,172} These conditions were applied to the cross-

coupling of iodoaziridine **20j** with phenyl boronic acid pinacol ester. Degradation to *p*-toluenesulfonamide was observed under the reaction conditions, presumably due to the high reaction temperatures in combination with the biphasic solvent system employed.

2.4.2.3: Conclusions: Pd Catalysis

Assessment of a selection of literature Pd catalysed Suzuki cross-coupling conditions has led to the formation of *cis*-aziridine **42**, observed via ^1H NMR spectroscopy. The stable PEPPSI-IPr catalyst in combination with PhB(OH)_2 was shown to afford **42** in 5% ^1H NMR yield. However, the use of biphasic reaction systems in combination with moderately high reaction temperatures, commonly employed in Suzuki couplings led to undesired degradation of the reaction mixture to *p*-tolylsulfonamide. Generation of Pd-NHC complexes in situ from Pd and imidazolium salts, using Cs_2CO_3 , led to formation of tosyl *N*-Ts aziridine **43**, implying the formation of an aziridinyl radical species under the basic reaction conditions. Monophosphine ligand systems, in particular Buchwald ligands, in combination with Pd(OAc)_2 were shown to be ineffective towards the desired cross-coupling, with degradation mainly observed. The commonly used basic and biphasic reaction conditions have shown to lead to undesired degradation pathways. Other cross-coupling partners are yet to be evaluated which could circumvent these issues, including 9-BBN reagents, PhBF_3K salts and boronate species.¹⁴⁶ An extensive screen of Pd/ligand combinations is also yet to be undertaken.

2.4.3.1: Iron Catalysed Iodoaziridine Cross-Coupling

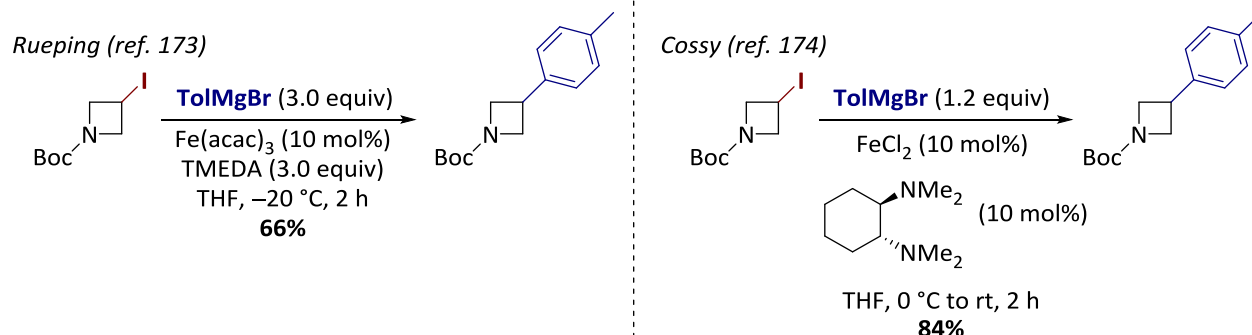
Palladium and nickel salts are commonly employed in cross-coupling reactions, due to the variety of ligands available to fine tune the electronics of the transition metal centre for the desired reaction. However, the high toxicity combined with the expensive nature of both metal and ligand, has driven research into catalysis using more a sustainable and less toxic source of transition metal.^{xii} Not only can iron catalysis provide clear economical and sustainability advantages, the variety of oxidation states Fe can adopt can lead to different chemical reactivity to that demonstrated by Ni/Pd chemistry (*vide infra*).

Iron catalysed cross-coupling reactions between saturated heterocycles and Grignard reagents have recently been reported in the literature, forming new carbon-carbon bonds, keeping the ring intact

xii) a) Market price for Palladium: £15880 per kg. b) Market price for Iron Ore: £0.04 per kg (prices correct 31st March 2015). Information collected from www.infomine.com

during this process.^{173,174} Recent methodology has exploited the versatility of iron cross-coupling, arylating 3-iodoazetidine under simple and effective reaction conditions (**Scheme 45**).

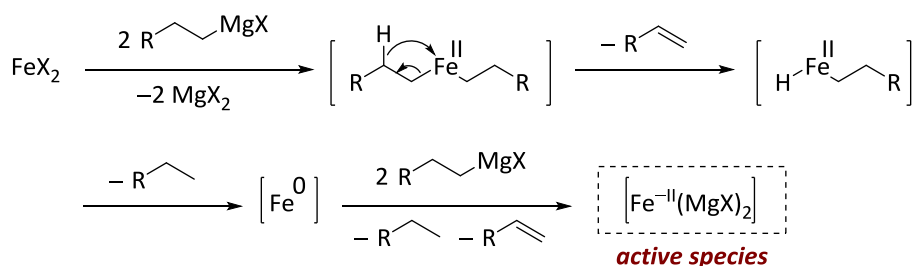
Scheme 45: Azetidine functionalisation, keeping ring intact during functionalisation process.



Mechanistic understanding of iron catalysed cross-coupling reactions is less established in comparison with nickel and palladium chemistry. A brief outline of current mechanistic hypothesis will be presented here, involving Fe(-II)/Fe(0) and Fe(0)/Fe(II) catalytic cycles. For a more detailed overview, including other postulated mechanisms, the reader is directed towards the following reviews: Furstner (2008),¹⁷⁵ von Wangelin (2009),¹⁷⁶ and Bolm (2008).¹⁷⁷

Early experimental evidence by Kochi and co-workers suggested that a “*reduced form of soluble iron*”, was an active catalytic species for the stereospecific cross-coupling of vinyl halides with alkyl Grignard reagents, in the presence of FeCl₃.^{178,179} The precise configuration of the active iron species was attributed to either an Fe(I) or Fe(0) species. A traditional catalytic cycle was then proposed, involving oxidative addition, transmetalation and reductive elimination to afford the coupled product and regenerate the active iron catalytic species.¹⁸⁰ Since this pioneering work, Bogdanovic has demonstrated that a 4 electron reduction occurs on reacting FeCl₂ with alkyl Grignard reagents (4 equiv Grignard, with respect to catalyst loading), leading to the formation of a cluster species of the form [Fe(MgX)₂] (**Scheme 46**).¹⁸¹

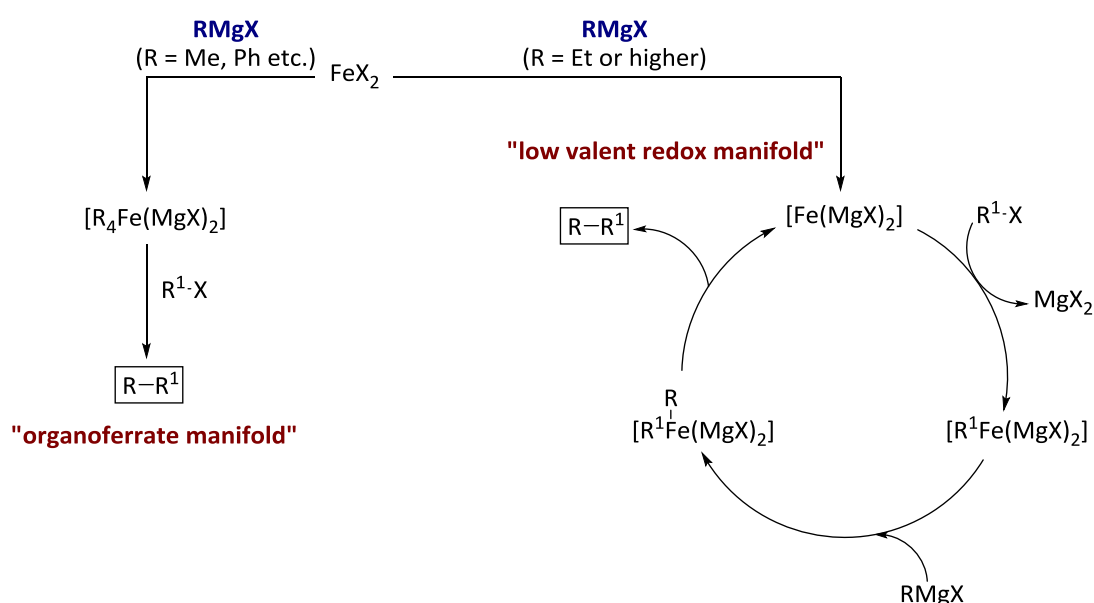
Scheme 46: Proposed formation of active iron species using 4 equiv alkyl Grignard reagent.



This low valent intermetallic catalyst was proposed to be the active species, with a formal negative charge at iron resulting in an overall Fe(-II)/Fe(0) catalytic cycle (contrasting to Fe(0)/Fe(II) cycle,

more associated with Pd/Ni chemistry) (**Scheme 47**).¹⁸² Work by Fürstner has supported this mechanism by revealing that active Fe(0) powder is not sufficient to promote cross-coupling reactions, but is activated upon reaction with excess Grignard reagent.^{183,184} Different mechanistic pathways have been proposed for Grignard reagents possessing no β -hydrogens (e.g. MeMgBr, PhMgBr) supported by experimental evidence.¹⁸² Exhaustive alkylation of the iron centre by the Grignard reagent, followed by transfer of the organic residue to reactive electrophiles (e.g. acid chlorides) affords coupled products.

Scheme 47: Proposed reaction pathways for iron catalysis using Grignard reagents.



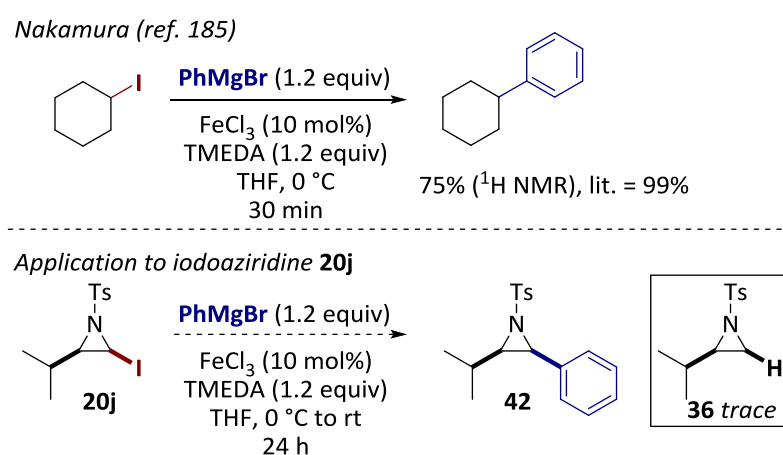
Although this catalytic pathway has been largely attributed to the reaction of aryl halides/triflates with Grignard reagents, the iron catalysed cross-coupling of alkyl halides with alkyl Grignard reagents has also been extensively explored.^{185,186,187} Other mechanisms for these couplings have been proposed, involving alkyl radical intermediates generated via single electron transfer, resulting in an overall Fe(0)/Fe(II) catalytic cycle.¹⁸⁶ Due to radical intermediates being postulated and cross-coupling success demonstrated in the literature with alkyl halides, we believed exploring iron catalysis was a viable strategy in order to functionalise *N*-Ts iodoaziridines, keeping the ring intact during this process. In this section a range of literature conditions will be assessed, exploring the reactivity of *N*-Ts iodoaziridines to Fe salts and Grignard reagents.

2.4.3.2: Assessment of Literature Conditions

Nakamura and co-workers have previously reported the iron catalysed cross-coupling of primary and secondary alkyl halides with aryl Grignard reagents, using TMEDA as a stoichiometric additive.¹⁸⁵ The

reaction conditions were successfully evaluated using iodocyclohexane and phenyl magnesium bromide under the reported FeCl_3 /TMEDA catalytic system in 75% yield (via ^1H NMR spectroscopy) (**Scheme 48**). Application of these conditions to iodoaziridine **20j** resulted in no apparent formation of the expected arylated aziridine **42**, but trace amounts of dehalogenated aziridine **36** were present. TLC analysis of the reaction mixture at 0 °C indicated only starting iodoaziridine **20j**, even upon after warming the reaction mixture to room temperature overnight.

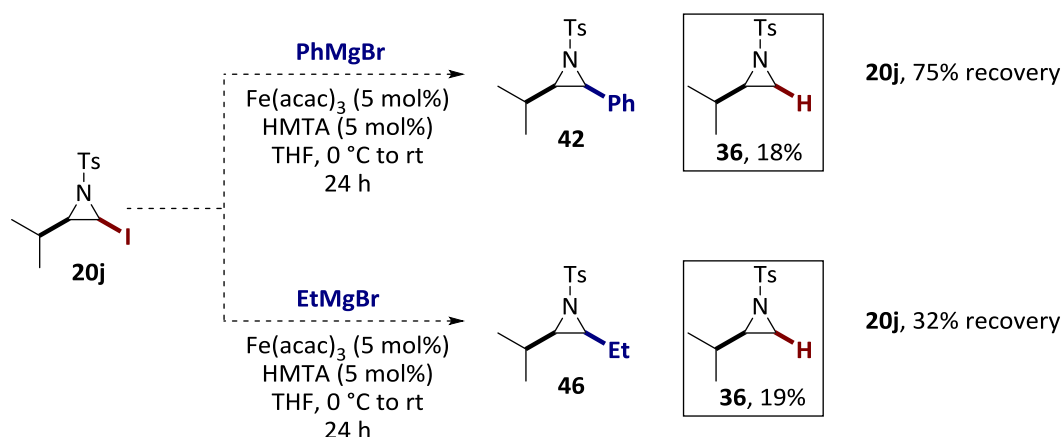
Scheme 48: Assessment of Nakamura's iron cross-coupling reaction conditions.



Bedford and co-workers have also demonstrated that FeCl_3 can be employed with simple amine ligands, forming active catalysts in situ, and are suitable to efficiently couple Grignard reagents with primary and secondary alkyl halides.¹⁸⁸ Advantageously under Bedford's reaction conditions, it was shown that no dropwise addition of the Grignard was required to maintain reaction progress, unlike earlier conditions outlined by Nakamura.¹⁸⁵ Bedford's conditions were first evaluated using iodocyclohexane, employing both DABCO and TMEDA as additives. Both additives returned excellent yields for the arylated cyclohexene, in accordance with observations made by Bedford. Applying the DABCO conditions to both iodoaziridine **20a** and **20i**, led to no desired arylated aziridine but only trace amounts of the corresponding dehalogenated aziridines.

Cahiez has published an array of iron catalysed alkylations of aromatic Grignard reagents with amine additives under mild reaction conditions.¹⁸⁶ 2-Bromobutane was chosen as a suitable substrate to investigate the reaction protocol, with HMTA demonstrated to have an influential effect on the iron catalysed cross-coupling between the alkyl bromide and phenyl magnesium bromide. Under identical reaction conditions to those described by Cahiez a similar yield for the arylated butane was observed by ^1H NMR spectroscopy (77% by ^1H NMR). Cahiez's conditions were applied to iodoaziridine **20j** (**Scheme 49**).

Scheme 49: Applying Cahiez's conditions to iodoaziridine **20j**.

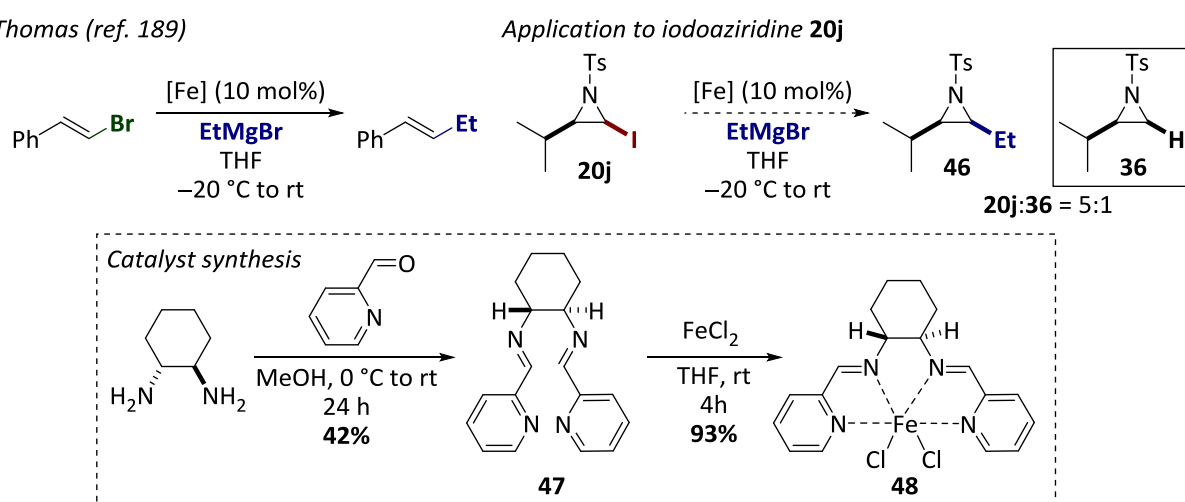


Both PhMgBr and EtMgBr were employed under identical reaction conditions, in potential iron catalysed cross-coupling reactions with iodoaziridine **20j**. No desired cross coupled products were observed by ¹H NMR spectroscopy, although the presence of dehalogenated aziridine **36** in both cases suggested undesired reactivity under the reaction conditions. In an interesting comparison between the use of PhMgBr and EtMgBr, excellent recovery of aziridine was observed when employing PhMgBr, whereas EtMgBr displayed more common aziridine degradation products (*p*-toluenesulfonamide). Stability studies were conducted, individually stirring each reaction component with iodoaziridine **20j** in THF. In the presence of various Fe salts and amine ligands, iodoaziridine **20j** was returned quantitatively. However, treatment of **20j** with EtMgBr at room temperature led to the formation of dehalogenated aziridine **36**, with decomposition of iodoaziridine **20j** to *p*-toluenesulfonamide also evident under the reaction conditions. This suggested that iodine–Grignard exchange was occurring, forming a highly unstable aziridinyl magnesium species, leading to protonation or decomposition of this metallated aziridine. Similar dehalogenation reactions have also been observed by Fürstner and co-workers when employing both aryl bromides and aryl iodides in iron catalysed cross-coupling reactions with alkyl Grignard reagents.¹⁸³ The formation of dehalogenated aromatics was attributed to the highly reductive nature of the active iron catalyst, causing dehalogenation via single electron transfer protocols.

Dehalogenation of iodoaziridine **20j** was also prominent on evaluation of reaction conditions outlined by Thomas and co-workers (**Scheme 50**).¹⁸⁹ The bench stable Fe(II) complex **48** was prepared according to literature procedures.^{189,190} Condensation of *trans*-(±)-diaminocyclohexane with 2.0 equiv of 2-pyridinecarboxaldehyde afforded salen ligand **47** in 42% yield, and further complexation with FeCl₂ furnished Fe(II) complex **48**. Unfortunately under Thomas's optimised reaction conditions, a 5:1 ratio of starting iodoaziridine **20j** and dehalogenated aziridine **36** was observed in the crude reaction mixture.

Scheme 50: Application of Thomas's cross-coupling conditions.

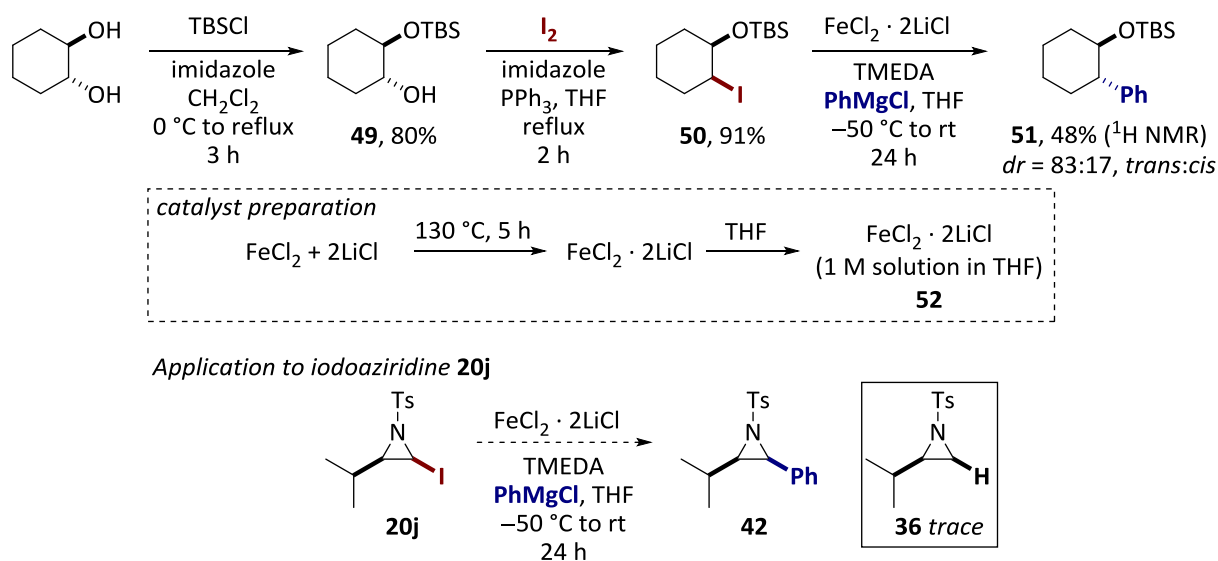
Thomas (ref. 189)



Attentions were then focused towards more recent conditions reported by Knochel and co-workers on iron catalysed cross-coupling of *N*-heterocyclic bromides with arylmagnesium reagents.¹⁹¹ In comparison with sp^2 - sp^3 iron catalysed carbon-carbon bond formation, the construction of sp^2 - sp^2 carbon-carbon bonds is less established in the literature due to the formation of undesired homocoupling products. 2-Bromopyridine was chosen as a suitable substrate to investigate the protocol, with both $Fe(acac)_3$ and $FeCl_3$ furnishing comparable yields of the corresponding arylated pyridine upon coupling with $PhMgBr$, in good agreement with that reported in the literature. Further reports by Knochel indicated that employing isoquinoline as a ligand dramatically enhanced both the rate of cross-coupling and yield of desired product.¹⁹² Various iron salts were shown under these modified conditions to afford the desired arylated pyridine in moderate yields. The most effective reaction conditions with were applied to iodoaziridine **20j**. From analysis of the crude 1H NMR spectra, the only identifiable product was dehalogenated aziridine **36** in 10% yield. No cross-coupled product was observed, although after this time period, only 10% starting iodoaziridine **20j** was remaining by 1H NMR. Attempts to isolate any other products via column chromatography were unsuccessful.

A highly diastereoselective iron catalysed sp^2 - sp^3 coupling between functionalised iodocyclohexanes and aryl Grignard reagents, formed from their corresponding aryl bromides, has also recently been reported by Knochel.¹⁹³ Preparation of the complex $FeCl_2 \cdot 2LiCl$ was found to be productive in the coupling protocol preferentially giving the thermodynamically stable *trans*-substituted products with excellent diastereoselectivity. Both iron complex **52** and functionalised iodocyclohexane **50** were accessed from literature procedures in order to assess the methodology (**Scheme 51**).

Scheme 51: Preparation of functionalised iodide **50** and iron complex **52** and attempted cross-coupling with PhMgBr.



Mono-protection of *trans*-cyclohexanediol using TBSCl afforded cyclohexanol **49** in good yield. Substitution of the free alcohol under Appel-like conditions with iodide afforded *cis*-iodocyclohexane **50** with inversion of stereochemistry at the reacting centre. Submission of iodocyclohexane **50** under Knochel's optimised conditions returned the expected arylated cyclohexane **51** in modest ¹H NMR yield and identical diastereoselectivity in comparison with the literature (lit. = 86% yield; *dr* = 83:17, *trans*:*cis*). The slow addition of the Grignard reagent required at -50 °C proved problematic due to precipitation of the Grignard reagent from the solution. However these conditions were then applied to iodoaziridine **20j**, with only trace amounts of unsubstituted aziridine **36** present after 24 h at rt.

2.4.3.3: Conclusions: Fe Catalysis

Literature conditions demonstrating Fe catalysed cross-coupling of both aryl halides and alkyl halides with Grignard reagents have been applied to *N*-Ts iodoaziridines. Although a variety of Fe salts, ligands and additives are yet to be explored, early experimental evidence has suggested that dehalogenation is occurring under the highly reductive conditions, with no desired cross-coupled aziridine observed under the conditions examined. Dehalogenation is proposed to occur via either an iodine-Grignard exchange, followed by quenching of the unstable aziridinyl magnesium intermediate or via a two electron reduction from the highly reduced active Fe species. Successful iron catalysed cross-couplings of iodo-azetidines have been recently described in the literature,^{173,174} employing conditions yet to be evaluated on *N*-Ts iodoaziridines. The observed dehalogenation with iodoaziridine **20j** in comparison with these systems could potentially be attributed to the increased

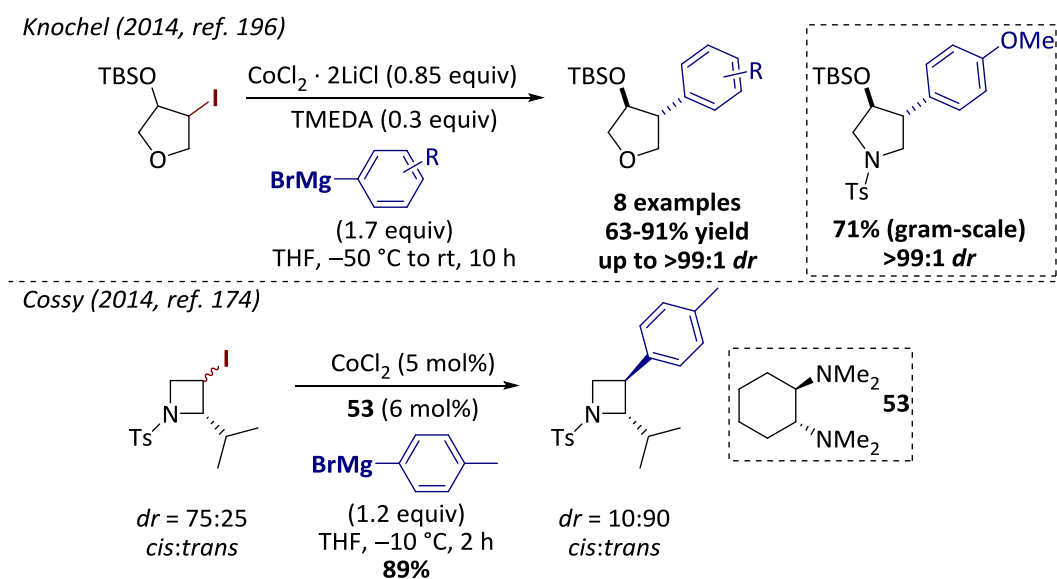
C-I bond reactivity (α -to *N* in the aziridine, β -to *N* in azetidine). These protocols have however demonstrated that Fe catalysis, employing saturated *N*-heterocycles as coupling partners can be adopted as a suitable approach to intact functionalisation. Further work should be aimed towards assessing these reaction conditions, with both aromatic and alkyl Grignard reagents shown to be suitable coupling partners.

2.4.4.1: Cobalt Catalysed Iodoaziridine Cross-Coupling

Since the development of the Co catalysed cross-coupling of bromobenzene with PhMgBr by Kharasch (1941),¹⁹⁴ there has been a significant growing interest in Co catalysed cross-coupling protocols. This is primarily due to the differing modes of reactivity available with Co salts in comparison to both Pd and Ni analogues (for example β -hydrogen elimination pathways of alkyl-cobalt intermediates have been shown not to be a limitation).¹⁹⁵ These approaches have also been deemed more sustainable and cheaper alternatives to Pd/Ni catalysed processes (in similar fashion to Fe catalysed protocols).^{xiii} Particular recent attention in the literature has been focused on sp^3 - sp^2 carbon-carbon bond formation, with many examples demonstrating high chemoselectivity and functional group compatibility. The wide range of cross-coupling transformations available when employing Co catalysis has recently been comprehensively reviewed by Cahiez (2010).¹⁹⁵ However despite the recent advances within Co catalysis, few diastereoselective Co catalysed cross-coupling reactions have been reported to date (**Scheme 52**). Building upon an earlier reported diastereoselective Fe catalysed cross-coupling of iodohydrins with Grignard reagents,¹⁹³ Knochel extended this protocol to functionalised saturated heterocycles using Co catalysis.¹⁹⁶ The use of sub-stoichiometric $CoCl_2 \cdot 2LiCl/TMEDA$ was demonstrated to be a highly efficient catalytic system in the preparation of *trans*-3,4-disubstituted tetrahydrofurans and pyrrolidines in excellent yields with *dr* up to >99:1.

xiii) a) Market price for Palladium: £15880 per kg. b) Market price for Cobalt: £18.32 per kg (prices correct 31st March 2015). Information collected from www.infomine.com

Scheme 52: Recent diastereoselective Co catalysed cross-couplings.



Cossy has also recently shown that a CoCl₂/diamine catalytic system (ligand **53**), was suitable to effect the chemoselective cross-coupling of a variety of saturated iodinated *N*-heterocycles with functionalised aromatic Grignard reagents, keeping the heterocyclic ring intact during this process.¹⁷⁴ A diastereoselective variant of the reaction was also reported, with the preparation of a *trans*-2,3-disubstituted azetidine in good yield and *dr*. The loss of stereochemical information of the starting 2,3-disubstituted iodo-azetidine (*dr* = 75:25, *cis:trans*) in the cross-coupled azetidine represented evidence for a planar radical intermediate, with subsequent preference for *trans*-diastereochemistry observed in the arylated azetidine (*dr* = 10:90, *cis:trans*).^{xiv} With cross-coupling success demonstrated in the literature for iodocyclohexanes, aryl iodides and more recently saturated functionalised *N*- and *O*-heterocycles, probing the reactivity of Co catalysts towards *N*-Ts iodoaziridines was deemed a plausible approach. The following section will assess the applicability of Co catalysis towards *N*-Ts iodoaziridines, keeping the aziridine ring intact during this functionalisation process.

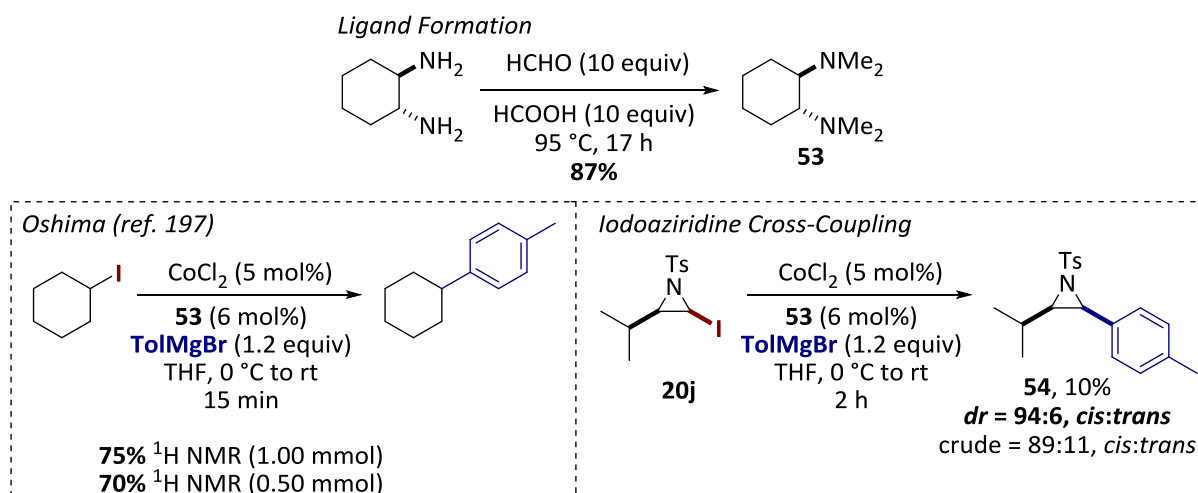
2.4.4.2: Assessment of Literature Conditions

Initially Oshima's conditions were evaluated, involving CoCl₂ and a simple diamine in combination with a Grignard reagent (**Scheme 53**).¹⁹⁷ An Eschweiler-Clarke reaction was employed to protect *trans*-diaminocyclohexane according to the method of Snyder and co-workers,¹⁹⁸ giving protected diamine **53** in excellent yield. The efficacy of the ligand was evaluated by employing **53** in a Co catalysed cross-coupling of iodocyclohexane with tolyl magnesium bromide as reported by Oshima.

xiv) Knochel and Cossy Co catalysed cross-couplings published in the literature after synthetic work finished.

The reaction was shown to be efficient on both the described scale and a more suitable reduced scale for potential iodoaziridine cross-coupling optimisation reactions (75% for repeated scale, 70% on reduced scale).

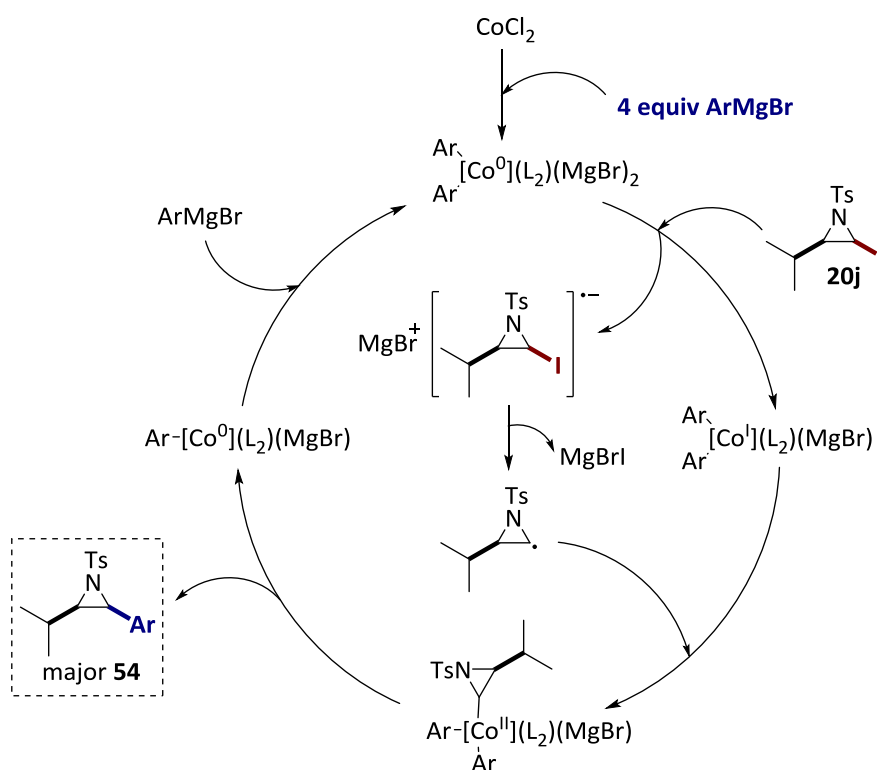
Scheme 53: Cobalt catalysis – Oshima conditions applied to iodoaziridine **20j**.



These conditions were then applied to *N*-Ts iodoaziridine **20j** coupling with *p*-tolylmagnesium bromide. Gratifyingly after 2 h at rt, cross-coupled aziridine was present in the ^1H NMR spectrum of the crude product, with *cis*-aziridine **54** present as the major diastereoisomer ($dr = 89:11$, *cis:trans*), isolated as a mixture of diastereoisomers in 10% yield.^{xv} The *cis*-stereochemistry of the major aziridine was assigned based on $^3J_{\text{H-H}}$ coupling constants observed in the ^1H NMR spectrum of the crude product for the aziridine ring proton, with values observed consistent with that reported in the literature for *cis*-aziridines (e.g. for major *cis*-aziridine **54**, CHTol, $\delta = 3.96$ ppm, $^3J_{\text{H-H}} = 7.1$ Hz; minor *trans*-aziridine **55**, CHTol, $\delta = 3.74$ ppm, $^3J_{\text{H-H}} = 4.7$ Hz).¹³¹ A tentative catalytic cycle is proposed for the formation of *cis*-aziridine **54** under the reaction conditions (**Figure 18**).¹⁹⁹

xv) Only fractions containing only **54** + **55** were combined to establish identity of product. Disparity in dr between crude and clean product could be due down to minor differences in R_f for two diastereoisomers.

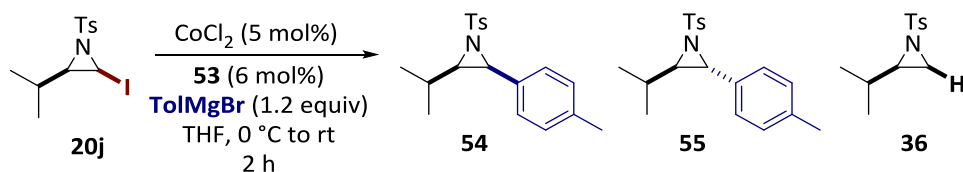
Figure 18: Proposed catalytic cycle for Co catalysed iodoaziridine cross-coupling.



It should be noted that the behaviour of the Co catalyst was shown to be dependent on the type of organic halide employed in the reaction. Both aryl and alkenyl halides were shown to react in a stereospecific manner via nonradical oxidative addition pathways with the active Co species, whereas alkyl halides reacted via radical based mechanisms. For the case of the Co catalysed cross-coupling of iodoaziridine **20j** with *p*-tolylmagnesium bromide, the active Co^0 species is generated upon reaction of CoCl_2 with 4 equiv Grignard reagent (with respect to the Co catalyst). Single electron transfer from the active electron rich 17 electron cobalt ate complex to iodoaziridine **20j** generates the iodoaziridine radical anion and a Co^{I} complex. Subsequent elimination of iodide from the iodoaziridine radical anion forms the reactive aziridinyl radical species, which recombines with the newly formed Co^{I} complex, affording a Co^{II} complex. Reductive elimination between the aziridine species and the aryl group from the Co^{II} complex, preferentially gives the *cis*-coupled product **54** and a Co^0 complex. The active Co species is regenerated upon reaction with an equivalent of the Grignard reagent. The reaction diastereoselectivity could be attributed to unfavourable steric clashes in the transition state, whereby the cobalt complex approaches from the less congested face of the aziridinyl radical intermediate. Potential steric clashes between the *N*-tosyl protecting group and the Co complex could lead to the preferential formation of the *cis*-substituted aziridine **54** over *trans*-aziridine **55**. The generation of both diastereoisomers under the reaction conditions also strongly supports the formation of a non planar radical intermediate, as previously proposed in the literature.

After this initial success, the effect of varying the addition time of *p*-tolylmagnesium bromide on the yield of cross-coupled aziridine **54** + **55** was assessed (Table 20).

Table 20: Effect of variation of Grignard addition time on yield of cross coupled aziridine **54** + **55**.



entry ^a	Grignard addition time	yield ^b		20j ^c	<i>dr</i> ^d (54:55)	recovery
		54 + 55	36			
1	5 s	20	22	26	90:10	68
2 ^e	5 s	34	11	0	96:4	45
3	5 min	31	8	37	89:11	76
4	1 h	23	10	39	94:6	72

^a Reaction conditions: aziridine **20j** (0.50 mmol), CoCl₂ (5 mol%), ligand **53** (6 mol%), THF (0.33 M), 0 °C; then addition of TolMgBr (1.2 equiv), 0 °C to rt, 2 h. ^b Yield determined by ¹H NMR spectroscopy with reference to an internal standard (1,3,5-trimethoxybenzene). ^c Unreacted iodoaziridine **20j**. ^d *dr* determined via comparison of CHN integrals. ^e 2.0 equiv TolMgBr used.

Addition of TolMgBr over 5 s to the reaction mixture at 0 °C (repeat of Oshima's reaction conditions) (Table 20, entry 1) led to an overall 20% ¹H NMR yield for cross-coupled aziridine **54** and **55**, predominately as the *cis*-diastereoisomer. Notably, a significant amount of dehalogenated aziridine **36** and starting iodoaziridine **20j** were observed in the ¹H NMR spectrum of the crude reaction mixture, possibly due to competing iodine–MgBr exchange and Grignard homocoupling pathways occurring faster than the desired iodoaziridine cross-coupling. Use of 2.0 equiv TolMgBr (instead of 1.2 equiv) afforded an increase in desired cross-coupled aziridine (entry 2), although no starting material was evident after 2 h at rt with significant decomposition of the reaction mixture evident. Variation in addition time from 5 min to 1 h appeared to lend stability to starting iodoaziridine **20j** under the reaction conditions, with an increase in yield for the desired cross-coupled products also observed (5 min dropwise addition time = 31% combined ¹H NMR yield for **54** and **55**). In all cases the iodoaziridine cross-coupling was shown to be diastereoselective for the *cis*-coupled aziridine **54** (ca. 9:1, *cis:trans*).

2.4.4.3: Conclusions: Co Catalysis

The use of CoCl₂ in combination with a simple diamine ligand (**53**),¹⁹⁷ has shown to be a suitable catalytic system to effect the desired cross-coupling of *N*-Ts iodoaziridine **20j** with *p*-tolylmagnesium

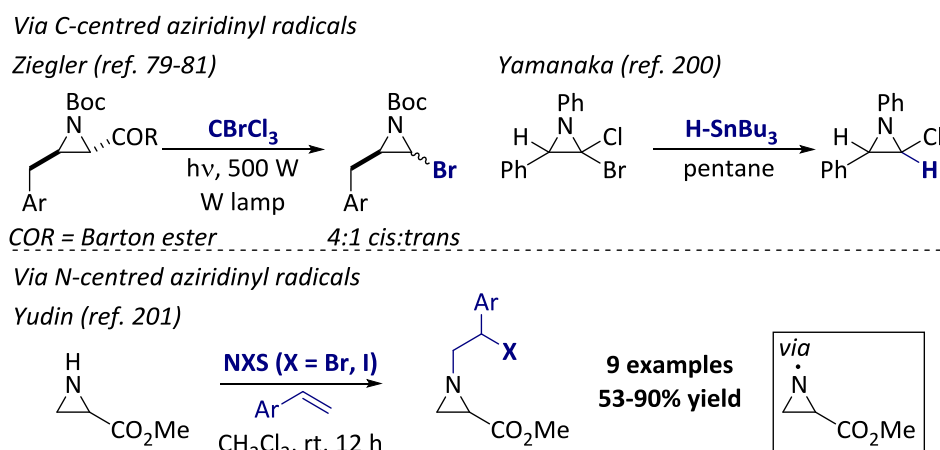
bromide, with the cross-coupled aziridine cleanly isolated for the first time. Early stage optimisation results have shown the cross-coupling reaction to be highly *cis*-selective affording the cross-coupled aziridine as a mixture of diastereoisomers (**54:55**, 89:11) in 31% ¹H NMR yield. Variation in Grignard addition time to the reaction mixture was shown to have an effect on both the conversion and stability of starting iodoaziridine **20j** under the reaction conditions. Many reaction parameters are yet to be investigated including tuning the diamine ligand,^{xvi} use of different Co salts, reaction temperature and time. With ongoing demand for more efficient synthetic methodology, Co catalysed *N*-Ts iodoaziridine cross-coupling could provide an excellent strategy into stereodefined aziridine derivatives, keeping the ring intact during this process. Advantageously, this methodology would also present a more desirable sustainable approach to aziridine cross-coupling, with previously developed methodology involving the use of either undesirable toxic aziridine derivatives, and/or palladium catalysis.⁶⁷⁻⁷⁰

xvi) Oshima (*ref.* 197), has demonstrated that the success of Co catalysed secondary alkyl halide–Grignard cross-coupling protocols was dependent on choice of ligand. Various *N,N*-ligands were examined with difference in ligand efficiency governed by ligand conformation, bite angle and steric demands.

2.5.1: Reactivity and Generation of Aziridinyl Radicals

Whereas aziridinyl anions have been frequently adopted in the literature to access aziridine derivatives (*vide supra*, **Section 1.6**, page 21), intact aziridine functionalisation via formation of reactive aziridinyl radical species is an approach which has received far less attention. The formation of aziridinyl radicals can be split into two classes: C-centred aziridine radicals and N-centred aziridine radicals (**Scheme 54**). Most notable approaches to C-centred aziridinyl radical species have been demonstrated by Ziegler, forming a mixture of bromoaziridines via a Barton decarboxylation bromination sequence from aziridine carboxylates.⁷⁹⁻⁸¹ Yamanaka has also demonstrated the formation of halogenated aziridines via aziridinyl radical intermediates. Selective reduction of 2,2-dihalogenated aziridines with H-SnBu₃ through a radical chain reaction afforded the corresponding dehalogenated aziridine, via a carbon centred radical species.²⁰⁰ Yudin has recently demonstrated a practical and simple approach to generation of N-centred aziridinyl radicals.²⁰¹ Treatment of methyl-2-aziridine carboxylate with either NIS or NBS, resulted in homolytic cleavage of the newly formed weak N-X bond, generating an N-centred aziridinyl radical. Subsequent reaction with styrene derivatives gave rise to a range of β -haloaziridines with *anti*-Markovnikov regioselectivity.

Scheme 54: Generation and reactivity of C- and N-centred aziridinyl radicals.



With C-centred aziridinyl radicals having been shown to undergo further synthetic transformations as demonstrated by Ziegler, and our interest in the reactivity and synthesis of C-heteroatom substituted aziridines,^{70,95,103-104,131} we were keen to explore the generation of aziridinyl radicals, trapping with diselenides to form selenium substituted aziridines (*selenoaziridine*). Organoselenium compounds have been shown to be important and versatile intermediates in organic synthesis, with a range of desirable synthetic transformations demonstrated in the literature.^{202,203} Installation of selenium onto the aziridine ring, would enable us to examine the effect of the heteroatom on the

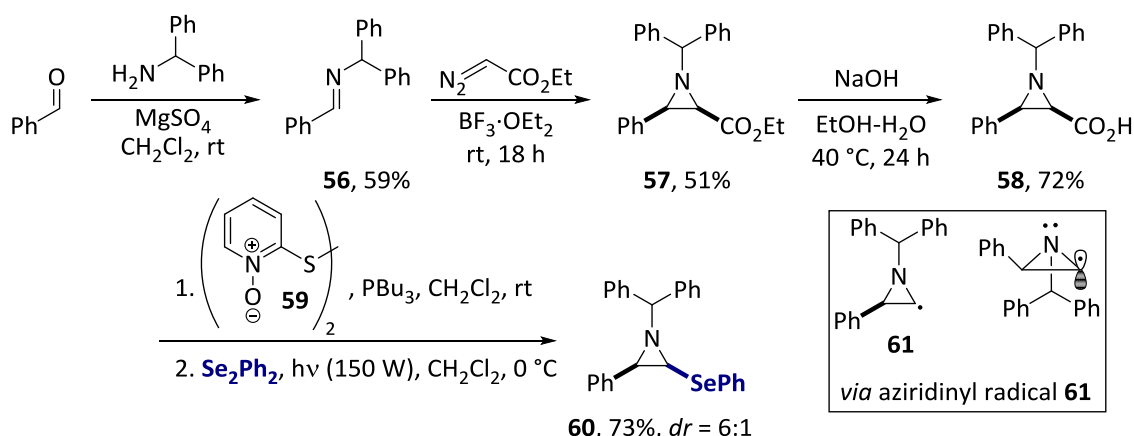
reactivity and stability of the aziridine ring.⁷¹ Previous work within the Bull Group had successfully demonstrated a synthetic approach to a selenoaziridine via a Barton decarboxylation and aziridine radical trapping sequence with diphenyl diselenide, affording a mixture of selenoaziridines, predominately as the *cis*-diastereoisomer.²⁰⁴ The formation of aziridinyl radicals from iodoaziridines will be mainly considered in this section, allowing for iodoaziridine functionalisation, keeping the ring intact during this process. The generation of an aziridinyl radical species would allow us to explore the stability of the radical and subsequent stereoselectivity observed on reaction with radical traps. The following section will be split into two parts, building upon both previous work in the Bull Group and previous described reactivity of *N*-Ts iodoaziridines (**Section 2.4**, page 84). In both sections, any origin of stereoselectivity obtained in the selenation step will be fully discussed.

- (i) synthesis of seleno-aziridines via a Barton decarboxylation selenation sequence.
- (ii) investigation into the formation of aziridinyl radicals from *N*-Ts iodoaziridines and subsequent reactivity with diselenides.

2.5.2: Access to Selenoaziridines via Barton Decarboxylation

Initially, *N*-diphenylmethyl protected aziridines were examined, due to well established literature methodology to access the corresponding aziridine carboxylates in both high enantiopurity and yield using chiral VAPOL (2,2'-diphenyl-[4-biphenanthrol]) catalysts.²⁰⁵ The conditions previously outlined by the Bull Group were replicated in order to assess the current methodology (**Scheme 55**).

Scheme 55: Route to access *cis*-selenoaziridine **60** via formation of Barton ester.



Condensation of benzaldehyde and benzhydramine afforded imine **56** and subsequent reaction with ethyl diazoacetate under Lewis acid catalysis afforded exclusively *cis*-aziridine ester **57** in moderate yield. Hydrolysis of aziridine ester **57** to aziridine acid **58** proved troublesome to purify due to the inherent ambiphilic nature of the aziridine. A reproducible procedure was however

established, with minor modification to the protocol previously reported, furnishing aziridine acid **58** in 72% yield. Preparation of *N*-oxide dimer **59** from commercially available mercaptopyridine *N*-oxide sodium salt,²⁰⁶ and addition to **58** in the presence of PBu₃ afforded the corresponding Barton ester *in situ*, with previous attempts to isolate the Barton ester being unsuccessful.²⁰⁴ Exposure to light (tungsten bulb, 150 W) resulted in a Barton decarboxylation sequence forming aziridinyl radical **61**, which was subsequently trapped by Se₂Ph₂ giving predominately *cis*-selenoaziridine **60** in good yield. The observed *cis*-diastereoselectivity is based on steric factors, with the bulky *N*-Bh protecting group protecting one face of the aziridine, causing attack of the aziridine radical on the top face leading to the preferential formation of *cis*-selenoaziridine **60**. Although this approach offered a diastereoselective synthesis of selenoaziridines, there were several limitations to the protocol:

- (i) the success of the installation of the Barton ester and subsequent decarboxylation step appeared to be reliant on the purity of aziridine acid **58**, which in turn was difficult to manipulate and synthesise;
- (ii) the variation in reaction set-up for the introduction of Se₂Ph₂ became hard to control, with multiple variables including distance of light source to reaction and the heat generated due to the proximity of the lamp;
- (iii) length of synthetic sequence (5 steps, including formation of Barton ester) was undesirable with multiple purification steps required;
- (iv) the atom-economy of the reaction was low, with the Barton ester needed to be installed *in situ* from the corresponding aziridine carboxylic acid to generate the necessary aziridine radical.

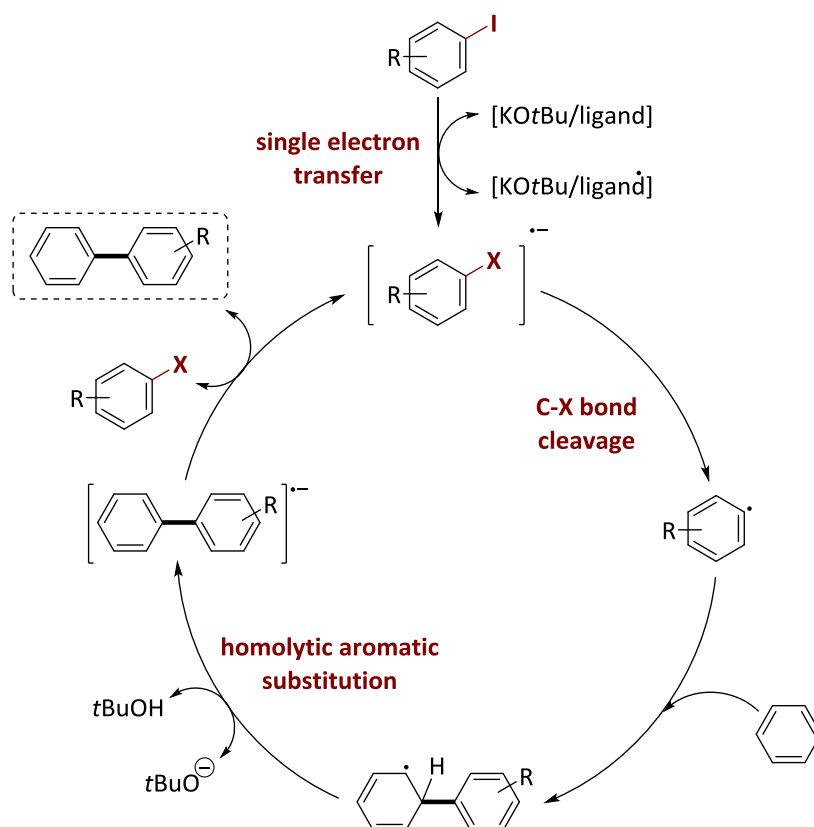
Overall, over a series of 5 separate reactions, yields for the final selenation step varied from 0-73%. As a consequence, alternative methodology to access selenoaziridines became desirable.

2.5.3: KOTBu as Single Electron Transfer Agent

The development of transition metal free cross-coupling reactions for the synthesis of important biaryl scaffolds has been of significant interest to synthetic chemists over the past decade, as a more sustainable alternative to traditional Pd, Ru and Rh chemistry. For excellent detailed reviews concerning transition metal free cross-coupling reactions, see Kwong (2013),²⁰⁷ and Shi (2014).²⁰⁸ Unactivated C-H arene bond functionalisation has been shown to occur with a range of aryl bromides and aryl iodides, in the presence of only a radical initiator through homolytic aromatic substitution.^{151,209,210} Alkoxide bases in combination with simple alcohols or amine ligands have been

shown to be suitable reagents for the generation of a radical aryl species. Since this pioneering work, several examples have been demonstrated in the literature (see highlighted reviews for further examples), with latter work suggesting that KOtBu alone is sufficient to promote biaryl cross-coupling reactions in the presence of an aryl halide and benzene (**Figure 19**).²¹¹

Figure 19: General proposed mechanism for coupling of aryl halides with benzene using KOtBu as SET reagent.

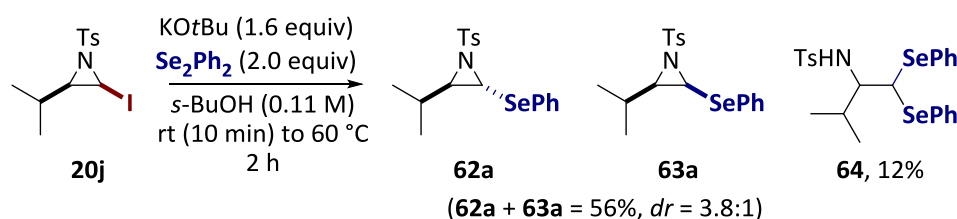


Current mechanistic hypothesis for this C-C bond formation has been surrounded in doubt due to the precise role of both reaction additives,^{212,213} and KOtBu in the reaction protocol.²¹⁴ Based on experimental findings within the literature, a tentative reaction mechanism has however been proposed. Single electron transfer from the KOtBu/ligand system to the aryl halide generates an aryl halide radical anion.^{215,216} Loss of the halide allows the formation of an aryl radical species which further undergoes a homolytic aromatic substitution pathway with benzene (typically used in excess as reaction solvent), to give a cyclohexadienyl radical. Deprotonation with base affords the corresponding biaryl radical anion, which then further acts as a SET reductant to give the desired biaryl motif and turnover the cycle.

2.5.4: Generation of Aziridinyl Radical from Iodoaziridines

From the previous studies into Ni catalysed iodoaziridine cross-coupling (*vide supra*, Section 2.4, page 84), it was evident that an aziridine radical species was being generated in the presence of KOtBu. Although the aziridine radical species was short lived under the reaction conditions due to proposed intermolecular *N*-Ts transfer, it was deemed plausible that this could be trapped using diphenyl diselenide (Scheme 56).

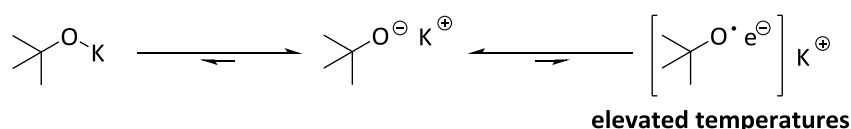
Scheme 56: Trapping of reactive intermediate with diphenyl diselenide.



Initial trapping of the proposed aziridinyl radical species formed under the reaction conditions with Se_2Ph_2 (2.0 equiv) was shown to be productive, affording 3 major products which were observed by ^1H NMR spectroscopy; *trans*-selenoaziridine **62a** (3.86 ppm, d, $J = 4.6$ Hz, CHSe); *cis*-selenoaziridine **63a** (4.26 ppm, d, $J = 6.8$ Hz, CHSe); and amino *gem*-diselenide **64** (4.22 ppm d, $J = 3.7$ Hz, CHSe_2). The major diastereoisomer was assigned as *trans*-selenoaziridine **62a** based on coupling constants. The mixture of selenoaziridines were successfully isolated in 56% yield, as a 3.8:1 *trans*:*cis* mixture with 12% of amino *gem*-diselenide **64** also isolated. The presence of selenoaziridines in the crude reaction mixture was also evident on closer inspection on the peak splittings present in the ^1H NMR spectrum. As ^{77}Se has a spin $I = 1/2$ and is of relatively low abundance (7.7%), Se satellites were visible in the ^1H NMR of the Se-aziridine mixtures, due to ^1H - ^{77}Se coupling.

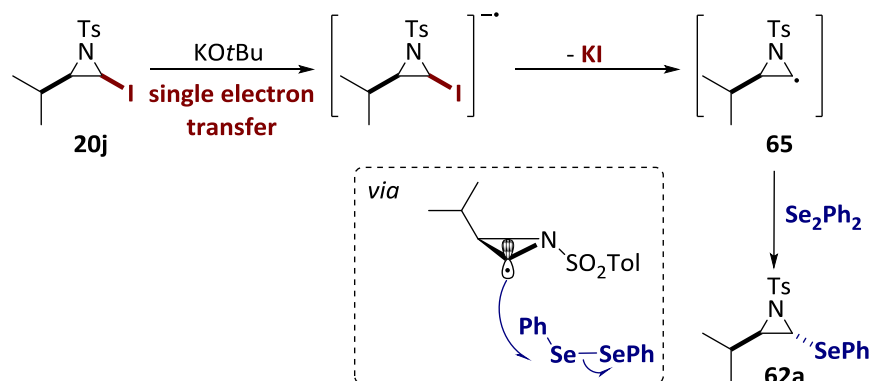
Wilden has recently suggested that a dynamic equilibrium is present in KOtBu between the charge separated species and a species that contains a loosely bound electron (Figure 20).²¹⁴

Figure 20: Proposed dynamic equilibrium between charged separated alkoxide and species that contains loosely bound electron.



At elevated reaction temperatures, this electron can be transferred to aryl halides to initiate aryl radical formation. Mechanistically in accordance with the literature, it is proposed that the KOtBu acts as a single electron transfer reagent, generating an iodoaziridine radical anion (Figure 21).

Figure 21: Proposed mechanism for selenoaziridine formation.



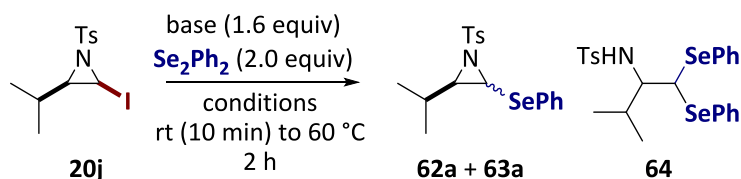
Elimination of iodide would afford the aziridinyl radical intermediate **65**. Nucleophilic radical attack on diphenyl diselenide would then afford selenoaziridine **62a**, predominately as the *trans*-diastereoisomer, with the diastereoselectivity arising from steric factors, with the relatively bulky PhSe group remaining away from the bulk of the *i*-Pr group present on the ring.

2.5.5.1: Reaction Optimisation

After this initial success, a systematic optimisation of the reaction was carried out. Reactions were set up in an N_2 filled glove box, sealed with a Teflon[®] cap and maintained under an inert atmosphere for the duration of the reaction. Reactions were then filtered through a short pad of silica to remove inorganic salts, with the filtrate examined by ^1H NMR with reference to an internal standard.

2.5.5.2: Initial Solvent and Base Screen

Various combinations of known SET promoters and common reaction solvents employed in the literature were examined (**Table 21**).

Table 21: Variation of solvent and base in SET protocol.

entry	conditions ^a	yield (%) ^b			<i>dr</i>
		62a + 63a	64	20j^c (<i>trans</i>:<i>cis</i>)^d	
1	KOtBu, 2-PrOH	53	16	0	7.1:1
2	KOtBu, <i>s</i> -BuOH	38	15	0	8.4:1
3	KOtBu, MeOH	2	0	82	1.3:1
4	KOtBu, 1,4-dioxane	44	7	0	1.3:1
5	KOtBu, THF	41	9	0	2.4:1
6	KOtBu, CH_2Cl_2	16	0	43	2.2:1
7	KOtBu, toluene	20	0	0	1.9:1
8	NaOEt, 2-PrOH	0	0	96	-
9	NaHMDS, 2-PrOH	32	11	8	3.4:1
10	Cs_2CO_3 , 2-PrOH	38	7	14	8.7:1
11	Ag_2CO_3 , 2-PrOH	0	0	97	-
12	no base, 2-PrOH	0	0	100	-

^a Reaction conditions: iodoaziridine **20j** (1.0 equiv), KOtBu (1.6 equiv), diphenyl diselenide (2.0 equiv), solvent (0.11 M), rt (10 min) to 60 °C (2 h). ^b Yield determined by ^1H NMR spectroscopy with reference to an internal standard (1,3,5-trimethoxybenzene). ^c Unreacted iodoaziridine **20j**. ^d *dr* obtained via comparison of CHN aziridine ring protons in crude ^1H NMR spectrum.

An interesting variation in diastereoselectivity was observed on changing the solvent employed in the reaction with KOtBu (**Table 21**, entries 1-7). Branched alcohols were shown to offer the best return for both the yield of the selenoaziridines and the *dr* of the mixture (entries 1-2), with 2-PrOH affording a 53% yield by ^1H NMR in 7.1:1 *dr* (*trans*:*cis*). Both 1,4-dioxane and THF (entries 4-5) afforded the desired selenoaziridine mixture, but with poor diastereoselectivity. The use of CH_2Cl_2 and toluene (entries 6-7) led to disappointing yields of selenoaziridine, also with poor diastereoselectivity. Although the use of *s*-BuOH offered an improved *dr*, at this early stage in reaction optimisation, it was deemed imperative to focus on maximising the yield of the desired selenoaziridine mixture. Therefore using 2-PrOH as solvent of choice, other group 1 metal alkoxides and bases were explored under the reaction conditions. NaOEt provided no desired selenoaziridine **62a + 63a**, with excellent recovery of starting iodoaziridine **20j** observed. Kappe has recently shown

that LiHMDS can be used in place of KOtBu to effect direct arylation of benzene with aryl bromides in the presence of catalytic amounts of 1,10-phenanthroline under high temperature and pressure.²¹⁷ Use of LiHMDS (entry 9) was shown to be productive, albeit affording **62a** + **63a** in reduced yields and diastereoselectivity. Chan has recently shown that caesium alkoxides can be employed in transition-metal free cross-coupling protocols, demonstrating the coupling of benzene and a range of aryl halides in the presence of a porphyrin catalyst.²¹⁸ Employing Cs₂CO₃ (entry 10), again afforded reduced yields of **62a** + **63a**, albeit in greater *dr* (8.7:1, *trans:cis*). The use of Ag₂CO₃ was shown to be ineffective under the reaction conditions with starting iodoaziridine **20j** exclusively returned. Importantly, the role of KOtBu in the reaction was shown to be crucial with **20j** returned quantitatively in its absence. This also confirmed that the proposed aziridinyl radical species was not being generated via a thermal or light induced C-I homolytic cleavage pathway. The combination of KOtBu/2-PrOH was therefore carried forward for further optimisation.

2.5.5.3: Temperature/Time Profiles

After the initial findings at 60 °C, an investigation of the temperature profile of the reaction was carried out, probing both the effect of temperature on product conversion and diastereoselectivity of the reaction. Identical reactions were set up in sealed vials in a glove box, to maintain both an inert atmosphere and a constant concentration of 2-PrOH upon varying reaction temperature. Individual data points were then collected at 10 min, 30 min, 60 min and 90 min (Figure 22). The *dr* observed for all of the data points collected were consistent with that observed from the preliminary experiments (*ca.* 7:1, *trans:cis*). Initially, the reaction was examined at room temperature with poor conversion to **62a** + **63a** observed (82% iodoaziridine **20j** left unreacted by ¹H NMR). Probing the reaction profile at 60 °C proved more encouraging, with an increase in ¹H NMR yield **62a** + **63a** observed upon reducing the reaction time from 2 h to 10 min, although with 13% **20j** present in the crude mixture (by ¹H NMR). The reduction in reaction time also aided the stability of **62a** + **63a** under the reaction conditions, with less of amino *gem*-diselenide **64** observed. It is postulated that prolonged reaction times results in the nucleophilic attack of the selenoaziridine mixture by excess phenylselenenyl radical generated under the reaction conditions, forming amino *gem*-diselenide **64**. Other ring opened products were also evident after prolonged reaction times, with the major of these products tentatively assigned as **66**, formed via nucleophilic attack of **62a** + **63a** by isopropoxide. Increasing the reaction time to 30 min, led to full consumption of iodoaziridine **20j**, but a reduction in yield for selenoaziridine mixture **62a** + **63a** due to the competing nucleophilic aziridine ring opening pathways. It was therefore postulated that a lower reaction temperature could prevent the rate of these pathways.

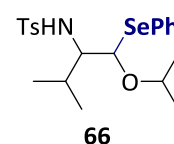
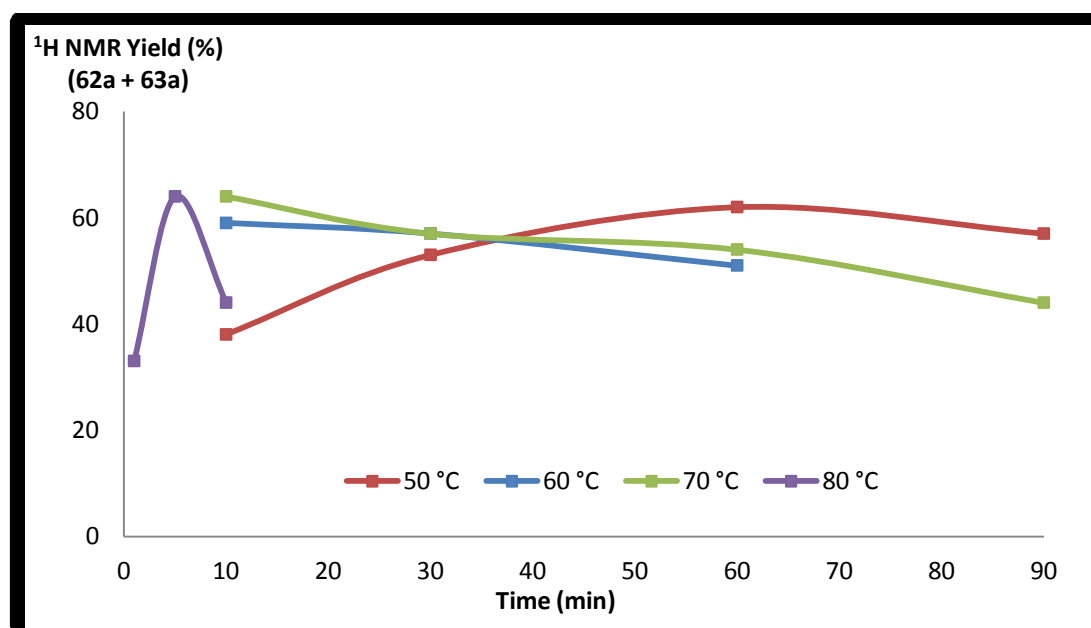


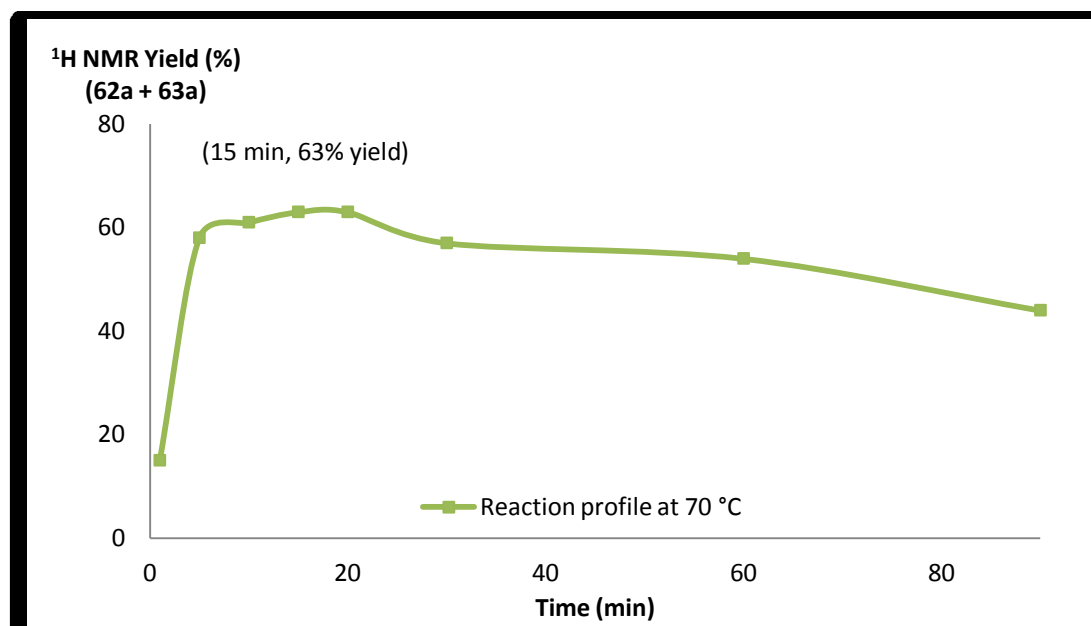
Figure 22: Effect of reaction temperature on yield of selenoaziridines **62a** + **63a**.^a



^a Yield determined by ¹H NMR spectroscopy with reference to an internal standard (1,3,5-trimethoxybenzene).

Exploring the reaction profile at 50 °C validated this, as longer reaction times led to less amino *gem*-diselenide present in the ¹H NMR spectra of the crude reaction mixture and a further improved yield of selenoaziridine mixture **62a** + **63a** (62% by ¹H NMR). However, the reduction in reaction temperature required >60 min to ensure full consumption of iodoaziridine **20j** under the reaction conditions. Increasing the reaction temperature to 70 °C enabled smooth conversion of **20j** to **62a** + **63a** after 10 min, with minimal starting iodoaziridine remaining after this short reaction time. As observed with lower temperatures, increasing reaction time led predominately to the formation of amino *gem*-diselenide **64**, although the rate of the formation of **64** was greatly enhanced at 70 °C. Rapid formation of the aziridinyl radical species and subsequent trapping with diphenyl diselenide occurred at 80 °C. After 5 min at 80 °C, a combined 64% ¹H NMR yield of selenoaziridines **62a** + **63a** was observed. This increased selenoaziridine formation is postulated to occur due to the increased rate of single electron transfer from the active alkoxide species to iodoaziridine **20j** at higher temperatures. Poor recovery of selenoaziridine mixture **62a** + **63a** was observed after 10 min at 80 °C, with products indicative of aziridine degradation (*p*-toluenesulfonamide) observed in the ¹H NMR spectra of the crude reaction mixture. Due to concerns with the instability of both starting materials and products at 80 °C, it was decided that 70 °C was the most suitable reaction temperature to effectively form the aziridinyl radical species without causing undesired degradation. A full study into the profile of the reaction was therefore carried out at 70 °C in order to maximise the yield of the selenoaziridine mixture **62a** + **63a** (Figure 23).

Figure 23: Effect of varying reaction time at 70 °C on yield of selenoaziridines **62a** + **63a**.^a

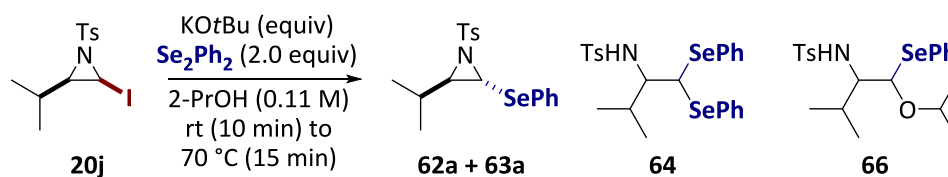


^a Yield determined by ¹H NMR spectroscopy with reference to an internal standard (1,3,5-trimethoxybenzene).

The optimum reaction time was 15 min, which represented a 63% ¹H NMR yield for **62a** + **63a**. The propensity of iodoaziridine **20j** to form the reactive aziridinyl radical species at 70 °C is evident after extremely short reaction times (1 min), with **62a** + **63a** observed in 15% ¹H NMR yield (*dr* = 12:1 *trans:cis*). Increasing reaction time led to the increased consumption of iodoaziridine **20j** and increased yields for **62a** + **63a**, with the *dr* of the mixture remaining constant (7:1 *trans:cis*). After 15 min at 70 °C, with starting iodoaziridine **20j** having been consumed, the resulting selenoaziridine mixture was shown to undergo degradation, due to selenoaziridine ring opening processes.

2.5.5.4: Equivalents of Base and Diselenide

Next the effect of the equivalents of KOtBu and diphenyl diselenide employed in the protocol were evaluated, under the ongoing optimisation conditions (**Table 22**).

Table 22: Effect of changing equivalents of KOtBu employed in reaction protocol.

entry ^a	KOtBu equiv	yield (%) ^b				<i>dr</i>	
		62a + 63a	64	66	20j ^c (<i>trans</i> : <i>cis</i>) ^d		
1	1.0	39	1	2	31	7.0:1	
2	1.2	44	1	2	29	6.7:1	
3	1.4	48	1	2	29	7.1:1	
4	1.6	59	6	3	5	7.6:1	
5	1.8	58	13	7	0	7.4:1	
6	2.0	54	15	2	0	8.1:1	

^a Reaction conditions: iodoaziridine **20j** (1.0 equiv), KOtBu (equiv), diphenyl diselenide (2.0 equiv), 2-PrOH (0.11 M), rt (10 min) to 70 °C (15 min). ^b Yield determined by ¹H NMR spectroscopy with reference to an internal standard (1,3,5-trimethoxybenzene). ^c Unreacted iodoaziridine **20j**. ^d *dr* obtained via comparison of CHN aziridine ring protons in crude ¹H NMR spectrum.

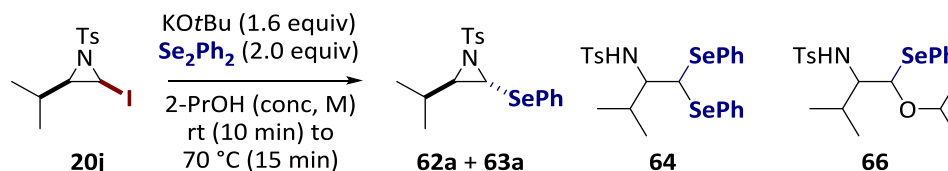
Varying the equivalents of KOtBu used from 1.0 equiv to 2.0 equiv had a dramatic effect on conversion of iodoaziridine **20j** and the yield of selenoaziridine mixture **62a + 63a**. Reducing the equivalents of KOtBu to 1.0 equiv led to a reduced yield (**Table 22**, entry 1), with the majority of the reaction mixture left as unreacted starting iodoaziridine **20j**. Increasing the equivalents of KOtBu up to 1.4 equiv, led to increased formation of **62a + 63a** (entries 2-3), but still with unreacted iodoaziridine **20j** present. However, slightly increasing the excess of KOtBu to 1.6 equiv enabled almost complete conversion of iodoaziridine **20j** to **62a + 63a** (entry 4).^{xvii} Complete conversion was achieved utilising both 1.8 and 2.0 equiv KOtBu. However, as a consequence, increased formation of amino *gem*-diselenide **64** was observed, therefore it was decided that 1.6 equiv KOtBu was optimum for the reaction protocol. In an analogous fashion, the equivalents of diphenyl diselenide were also explored, varying the equivalents from 1.0 equiv to 2.0 equiv, utilising 1.6 equiv KOtBu. In general, the amount of diphenyl diselenide employed (1.0 to 2.0 equiv), had no effect on the yield of **62a + 63a**, or ring opened amino *gem*-diselenide **64**, therefore 2.0 equiv Se₂Ph₂ was carried forward.

xvii) 1.6 equiv KOtBu used by Fu and co-workers in Ni catalysed cross-coupling of alkyl halides with boronic acids (*ref.* 142).

2.5.5.5: Reaction Concentration and Solvent

Next the effect of reaction concentration and choice of solvent was investigated under the ongoing optimisation conditions (**Table 23**).

Table 23: Effect of reaction concentration on reaction protocol.



entry ^a	concentration (M)	yield (%) ^b				<i>dr</i> 20j ^c (<i>trans:cis</i>) ^d
		62a + 63a	64	66	20j ^c	
1	neat	28	14	0	8	1.3:1
2	2.00	29	7	3	7	2.7:1
3	1.00	41	7	3	4	4.1:1
4	0.50	49	7	3	3	4.6:1
5	0.10	57	6	4	5	6.9:1
6	0.05	53	3	4	10	6.2:1

^a Reaction conditions: iodoaziridine **20j** (1.0 equiv), KOtBu (1.6 equiv), diphenyl diselenide (2.0 equiv), 2-PrOH (concentration, M), rt (10 min) to 70 °C (15 min). ^b Yield determined by ^1H NMR spectroscopy with reference to an internal standard (1,3,5-trimethoxybenzene). ^c Unreacted iodoaziridine **20j**. ^d *dr* obtained via comparison of CHN aziridine ring protons in crude ^1H NMR spectrum.

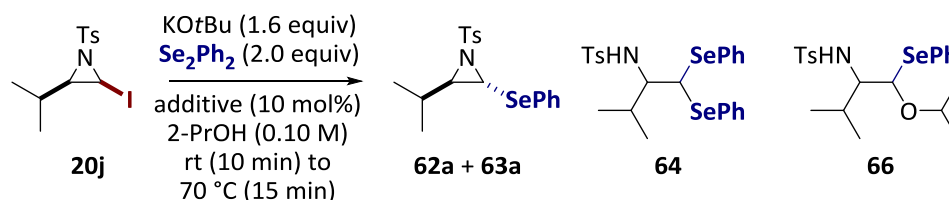
The reaction was first evaluated in the absence of solvent to examine the sole effect of KOtBu as a single electron transfer reagent (**Table 23**, entry 1). In agreement with Wilden and Ashby,²¹⁴⁻²¹⁶ KOtBu was shown to act as a single electron transfer reagent in the absence of any solvent and ligand systems, generating selenoaziridine mixture **62a + 63a** in a reasonable 28% yield at 70 °C. A loss in recovery of aziridine, with decomposition to *p*-toluenesulfonamide was however observed, presumably due to the harsh reaction conditions. A general trend was then observed upon reducing the reaction concentration from 2.00 M to 0.05 M (entries 2-6), whereby both an increase in yield and *dr* of **62a + 63a** was obtained. Reducing the reaction concentration to 0.10 M proved the most effective in terms of both yield and *dr* of **62a + 63a**. Disappointingly, further reduction in concentration led to incomplete conversion of starting iodoaziridine **20j**. With several of the reaction parameters investigated, it was considered pertinent to reinvestigate choice of reaction solvent, using the previous result with 2-PrOH (**Table 23**, entry 5) as a reaction control. Use of primary

substituted alcohols EtOH and *n*-BuOH had no positive impact on the yield of the desired selenoaziridine mixture **62a** + **63a**. For the duration of both of these reactions, the reaction components remained fully in solution, whereas under 2-PrOH conditions this only occurred for the initial few minutes at 70 °C. Increasing the steric bulk of the alcohol to *t*-BuOH had a small positive effect on the yield of **62a** + **63a** rising to 62% (¹H NMR yield), although a reduction in *dr* was noticeable (7.0:1 for 2-PrOH, 2.9:1 for *t*-BuOH). More noticeably with *t*-BuOH, conversion to **62a** + **63a** was evidently cleaner. No products arising from selenoaziridine ring opening process by *t*-butoxide were evident in the crude reaction mixture. A 1:1 mix of 2-PrOH:*t*-BuOH was employed in order to have a positive impact on both yield and *dr* of **62a** + **63a**, but did not offer any dramatic improvements. Set on the single solvent 2-PrOH system, the effect of water was assessed. To our surprise, both the addition of an aliquot of water to the sealed reaction vessel and use of “wet” 2-PrOH,^{xviii} had no effect on the yield **62a** + **63a**. Nevertheless, in an attempt to control the levels of H₂O present in the reaction mixture, dry 2-PrOH was carried forward as the solvent of choice.

2.5.5.6: Role of Additives

The effect of additives (10 mol%) were next investigated under the reaction optimisation (**Table 24**).

Table 24: Effect of reaction additives on reaction protocol.



entry ^a	additive (10 mol%)	yield (%) ^b				<i>dr</i>
		62a + 63a	64	66	20j ^c (<i>trans</i> : <i>cis</i>) ^d	
1	none	55	4	7	3	6.2:1
2	1,10-phenanthroline ^{xix}	57	6	6	4	6.1:1
3	isoquinoline	18	9	10	16	5.8:1
4	HMTA	5	13	0	8	<i>trans</i>

^a Reaction conditions: iodoaziridine **20j** (1.0 equiv), KOtBu (1.6 equiv), diphenyl diselenide (2.0 equiv), additive (10 mol%), solvent (0.10 M), rt (10 min) to 70 °C (15 min). ^b Yield determined by ¹H NMR spectroscopy with reference to an internal standard (1,3,5-trimethoxybenzene). ^c Unreacted iodoaziridine **20j**. ^d *dr* obtained via comparison of CHN aziridine ring protons in crude ¹H NMR spectrum.

xviii) “Wet” 2-PrOH refers to use of Winchester HPLC grade 2-PrOH (≥99.9%)

xix) Purified 1,10-phenanthroline used according to method of Wilden and co-workers (*ref.* 214).

Wilden has shown that equimolar mixtures of 1,10-phenanthroline and KOtBu led to the collapse of the 9H singlet for KOtBu in the ^1H NMR spectrum. It is suggested that 1,10-phenanthroline removes the loosely bound electron from the alkoxide species, which can then be transferred to aryl halides. Addition of 10 mol% 1,10-phenanthroline to the system (**Table 24**, entry 2), had no major impact on the yield of **62a** + **63a** (in comparison with control reaction – entry 1). The effect of isoquinoline was next assessed (entry 3), with Knochel and co-workers recently demonstrating its use as an effective additive in Fe and Co catalysed cross-coupling of *N*-heteroaryl halides with aryl magnesium reagents.¹⁹² Addition of 10 mol% isoquinoline led to an overall reduction in yield for **62a** + **63a**, with more products arising from aziridine ring opening present in the crude ^1H NMR spectrum. A potential explanation for this observation could be due to an increased rate of formation of **62a** + **63a** under the reaction conditions, with it further degrading under the prolonged reaction conditions. The use of HMTA proved detrimental to the reaction (entry 4), with poor recovery of aziridine observed. 1-Aminoisoquinoline and 1,2,3,4-tetrahydroquinoline were also evaluated, with both additives also returning complex crude mixtures upon analysis of their corresponding ^1H NMR spectra.

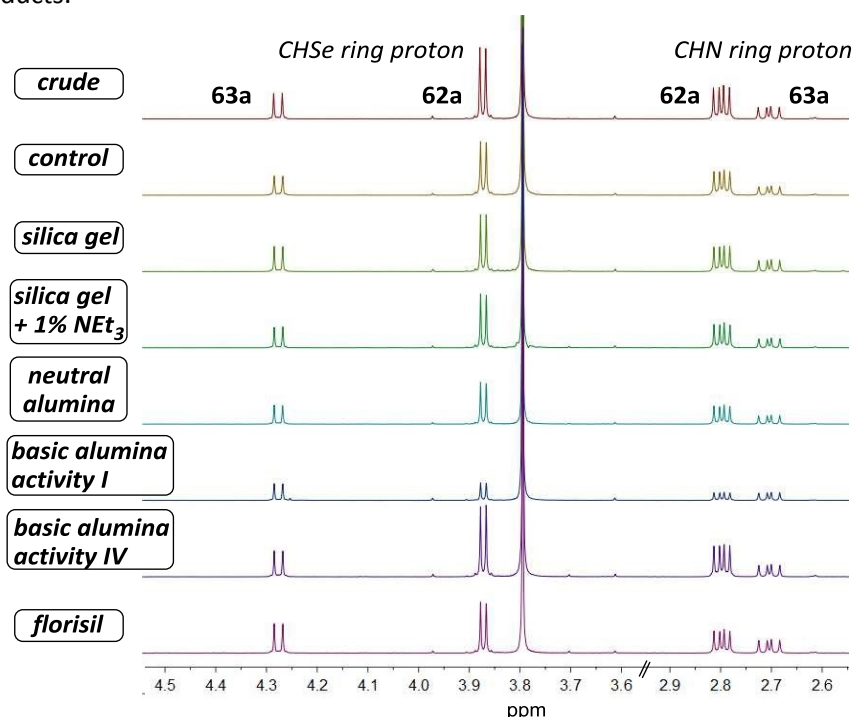
Kwong has previously screened a variety of alcohols, amino alcohols and organocatalysts in the KOtBu promoted cross-coupling of aryl halides with benzene, with the use of amines and alcohols shown to be beneficial in the yield of desired biaryl.²¹⁰ The precise role of such reaction additives in KOtBu promoted biaryl cross-coupling reactions has been of significant recent interest, and now well documented within the literature.^{212,213} For example, oxidation of alcohols has shown to be most likely under cross-coupling reaction conditions forming ketones, which act as precursors to electron rich enolates that can act as organic-super electron-donors.²¹³ Future work could be aimed towards screening a range of alcohols, amino alcohols and organocatalysts in the reaction protocol. It has been shown that lower reaction temperatures can be utilised in the presence of such additives, which would afford greater stability to iodoaziridine **20j** and **62a** + **63a** under the reaction conditions (see reaction temperature profiles, **Section 2.5.5.3**, page 116),

2.5.5.7: Choice of Work Up & Stationary Phase for Purification

Although the isolated yields were corresponding to the yields obtained by ^1H NMR spectroscopy, there was a significant reduction in *dr* from the crude reaction mixture to that observed after purification (reaction *dr* = ~6:1, *trans:cis* – cf. isolated product, *dr* = 3.8:1). Various reaction work-ups were evaluated in order to assess any potential degradation/epimerisation prior to purification, with the known effect of silica gel on sensitive functional groups having been previously demonstrated (*vide supra*, **Section 2.2.4**, page 59). Celite and silica gel were directly compared, with celite having

no effect on recovery or *dr* of selenoaziridine mixture **62a** + **63a**. Aqueous work-ups including 1 N HCl and sat. aq. NaHCO₃ were also evaluated, with 1 N HCl causing degradation of **62a** + **63a**, and sat. aq. NaHCO₃ returning similar yields and diastereoselectivities to those observed when employing only filtration through a short pad of silica gel. Content with the reaction work-up, attention was focused on assessing the choice of stationary phase for purification. A screen of potential stationary phases for purification was therefore carried out, according to the method developed for *N*-Ts iodoaziridines (*vide supra*, Section 2.2.4, page 59).^{103,104} A pure mixture of *trans*-selenoaziridine **62a** and *cis*-selenoaziridine **63a** (*trans*:*cis* = 2.5:1) was submitted to the conditions of the protocol in order to assess whether the stationary phase had any effect on the recovery or diastereoisomeric ratio (**Figure 24**).

Figure 24: Stationary phase stability study, highlighting the effect of choice of stationary phase on *dr* of isolated products.



Analysis of the crude and control reactions by ¹H NMR spectroscopy showed no degradation or reduction in *dr* of the selenoaziridine mixture (**Figure 24** and **Table 25**, entries 1-2). However, treating the selenoaziridine mixture with silica gel caused a minor loss in recovery, but also more interestingly a significant reduction in the *dr* of the mixture (entry 3). This reduction in *dr* was observed with the majority of stationary phases examined. Remarkably, a 1:1 mixture of *trans*:*cis* selenoaziridines was observed, when treating the original selenoaziridine mixture with basic alumina (activity I), with a considerable loss in recovery (entry 6). This significant epimerisation and loss of recovery is believed to occur via deprotonation of the highly acidic CHSePh aziridine ring proton by

the active sites on the basic alumina leading to aziridine degradation and scrambling of stereochemistry at this centre.

Table 25: Stationary phase stability study protocol for selenoaziridines **62a** and **63a**.

entry	stationary phase	62a (%) ^a	63a (%) ^a	recovery (62a + 63a) (%) ^a	<i>dr</i> ^b (62a:63a)
1	crude	72	28	100	2.5:1
2	control ^c	72	28	100	2.5:1
3	silica gel	66	33	99	2.0:1
4	silica gel + 1% Et ₃ N	70	30	100	2.3:1
5	neutral alumina	66	34	100	1.9:1
6	basic alumina (activity I) ^d	23	23	46	1:1
7	basic alumina (activity IV) ^e	72	28	100	2.5:1
8	florisil	62	38	100	1.6:1

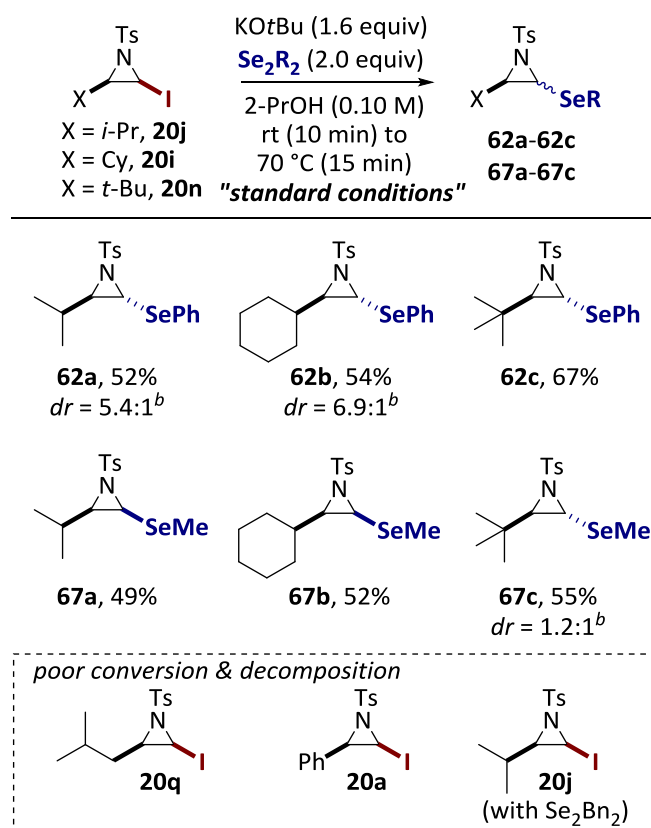
^a Yield determined by ¹H NMR spectroscopy with reference to an internal standard (1,3,5-trimethoxybenzene). ^b *dr* obtained via comparison of integrals for CHN aziridine ring protons in crude ¹H NMR spectrum. ^c Sample of crude **62a** + **63a** stirred in 10% Et₂O/hexane. ^d Basic alumina (activity I) oven-dried for 24 h, and cooled under reduced pressure prior to use. ^e Basic alumina (activity IV) prepared by addition of water (10% w/v) to basic alumina (activity I).

This degradation and epimerisation could be prevented by deactivating basic alumina (activity I) to basic alumina (activity IV), whereby the product retained the *dr* observed in the ¹H NMR spectrum of the crude reaction mixture and showed quantitative recovery of material (entry 7). Pleasingly, using column chromatography on deactivated basic alumina (activity IV) enabled the reduction in levels of epimerisation observed with silica gel and isolate *trans*-selenoaziridine **62a** in a 52% yield (crude *dr* = 6.7:1 *trans:cis*, purified mixture = 5.4:1; *cf.* purification using silica gel, *dr* = 3.8:1).

2.5.6: Reaction Scope

The scope of the reaction was investigated by varying both the source of *N*-Ts iodoaziridine and diselenide (**Scheme 57**). As a consequence of the stationary phase stability study, it was decided that basic alumina (activity IV) was suitable for the purification of the remainder of the scope to minimise any potential epimerisation of the selenoaziridine products.

Scheme 57: Reaction scope for KOtBu mediated aziridinyl radical formation and trapping with diselenides.^a



^a Reaction conditions: aziridine (0.27 mmol), KOtBu (1.6 equiv), diselenide (2.0 equiv), 2-propanol (0.10 M), rt (10 min) to 70 °C (15 min). ^b *dr* calculated from crude ¹H NMR mixture.

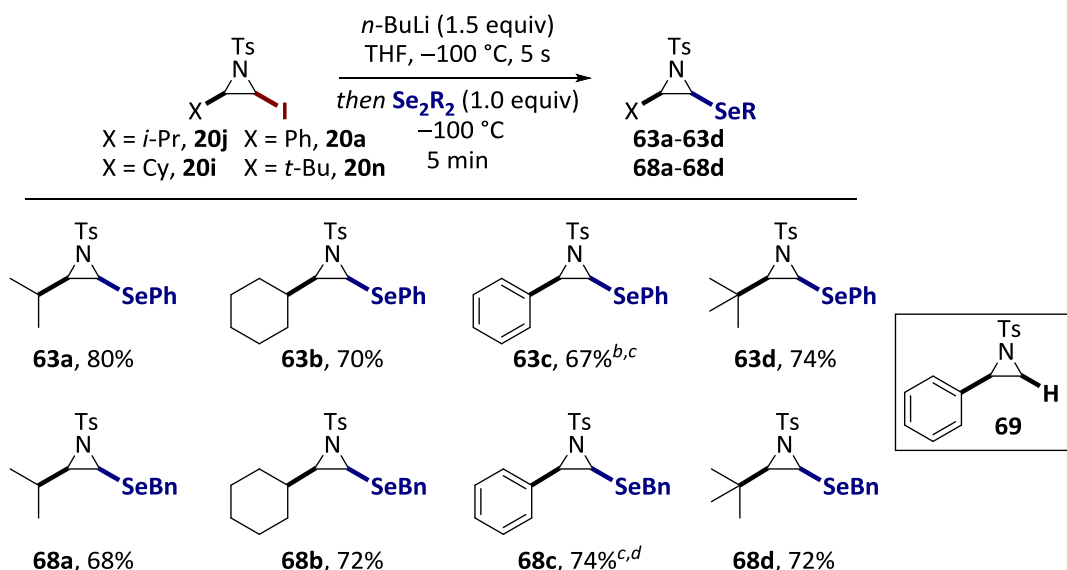
Under the standard reaction conditions, with purification on deactivated basic alumina (activity IV), the reaction showed good tolerance for the formation of secondary alkyl substituted aziridinyl seleno-ethers **62a** and **62b** in good yield and *dr*. The *dr* of the final products after purification closely resembled the *dr* observed in the crude ¹H NMR spectrum, demonstrating the effectiveness of the stationary phase stability study. Reaction of the *tert*-butyl substituted iodoaziridine **20n** with diphenyl diselenide resulted in the exclusive formation of *trans*-substituted selenoaziridine **62c** in excellent yield. This is presumably due to the steric demands of the *tert*-butyl group preventing attack of the aziridinyl radical on diphenyl diselenide from the top face of the aziridine. Interestingly, submission of Ph substituted iodoaziridine **20a** under the "standard conditions" only afforded 5% yield (by ¹H NMR) of a 5.6:1 (*trans*:*cis*) mixture of selenoaziridines. Attempts at lowering the reaction temperature to both 50 °C and 60 °C, led to reduced yields (by ¹H NMR) and increased amounts of unreacted iodoaziridine **20a**. It was postulated the high reaction temperatures were leading to radical induced thermal decomposition of the aromatic substituted iodoaziridine, but submission to the "standard conditions" in the absence of KOtBu led to quantitative recovery of iodoaziridine **20a**, showing the requirement of KOtBu to generate the aziridinyl radical species. Poor conversion was

also observed with primary substituted iodoaziridine **20q**, with decomposition to *p*-toluenesulfonamide being the major product observed in the crude ^1H NMR spectrum. A mixture of sulfur substituted aziridines were also accessed in a yield of 22% by ^1H NMR (*dr* = 1.6:1 *trans:cis*), on reaction of diphenyl disulfide with **20j** under the standard conditions. On changing diselenide to dimethyl diselenide, a reversal in diastereoselectivity was observed for secondary alkyl substituted iodoaziridines **20j** and **20i**, highlighting the preference for *cis*-substitution. Reaction of dimethyl diselenide with both iodoaziridine **20j** and **20i** resulted in the formation of exclusively the *cis*-substituted selenoaziridines **67a** and **67b** respectively in good yields. Employing *tert*-butyl substituted iodoaziridine **20n** resulted in the formation of 1.2:1 mixture (*trans:cis*) of selenoaziridine **67c**. The reversal in diastereoselectivity can be attributed to the increased steric bulk of the *tert*-butyl group present on the aziridine ring. Use of dibenzyl diselenide under the “standard conditions” with iodoaziridine **20j** resulted in a combined 38% ^1H NMR yield for the mixture of selenoaziridines, with a significant drop in *dr* observed. As a consequence, the further use of dibenzyl diselenide as a radical trap was not continued.

2.5.7: Access to *cis*-Selenoaziridines via Iodine–Lithium Exchange

It was envisaged that the previous conditions developed for the stereospecific functionalisation of iodoaziridines via an aziridinyl lithium, generated by iodine–lithium exchange, would be suitable for the preparation of a library of *cis*-selenoaziridines (see **Section 2.3**, page 71). A range of iodoaziridines and diselenides was successfully employed as shown below (**Scheme 58**), affording *cis*-selenoaziridines with retention of stereochemistry after iodine–lithium exchange. A slight modification in the optimised reaction conditions was adopted to account for the reduced solubility of diphenyl diselenide in THF, with the equivalents of electrophile being reduced from 3.0 equiv to 1.0 equiv. This was to ensure a minimisation in the warming of the reaction mixture upon rapid addition of electrophile, ensuring the stability of the aziridinyl lithium under the reaction conditions. A range of *cis*-selenoaziridines were successfully accessed under the modified reaction conditions, with purification occurring on silica gel without any significant decomposition observed. The *cis*-stereochemistry was assigned based upon coupling constants and comparison with their *trans*-counterparts which were successfully accessed using the SET protocol.

Scheme 58: Reaction scope for KOtBu mediated aziridinyll radical formation and trapping with diselenides.^a



^a Reaction conditions: *n*-BuLi (1.5 equiv), THF (0.065 M), $-100\text{ }^{\circ}\text{C}$, addition of aziridine (0.27 mmol) in THF, 5 s; then diselenide (1.0 equiv), THF, $-100\text{ }^{\circ}\text{C}$, 5 min. ^b Contained **69** as an inseparable impurity (7% yield). ^c Yield calculated based on desired product only. ^d Contained **69** as an inseparable impurity (6% yield).

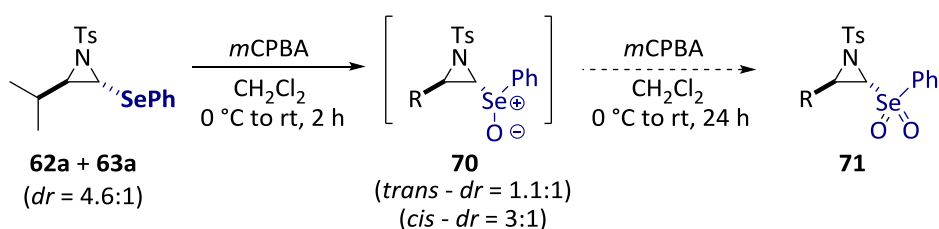
Secondary alkyl substituted iodoaziridines **20j** and **20i** successfully reacted with diphenyl diselenide affording the corresponding *cis*-selenoaziridines **63a-63b** in high yield. Phenyl substituted iodoaziridine **20a** was again shown to react exclusively at the pre-assigned position, with no evidence of competing benzylic deprotonation under the reaction conditions affording *cis*-selenoaziridine **63c**. Problems were unfortunately encountered upon purification due to the co-elution of unsubstituted aziridine **69**, arising from the competing protonation of the highly reactive aziridinyllithium intermediate. Impressively, the *tert*-butyl substituted iodoaziridine **20n** could be successively employed in the stereospecific lithiation/trapping sequence with diphenyl diselenide to afford exclusively *cis*-selenoaziridine **63d** in excellent yield. Similar reactivity of the free phenylselenenyl anion with the BuLi exchange product was observed with the formation of *n*-BuSePh in the crude spectra for **63a-63d** (see **Section 2.3**, page 77), potentially preventing undesired ring opening pathways. As previously under the SET reaction conditions, dimethyl diselenide was explored as a potential reacting partner for the aziridinyllithium intermediate. However under the optimised reaction conditions, only minor conversion to the expected *cis*-selenoaziridine was observed (<5%), with unsubstituted aziridine **36** as the major product. This implies that complete iodine–lithium exchange occurred, but due to the reduced electrophilicity of dimethyl diselenide, the highly reactive aziridinyllithium species was quenched with a proton source prior to reaction. To access the desired product, warming the reaction mixture towards $-90\text{ }^{\circ}\text{C}$ would be recommended.

in order to enhance the reactivity of the aziridinyllithium intermediate, as shown previously (**Section 2.3.5**, page 79). Reaction with dibenzyl diselenide was shown to be unproductive under the SET reaction conditions, with both diminished yields and diastereoselectivity observed. Under the stereospecific lithiation protocol, dibenzyl diselenide was shown to be reactive with a range of iodoaziridines, affording exclusively the *cis*-substituted selenoaziridines **68a-68d** in all cases in excellent yields. For the case of phenyl substituted selenoaziridine **68c**, the corresponding dehalogenated aziridine **69** was again observed as an inseparable impurity after silica gel chromatography. The quoted yield above (**Scheme 58**), is based on the yield of the desired selenoaziridine only. Again, *n*-BuSeBn was observed as a byproduct of the lithiation/trapping protocol for **68a-68d**.

2.5.8: Oxidation of Selenoaziridines

Selenoxides are common organoselenium species, which have shown to be important intermediates in organic synthesis due to their ability to undergo a wide range of transformations including sigmatropic rearrangements, *syn*-eliminations and selenoxide–metal exchange.^{202,203} Treatment of selenoaziridines **62a + 63a** with *m*CPBA furnished the corresponding mixture of aziridine selenoxides **70** as a mixture of diastereoisomers (*trans* - 1.1:1 *major:minor*, *cis* - 3:1 *major:minor*, via ¹H NMR spectroscopy) (**Scheme 59**).

Scheme 59: Oxidation of selenoaziridnes **62a + 63a** with *m*CPBA.^a



^a Reaction conditions: *m*CPBA (1.1 equiv), CH₂Cl₂ (0.03 M), 0 °C to rt, 2 h.

Although conversion to aziridine selenoxide **70** was clean, purification via silica gel chromatography to remove excess *m*CPBA and baseline impurities led to degradation of the reaction mixture. Use of 2.5 equiv *m*CPBA failed to give the expected aziridine selenone **71**, with only selenoxide **70** present by TLC analysis of the reaction mixture. This was also evident upon the addition of an extra equivalent of *m*CPBA to the reaction mixture in an attempt to force a second oxidation. Degradation to *p*-toluenesulfonamide was also observed by ¹H NMR spectroscopy.

2.5.9: Conclusions

N-Ts Iodoaziridines have shown to be suitable precursors to aziridinyl radicals, generated via a single electron transfer from KO^tBu. The resulting aziridinyl radicals were successfully trapped with a range of diselenides to afford *N*-Ts selenoaziridines for the first time. The diastereoselectivity of the reaction was shown to be dependent on both the size of the substituent already present on the ring, and the size of the diselenide. In general the use of diphenyl diselenide led to predominately the *trans*-diastereoisomer, whereas the use of dimethyl diselenide led to the formation of the *cis*-diastereoisomer. An iodine–lithium exchange protocol, previously developed for *N*-Ts iodoaziridines,¹³¹ was also demonstrated to be suitable for the stereospecific formation of a range of *cis*-selenoaziridines.

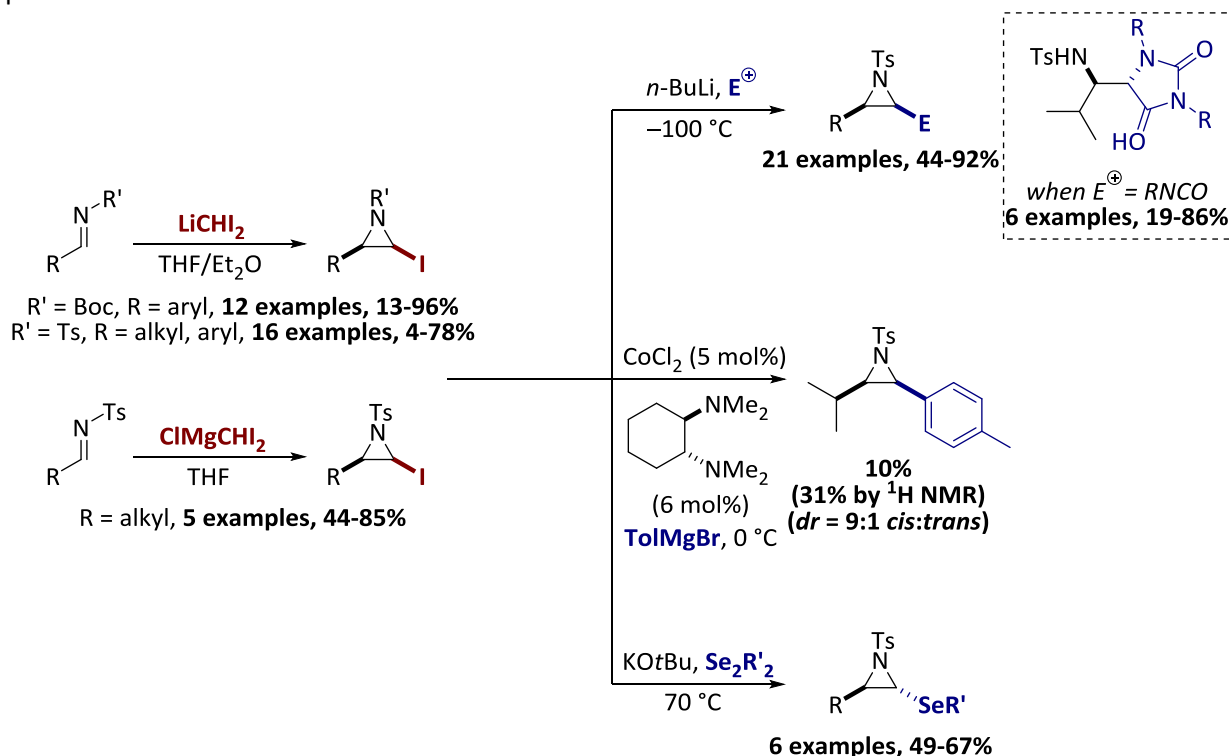
3: Conclusions and Future Work

Iodoaziridines were designed as potential precursors from which to access a wide variety of aziridine derivatives through the functionalisation of the intact ring involving the C-I bond. This has been achieved through:

- (i) iodine–lithium exchange, trapping the aziridinyl lithium intermediate with electrophiles;
- (ii) Co-catalysed aziridine cross-coupling with Grignard reagents;
- (iii) SET using KOtBu, forming aziridinyl radicals and trapping with diselenides to afford novel selenium substituted aziridines.

The formation and further interesting reactivity of iodoaziridines has enabled the development of novel methodology to access aziridine derivatives (**Figure 25**).

Figure 25: Synthesis of iodoaziridines and their functionalisation, keeping the ring intact during this process.



Iodoaziridine Formation

The addition of LiCHI_2 to imines at low temperature has enabled the preparation of an iodoaziridine for the first time, in a one pot addition-cyclisation protocol, with a highly diastereoselective 3-*exo-tet* cyclisation resulting in the exclusive formation of *cis*-iodoaziridines. Variation in *N*-protecting group

from *N*-Boc to *N*-Ts was shown to expand the scope of the reaction, tolerating both aromatic and alkyl substituted imines. A stationary phase stability study protocol has also been developed to identify the optimum choice of stationary phase for purification. Deactivated basic alumina (activity IV) was shown to be most suitable for the case for the purification of *N*-Ts iodoaziridines, with the use of silica gel leading to rearrangement. The protocol using alkyl *N*-Ts imines was further improved by employing ClMgCHI_2 , formed via iodine–magnesium exchange, under similar reaction conditions.

Functionalisation of the Intact Iodoaziridine

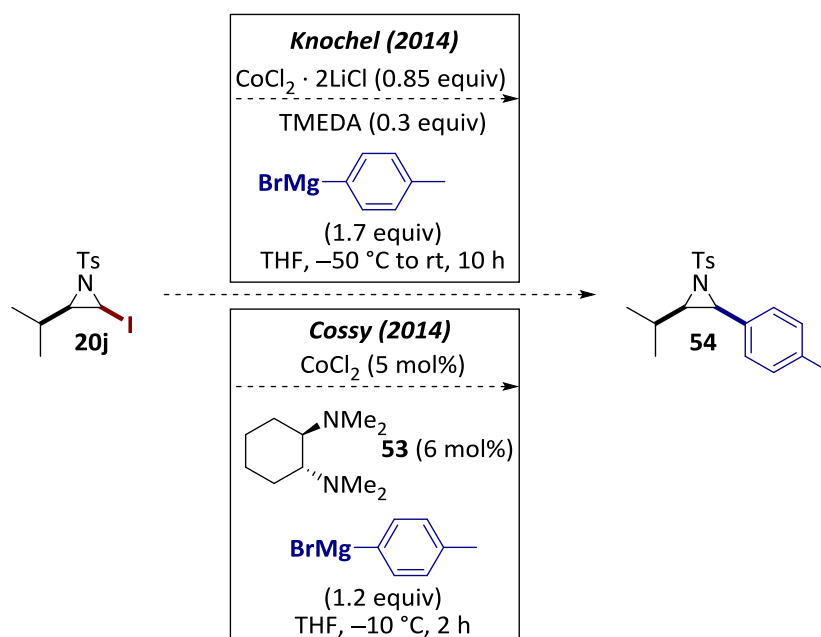
The *N*-Ts iodoaziridine was then demonstrated to be a suitable scaffold for further functionalisation, keeping the ring intact during this process. Stereospecific iodine–lithium exchange was shown to occur at $-100\text{ }^\circ\text{C}$, affording an unstabilized aziridinyl lithium species. This could be subsequently trapped, upon reaction with a range of suitable electrophiles, exclusively affording *cis*-aziridines with retention of stereochemistry at the reacting centre. Use of transition metal catalysed cross-coupling reactions, employing the iodoaziridine as the electrophilic cross-coupling partner, led to unexpected reactivity of *N*-Ts iodoaziridines under these conditions. Use of well established Ni catalysed $\text{sp}^3\text{--}\text{sp}^2$ alkyl-aryl Suzuki cross-coupling conditions led to the formation of an aziridinyl radical species under the reaction conditions, preventing the formation of the desired cross-coupled aziridine due to degradation and intermolecular reactivity. Whereas Pd and Fe catalysed processes were shown to be less reactive towards the *N*-Ts iodoaziridine, due to competing dehalogenation in the latter case, the use of Co catalysis was shown to be more productive. The use of CoCl_2 in combination with a simple diamine ligand enabled the first transition metal catalysed cross-coupling of an iodoaziridine with TMgBr , furnishing the corresponding arylated aziridine in 10% yield (31% ^1H NMR yield), with *dr* = 90:10 (*cis:trans*). KOtBu has also shown to be an effective SET reagent, generating an aziridinyl radical species, with optimisation demonstrating this is most effective under relatively mild reaction conditions. The aziridinyl radical species was trapped with diphenyl diselenide, enabling the preparation of a range of *cis*- and *trans*- selenium substituted aziridines for the first time. The diastereoselectivity of the reaction was shown to rely on steric factors, with both the steric demand of the ring substituent and diselenide investigated. *cis*-Selenoaziridines were also exclusively accessed via stereospecific iodine–lithium exchange on a range of alkyl and aryl iodoaziridines, trapping the resulting aziridinyl lithium intermediates with diselenides.

Future Work – (a) Co catalysis

Further investigation into the Co catalysed cross-coupling of *N*-Ts iodoaziridines with Grignard reagents should be firstly considered, due to the successful nature of the conditions previously

outlined (*vide supra*, **Section 2.4.4**, page 103). With both Cossy,¹⁷⁴ and Knochel,¹⁹⁶ having demonstrated diastereoselective Co catalysed cross-coupling of saturated *N*-heterocycles with Grignard reagents since the preliminary results with *N*-Ts iodoaziridine **20j**, immediate future work should consider analysing similar catalytic systems which are outlined below (**Scheme 60**). Reaction parameters are yet to be fully investigated, including the optimal choice of Co salt and ligand, with previous reports suggesting that fine tuning the electronic properties of the ligand can be crucial to the success of the cross-coupling reaction. Both a variety of common Co salts and ligands employed in Co catalysed cross-coupling reactions are commercially available and of low cost, or are accessible via short synthetic sequences (*e.g.* salen ligands), providing an excellent starting point for further reaction optimisation. The diastereochemistry of the resulting aziridine products will give further insight into the mechanism of Co catalysed processes.

Scheme 60: Potential Co catalysed cross-coupling conditions to investigate.



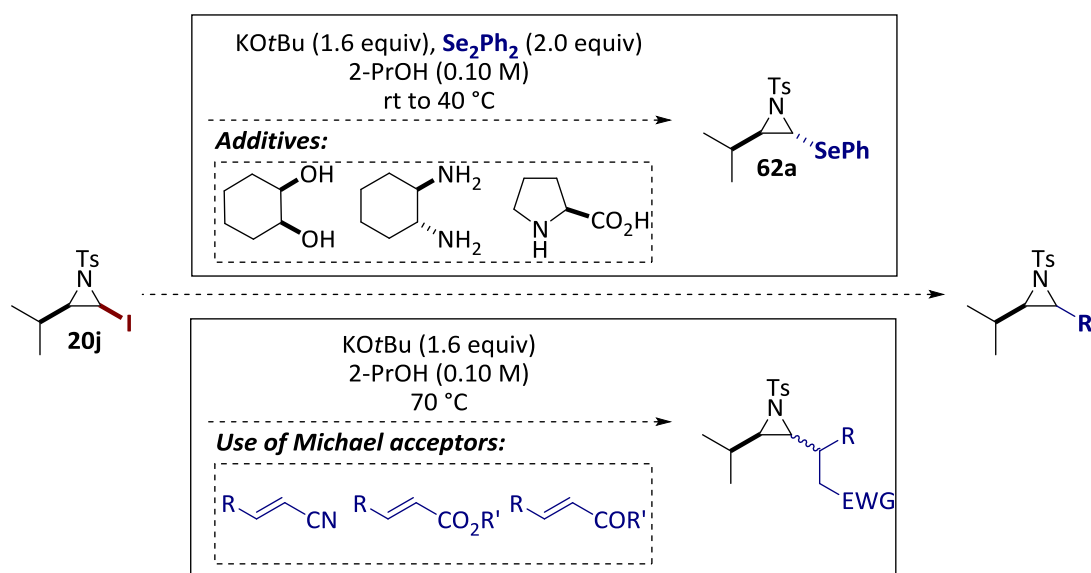
Future Work – (b) KOTBu as SET Reagent: Use of Additives & C-C bond Formation

N-Ts iodoaziridines were successfully demonstrated to be suitable precursors to aziridinyl radicals, via a KOTBu mediated single electron transfer pathway. As previously outlined in **Section 2.5.3** (page 111), the role of reaction additives has been established, with the formation of organic-super electron donors responsible for the SET pathway.^{212,213} Future work should be aimed towards screening a range of alcohols, amino alcohols and organocatalysts in the reaction protocol. This could lend stability to both the iodoaziridine and product selenoaziridine under the reaction conditions, with lower temperatures shown to be required for aryl radical formation in the presence of suitable organic additives. A screen of 1,2-alcohols, 1,2-diamines and amino acids are suggested in

combination with lower reaction temperatures (rt to 40 °C) in order to probe the effect of the additives on the formation of the desired aziridiny radical (**Scheme 61**).

The formation of new carbon-carbon bonds using this methodology is also yet to be explored. It is envisaged that the addition of the aziridiny radical can occur under mild reaction conditions, using an excess of benzene as an effective trap. This has successfully been demonstrated in the literature on numerous occasions for sp^2 - sp^2 C-C bond formation. More activated carbon electrophiles should also be considered, such as common Michael acceptors (*e.g.* acrylates).

Scheme 61: Investigate additives used in aziridiny radical formation and formation of new carbon-carbon bonds.



4: Experimental

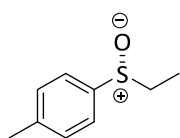
General Experimental Considerations: All nonaqueous reactions were run under an inert atmosphere (argon) with flame-dried glassware using standard techniques. Anhydrous solvents were obtained by filtration through drying columns (THF, diethyl ether, CH₂Cl₂, hexane). Flash column chromatography was performed using 230-400 mesh silica or 50-200 μ m Brockmann basic alumina (activity IV) with the indicated solvent system according to standard techniques. Analytical thin-layer chromatography (TLC) was performed on precoated, glass-backed silica gel plates. Visualisation of the developed chromatogram was performed by UV absorbance (254 nm), aqueous potassium permanganate stain, ninhydrin solution in ethanol, phosphomolybdic acid solution in ethanol or a vanillin solution. Infrared spectra (ν_{max} , FTIR ATR) were recorded in reciprocal centimeters (cm⁻¹). Nuclear magnetic resonance spectra were recorded on 400 MHz or 500 MHz spectrometers. Chemical shifts for ¹H NMR spectra are recorded in parts per million from tetramethylsilane with the solvent resonance as the internal standard (chloroform, δ = 7.27 ppm). Data is reported as follows: chemical shift [multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet and br = broad), coupling constant in Hz, integration, assignment]. ¹³C NMR spectra were recorded with complete proton decoupling. Chemical shifts are reported in parts per million from tetramethylsilane with the solvent resonance as the internal standard (¹³CDCl₃: 77.0 ppm). ¹⁹F NMR spectra were recorded with complete proton decoupling. Chemical shifts are reported in parts per million referenced to the standard monofluorobenzene: -113.5 ppm. *J* values are reported in Hz. Assignments of ¹H/¹³C spectra were made by the analysis of δ/J values, and COSY, HSQC, and HMBC experiments as appropriate. Melting points are uncorrected.

Reagents: HMDS was freshly distilled under an Ar atmosphere prior to use over KOH pellets. Commercial organometallic solutions were either titrated against salicylhydrazine,²¹⁹ or a mixture of *s*-BuOH/1,10-phenanthroline.²²⁰ All other commercial reagents were used as supplied, or purified by standard techniques where necessary.¹⁰⁷

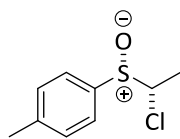
Procedure for obtaining deactivated basic alumina: Commercial alumina is classed as activity I. To alter the activity to basic alumina (activity IV), 10% w/v water must be added to basic alumina (activity I) and evenly distributed.^{103-107,221}

Iodoaziridine and amino *gem*-diiodide melting points: Iodoaziridines and diiodides decomposed upon heating (>100 °C), therefore accurate melting points have not been determined.

Cross-Coupling of Aziridinyl Sulfoxides

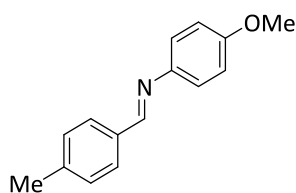


Ethyl-4-tolyl sulfoxide (4). *m*CPBA (22.4 g, 130 mmol, 1.3 equiv) was added in portions at $-10\text{ }^{\circ}\text{C}$ to a solution of ethyl tolyl sulfide (8.00 g, 52.5 mmol, 1.0 equiv) in CH_2Cl_2 (250 mL). The reaction was then warmed to $0\text{ }^{\circ}\text{C}$ in an ice bath. Reaction progress was monitored by thin layer chromatography. After 1 h at $0\text{ }^{\circ}\text{C}$, the reaction was then quenched by the addition of NaI solution (aq, 10% w/v, 150 mL). The organic layer was separated and washed with aqueous NaOH (200 mL, 0.5 M). The aqueous mixture was then extracted with CH_2Cl_2 ($2 \times 100\text{ mL}$) and EtOAc ($2 \times 100\text{ mL}$). The organic extracts were then combined, dried (Na_2SO_4), filtered and solvent removed under reduced pressure. Purification by flash chromatography (50% EtOAc/hexane) afforded the racemic sulfoxide **4** (8.11 g, 92%) as a colourless oil: $R_f = 0.21$ (80% EtOAc/hexane); ^1H NMR (400 MHz, CDCl_3) δ 7.50 (d, $J = 8.0\text{ Hz}$, 2H, $2 \times \text{Tol-H}$), 7.33 (d, $J = 8.0\text{ Hz}$, 2H, $2 \times \text{Tol-H}$), 2.87 (m, 1H, CH_2), 2.77 (m, 1H, CH_2), 2.42 (s, 3H, Tol-CH_3), 1.19 (t, $J = 7.4\text{ Hz}$, 3H, CH_3); ^{13}C NMR (101 MHz, CDCl_3) δ 141.3 (SOTol-C quat.), 139.9 (SOTolC- CH_3 quat.), 129.8 ($2 \times \text{SOTol-C}$), 124.1 ($2 \times \text{SOTol-C}$), 50.3 (CH_2), 21.3 (SOTol- CH_3), 6.0 (CH_3). The observed data is consistent with that previously reported in the literature.²²²

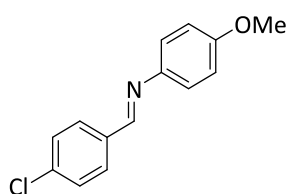


1-Chloromethyl-4-tolyl sulfoxide (5). Prepared according to the procedure of Blakemore and co-workers.²²³ *N*-Chlorosuccinimide (10.45 g, 78.3 mmol, 1.0 equiv) was added to a solution of sulfoxide **4** (13.17 g, 78.3 mmol, 1.0 equiv) in CH_2Cl_2 (250 mL), with the resulting mixture stirred at rt for 2 h. The reaction was quenched by addition of a NaI solution (aq, 10% w/v, 200 mL) and was washed with $\text{Na}_2\text{S}_2\text{O}_3$ solution (aq, 10% w/v, 100 mL). The aqueous layer was extracted with EtOAc ($2 \times 100\text{ mL}$), organic extracts combined, dried (Na_2SO_4), and the solvent removed under reduced pressure to afford a yellow oil. Purification by flash column chromatography (50% EtOAc/hexane) afforded α -chlorosulfoxide **5**, as a mixture of diastereoisomers (14.94 g, 96%) (8:1 *syn:anti*) as a yellow oil: $R_f = 0.25$ (50% EtOAc/hexane); ν_{max} (film)/ cm^{-1} 3052, 3024, 2925, 1602, 1496, 1449, 1400, 1218, 1083, 1055 (s, S=O), 1016, 813, 742; ^1H NMR (400 MHz, CDCl_3) δ 7.65–7.53 (m, 4H, $4 \times \text{Tol-H}$, 2H^{syn} and 2H^{anti}), 7.39–7.30 (m, 4H, $4 \times \text{Tol-H}$, 2H^{syn} and 2H^{anti}), 4.69 (q, $J = 6.7\text{ Hz}$, 1H, ClCH^{syn}), 4.51 (q, $J = 6.7\text{ Hz}$, 1H, $\text{ClCH}^{\text{anti}}$), 2.43 (s, 6H, $\text{Tol-CH}_3^{\text{syn}}$ and $\text{Tol-CH}_3^{\text{anti}}$), 1.76 (d, $J = 6.7\text{ Hz}$, 3H, $\text{ClHC-CH}_3^{\text{anti}}$), 1.60 (d, $J = 6.7\text{ Hz}$, 3H, $\text{ClHC-CH}_3^{\text{syn}}$); ^{13}C NMR (101 MHz, CDCl_3), major (*syn*) δ 142.6 (SOTol-C quat.), 135.3 (SOTolC- CH_3 quat.), 129.5 ($2 \times \text{SOTol-C}$), 125.8 ($2 \times \text{SOTol-C}$), 70.8 (CHCl), 21.5 (SOTol- CH_3), 17.1 (CH_3). The observed data is consistent with that previously reported in the literature.^{64,223}

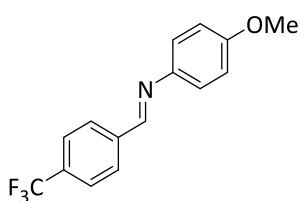
Synthesis of *N*-PMP Imines 6a-6d, General Procedure 1: Prepared according to the procedure of Danheiser and co-workers.²²⁴ The relevant aldehyde (23.0 mmol, 1.0 equiv) was added to a stirred suspension of *p*-anisidine (2.82 g, 23.0 mmol, 1.0 equiv) and MgSO₄ (2.75 g) in CH₂Cl₂ (50 mL), and the resulting mixture was stirred at rt for 24 h. The mixture was then filtered and washed with CH₂Cl₂ (2 × 50 mL). The filtrate was evaporated to afford the crude imine which was purified by recrystallisation (EtOH) to afford the corresponding imine.



(*E*)-*N*-4-Methylbenzylidene-4-methoxyaniline (6b). Prepared according to **General Procedure 1** described above, starting from 4-tolualdehyde (3.14 mL, 23.0 mmol) afforded imine **6b** (3.74 g, 72%) as yellow crystals: mp = 82–84 °C (lit.²²⁵ = 88–90 °C); *R*_f = 0.44 (25% EtOAc/hexane); *v*_{max} (film)/cm⁻¹ 3002, 2968, 2915, 2889, 2840, 1624 (s, C=N), 1501, 1237, 1031, 836; ¹H NMR (400 MHz, CDCl₃) δ 8.46 (s, 1H, HC=N), 7.80 (d, *J* = 8.1 Hz, 2H, 2 × Tol-H), 7.31–7.26 (m, 2H, 2 × Tol-H), 7.24 (d, *J* = 8.9 Hz, 2H, 2 × MeOAr-H), 6.94 (d, *J* = 8.7 Hz, 2H, 2 × MeOAr-H), 3.84 (s, 3H, OCH₃), 2.43 (s, 3H, Tol-CH₃); ¹³C NMR (101 MHz, CDCl₃) δ 158.3 (C=N), 158.0 (ArC-OCH₃ quat.), 145.0 (CN-CArOCH₃ quat.), 141.4 (TolC-CH₃ quat.), 133.8 (TolC-CN quat.), 129.4 (2 × Tol-C), 128.5 (2 × Tol-C), 122.1 (2 × MeOAr-C), 114.3 (2 × MeOAr-C), 55.4 (OCH₃), 21.5 (Tol-CH₃). The observed data was consistent with that previously reported in the literature.²²⁵

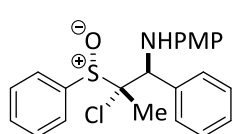


(*E*)-*N*-4-Chlorobenzylidene-4-methoxyaniline (6c). Prepared according to **General Procedure 1** described above, starting from 4-chlorobenzaldehyde (3.25 g, 23.0 mmol) afforded imine **6c** (3.84g, 68%) as silver crystals: mp = 115–117 °C (lit.²²⁶ = 127–129 °C); *R*_f = 0.44 (25% EtOAc/hexane); *v*_{max} (film)/cm⁻¹ 3013, 2964, 2882, 2840, 1620 (s, C=N), 1246, 835; ¹H NMR (400 MHz, CDCl₃) δ 8.45 (s, 1H, CHN), 7.84 (d, *J* = 8.4 Hz, 2H, 2 × ClAr-H), 7.44 (d, *J* = 8.4 Hz, 2H, 2 × ClAr-H), 7.25 (d, *J* = 8.9 Hz, 2H, 2 × MeOAr-H), 6.95 (d, *J* = 8.9 Hz, 2H, 2 × MeOAr-H), 3.84 (s, 3H, OCH₃); ¹³C NMR (100 MHz, CDCl₃) δ 158.5 (ArC-OCH₃ quat.), 156.6 (C=N), 144.4 (MeOAr-CN quat.), 136.9 (Cl-CAr quat.), 134.9 (ClArC-CN quat.), 129.6 (2 × ClAr-C), 129.2 (2 × ClAr-C), 122.2 (2 × MeOAr-C), 114.4 (2 × MeOAr-C), 55.5 (OCH₃). The observed data was consistent with that previously reported in the literature.²²⁶



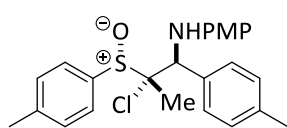
(*E*)-*N*-4-Trifluoromethylbenzylidene-4-methoxyaniline (6d). Prepared according to **General Procedure 1** described above, starting from 4-trifluoromethylbenzaldehyde (2.81 g, 23.0 mmol) afforded imine **6d** (4.70 g, 73%) as beige crystals: mp = 116–118 °C (lit.²²⁷ = 124 °C); *R*_f = 0.53 (25%

EtOAc/hexane); ^1H NMR (400 MHz, CDCl_3) δ 8.54 (s, 1H, CHN), 8.01 (d, J = 8.1 Hz, 2H, $2 \times \text{F}_3\text{CAr-H}$), 7.72 (d, J = 8.1 Hz, 2H, $2 \times \text{F}_3\text{CAr-H}$), 7.29 (d, J = 8.9 Hz, 2H, $2 \times \text{MeOAr-H}$), 6.96 (d, J = 8.9 Hz, 2H, $2 \times \text{MeOAr-H}$), 3.85 (s, 3H OCH_3); ^{13}C NMR (101 MHz, CDCl_3) δ 158.8 (ArC-OCH_3 quat.), 156.2 (C=N), 144.1 (CN-CArOCH_3 quat.), 139.6 ($\text{F}_3\text{CAr-C}$ quat.), 132.3 (q, J = 32.3 Hz, $\text{F}_3\text{C-CAr}$ quat.), 128.7 ($2 \times \text{F}_3\text{CAr-C}$), 125.7 (q, J = 3.8 Hz, $2 \times \text{F}_3\text{CAr-C}$), 123.9 (q, J = 272.1 Hz, $\text{F}_3\text{C-CAr}$ quat.), 122.4 ($2 \times \text{MeOAr-C}$), 114.5 ($2 \times \text{MeOAr-C}$), 55.5 (OCH_3). The observed data was consistent with that previously reported in the literature.^{227,228}



(1R*,2R*)-2-Chloro-1-(4-methoxyphenylamino)-1-phenyl-2-(4-tolylsulfinyl)propane (7a). Prepared according to the procedure of Satoh and co-workers.⁶⁴

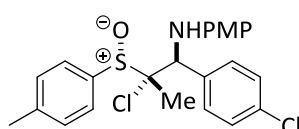
n-BuLi (1.60 M solution in hexane, 7.73 mL, 12.36 mmol, 1.2 equiv) was added to a solution of diisopropylamine (1.88 mL, 13.39 mmol, 1.3 equiv) in THF (20 mL) at -78°C . After 30 minutes at -78°C , a solution of α -chlorosulfoxide **5** (2.09 g, 10.30 mmol, 1.0 equiv) in THF (10 mL) was added dropwise to the reaction mixture. After a further 10 minutes stirring at -78°C , a solution of imine **6a** (2.61 g, 12.36 mmol, 1.2 equiv) in THF (10 mL) was added dropwise to the reaction mixture. The resulting solution was stirred at -78°C , monitoring reaction progress by thin layer chromatography. After 1 h at -78°C , the reaction was quenched by the addition of sat. aq. NH_4Cl solution (100 mL). The aqueous mixture was extracted with CHCl_3 (3×75 mL). The organic extracts were combined, washed with sat. aq. NH_4Cl solution (100 mL), dried (Na_2SO_4), filtered and the solvent removed under reduced pressure. Purification by trituration (10:1 EtOAc: hexane) afforded β -chloroamine **7a** (2.62 g, 61 %) as a white solid: mp = $165\text{--}166^\circ\text{C}$ (lit.⁶⁴ = $165\text{--}168^\circ\text{C}$); R_f = 0.34 (25% EtOAc/hexane); ν_{max} (film)/ cm^{-1} 3304 (br, NH), 1517, 1458, 1241, 1182, 1091, 1038 (s, S=O), 910, 812, 729, 704; ^1H NMR (400 MHz, CDCl_3) δ 7.65–7.60 (m, 2H, $2 \times \text{Tol-H}$), 7.45–7.39 (m, 2H, $2 \times \text{Tol-H}$), 7.33–7.28 (m, 3H, $3 \times \text{Ph-H}$), 7.23–7.18 (m, 2H, $2 \times \text{Ph-H}$), 6.66–6.61 (m, 2H, $2 \times \text{MeOAr-H}$), 6.42–6.37 (m, 2H, MeOAr-H), 5.76 (d, J = 2.0 Hz, 1H, NH), 4.36 (d, J = 2.0 Hz, 1H, ClCC-H), 3.69 (s, 3H, OCH_3), 2.40 (s, 3H, Tol- CH_3), 1.85 (s, 3H, CH_3); ^{13}C NMR (101 MHz, CDCl_3) δ 152.3 (ArC-OMe quat.) 143.0 (Tol- C(S=O) quat.), 140.6 ($\text{CH}_3\text{OAr-CN}$ quat.), 137.4 (ArC-CH_3 quat.), 134.2 (Ph-C quat.), 129.3 ($2 \times \text{Tol-C}$), 129.2 ($2 \times \text{Tol-C}$), 128.2 (Ph-C), 128.1 ($2 \times \text{Ph-C}$), 127.5 ($2 \times \text{Ph-C}$), 115.2 ($2 \times \text{MeOAr-C}$), 115.0 ($2 \times \text{MeOAr-C}$), 83.2 (PhCHN), 67.0 ($\text{H}_3\text{C-CCl}$), 55.6 (OCH_3), 23.0 (Tol- CH_3), 22.0 (ClC- CH_3 quat.). The observed data is consistent with that previously reported in the literature.⁶⁴



(1R*,2R*)-2-Chloro-1-(4-methoxyphenylamino)-1-(4-tolyl)-2-(4-tolylsulfinyl)propane (7b). Prepared according to the procedure of Satoh and co-workers.⁶⁴

n-BuLi (1.45 M solution in hexane, 8.17 mL, 11.84 mmol, 1.2

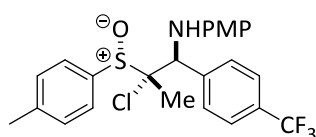
equiv) was added to a solution of diisopropylamine (1.80 mL, 12.83 mmol, 1.3 equiv) in THF (20 mL) at -78°C . After 30 minutes at -78°C , a solution of α -chlorosulfoxide **5** (2.00 g, 9.87 mmol, 1.0 equiv) in THF (10 mL) was added dropwise to the reaction mixture. After a further 10 minutes stirring at -78°C , a solution of imine **6b** (2.67 g, 11.84 mmol, 1.2 equiv) in THF (10 mL) was added dropwise to the reaction mixture. The resulting solution was stirred at -78°C , monitoring reaction progress by thin layer chromatography. After 90 mins at -78°C the reaction was quenched by the addition of sat. aq. NH_4Cl solution (100 mL). The aqueous mixture was extracted with CHCl_3 (3×75 mL), organic extracts combined, washed with sat. aq. NH_4Cl solution (100 mL), dried (Na_2SO_4), filtered and solvent removed under reduced pressure. Purification by trituration (10:1 EtOAc: hexane) afforded β -chloroamine **7b** (1.84 g, 44 %) as a white solid: mp = $135\text{--}142^{\circ}\text{C}$; R_f = 0.26 (25% EtOAc/hexane); ν_{max} (film)/ cm^{-1} 3304 (NH), 1595, 1372, 1251, 1241, 1177, 1113, 1031 (s, S=O), 1012, 824, 809; ^1H NMR (400 MHz, CDCl_3) δ 7.61 (d, J = 7.9 Hz, 2H, 2 $\times$ SOTol-H), 7.30 (d, J = 7.7 Hz, 2H, 2 $\times$ Tol-H), 7.20 (d, J = 7.9 Hz, 2H, 2 $\times$ SOTol-H), 7.11 (d, J = 7.8 Hz, 2H, 2 $\times$ Tol-H), 6.64 (d, J = 8.7 Hz, 2H, 2 $\times$ MeOAr-H), 6.41 (d, J = 9.0 Hz, 2H, 2 $\times$ MeOAr-H), 5.77 (br s, 1H, NH), 4.34 (s, 1H, CHN), 3.68 (s, 3H, Ar-OCH₃), 2.38 (s, 3H, SOTol-CH₃), 2.32 (s, 3H, Tol-CH₃), 1.83 (s, 3H, C(Cl)CH₃); ^{13}C NMR (101 MHz, CDCl_3) δ 152.3 (ArC-OMe quat.), 142.9 (Tol-C(S=O) quat.), 140.6 (CH₃OAr-CN quat.), 138.0 (TolC-CH₃ quat.), 134.3 (TolC-CHN quat.), 134.2 (SOTolC-CH₃ quat.), 129.21 (2 $\times$ SOTol-C), 129.16 (2 $\times$ Tol-C), 128.9 (2 $\times$ Tol-C), 127.5 (2 $\times$ SOTol-C), 115.3 (2 $\times$ MeOAr-C), 114.5 (2 $\times$ MeOAr-C), 83.5 (H₃C-CCl quat.), 66.7 (CHN), 55.6 (OCH₃), 21.8 (SOTol-CH₃), 21.5 (ClC-CH₃), 21.2 (Tol-CH₃); HRMS (ESI⁺) m/z Calculated for $\text{C}_{24}\text{H}_{27}\text{ClINO}_2\text{S}^+ [\text{M}+\text{H}]^+$: 428.1451; Found: 428.1448.



(1R*,2R*)-2-Chloro-1-(4-methoxyphenylamino)-1-(4-chlorobenzene)-2-(4-tolylsulfinyl)propane (7c). Prepared according to the procedure of Satoh and co-workers.⁶⁴ *n*-BuLi (2.20 M solution in hexane, 1.68 mL, 3.70

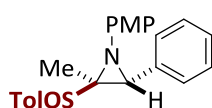
mmol, 1.0 equiv) was added to a solution of diisopropylamine (570 μL , 4.07 mmol, 1.1 equiv) in THF (20 mL) at -78°C . After 30 minutes at -78°C , a solution of α -chlorosulfoxide **5** (750 mg, 3.70 mmol, 1.0 equiv) in THF (6 mL) was added dropwise to the reaction mixture. After a further 10 minutes stirring at -78°C , a solution of imine **6c** (910 mg, 3.70 mmol, 1.0 equiv) in THF (6 mL) was added dropwise to the reaction mixture. The resulting solution was stirred at -78°C , monitoring reaction progress by thin layer chromatography. After 2 h, the reaction was quenched by the addition of sat. aq. NH_4Cl solution (75 mL). The aqueous mixture was extracted with CHCl_3 (3×75 mL), organic extracts combined, dried (Na_2SO_4), filtered and the solvent removed under reduced pressure. Purification by flash chromatography (20% diethyl ether/hexane) afforded β -chloroamine **7c** (723 mg, 44 %) as a white solid: mp = $150\text{--}151^{\circ}\text{C}$; R_f = 0.23 (25% EtOAc/hexane); ν_{max} (film)/ cm^{-1} 3337

(NH), 2834, 1598, 1511, 1494, 1441, 1413, 1382, 1237, 1183, 1087, 1039 (s, S=O), 1015, 851, 813, 735; ^1H NMR (400 MHz, CDCl_3) δ 7.61 (d, J = 8.2 Hz, 2H, 2 $\times$ SOTol-H), 7.36 (d, J = 8.6 Hz, 2H, 2 $\times$ ClAr-H), 7.28 (d, J = 8.6 Hz, 2H, 2 $\times$ ClAr-H), 7.19 (d, J = 8.2 Hz, 2H, 2 $\times$ SOTol-H), 6.64 (d, J = 9.0 Hz, 2H, 2 $\times$ MeOAr-H), 6.38 (d, J = 9.0 Hz, 2H, 2 $\times$ MeOAr-H), 5.82 (br s, 1H, NH), 4.28 (br s, 1H, CHN), 3.69 (s, 3H, Ar-OCH₃), 2.38 (s, 3H, SOTol-CH₃), 1.88 (s, 3H, C(Cl)CH₃); ^{13}C NMR (101 MHz, CDCl_3) δ 152.5 (ArC-OMe quat.), 143.1 (Tol-C(S=O) quat.), 140.2 (CH₃OAr-CN quat.), 136.0 (ClAr-C quat.), 134.1 (NHC-CarCl quat.), 133.9 (TolC-CH₃ quat.), 130.6 (2 $\times$ ClAr-C), 129.3 (2 $\times$ Tol-C), 128.4 (2 $\times$ ClAr-C), 127.4 (2 $\times$ Tol-C), 115.3 (2 $\times$ MeOAr-C), 114.6 (2 $\times$ MeOAr-C), 82.5 (H₃C-CCl quat.), 66.2 (CHN), 55.6 (OCH₃), 21.6 (Ar-CH₃), 21.5 (ClC-CH₃); HRMS (ESI⁺) m/z Calculated for $\text{C}_{23}\text{H}_{24}\text{Cl}_2\text{NO}_2\text{S}^+$ [M+H]⁺: 448.0899; Found: 448.0905.



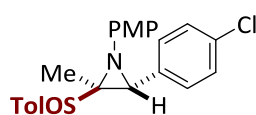
(1R*,2R*)-2-Chloro-1-(4-methoxyphenylamino)-1-(4-trifluoromethylbenzene)-2-(4-tolylsulfinyl)propane (7d).

Prepared according to the procedure of Satoh and co-workers.⁶⁴ *n*-BuLi (1.60 M solution in hexane, 2.31 mL, 3.70 mmol, 1.0 equiv) was added to a solution of diisopropylamine (0.52 mL, 3.70 mmol, 1.0 equiv) in THF (20 mL) at -78°C . After 30 minutes at -78°C , a solution of α -chlorosulfoxide **5** (753 mg, 3.71 mmol, 1.0 equiv) in THF (7 mL) was added dropwise to the reaction mixture. After a further 15 minutes stirring at -78°C , a solution of imine **6d** (1.03 g, 3.71 mmol, 1.0 equiv) in THF (7 mL) was added dropwise to the reaction mixture. The resulting solution was stirred at -78°C , monitoring reaction progress by thin layer chromatography. After 2 h, the reaction was quenched by the addition of sat. aq. NH_4Cl solution (100 mL). The aqueous mixture was extracted with CHCl_3 (3 $\times$ 75 mL). The organic extracts were combined, dried (Na_2SO_4), filtered and the solvent removed under reduced pressure. Purification by flash chromatography (25% EtOAc/hexane) afforded β -chloroamine **7d** (544 mg, 34 %) as a white solid: R_f = 0.22 (25% EtOAc/hexane); ν_{max} (film)/ cm^{-1} 3334 (NH), 3003, 2836, 1511, 1324, 1237, 1165, 1121, 1067, 1037 (s, S=O), 1016; ^1H NMR (400 MHz, CDCl_3) δ 7.64 (d, J = 8.2 Hz, 2H, 2 $\times$ SOTol-H), 7.57 (br s, 4H, 4 $\times$ F₃CAr-H), 7.21 (d, J = 8.2 Hz, 2H, 2 $\times$ SOTol-H), 6.66 (d, J = 8.9 Hz, 2H, 2 $\times$ MeOAr-H), 6.38 (d, J = 8.9 Hz, 2H, 2 $\times$ MeOAr-H), 5.88 (br s, 1H, NH), 4.41 (br s, 1H, CHN), 3.69 (s, 3H, Ar-OCH₃), 2.39 (s, 3H, SOTol-CH₃), 1.88 (s, 3H, C(Cl)CH₃); ^{13}C NMR (101 MHz, CDCl_3) δ 152.5 (ArC-OMe quat.), 143.2 (Tol-C(S=O) quat.), 141.6 (F₃CArC-CHN quat.), 140.0 (CH₃OArC-NH quat.), 133.7 (TolC-CH₃ quat.), 130.3 (q, J = 32.4 Hz, F₃C-CAr quat.), 129.6 (2 $\times$ F₃CAr-C), 129.3 (2 $\times$ Tol-C), 127.4 (2 $\times$ Tol-C), 124.0 (q, J = 3.5 Hz, 2 $\times$ F₃CAr-C), 123.9 (q, J = 272.1 Hz, F₃C-CAr quat.), 115.2 (2 $\times$ MeOAr-C), 114.5 (2 $\times$ MeOAr-C), 82.3 (H₃C-CCl quat.), 66.1 (CHN), 54.5 (OCH₃), 21.5 (Tol-CH₃ and ClC-CH₃); HRMS (ESI⁺) m/z Calculated for $\text{C}_{24}\text{H}_{24}\text{ClF}_3\text{NO}_2\text{S}^+$ [M+H]⁺: 482.1160; Found: 482.1163.



2-Methyl-1-(4-methoxyphenyl)-3-phenyl-2-(4-tolylsulfinyl) aziridine (8a).

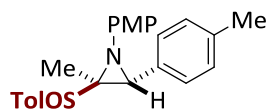
Prepared according to the procedure of Satoh and co-workers.⁶⁴ KOtBu (1.0 M in THF, 27.5 mL, 27.5 mmol, 2.5 equiv) was added to a solution of β -chloroamine **7a** (4.55 g, 11.0 mmol, 1.0 equiv) in THF (100 mL). The reaction mixture was heated under reflux for 15 min and then quenched with sat. aq. NH_4Cl solution (50 mL). The layers were separated and the aqueous layer was extracted with CHCl_3 (3 $\times$ 50 mL). The combined organic layers were dried (Na_2SO_4), filtered and the solvent removed under reduced pressure to give a yellow oil. Purification by flash column chromatography (20% EtOAc/hexane) afforded sulfinyl aziridine **8a** (3.91 g, 94%) as light yellow crystals: mp = 92–94 °C (lit.⁶⁴ = 88–91 °C); R_f = 0.24 (30% EtOAc/hexane); ν_{max} (film)/ cm^{-1} 3046, 2996, 2931, 2839, 1602, 1503, 1448, 1402, 1297, 1235, 1183, 1084, 1035 (s, S=O), 842, 813, 701; ^1H NMR (400 MHz, CDCl_3) δ 7.61 (d, J = 7.8 Hz, 2H, 2 $\times$ Tol-H), 7.42–7.29 (m, 7H, 2 $\times$ Tol-H and 5 $\times$ Ph-H), 7.01 (d, J = 8.7 Hz, 2H, 2 $\times$ MeOAr), 6.88 (d, J = 8.7 Hz, 2H, 2 $\times$ MeOAr), 4.54 (s, 1H, NC-H), 3.80 (s, 3H, ArOCH_3), 2.42 (s, 3H, Tol- CH_3), 1.06 (s, 3H, NC- CH_3); ^{13}C NMR (100 MHz, CDCl_3) δ 155.5 (ArC-OMe quat.), 142.7 (Tol-C(S=O) quat.), 140.8 (Ar-CN quat.), 138.3 (ArC- CH_3 quat.), 135.2 (Ph-C quat.), 130.0 (2 $\times$ Tol-C), 128.4 (2 $\times$ Tol-C), 127.7 (2 $\times$ Ph-C), 127.6 (Ph-C), 126.6 (2 $\times$ Ph-C), 120.3 (2 $\times$ MeOAr-C), 114.6 (2 $\times$ MeOAr-C), 64.4 (OCH_3), 55.6 ($\text{H}_3\text{CC}(\text{SO})$), 41.4 (PhCNH), 21.6 (Tol- CH_3), 14.0 (CH_3). The observed data is consistent with that previously reported in the literature.⁶⁴



2-Methyl-1-(4-methoxyphenyl)-3-(4-chlorophenyl)-2-(4-tolylsulfinyl) aziridine (8b).

Prepared according to the procedure of Satoh and co-workers.⁶⁴ KOtBu (1.0 M in THF, 3.69 mL, 3.69 mmol, 2.5 equiv) was added to a solution of β -chloroamine **7b** (662 mg, 1.48 mmol, 1.0 equiv) in THF (25 mL). The reaction mixture was heated under reflux for 45 min and then quenched with sat. aq. NH_4Cl solution (50 mL). The layers were separated and the aqueous layer was extracted with CHCl_3 (3 $\times$ 30 mL). The combined organic layers were dried (Na_2SO_4), filtered and the solvent removed under reduced pressure to give an orange oil. Purification by flash column chromatography (25% EtOAc/hexane) afforded sulfinyl aziridine **8b** (250 mg, 41%) as red/orange crystals: mp = 61–63 °C; R_f = 0.14 (25% EtOAc/hexane); ν_{max} (film)/ cm^{-1} 3040, 2997, 2929, 2835, 1505, 1491, 1236, 1086, 1039 (s, S=O), 730; ^1H NMR (400 MHz, CDCl_3) δ 7.58 (d, J = 8.2 Hz, 2H, 2 $\times$ SOTol-H), 7.34–7.31 (m, 6H, 2 $\times$ SOTol-H and 4 $\times$ ClAr-H), 6.98 (d, J = 8.9 Hz, 2H, 2 $\times$ MeOAr-H), 6.87 (d, J = 8.9 Hz, 2H, 2 $\times$ MeOAr-H), 4.49 (s, 1H, NC-H), 3.79 (s, 3H, OCH_3), 2.42 (s, 3H, SOTol- CH_3), 1.02 (s, 3H, NC- CH_3); ^{13}C NMR (101 MHz, CDCl_3) δ 155.5 (ArC-OMe quat.), 142.6 (Tol-C(S=O) quat.), 140.3 (MeOAr-CN quat.), 138.0 (SOTolC- CH_3 quat.), 133.7 (ClArC-CHN quat.), 133.4 (ArC-Cl quat.), 129.9 (2 $\times$ SOTol-C), 128.9 (2 $\times$ ClAr-C), 128.5 (2 $\times$ SOTol-C),

126.3 (2 × ClAr-C), 120.2 (2 × MeOAr-C), 114.5 (2 × MeOAr-C), 64.4 (OCH₃), 55.4 (H₃C-C(SO) quat.), 40.8 (CHN), 21.5 (SOTol-CH₃), 13.8 (CH₃); HRMS (ESI⁺) *m/z* Calculated for C₂₃H₂₃ClNO₂S⁺ [M+H]⁺: 412.1133; Found: 412.1134.

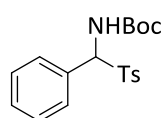


2-Methyl-1-(4-methoxyphenyl)-3-(4-tolyl)-2-(4-tolylsulfinyl)aziridine (8c).

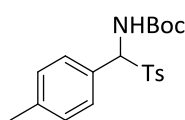
Prepared according to the procedure of Satoh and co-workers.⁶⁴ KOtBu (1.0 M in THF, 9.64 mL, 9.64 mmol, 2.5 equiv) was added to a solution of β -chloroamine **7c** (1.65 g, 3.86 mmol, 1.0 equiv) in THF (50 mL). The reaction was then heated under reflux, monitoring the reaction progress by thin layer chromatography. After 1 h at reflux, the reaction mixture was cooled and quenched by the addition of sat. aq. NH₄Cl solution (50 mL). The aqueous mixture was extracted with CHCl₃ (3 × 75 mL). The organic extracts were combined, dried (Na₂SO₄), filtered and the solvent removed under reduced pressure. Purification by flash chromatography (20% EtOAc/hexane) afforded sulfinyl aziridine **8c** (1.29 g, 85 %) as a pale orange solid: mp = 59–61 °C; *R_f* = 0.23 (25% EtOAc/hexane); ν_{max} (film)/cm⁻¹ 3035, 2923, 2834, 1598, 1504, 1234, 1038 (s, S=O), 910, 814, 730; ¹H NMR (400 MHz, CDCl₃) δ 7.61 (d, *J* = 8.2 Hz, 2H, 2 × SOTol-H), 7.32 (d, *J* = 8.0 Hz, 2H, 2 × Tol-H), 7.27 (m, 2H, 2 × SOTol-H), 7.16 (d, *J* = 8.0 Hz, 2H, 2 × Tol-H), 6.99 (d, *J* = 8.9 Hz, 2H, 2 × MeOAr-H), 6.87 (d, *J* = 8.9 Hz, 2H, 2 × MeOAr-H), 4.51 (s, 1H, CHN), 3.80 (s, 3H, Ar-OCH₃), 2.42 (s, 3H, SOTol-CH₃), 2.35 (s, 3H, Tol-CH₃), 1.06 (s, 3H, CH₃); ¹³C NMR (101 MHz, CDCl₃) δ 155.3 (ArC-OMe quat.), 142.4 (Tol-C(S=O) quat.), 140.6 (MeOAr-CN quat.), 138.2 (SOTolC-CH₃ quat.), 137.2 (TolC-CH₃ quat.), 131.9 (TolC-CHN quat.), 129.8 (2 × SOTol-C), 129.0 (2 × SOTol-C), 127.5 (2 × Tol-C), 126.4 (2 × Tol-C), 120.2 (2 × MeOAr-C), 114.4 (2 × MeOAr-C), 64.1 (Ar-OCH₃), 55.4 (H₃C-C(SO) quat.), 41.4 (CHN), 21.4 (SOTol-CH₃), 21.1 (Tol-CH₃), 13.6 (CH₃); HRMS (ESI⁺) *m/z* Calculated for C₂₄H₂₆NO₂S⁺ [M+H]⁺: 392.1679; Found: 392.1680.

N-Boc Iodoaziridines (Section 2.1)

Synthesis of N-Boc Imine-HSO₂Tol Adducts 9a-9o, General Procedure 2: Prepared according to the procedure of Jacobsen and co-workers.¹⁰⁰ The appropriate aldehyde (13.5 mmol, 1.5 equiv) was added to a stirred suspension of *tert*-butyl carbamate (1.06 g, 9.00 mmol, 1.0 equiv) and sodium *p*-toluenesulfinate (3.21 g, 18.0 mmol, 2.0 equiv) in methanol and water (1:2, 30 mL). Formic acid (98%, 2.0 mL) was added dropwise to the reaction mixture and was stirred for 48 h at rt, during which time the product precipitated as a white solid. The reaction mixture was then filtered under reduced pressure, and the solid purified via trituration with water (100 mL) and diethyl ether (100 mL). Purification via drying under reduced pressure afforded the relevant N-Boc imine-HSO₂Tol adduct.

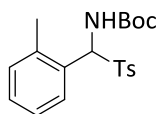


[(Phenyl-(4-tolylsulfonyl)-methyl)-*tert*-butylcarbamate (9a). Reaction performed on a 25.6 mmol scale. Prepared according to **General Procedure 2** described above starting from benzaldehyde (3.91 mL, 38.4 mmol) afforded imine-HSO₂Tol adduct **9a** (8.38 g, 91%) as a white solid: mp = 183–185 °C (lit.²²⁹ = 177–178 °C); $\nu_{\max}$ (film)/cm⁻¹ 2987, 1692 (C=O), 1598, 1511, 1500, 1392, 1368, 1300, 1250, 1140, 1085, 1050, 1022, 881, 751; ¹H NMR (400 MHz, CDCl₃) δ 7.81 (d, *J* = 8.1 Hz, 2H, 2 × SO₂Tol-H), 7.47–7.42 (m, 5H, 5 × Ph-H), 7.35 (d, *J* = 8.1 Hz, 2H, 2 × SO₂Tol-H), 5.90 (d, *J* = 10.8 Hz, 1H, NH), 5.73 (d, *J* = 10.8 Hz, 1H, CHN), 2.45 (s, 3H, SO₂Tol-CH₃), 1.29 (s, 9H, C(CH₃)₃); ¹³C NMR (101 MHz, CDCl₃) δ 153.5 (C=O quat.), 145.0 (SO₂Tol-C quat.), 133.7 (SO₂TolC-CH₃ quat.), 130.0 (Ph-C quat.), 129.7 (2 × Ph-C), 129.6 (2 × SO₂Tol-C), 129.5 (2 × SO₂Tol-C), 128.9 (Ph-C), 128.7 (2 × Ph-C), 81.1 (C(CH₃)₃ quat.), 73.8 (HC-NH), 27.9 (C(CH₃)₃), 21.6 (SO₂Tol-CH₃); HRMS (ESI⁺) *m/z* Calculated for C₁₉H₂₃NNaO₄S⁺ [M+Na]⁺: 384.1245; Found: 384.1231. Observed data was consistent with that found in the literature.¹⁰⁰



[(4-Tolyl-(4-tolylsulfonyl)-methyl)-*tert*-butylcarbamate (9b). Prepared according to **General Procedure 2** described above starting from 4-tolualdehyde (1.60 mL, 13.5 mmol) afforded imine-HSO₂Tol adduct **9b** (2.57 g, 79%) as a white solid: mp = 183–185 °C (lit.²²⁹ = 183–185 °C); $\nu_{\max}$ (film)/cm⁻¹ 3362, 3005, 1695 (C=O), 1603, 1522, 1515, 1469, 1368, 1317, 1307, 1247, 1139, 1085, 1052, 883, 803, 771; ¹H NMR (400 MHz, CDCl₃) δ 7.79 (d, *J* = 8.2 Hz, 2H, 2 × SO₂Tol-H), 7.33 (d, *J* = 8.1 Hz, 4H, 2 × SO₂Tol-H and 2 × Tol-H), 7.23 (d, *J* = 8.0 Hz, 2H, 2 × Tol-H), 5.85 (d, *J* = 10.8 Hz, 1H, NH), 5.68 (d, *J* = 10.8 Hz, 1H, CHN), 2.44 (s, 3H, SO₂Tol-CH₃), 2.38 (s, 3H, Tol-CH₃), 1.27 (s, 9H, C(CH₃)₃); ¹³C NMR (101 MHz, CDCl₃) δ 153.4 (C=O quat.), 144.8 (SO₂Tol-C quat.), 139.8 (TolC-CH₃ quat.), 133.8 (SO₂TolC-CH₃ quat.), 129.6 (2 × SO₂Tol-C), 129.4 (2 × Tol-C), 129.3 (2 × SO₂Tol-C), 128.7 (2 × Tol-C), 126.8 (Tol-C quat.), 80.9 (C(CH₃)₃ quat.), 73.6 (HC-NH), 27.9

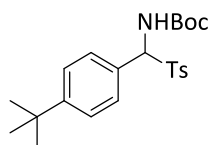
(C(CH₃)₃), 21.6 (SO₂Tol-CH₃), 21.2 (Tol-CH₃). Observed data (IR, ¹H NMR, ¹³C NMR) was consistent with that found in the literature.²³⁰



[(2-Tolyl-(4-tolylsulfonyl)-methyl)-tert-butylcarbamate (9c). Prepared according to

General Procedure 2 described above starting from 2-tolualdehyde (1.56 mL, 13.5 mmol) afforded imine-HSO₂Tol adduct **9c** (1.00 g, 25%) as a white solid: mp =

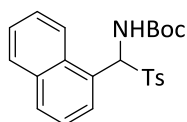
147–149 °C (lit.²³⁰ = 152–154 °C); $\nu_{\max}$ (film)/cm⁻¹ 3352, 2984, 1704 (C=O), 1603, 1525, 1494, 1371, 1318, 1303, 1291, 1139, 1084, 1049, 1021, 910, 884, 712; ¹H NMR (400 MHz, CDCl₃) δ 7.80 (d, *J* = 7.9 Hz, 2H, 2 × SO₂Tol-H), 7.48–7.41 (m, 1H, Tol-H), 7.37–7.29 (m, 5H, 3 × Tol-H and 2 × SO₂Tol-H), 6.20 (d, *J* = 10.8 Hz, 1H, NH), 5.75 (d, *J* = 10.8 Hz, 1H, CHN), 2.44 (s, 3H, SO₂Tol-CH₃), 2.43 (s, 3H, Tol-CH₃), 1.26 (s, 9H, C(CH₃)₃); ¹³C NMR (101 MHz, CDCl₃) δ 153.6 (C=O quat.), 144.9 (SO₂Tol-C quat.), 138.1 (TolC-CH₃ quat.), 134.2 (SO₂TolC-CH₃ quat.), 130.7 (Tol-C quat.), 129.6 (2 × SO₂Tol-C), 129.5 (Tol-C), 129.3 (2 × SO₂Tol-C), 129.2 (Tol-C), 127.5 (Tol-C), 126.4 (Tol-C), 81.0 (C(CH₃)₃ quat.), 69.8 (HC-NH), 28.0 (C(CH₃)₃), 21.7 (SO₂Tol-CH₃), 19.8 (Tol-CH₃). Observed data (IR, ¹H NMR, ¹³C NMR) was consistent with that found in the literature.²³⁰



[(4-tert-Butylphenyl-(4-tolylsulfonyl)-methyl)-tert-butylcarbamate (9d).

Prepared according to **General Procedure 2** described above starting from 4-tert-butylbenzaldehyde (2.26 mL, 13.5 mmol) afforded imine-HSO₂Tol adduct **9d**

(2.20 g, 59%) as a white solid: mp = 173–174 °C; $\nu_{\max}$ (film)/cm⁻¹ 2973, 1708 (C=O), 1510, 1318, 1306, 1246, 1140, 1086; ¹H NMR (400 MHz, CDCl₃) δ 7.81 (d, *J* = 8.2 Hz, 2H, 2 × SO₂Tol-H), 7.45 (d, *J* = 8.5 Hz, 2H, 2 × *t*-BuAr-H), 7.39 (d, *J* = 8.5 Hz, 2H, 2 × *t*-BuAr-H), 7.34 (d, *J* = 8.2 Hz, 2H, 2 × SO₂Tol-H), 5.87 (d, *J* = 10.8 Hz, 1H, NH), 5.71 (d, *J* = 10.8 Hz, 1H, CHN), 2.43 (s, 3H, SO₂Tol-CH₃), 1.33 (s, 9H, OC(CH₃)₃), 1.25 (s, 9H, C(CH₃)₃); ¹³C NMR (101 MHz, CDCl₃) δ 153.4 (C=O quat.), 152.9 (ArC-C(CH₃)₃ quat.), 144.8 (SO₂Tol-C quat.), 133.9 (SO₂TolC-CH₃ quat.), 129.6 (2 × SO₂Tol-C), 129.5 (2 × SO₂Tol-C), 128.6 (2 × *t*-BuAr-C), 126.8 (*t*-BuAr-C quat.), 125.7 (2 × *t*-BuAr-C), 80.9 (OC(CH₃)₃ quat.), 73.6 (HC-NH), 34.7 (ArC-C(CH₃)₃ quat.), 31.2 (ArC-C(CH₃)₃), 27.9 (OC(CH₃)₃), 21.6 (SO₂Tol-CH₃). Observed data consistent with that found in the literature.²³⁰



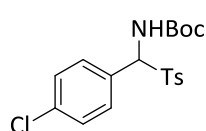
[(1-Naphthyl-(4-tolylsulfonyl)-methyl)-tert-butylcarbamate (9e). Prepared

according to **General Procedure 2** described above starting from 1-naphthaldehyde (1.83 mL, 13.5 mmol) afforded imine-HSO₂Tol adduct **9e** (3.45 g,

62%) as a white solid: mp = 153–154 °C; $\nu_{\max}$ (film)/cm⁻¹ 3359, 3005, 1695, 1599,

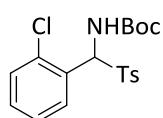
1525, 1508, 1364, 1317, 1307, 1247, 1139, 1084, 1052, 803, 751; ¹H NMR (400 MHz, CDCl₃) δ 8.13 (d,

$J = 8.4$ Hz, 1H, Ar-H), 7.94 (d, $J = 8.1$ Hz, 1H, Ar-H), 7.91–7.84 (m, 3H, Ar-H and $2 \times \text{SO}_2\text{Tol-H}$), 7.77 (d, $J = 7.3$ Hz, 1H, Ar-H), 7.61–7.49 (m, 3H, $3 \times \text{Ar-H}$), 7.34 (d, $J = 8.0$ Hz, 2H, $2 \times \text{SO}_2\text{Tol-H}$), 6.82 (d, $J = 10.5$ Hz, 1H, NH), 5.87 (d, $J = 10.5$ Hz, 1H, CHN), 2.43 (s, 3H, $\text{SO}_2\text{Tol-CH}_3$), 1.28 (s, 9H, $\text{C}(\text{CH}_3)_3$); ^{13}C NMR (101 MHz, CDCl_3) δ 153.6 (C=O quat.), 145.0 ($\text{SO}_2\text{Tol-C}$ quat.), 134.2 (Ar-C quat.), 133.6 ($\text{SO}_2\text{TolC-CH}_3$ quat.), 131.7 (Ar-C quat.), 130.4 (Ar-C), 129.7 ($2 \times \text{SO}_2\text{Tol-C}$), 129.4 ($2 \times \text{SO}_2\text{Tol-C}$), 128.8 (Ar-C), 127.1 (Ar-C), 126.5 (Ar-C), 126.0 (Ar-C), 125.0 (Ar-C), 122.9 (Ar-C), 122.9 (Ar-C), 81.1 ($\text{C}(\text{CH}_3)_3$ quat.), 69.0 (HC-NH), 27.9 ($\text{C}(\text{CH}_3)_3$), 21.6 ($\text{SO}_2\text{Tol-CH}_3$). Observed data (IR, ^1H NMR, ^{13}C NMR) was consistent with that found in the literature.¹⁰⁰



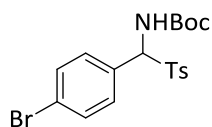
[(4-Chlorophenyl)-(4-tolylsulfonyl)-methyl]-tert-butylcarbamate (9f). Prepared

according to **General Procedure 2** described above starting from 4-chlorobenzaldehyde (1.91 g, 13.5 mmol) afforded imine- HSO_2Tol adduct **9f** (926 mg, 26%) as a white solid: mp = 171–173 °C (lit.²²⁹ = 174–175 °C); ν_{max} (film)/ cm^{-1} 3390, 2973, 1700, 1603, 1495, 1371, 1305, 1247, 1164, 1141, 1084, 1052, 1017, 717; ^1H NMR (400 MHz, CDCl_3) δ 7.79 (d, $J = 7.8$ Hz, 2H, $2 \times \text{SO}_2\text{Tol-H}$), 7.40–7.37 (m, 4H, $4 \times \text{ClAr-H}$), 7.34 (d, $J = 8.0$ Hz, 2H, $2 \times \text{SO}_2\text{Tol-H}$), 5.89 (d, $J = 10.6$ Hz, 1H, NH), 5.81 (d, $J = 10.6$ Hz, 1H, CHN), 2.44 (s, 3H, $\text{SO}_2\text{Tol-CH}_3$), 1.26 (s, 9H, $\text{C}(\text{CH}_3)_3$); ^{13}C NMR (101 MHz, CDCl_3) δ 153.4 (C=O quat.), 145.2 ($\text{SO}_2\text{Tol-C}$ quat.), 135.9 (ClArC-Cl quat.), 133.5 ($\text{SO}_2\text{TolC-CH}_3$ quat.), 130.2 ($2 \times \text{ClAr-C}$), 129.7 ($2 \times \text{SO}_2\text{Tol-C}$), 129.5 ($2 \times \text{SO}_2\text{Tol-C}$), 128.9 ($2 \times \text{ClAr-C}$), 128.6 (ClAr-C quat.), 81.3 ($\text{C}(\text{CH}_3)_3$ quat.), 73.1 (CH-NH), 27.9 ($\text{C}(\text{CH}_3)_3$), 21.6 ($\text{SO}_2\text{Tol-CH}_3$). Observed data was consistent with that found in the literature.^{229,230}



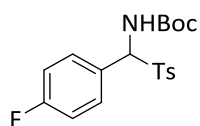
[(2-Chlorophenyl)-(4-tolylsulfonyl)-methyl]-tert-butylcarbamate (9g). Prepared

according to **General Procedure 2** described above starting from 2-chlorobenzaldehyde (1.52 mL, 13.5 mmol) afforded imine- HSO_2Tol adduct **9g** (3.03 g, 57%) as a white solid: mp = 147–148 °C; ν_{max} (film)/ cm^{-1} 3352, 2987, 1704, 1603, 1518, 1501, 1480, 1371, 1320, 1249, 1144, 1085, 1045, 1021, 911, 729; ^1H NMR (400 MHz, CDCl_3) δ 7.81 (d, $J = 8.0$ Hz, 2H, $2 \times \text{SO}_2\text{Tol-H}$), 7.60–7.52 (m, 1H, ClAr-H), 7.40–7.30 (m, 5H, $3 \times \text{ClAr-H}$ and $2 \times \text{SO}_2\text{Tol-H}$), 6.57 (d, $J = 10.8$ Hz, 1H, NH), 5.82 (d, $J = 10.8$ Hz, 1H, CHN), 2.44 (s, 3H, $\text{SO}_2\text{Tol-CH}_3$), 1.30 (s, 9H, $\text{C}(\text{CH}_3)_3$); ^{13}C NMR (101 MHz, CDCl_3) δ 153.5 (C=O quat.), 145.2 ($\text{SO}_2\text{Tol-C}$ quat.), 135.3 (ArC-Cl quat.), 133.9 ($\text{SO}_2\text{TolC-CH}_3$ quat.), 130.8 (ClAr-C), 129.8 (ClAr-C), 129.7 ($2 \times \text{SO}_2\text{Tol-C}$), 129.3 ($2 \times \text{SO}_2\text{Tol-C}$ and ClAr-C), 129.0 (ClAr-C quat.), 127.2 (ClAr-C), 81.2 ($\text{C}(\text{CH}_3)_3$ quat.), 70.0 (HC-NH), 27.9 ($\text{C}(\text{CH}_3)_3$), 21.6 ($\text{SO}_2\text{Tol-CH}_3$).



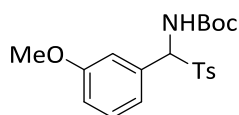
[(4-Bromophenyl)-(4-tolylsulfonyl)-methyl]-*tert*-butylcarbamate (9h).

Prepared according to **General Procedure 2** described above starting from 4-bromobenzaldehyde (1.89 g, 13.5 mmol, 1.02 equiv), *tert*-butyl carbamate (1.17 g, 10.2 mmol, 1.00 equiv) and sodium *p*-toluenesulfinate (1.78 g, 10.2 mmol, 1.00 equiv) afforded imine- HSO_2Tol adduct **9h** (3.77g, 84%) as a white solid: mp = 194–197 °C (lit.²³⁰ = 172–173 °C, lit.²³¹ = 180–182 °C); ν_{max} (film)/ cm^{-1} 3390, 2973, 1700, 1603, 1495, 1371, 1305, 1247, 1164, 1141, 1084, 1052, 1017, 717; ^1H NMR (400 MHz, CDCl_3) δ 7.78 (d, J = 8.1 Hz, 2H, 2 $\times$ $\text{SO}_2\text{Tol-H}$), 7.56 (d, J = 8.5 Hz, 2H, 2 $\times$ BrAr-H), 7.35 (d, J = 8.1 Hz, 2H, 2 $\times$ $\text{SO}_2\text{Tol-H}$), 7.32 (d, J = 8.5 Hz, 2H, 2 $\times$ BrAr-H), 5.85 (d, J = 10.5 Hz, 1H, NH), 5.66 (d, J = 10.5 Hz, 1H, CHN), 2.44 (s, 3H, $\text{SO}_2\text{Tol-CH}_3$), 1.27 (s, 9H, $\text{C}(\text{CH}_3)_3$); ^{13}C NMR (101 MHz, CDCl_3) δ 153.4 (C=O quat.), 145.3 ($\text{SO}_2\text{Tol-C}$ quat.), 133.4 ($\text{SO}_2\text{TolC-CH}_3$ quat.), 131.9 (2 $\times$ BrAr-C), 130.4 (2 $\times$ BrAr-C), 129.8 (2 $\times$ $\text{SO}_2\text{Tol-C}$), 129.5 (2 $\times$ $\text{SO}_2\text{Tol-C}$), 129.1 (BrAr-C quat.), 124.1 (ArC-Br quat.), 81.3 ($\text{C}(\text{CH}_3)_3$ quat.), 73.1 (HC-NH), 27.9 ($\text{C}(\text{CH}_3)_3$), 21.6 ($\text{SO}_2\text{Tol-CH}_3$). Observed data (IR, ^1H NMR, ^{13}C NMR) consistent with that reported in the literature.^{100,230,231}



[(4-Fluorophenyl)-(4-tolylsulfonyl)-methyl]-*tert*-butylcarbamate (9i).

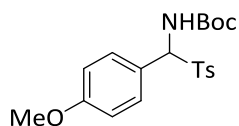
Prepared according to **General Procedure 2** described above starting from 4-fluorobenzaldehyde (1.42 mL, 13.5 mmol) afforded imine- HSO_2Tol adduct **9i** (1.93 g, 56%) as a white solid: mp = 162–165 °C (lit.²³⁰ = 168–170 °C); ν_{max} (film)/ cm^{-1} 3352, 2987, 1700, 1610, 1504, 1375, 1316, 1304, 1287, 1231, 1161, 1140, 1087, 1049, 1017, 912, 729; ^1H NMR (400 MHz, CDCl_3) δ 7.78 (d, J = 8.1 Hz, 2H, 2 $\times$ $\text{SO}_2\text{Tol-H}$), 7.43 (dd, J = 5.1, 8.5 Hz, 2H, 2 $\times$ FAr-H), 7.35 (d, J = 8.1 Hz, 2H, 2 $\times$ $\text{SO}_2\text{Tol-H}$), 7.11 (t, J = 8.6 Hz, 2H, 2 $\times$ FAr-H), 5.87 (d, J = 10.8 Hz, 1H, NH), 5.67 (d, J = 10.8 Hz, 1H, CHN), 2.44 (s, 3H, $\text{SO}_2\text{Tol-CH}_3$), 1.27 (s, 9H, $\text{C}(\text{CH}_3)_3$); ^{13}C NMR (101 MHz, CDCl_3) δ 163.5 (d, J = 249.5 Hz, ArC-F quat.), 153.5 (C=O quat.), 145.1 ($\text{SO}_2\text{Tol-C}$ quat.), 133.5 ($\text{SO}_2\text{TolC-CH}_3$ quat.), 130.8 (d, J = 8.1 Hz, 2 $\times$ FAr-C), 129.7 (2 $\times$ $\text{SO}_2\text{Tol-C}$), 129.4 (2 $\times$ $\text{SO}_2\text{Tol-C}$), 125.9 (d, J = 3.0 Hz, FAr-C quat.), 115.8 (d, J = 21.7 Hz, 2 $\times$ FAr-C), 81.2 ($\text{C}(\text{CH}_3)_3$ quat.), 73.1 (HC-NH), 27.9 ($\text{C}(\text{CH}_3)_3$), 21.6 ($\text{SO}_2\text{Tol-CH}_3$). Observed data (IR, ^1H NMR, ^{13}C NMR) consistent with that reported in the literature.¹⁰⁰



[(3-Methoxyphenyl)-(4-tolylsulfonyl)-methyl]-*tert*-butylcarbamate (9j).

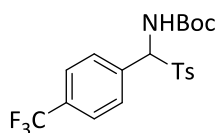
Prepared according to **General Procedure 2** described above starting from 3-methoxybenzaldehyde (1.64 mL, 13.5 mmol) afforded imine- HSO_2Tol adduct **9j** (2.95 g, 84%) as a white solid: mp = 162–163 °C; ν_{max} (film)/ cm^{-1} 2967, 1694 (C=O), 1502, 1317, 1287, 1257, 1146, 1086; ^1H NMR (400 MHz, CDCl_3) δ 7.79 (d, J = 8.2 Hz, 2H, 2 $\times$ $\text{SO}_2\text{Tol-H}$), 7.35–7.31 (m, 3H, 2 $\times$ $\text{SO}_2\text{Tol-H}$ and MeOAr-H), 7.02 (d, J = 7.7 Hz, 2H, 2 $\times$ MeOAr-H), 6.98–6.96 (m, 2H, 2 $\times$ MeOAr-H), 5.85 (d, J = 10.5 Hz, 1H, NH), 5.69 (d, J = 10.7 Hz, 1H, CHN), 3.82 (s, 3H, Ar-OCH₃), 2.44 (s,

3H, SO₂Tol-CH₃), 1.28 (s, 9H, C(CH₃)₃); ¹³C NMR (101 MHz, CDCl₃) δ 159.6 (ArC-OMe quat.), 153.5 (C=O quat.), 145.0 (SO₂Tol-C quat.), 133.8 (SO₂TolC-CH₃ quat.), 131.4 (MeOAr-C quat.), 129.7 (MeOAr-C), 129.6 (2 × SO₂Tol-C), 129.5 (2 × SO₂Tol-C), 121.1 (MeOAr-C), 115.5 (MeOAr-C), 114.4 (MeOAr-C), 81.1 (C(CH₃)₃ quat.), 73.8 (HC-NH), 55.3 (OCH₃), 27.9 (C(CH₃)₃), 21.6 (SO₂Tol-CH₃).



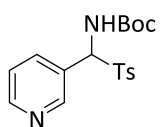
[(4-Methoxybenzene-(4-tolylsulfonyl)-methyl)-tert-butylcarbamate (9k).

Prepared according to **General Procedure 2** described above starting from 4-methoxybenzaldehyde (1.64 mL, 13.5 mmol) afforded imine-HSO₂Tol adduct **9k** (2.85 g, 81%) as a white solid: mp = 166–167 °C (lit.²²⁹ = 179–180 °C, lit.²³⁰ = 155–156 °C); $\nu_{\max}$ (film)/cm⁻¹ 2962, 1711 (C=O), 1614, 1508, 1312, 1245, 1137, 1084, 1028; ¹H NMR (400 MHz, CDCl₃) δ 7.79 (d, *J* = 8.2 Hz, 2H, 2 × SO₂Tol-H), 7.36 (d, *J* = 8.7 Hz, 2H, 2 × MeOAr-H), 7.33 (d, *J* = 8.2 Hz, 2H, 2 × SO₂Tol-H), 6.94 (d, *J* = 8.7 Hz, 2H, 2 × MeOAr-H), 5.84 (d, *J* = 10.6 Hz, 1H, NH), 5.67 (d, *J* = 10.6 Hz, 1H, CHN), 3.83 (s, 3H, Ar-OCH₃), 2.43 (s, 3H, SO₂Tol-CH₃), 1.27 (s, 9H, C(CH₃)₃); ¹³C NMR (101 MHz, CDCl₃) δ 160.7 (ArC-OMe quat.), 153.5 (C=O quat.), 144.8 (SO₂Tol-C quat.), 133.9 (SO₂TolC-CH₃ quat.), 130.1 (2 × MeOAr-C), 129.6 (2 × SO₂Tol-C), 129.4 (2 × SO₂Tol-C), 121.9 (MeOAr-C quat.), 114.2 (2 × MeOAr-C), 81.0 (C(CH₃)₃ quat.), 73.4 (HC-NH), 55.3 (OCH₃), 27.9 (C(CH₃)₃), 21.6 (SO₂Tol-CH₃). Observed data (IR, ¹H NMR, ¹³C NMR) consistent with that reported in the literature.¹⁰⁰



[(4-Trifluoromethylphenyl)-(4-tolylsulfonyl)-methyl]-tert-butylcarbamate (9l).

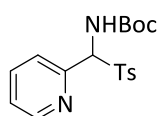
Prepared according to **General Procedure 2** described above starting from 4-trifluoromethylbenzaldehyde (1.84 mL, 13.5 mmol) afforded imine-HSO₂Tol adduct **9l** (2.29 g, 59%) as a white solid: mp = 180–181 °C (lit.²³⁰ = 179–180 °C); $\nu_{\max}$ (film)/cm⁻¹ 3352, 2987, 1700, 1610, 1504, 1375, 1316, 1287, 1231, 1087, 1049, 1017, 729; ¹H NMR (400 MHz, CDCl₃) δ 7.80 (d, *J* = 8.2 Hz, 2H, 2 × SO₂Tol-H), 7.68 (d, *J* = 8.3 Hz, 2H, 2 × F₃C-Ar-H), 7.59 (d, *J* = 8.3 Hz, 2H, 2 × F₃C-Ar-H), 7.36 (d, *J* = 8.2 Hz, 2H, 2 × SO₂Tol-H), 5.96 (d, *J* = 10.8 Hz, 1H, NH), 5.83 (d, *J* = 10.8 Hz, 1H, CHN), 2.45 (s, 3H, SO₂Tol-CH₃), 1.27 (s, 9H, C(CH₃)₃); ¹³C NMR (101 MHz, CDCl₃) δ 153.4 (C=O quat.), 145.5 (SO₂Tol-C quat.), 134.0 (F₃C-Ar-C quat.), 133.4 (SO₂TolC-CH₃ quat.), 131.8 (q, *J* = 32.8 Hz, F₃C-Ar quat.), 129.8 (2 × F₃C-Ar-C), 129.5 (2 × SO₂Tol-C), 129.4 (2 × SO₂Tol-C), 125.6 (q, *J* = 3.1 Hz, 2 × F₃C-Ar-C), 124.8 (q, *J* = 272.7 Hz, F₃C-C-Ar), 81.5 (C(CH₃)₃ quat.), 73.2 (HC-NH), 27.9 (C(CH₃)₃), 21.7 (SO₂Tol-CH₃). Observed data consistent with that reported in the literature.²³⁰



[(Pyridin-3-yl)-(4-tolylsulfonyl)-methyl]-tert-butylcarbamate (9m).

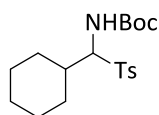
Prepared according to **General Procedure 2** described above starting from 3-pyridinecarboxaldehyde (1.28 mL, 13.5 mmol) afforded imine-HSO₂Tol adduct **9m**

(1.40 g, 43%) as a white solid: mp = 161–163 °C; $\nu_{\max}$ (film)/cm⁻¹ 3209, 3067, 2983, 1716, 1536, 1301, 1165, 1140, 1082, 1046, 715; ¹H NMR (400 MHz, CDCl₃) δ 8.68 (dd, J = 1.4, 4.8 Hz, 1H, Ar-H), 8.67–8.63 (m, 1H, Ar-H), 7.89–7.83 (m, 1H, Ar-H), 7.80 (d, J = 8.2 Hz, 2H, 2 $\times$ SO₂Tol-H), 7.43–7.32 (m, 3H, Ar-H and 2 $\times$ SO₂Tol-H), 6.02–5.79 (m, 2H, NH and CHN), 2.45 (s, 3H, SO₂Tol-CH₃), 1.28 (s, 9H, C(CH₃)₃); ¹³C NMR (101 MHz, CDCl₃) δ 153.6 (C=O quat.), 150.6 (Ar-C), 149.9 (Ar-C), 145.5 (SO₂Tol-C quat.), 136.3 (Ar-C quat.), 133.2 (SO₂TolC-CH₃ quat.), 129.8 (2 $\times$ SO₂Tol-C), 129.5 (2 $\times$ SO₂Tol-C), 126.6 (Ar-C), 123.5 (Ar-C), 81.4 (C(CH₃)₃ quat.), 71.9 (HC-NH), 27.9 (C(CH₃)₃), 21.6 (SO₂Tol-CH₃). Observed data consistent with that reported in the literature.¹⁰⁰



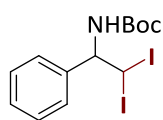
[(Pyridin-2-yl-(4-tolylsulfonyl)-methyl)-tert-butylcarbamate (9n)]. Prepared according

to **General Procedure 2** described above starting from 2-pyridinecarboxaldehyde (1.28 mL, 13.5 mmol) afforded imine-HSO₂Tol adduct **9n** (1.32 g, 40%) as a white solid: mp = 160–162 °C; $\nu_{\max}$ (film)/cm⁻¹ 3419, 2970, 1711, 1488, 1320, 1143, 1086, 809; ¹H NMR (400 MHz, CDCl₃) δ 8.60 (d, J = 3.9 Hz, 2 $\times$ Ar-H), 7.78–7.61 (m, 4H, 2 $\times$ Ar-H and 2 $\times$ SO₂Tol-H), 7.35–7.30 (m, 3H, Ar-H and 2 $\times$ SO₂Tol-H), 6.77 (d, J = 9.2 Hz, 1H, NH), 6.00 (d, J = 9.2 Hz, 1H, CHN), 2.42 (s, 3H, SO₂Tol-CH₃), 1.27 (s, 9H, C(CH₃)₃); ¹³C NMR (101 MHz, CDCl₃) δ 153.6 (C=O quat.), 149.4 (Ar-C), 144.9 (SO₂Tol-C quat.), 148.0 (Ar-C quat.), 136.5 (Ar-C), 133.4 (SO₂TolC-CH₃ quat.), 129.8 (2 $\times$ SO₂Tol-C), 129.5 (2 $\times$ SO₂Tol-C), 125.5 (Ar-C), 80.6 (C(CH₃)₃ quat.), 74.4 (HC-NH), 27.9 (C(CH₃)₃), 21.6 (SO₂Tol-CH₃). **Note:** Rotamers present in ¹H spectra for (NH + CHN) and pyridine protons. Major peaks given in experimental.

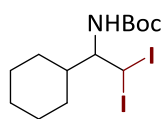


[(Cyclohexyl-(4-tolylsulfonyl)-methyl)-tert-butylcarbamate (9o)]. Prepared according

to **General Procedure 2** described above starting from cyclohexanecarboxaldehyde (3.87 mL, 32.0 mmol), *tert*-butyl carbamate (2.50 g, 21.4 mmol) and sodium *p*-toluenesulfinate (7.56 g, 42.5 mmol) afforded imine-HSO₂Tol adduct **9o** (5.78 g, 74%) as a white solid: mp = 146–148 °C (lit.²²⁹ = 151–154 °C); $\nu_{\max}$ (film)/cm⁻¹ 3361, 2924, 2552, 1696 (C=O), 1497, 1368, 1313, 1297, 1256, 1164, 1137, 1085, 656; ¹H NMR (400 MHz, CDCl₃) δ 7.75 (d, J = 8.2 Hz, 2H, 2 $\times$ SO₂Tol-H), 7.31 (d, J = 8.2 Hz, 2H, 2 $\times$ SO₂Tol-H), 5.18 (d, J = 11.2 Hz, 1H, NH), 4.67 (dd, J = 3.6, 11.2 Hz, 1H, CHN), 2.40 (s, 3H, SO₂Tol-CH₃), 2.13 (d, J = 12.4 Hz, 1H, Cy-H), 1.82–1.64 (m, 5H, 5 $\times$ Cy-H), 1.41–1.32 (m, 2H, 2 $\times$ Cy-H), 1.23 (s, 9H, C(CH₃)₃), 1.14 (m, 3H, 3 $\times$ Cy-H); ¹³C NMR (101 MHz, CDCl₃) δ 154.0 (C=O quat.), 144.5 (SO₂Tol-C quat.), 134.9 (SO₂TolC-CH₃ quat.), 129.5 (2 $\times$ SO₂Tol-C), 128.9 (2 $\times$ SO₂Tol-C), 80.4 (C(CH₃)₃ quat.), 74.3 (HC-NH), 36.2 (CH), 30.5 (CH₂), 27.8 (C(CH₃)₃), 27.2 (CH₂), 25.9 (CH₂), 25.6 (CH₂), 25.5 (CH₂), 21.4 (SO₂Tol-CH₃). **Note:** Rotamers present (major:minor = 85:15). Peaks given for major rotamer. Observed data consistent with that reported in the literature.²³⁰

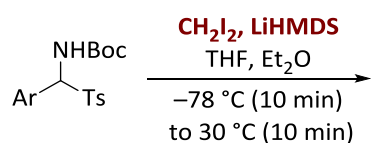


(2,2-Diiodo-1-phenyl-ethyl)-tert-butylcarbamate (10a). Diiodomethane (145 μL , 1.80 mmol, 3.0 equiv) in THF (1.6 mL) was added dropwise to a solution of LiHMDS (1.0 M solution in THF, 1.56 mL, 1.56 mmol, 2.6 equiv) in THF (6.0 mL) and diethyl ether (3.0 mL) at -78°C in the dark. After 20 minutes at -78°C , a solution of imine- HSO_2Tol adduct **9a** (217 mg, 0.60 mmol, 1.0 equiv) in THF (3 mL) was added dropwise to the reaction mixture. After a further 10 minutes at -78°C , the reaction was quenched by the addition of saturated aqueous sodium bicarbonate solution (40 mL). The aqueous solution was extracted with CH_2Cl_2 (3×30 mL) and the organic extracts were combined, dried (Na_2SO_4), filtered and solvent removed under reduced pressure. Purification by flash chromatography (10% diethyl ether/hexane) afforded amino *gem*-diiodide **10a** (232 mg, 80%) as a white solid: $R_f = 0.10$ (10% diethyl ether/hexane); ν_{max} (film)/ cm^{-1} 2980, 1699 (C=O), 1490, 1366, 1244, 1160, 1047; ^1H NMR (400 MHz, CDCl_3) δ 7.40–7.35 (m, 5H, 5 $\times$ Ph-H), 5.46 (br s, 1H, CHI_2), 5.37 (br s, 1H, NH), 4.90 (br s, 1H, CHPh), 1.51 (s, 9H, $\text{C}(\text{CH}_3)_3$); ^{13}C NMR (101 MHz, CDCl_3) δ 154.8 (C=O quat.), 138.7 (Ph-C quat.), 128.6 (Ph-C), 128.3 (2 $\times$ Ph-C), 126.7 (2 $\times$ Ph-C), 80.5 ($\text{C}(\text{CH}_3)_3$ quat.), 62.2 (CHN), 28.3 ($\text{C}(\text{CH}_3)_3$), -14.7 (CHI_2); HRMS (ESI^+) m/z Calculated for $\text{C}_9\text{H}_{10}\text{I}_2\text{NO}_2^+$ [$\text{M}-\text{tBu}+2\text{H}$] $^+$: 417.8795; Found: 417.8794.



(2,2-Diiodo-1-cyclohexyl-ethyl)-tert-butylcarbamate (10o). Diiodomethane (145 μL , 1.80 mmol, 3.0 equiv) in THF (1.6 mL) was added dropwise to a solution of LiHMDS (1.0 M solution in THF, 1.56 mL, 1.56 mmol, 2.6 equiv) in THF (6.0 mL) and diethyl ether (3.0 mL) at -78°C in the dark. After 20 minutes at -78°C , a solution of imine- HSO_2Tol adduct **9o** (222 mg, 0.60 mmol, 1.0 equiv) in THF (3.0 mL) was added dropwise to the reaction mixture. After 10 minutes at -78°C , the reaction was transferred to a water bath at 30°C for 30 minutes and then quenched by the addition of saturated aqueous sodium bicarbonate solution (40 mL). The aqueous mixture was extracted with CH_2Cl_2 (3×40 mL). The organic extracts were then combined, dried (Na_2SO_4), filtered and solvent removed under reduced pressure. Purification by flash chromatography (10% EtOAc/hexane) afforded amino *gem*-diiodide **10o** (83 mg, 29%) as a colourless oil: $R_f = 0.33$ (10% EtOAc/hexane); ν_{max} (film)/ cm^{-1} 2979, 2925, 2853, 1706 (C=O), 1495, 1366, 1240, 1163, 1056, 1017; ^1H NMR (400 MHz, CDCl_3) δ 5.50 (d, $J = 2.7$ Hz, 1H, CHI_2), 4.76 (d, $J = 10.3$ Hz, 1H, NH), 3.20 (ddd, $J = 2.7, 8.9, 10.3$ Hz, 1H, CHN), 1.88–1.61 (m, 5H, 5 $\times$ Cy-H), 1.49 (s, 9H, $\text{C}(\text{CH}_3)_3$), 1.33–0.86 (m, 6H, 6 $\times$ Cy-H); ^{13}C NMR (101 MHz, CDCl_3) δ 155.6 (C=O quat.), 79.7 ($\text{C}(\text{CH}_3)_3$ quat.), 63.1 (CHN), 43.8 (CH), 29.7 (CH_2), 28.9 (CH_2), 28.4 ($\text{C}(\text{CH}_3)_3$), 25.83 (CH_2), 25.79 (CH_2), 25.6 (CH_2), -15.1 (CHI_2); HRMS (ESI^+) m/z Calculated for $\text{C}_{13}\text{H}_{23}\text{I}_2\text{NO}_2^+$ [$\text{M}-\text{tBu}+2\text{H}$] $^+$: 417.8795; Found: 417.8794. **Note:** Rotamers observed for CHN, NH and CHI_2 protons. Peaks given for major rotamer.

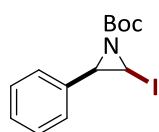
Formation of *cis*-*N*-Boc Iodoaziridines, General Procedure 3: Diiodomethane (145 μ L, 1.80 mmol,



3.0 equiv) in THF (1.6 mL) was added dropwise to a solution of LiHMDS (1.0 M solution in THF, 1.56 mL, 1.56 mmol, 2.6 equiv) in THF (6.0 mL) and diethyl ether (3.0 mL) at -78 $^{\circ}$ C in the dark. After 20 minutes at -78

$^{\circ}$ C, a solution of the imine-HSO₂Tol adduct (0.60 mmol, 1.0 equiv) in THF (2.0 mL) was added dropwise to the reaction mixture. After 10 minutes at -78 $^{\circ}$ C, the reaction flask was transferred to a water bath at 30 $^{\circ}$ C for 10 minutes and then quenched by the addition of saturated aqueous sodium bicarbonate solution (30 mL). The aqueous mixture was extracted with CH₂Cl₂ (3 $\times$ 30 mL). The organic extracts were combined, dried (Na₂SO₄), filtered and solvent removed under reduced pressure. Purification by flash chromatography (10% diethyl ether/hexane) afforded the *cis*-iodoaziridine.

General Procedure 4: Identical to **General Procedure 3**, but the reaction was warmed to 30 $^{\circ}$ C for 30 minutes.

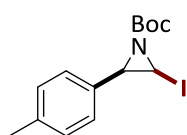


***cis*-($\pm$)-2-iodo-3-phenyl-1-tert-butoxycarbonylaziridine (11a).** Prepared according to

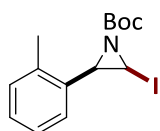
General Procedure 3 described above starting from imine-HO₂STol adduct **9a** (217 mg, 0.60 mmol). Purification by flash chromatography (10% diethyl ether/hexane)

afforded *cis*-iodoaziridine **11a** (172 mg, 83%) as a colourless oil: R_f = 0.37 (20% diethyl ether/hexane); $\nu_{\max}$ (film)/cm⁻¹ 2981, 1724 (C=O), 1610, 1496, 1478, 1458, 1399, 1372, 1320, 1306, 1285, 1258, 1230, 1147, 1078, 1029; ¹H NMR (400 MHz, CDCl₃) δ 7.43–7.34 (m, 5H, 5 $\times$ Ph-H), 4.72 (d, J = 5.4 Hz, 1H, CHI), 3.59 (d, J = 5.4 Hz, 1H, CHPh), 1.51 (s, 9H, C(CH₃)₃); ¹³C NMR (101 MHz, CDCl₃) δ 159.6 (C=O quat.), 134.8 (Ph-C quat.), 128.4 (Ph-C), 128.0 (2 $\times$ Ph-C), 127.5 (2 $\times$ Ph-C), 82.9 (C(CH₃)₃ quat.), 43.1 (PhCHN), 27.9 (C(CH₃)₃), 18.2 (CHI); HRMS (ESI⁺) m/z Calculated for C₁₃H₁₇INO₂⁺ [M+H]⁺: 346.0298; Found: 346.0295.

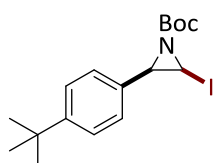
Alternative procedure from diiodide (10a): Cesium carbonate (299 mg, 0.85 mmol, 2.0 equiv) was added to a solution of diiodide **10a** (200 mg, 0.42 mmol) in *N,N*-dimethylformamide (10 mL) at rt, monitoring reaction progress via thin layer chromatography. After 15 h at rt, diethyl ether (50 mL) was added to the reaction mixture. The reaction mixture was then washed with water (50 mL) and brine (50 mL). The organic layer was then dried (Na₂SO₄), filtered and the solvent removed under reduced pressure. Purification by flash chromatography (10% EtOAc/hexane) afforded *cis*-iodoaziridine **11a** (83 mg, 54%) as a colourless oil. Data observed identical to that reported above.



***cis*-(±)-2-iodo-3-(4-tolyl)-1-tert-butoxycarbonylaziridine (11b).** Prepared according to **General Procedure 3** described above starting from imine-HO₂STol adduct **9b** (226 mg, 0.60 mmol). Purification by flash chromatography (10% EtOAc/hexane) afforded *cis*-iodoaziridine **11b** (208 mg, 96%) as a colourless oil: R_f = 0.45 (20% EtOAc/hexane); $\nu_{\max}$ (film)/cm⁻¹ 2981, 1724 (C=O), 1525, 1455, 1391, 1368, 1315, 1298, 1280, 1253, 1149, 1082, 974, 862; ¹H NMR (400 MHz, CDCl₃) δ 7.24 (d, J = 8.3 Hz, 2H, 2 × Tol-H), 7.20 (d, J = 8.3 Hz, 2H, 2 × Tol-H), 4.71 (d, J = 5.4 Hz, 1H, CHI), 3.55 (d, J = 5.4 Hz, 1H, CHTol), 2.38 (s, 3H, Tol-CH₃), 1.51 (s, 9H, C(CH₃)₃); ¹³C NMR (101 MHz, CDCl₃) δ 159.7 (C=O quat.), 138.3 (Tol-C quat.), 131.8 (Tol-C quat.), 128.8 (2 × Tol-C), 127.4 (2 × Tol-C), 82.9 (C(CH₃)₃ quat.), 43.2 (TolCHN), 27.9 (C(CH₃)₃), 21.3 (Tol-CH₃), 18.7 (CHI); HRMS (ESI⁺) m/z Calculated for C₁₇H₁₉NO₂⁺ [M-I+H]⁺: 233.1410; Found: 233.1435.



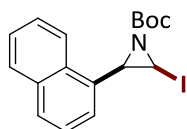
***cis*-(±)-2-iodo-3-(2-tolyl)-1-tert-butoxycarbonylaziridine (11c).** Prepared according to **General Procedure 3** described above starting from imine-HO₂STol adduct **9c** (226 mg, 0.60 mmol). Purification by flash chromatography (10% EtOAc/hexane) afforded *cis*-iodoaziridine **11c** (192 mg, 89%) as a colourless oil: R_f = 0.14 (10% EtOAc/hexane); $\nu_{\max}$ (film)/cm⁻¹ 2981, 1723 (C=O), 1494, 1480, 1462, 1392, 1304, 1282, 1252, 1235, 1204, 1148, 1082, 970, 788; ¹H NMR (400 MHz, CDCl₃) δ 7.37 (d, J = 7.6 Hz, 1H, Tol-H), 7.33–7.20 (m, 3H, 3 × Tol-H), 4.76 (d, J = 5.3 Hz, 1H, CHI), 3.59 (d, J = 5.3 Hz, 1H, CHTol), 2.36 (s, 3H, Tol-CH₃), 1.54 (s, 9H, C(CH₃)₃); ¹³C NMR (101 MHz, CDCl₃) δ 159.7 (C=O quat.), 136.0 (Tol-C quat.), 133.6 (Tol-C quat.), 129.6 (Tol-C), 128.2 (Tol-C), 127.7 (Tol-C), 125.7 (Tol-C), 82.8 (C(CH₃)₃ quat.), 42.5 (TolCHN), 27.9 (C(CH₃)₃), 18.9 (Tol-CH₃), 17.0 (CHI); HRMS (ESI⁺) m/z Calculated for C₁₄H₁₉INO₂⁺ [M+H]⁺: 360.0455; Found: 360.0471.



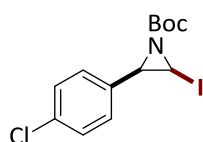
***cis*-(±)-2-iodo-3-(4-tert-butylphenyl)-1-tert-butoxycarbonylaziridine (11d).**

Prepared according to **General Procedure 3** described above starting from imine-HO₂STol adduct **9d** (251 mg, 0.60 mmol). Purification by flash chromatography (10% EtOAc/hexane) afforded *cis*-iodoaziridine **11d** (160 mg,

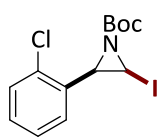
67%) as a colourless oil: R_f = 0.34 (10% EtOAc/hexane); $\nu_{\max}$ (film)/cm⁻¹ 2965, 1725 (C=O), 1391, 1368, 1280, 1253, 1148, 844; ¹H NMR (400 MHz, CDCl₃) δ 7.42 (d, J = 8.3 Hz, 2H, 2 × *t*-BuAr-H), 7.29 (d, J = 8.3 Hz, 2H, 2 × *t*-BuAr-H), 4.73 (d, J = 5.4 Hz, 1H, CHI), 3.56 (d, J = 5.4 Hz, 1H, CHAr), 1.51 (s, 9H, C(CH₃)₃), 1.36 (s, 9H, ArC(CH₃)₃); ¹³C NMR (101 MHz, CDCl₃) δ 159.7 (C=O quat.), 151.3 (*t*-BuArC-C(CH₃)₃ quat.), 131.7 (*t*-BuAr-C quat.), 127.1 (2 × *t*-BuAr-C), 124.9 (2 × *t*-BuAr-C), 82.7 (OC(CH₃)₃ quat.), 43.1 (ArCHN), 34.6 (Ar-C(CH₃)₃ quat.), 31.3 (Ar-C(CH₃)₃), 27.9 (OC(CH₃)₃), 18.6 (CHI); HRMS (ESI⁺) m/z Calculated for C₁₇H₂₇NO₂⁺ [M-I+H]⁺: 275.1880; Found: 275.1879.



***cis*-(±)-2-iodo-3-(1-naphthenyl)-1-tert-butoxycarbonylaziridine (11e).** Prepared according to **General Procedure 4** described above starting from imine-HO₂Stol adduct **9e** (247 mg, 0.60 mmol). Purification by flash chromatography (10% EtOAc/hexane) afforded *cis*-iodoaziridine **11e** (219 mg, 92%) as a colourless oil: R_f = 0.46 (20% EtOAc/hexane); $\nu_{\max}$ (film)/cm⁻¹ 2981, 1722 (C=O), 1511, 1483, 1369, 1347, 1291, 1249, 1205, 1149, 1092, 1047, 967, 802; ¹H NMR (400 MHz, CDCl₃) δ 8.03–8.01 (m, 1H, Ar-H), 7.96–7.94 (m, 1H, Ar-H), 7.91 (d, J = 8.3 Hz, 1H, Ar-H), 7.65–7.50 (m, 4H, 4 × Ar-H), 4.93 (d, J = 5.4 Hz, 1H, CHI), 4.09 (d, J = 5.4 Hz, 1H, CHAr), 1.57 (s, 9H, C(CH₃)₃); ¹³C NMR (101 MHz, CDCl₃) δ 159.8 (C=O quat.), 133.2 (Ar-C quat.), 131.2 (Ar-C quat.), 131.0 (Ar-C quat.), 128.8 (Ar-C), 128.7 (Ar-C), 126.4 (Ar-C), 126.1 (Ar-C), 126.0 (Ar-C), 125.3 (Ar-C), 122.7 (Ar-C), 83.0 (C(CH₃)₃ quat.), 42.4 (ArCHN), 28.0 (C(CH₃)₃), 16.8 (CHI); HRMS (ESI⁺) m/z Calculated for C₁₇H₁₉NO₂⁺ [M-I+H]⁺: 269.1410; Found: 269.1423.

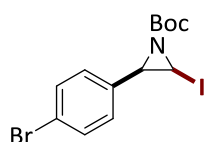


***cis*-(±)-2-iodo-3-(4-chlorophenyl)-1-tert-butoxycarbonylaziridine (11f).** Prepared according to the **General Procedure 3** described above starting from imine-HO₂Stol adduct **9f** (237 mg, 0.60 mmol). Purification by flash chromatography (10% EtOAc/hexane) afforded *cis*-iodoaziridine **11f** (117 mg, 51%) as a colourless oil: R_f = 0.20 (10% EtOAc/hexane); $\nu_{\max}$ (film)/cm⁻¹ 2984, 1724 (C=O), 1494, 1598, 1420, 1392, 1369, 1308, 1289, 1276, 1252, 1146, 1089, 1015, 970, 842; ¹H NMR (400 MHz, CDCl₃) δ 7.36 (d, J = 8.4 Hz, 2H, 2 × ClAr-H), 7.28 (d, J = 8.4 Hz, 2H, 2 × ClAr-H), 4.70 (d, J = 5.4 Hz, 1H, CHI), 3.55 (d, J = 5.4 Hz, 1H, CHAr), 1.51 (s, 9H, C(CH₃)₃); ¹³C NMR (101 MHz, CDCl₃) δ 159.3 (C=O quat.), 134.2 (ClAr-C quat.), 133.4 (ClAr-C quat.), 128.8 (2 × ClAr-C), 128.3 (2 × ClAr-C), 83.1 (C(CH₃)₃ quat.), 42.4 (ArCHN), 27.9 (C(CH₃)₃), 17.8 (CHI); HRMS (ESI⁺) m/z Calculated for C₁₃H₁₆ClINO₂⁺ [M+H]⁺: 379.9909; Found: 379.9923.



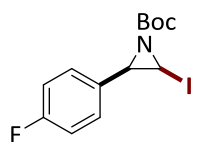
***cis*-(±)-2-iodo-3-(2-chlorophenyl)-1-tert-butoxycarbonylaziridine and *trans*-(±)-2-iodo-3-(2-chlorophenyl)-1-tert-butoxycarbonylaziridine (11g).** Prepared according to **General Procedure 4** described above starting from imine-HO₂Stol adduct **9g** (238 mg, 0.60 mmol). Purification by flash chromatography (10% EtOAc/petroleum ether) afforded a 88:12 (*cis*:*trans*) mixture of iodoaziridines **11g** (118 mg, 52%) as a colourless oil: R_f = 0.31 (10% EtOAc/petroleum ether); $\nu_{\max}$ (film)/cm⁻¹ 2984, 1726 (C=O), 1483, 1441, 1396, 1369, 1301, 1290, 1276, 1253, 1224, 1147, 1054, 967, 851, 750. ***cis*-aziridine:** ¹H NMR (400 MHz, CDCl₃) δ 7.44–7.34 (m, 4H, 4 × ClAr-H), 4.77 (d, J = 5.4 Hz, 1H, CHI), 3.80 (d, J = 5.4 Hz, 1H, CHAr), 1.54 (s, 9H, C(CH₃)₃); ¹³C NMR (400 MHz, CDCl₃) δ 159.4 (C=O quat.), 133.4 (ClAr-C quat.), 133.3 (ClAr-C quat.), 130.0 (ClAr-C), 129.5 (ClAr-C), 129.0 (ClAr-C), 126.5 (ClAr-C), 83.0

(C(CH₃)₃ quat.), 42.2 (ArCHN), 27.9 (C(CH₃)₃), 16.3 (CHI); **trans-aziridine**: ¹H NMR (400 MHz, CDCl₃) δ 7.36–7.27 (m, 4H, 4 × Ar-H), 4.01 (d, *J* = 2.3 Hz, 1H, CHI), 3.84 (d, *J* = 2.3 Hz, 1H, CHAr), 1.56 (s, 9H, C(CH₃)₃); ¹³C NMR (400 MHz, CDCl₃) δ 157.2 (C=O quat.), 134.3 (ClAr-C quat.), 133.8 (ClAr-C quat.), 129.30 (ClAr-C), 129.25 (ClAr-C), 127.0 (ClAr-C), 126.9 (ClAr-C), 83.3 (C(CH₃)₃ quat.), 46.1 (ArCHN), 28.0 (C(CH₃)₃), 10.2 (CHI); HRMS (ESI⁺) *m/z* Calculated for C₁₃H₁₆ClINO₂⁺ [M+H]⁺: 379.9909; Found: 379.9907.



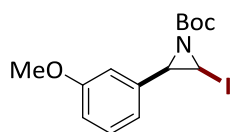
***cis*-(±)-2-iodo-3-(4-bromophenyl)-1-tert-butoxycarbonylaziridine (11h).**

Prepared according to **General Procedure 3** described above starting from imine-HO₂STol adduct **9h** (264 mg, 0.60 mmol). Purification by flash chromatography (10% EtOAc/hexane) afforded *cis*-iodoaziridine **11h** (100 mg, 42%) as a colourless oil: *R_f* = 0.39 (20% EtOAc/hexane); *v*_{max} (film)/cm⁻¹ 2984, 1725 (C=O), 1490, 1424, 1369, 1307, 1290, 1276, 1253, 1149, 1069, 1011, 974, 842; ¹H NMR (400 MHz, CDCl₃) δ 7.52 (d, *J* = 8.4 Hz, 2H, 2 × BrAr-H), 7.22 (d, *J* = 8.4 Hz, 2H, 2 × BrAr-H), 4.69 (d, *J* = 5.4 Hz, 1H, CHI), 3.53 (d, *J* = 5.4 Hz, 1H, CHAr), 1.50 (s, 9H, C(CH₃)₃); ¹³C NMR (101 MHz, CDCl₃) δ 159.3 (C=O quat.), 134.0 (Br-CAr quat.), 131.2 (2 × BrAr-C), 129.2 (2 × BrAr-C), 122.5 (BrArC-CH quat.), 83.1 (C(CH₃)₃ quat.), 42.5 (ArCHN), 27.9 (C(CH₃)₃), 17.7 (CHI); HRMS (ESI⁺) *m/z* Calculated for C₁₃H₁₆⁷⁹BrINO₂⁺ [M+H]⁺: 423.9404; Found: 423.9420.



***cis*-(±)-2-iodo-3-(4-fluorophenyl)-1-tert-butoxycarbonylaziridine (11i).**

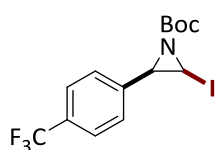
Prepared according to **General Procedure 3** described above starting from imine-HO₂STol adduct **9i** (228 mg, 0.60 mmol). Purification by flash chromatography (10% EtOAc/hexane) afforded *cis*-iodoaziridine **11i** (165 mg, 76%) as a colourless oil: *R_f* = 0.14 (10% EtOAc/hexane); *v*_{max} (film)/cm⁻¹ 2984, 1724 (C=O), 1609, 1512, 1483, 1462, 1427, 1396, 1369, 1308, 1281, 1254, 1146, 1099, 1078, 1015, 970; ¹H NMR (400 MHz, CDCl₃) δ 7.36–7.28 (m, 2H, 2 × FAr-H), 7.13–7.03 (m, 2H, 2 × FAr-H), 4.70 (d, *J* = 5.2 Hz, 1H, CHI), 3.56 (d, *J* = 5.2 Hz, 1H, CHAr), 1.51 (s, 9H, C(CH₃)₃); ¹³C NMR (101 MHz, CDCl₃) δ 162.7 (d, *J* = 247.1 Hz, Ar-CF quat.), 159.4 (C=O quat.), 130.6 (d, *J* = 3.1 Hz, FAr-C quat.), 129.2 (d, *J* = 8.4 Hz, 2 × FAr-C), 115.0 (d, *J* = 21.9 Hz, 2 × FAr-C), 83.0 (C(CH₃)₃ quat.), 42.4 (ArCHN), 27.8 (C(CH₃)₃), 18.2 (CHI); ¹⁹F NMR (377 MHz, CDCl₃) δ -113.3 (C-F); HRMS (ESI⁺) *m/z* Calculated for C₁₃H₁₆FINO₂⁺ [M+H]⁺: 364.0204; Found: 364.0228.



***cis*-(±)-2-iodo-3-(3-methoxyphenyl)-1-tert-butoxycarbonylaziridine (11j).**

Prepared according to **General Procedure 3** described above starting from imine-HO₂STol adduct **9j** (235 mg, 0.60 mmol). Purification by flash chromatography (10% EtOAc/hexane) on neutral alumina afforded *cis*-iodoaziridine **11j** (174 mg,

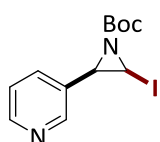
77%) as a colourless oil: R_f = 0.45 (10% EtOAc/hexane); $\nu_{\max}$ (film)/ cm^{-1} 2980, 1723 (C=O), 1392, 1369, 1279, 1252, 1145, 1043, 840; ^1H NMR (400 MHz, CDCl_3) δ 7.30 (t, J = 7.4 Hz, 1H, MeOAr-H), 6.96–6.88 (m, 3H, 3 $\times$ MeOAr-H), 4.71 (d, J = 5.4 Hz, 1H, CHI), 3.84 (s, 3H, OCH_3), 3.57 (d, J = 5.4 Hz, 1H, CHAr), 1.51 (s, 9H, $\text{C}(\text{CH}_3)_3$); ^{13}C NMR (400 MHz, CDCl_3) δ 159.5 (C=O quat.), 159.3 (ArC- OCH_3 quat.), 136.3 (MeOAr-C quat.), 129.1 (MeOAr-C), 119.8 (MeOAr-C), 114.2 (MeOAr-C), 112.6 (MeOAr-C), 82.8 ($\text{C}(\text{CH}_3)_3$ quat.), 55.2 (Ar- OCH_3), 43.0 (ArCHN), 27.8 ($\text{C}(\text{CH}_3)_3$), 18.0 (CHI); HRMS (ESI^+) m/z Calculated for $\text{C}_{14}\text{H}_{19}\text{INO}_3^+$ $[\text{M}+\text{H}]^+$: 376.0404; Found: 376.0415.



***cis*-(±)-2-iodo-3-(4-trifluoromethylphenyl)-1-tert-butoxycarbonylaziridine (11l).**

Prepared according to **General Procedure 3** described above starting from imine- HO_2STol adduct **9l** (258 mg, 0.60 mmol). Purification by flash chromatography (5% EtOAc/hexane) afforded *cis*-iodoaziridine **11l** (30 mg, 13%)

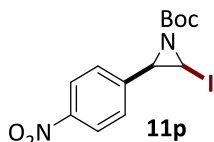
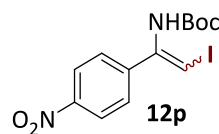
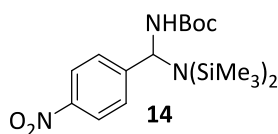
as a colourless oil: R_f = 0.19 (10% EtOAc/hexane); $\nu_{\max}$ (film)/ cm^{-1} 2984, 1729 (C=O), 1323, 1285, 1151, 1128, 1128, 1066, 855; ^1H NMR (400 MHz, CDCl_3) δ 7.65 (d, J = 8.3 Hz, 2H, 2 $\times$ $\text{F}_3\text{CAr-H}$), 7.47 (d, J = 8.4 Hz, 2H, 2 $\times$ $\text{F}_3\text{CAr-H}$), 4.72 (d, J = 5.4 Hz, 1H, CHI), 3.63 (d, J = 5.4 Hz, 1H, CHAr), 1.52 (s, 9H, $\text{C}(\text{CH}_3)_3$); ^{13}C NMR (500 MHz, CDCl_3) δ 159.2 (C=O quat.), 138.8 ($\text{F}_3\text{CAr-C}$ quat.), 130.5 (q, J = 32.5 Hz, $\text{F}_3\text{C-CAr}$ quat.), 127.9 (2 $\times$ $\text{F}_3\text{CAr-C}$), 125.1 (q, J = 3.6 Hz, 2 $\times$ $\text{F}_3\text{CAr-C}$), 124.1 (q, J = 272.2 Hz, $\text{F}_3\text{C-CAr}$), 83.3 ($\text{C}(\text{CH}_3)_3$ quat.), 42.5 (CHN), 27.9 ($\text{C}(\text{CH}_3)_3$), 17.0 (CHI); ^{19}F NMR (470 MHz, CDCl_3) δ -62.7 (CF_3); HRMS (ESI^+) m/z Calculated for $\text{C}_{14}\text{H}_{16}\text{F}_3\text{INO}_2^+$ $[\text{M}+\text{H}]^+$: 414.0172; Found: 414.0183.



***cis*-(±)-2-iodo-3-(pyridin-3-yl)-1-tert-butoxycarbonylaziridine (11m).**

Prepared according to **General Procedure 3** described above starting from imine- HO_2STol adduct **9m** (219 mg, 0.60 mmol). Purification by flash chromatography (40%

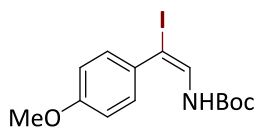
EtOAc/hexane) afforded *cis*-iodoaziridine **11m** (101 mg, 49%) as a yellow oil: R_f = 0.16 (40% EtOAc/hexane); $\nu_{\max}$ (film)/ cm^{-1} 2981, 1729 (C=O), 1370, 1293, 1252, 1152, 755; ^1H NMR (400 MHz, CDCl_3) δ 8.64 (br s, 2H, 2 $\times$ Ar-H), 7.66 (d, J = 7.7 Hz, 1H, Ar-H), 7.35 (br s, 1H, Ar-H), 4.72 (d, J = 5.4 Hz, 1H, CHI), 3.61 (d, J = 5.4 Hz, 1H, CHAr), 1.49 (s, 9H, $\text{C}(\text{CH}_3)_3$); ^{13}C NMR (101 MHz, CDCl_3) δ 159.1 (C=O quat.), 149.3 (Ar-C), 148.8 (Ar-C), 135.4 (Ar-C quat.), 131.0, (Ar-C) 123.0 (Ar-C), 83.3 ($\text{C}(\text{CH}_3)_3$ quat.), 40.8 (CHN), 27.8 ($\text{C}(\text{CH}_3)_3$), 17.1 (CHI); HRMS (ESI^+) m/z Calculated for $\text{C}_{12}\text{H}_{16}\text{IN}_2\text{O}_2^+$ $[\text{M}+\text{H}]^+$: 374.0251; Found: 374.0261.



***tert*-Butyl-*N*-[[bis(trimethylsilyl)amino](4-nitrophenyl)methyl]carbamate (14), *tert*-Butyl-*N*-[3-iodo-1-(4-nitrophenyl)prop-2-en-1-yl]carbamate (12p) and *cis*-(±)-2-iodo-3-(4-nitrophenyl)-1-*tert*-butoxycarbonylaziridine (11p).** Prepared according to **General Procedure 3** described above starting

from imine-HO₂STol adduct **9p** (244 mg, 0.60 mmol, 1.0 equiv). Purification by flash chromatography (5% EtOAc/hexane) afforded a mixture of compounds: **aminal 14**: (21 mg, 9%) as a colourless oil: R_f = 0.44 (10% EtOAc/hexane); $\nu_{\max}$ (film)/cm⁻¹ 2977, 2955, 1721, 1703, 1522 (NO₂), 1484, 1348 (NO₂), 1254, 1048, 855; ¹H NMR (400 MHz, CDCl₃) δ 8.20 (d, J = 8.8 Hz,

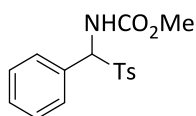
2H, 2 × H-ArNO₂), 7.60 (d, J = 8.8 Hz, 2H, 2 × H-ArNO₂), 6.10 (d, J = 8.8 Hz, 1H, NH), 5.07 (d, J = 8.8 Hz, 1H, CHN), 1.52 (s, 9H, C(CH₃)₃), 0.14 (s, 18H, [Si(CH₃)₃]₂); ¹³C NMR (101 MHz, CDCl₃) δ 151.9 (C=O quat.), 147.2 (C-ArNO₂ quat.), 127.6 (2 × C-ArNO₂), 123.4 (2 × C-ArNO₂), 110.0 (C-ArNO₂ quat.), 80.3 (C(CH₃)₃ quat.), 66.1 (CHN), 28.4 (C(CH₃)₃), 3.04 (N[Si(CH₃)₃]₂): **vinyl iodide 12p**: (25 mg, 11%) as a yellow oil: R_f = 0.21 (10% EtOAc/hexane); $\nu_{\max}$ (film)/cm⁻¹ 2980, 1707 (C=O), 1590, 1516 (NO₂), 1455, 1343 (NO₂), 1239, 1155, 856; ¹H NMR (400 MHz, CDCl₃) δ 8.22 (d, J = 8.9 Hz, 2H, 2 × H-ArNO₂), 7.54 (d, J = 8.9 Hz, 2H, 2 × H-ArNO₂), 6.46 (br s, 1H, NH), 6.01 (s, 1H, C=CHI), 1.37 (s, 9H, C(CH₃)₃); ¹³C NMR (101 MHz, CDCl₃) δ 152.2 (C=O quat.), 147.7 (CNH quat.), 143.8 (C-ArNO₂ quat.), 142.9 (C-ArNO₂ quat.), 127.2 (2 × C-ArNO₂), 123.7 (2 × C-ArNO₂), 82.0 (C(CH₃)₃ quat.), 69.2 (CHI), 28.0 (C(CH₃)₃): ***cis*-iodoaziridine 11p**: (4 mg, 2%) as a colourless oil: R_f = 0.15 (10% EtOAc/hexane); $\nu_{\max}$ (film)/cm⁻¹ 2981, 1729 (C=O), 1522 (NO₂), 1370, 1347 (NO₂), 1258, 1151, 853; ¹H NMR (400 MHz, CDCl₃) δ 8.28 (d, J = 8.8 Hz, 2H, 2 × H-ArNO₂), 7.55 (d, J = 8.8 Hz, 2H, 2 × H-ArNO₂), 4.75 (d, J = 5.4 Hz, 1H, CHI), 3.70 (d, J = 5.4 Hz, 1H, CHAr), 1.54 (s, 9H, C(CH₃)₃); ¹³C NMR (101 MHz, CDCl₃) δ 158.9 (C=O quat.), 128.5 (2 × C-ArNO₂), 123.4 (2 × C-ArNO₂), 83.6 (C(CH₃)₃ quat.), 42.2 (ArCHN), 27.9 (C(CH₃)₃), 16.4 (CHI).



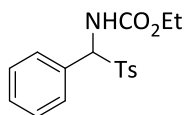
***tert*-Butyl[(*E*)-2-iodo-2-(4-methoxyphenyl)ethenyl]carbamate (15).**

Diiodomethane (145 μ L, 1.80 mmol, 3.0 equiv) in THF (1.6 mL) was added dropwise to a solution of LiHMDS (1.0 M solution in THF, 1.56 mL, 1.56 mmol, 2.6 equiv) in THF (6.0 mL) and diethyl ether (3.0 mL) at -78 °C in the dark. After 20 minutes at -78 °C, a solution of imine-HO₂STol adduct **9k** (235 mg, 0.60 mmol, 1.0 equiv) in THF (3 mL) was added dropwise to the reaction mixture. After 10 minutes at -78 °C, the reaction was then transferred to warm in a water bath at 30 °C for 10 minutes and then was then quenched by the addition of saturated aqueous sodium bicarbonate solution (40 mL). The aqueous mixture was extracted with CH₂Cl₂ (3 × 40 mL). The organic extracts were then combined, dried (Na₂SO₄), filtered and solvent removed under reduced pressure, affording crude *cis*-iodoaziridine **11k**. Upon purification by flash

chromatography on neutral alumina (5% EtOAc/hexane), rearrangement of *cis*-iodoaziridine **11k** afforded vinyl iodide **15** (77 mg, 34%) as a colourless oil: R_f = 0.47 (10% EtOAc/hexane); $\nu_{\max}$ (film)/ cm^{-1} 3404, 2978, 2934, 2836, 1726 (C=O), 1644, 1605, 1461, 1282, 1249, 1223, 1035, 829. ^1H NMR (400 MHz, CDCl_3) δ 7.37 (d, J = 8.7 Hz, 2H, 2 $\times$ MeOAr-H), 6.90 (d, J = 9.8 Hz, 1H, NH), 6.83 (d, J = 8.7 Hz, 2H, 2 $\times$ MeOAr-H), 6.63 (d, J = 9.8 Hz, 1H, CH), 3.82 (s, 3H, OCH_3), 1.52 (s, 9H, $\text{C}(\text{CH}_3)_3$); ^{13}C NMR (101 MHz, CDCl_3) δ 159.2 (MeO-CAr quat.), 152.4 (C=O), 132.7 (MeOAr-C quat.), 129.5 (2 $\times$ MeOAr-C), 127.7 (CH), 113.7 (2 $\times$ MeOAr-C), 81.6 ($\text{C}(\text{CH}_3)_3$ quat.), 80.0 (C-I quat.), 55.3 (OCH_3), 28.2 ($\text{C}(\text{CH}_3)_3$); HRMS (EI) m/z Calculated for $\text{C}_{14}\text{H}_{18}\text{INO}_3^+$ $[\text{M}]^+$: 375.0331; Found: 375.0295.

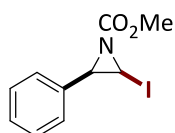


[(Phenyl-(4-tolylsulfonyl)-methyl)-methylcarbamate (16a). Benzaldehyde (3.05 mL, 30.0 mmol, 1.5 equiv) was added to a stirred suspension of methyl carbamate (1.50 g, 20.0 mmol, 1.0 equiv) and *p*-toluenesulfinate (7.13 g, 40.0 mmol, 2.0 equiv) in methanol and water (1:2, 75 mL). Formic acid (98%, 2.0 mL) was added dropwise and the resulting mixture was stirred for 24 h at rt. The reaction mixture was then filtered under reduced pressure, and the solid purified via trituration with water (150 mL) and diethyl ether (150 mL). Purification via drying under reduced pressure afforded imine-HSO₂Tol adduct **16a** (1.71 g, 27%) as a white solid: $\nu_{\max}$ (film)/ cm^{-1} 2974, 1704 (C=O), 1598, 1516, 1490, 1459, 1354, 1317, 1288, 1147, 1089, 1042, 956, 806; ^1H NMR (400 MHz, CDCl_3) δ 7.74 (d, J = 7.9 Hz, 2H, 2 $\times$ SO₂Tol-H), 7.48–7.37 (m, 5H, 5 $\times$ Ph-H), 7.34 (d, J = 7.9 Hz, 2H, 2 $\times$ SO₂Tol-H), 5.95–5.80 (m, 2H, NH and CHN), 3.59 (s, 3H, OCH_3), 2.47 (s, 3H, 2 $\times$ SO₂Tol-CH₃); ^{13}C NMR (101 MHz, CDCl_3) δ 155.1 (C=O quat.), 145.3 (SO₂Tol-C quat.), 133.4 (SO₂TolC-CH₃ quat.), 130.1 (Ph-C quat.), 129.9 (Ph-C), 129.7 (2 $\times$ SO₂Tol-C), 129.5 (2 $\times$ Ph-C), 128.8 (2 $\times$ SO₂Tol-C), 128.7 (2 $\times$ Ph-C), 74.3 (CHN), 53.0 (OCH_3), 21.8 (SO₂Tol-CH₃); HRMS (ESI⁺) m/z Calculated for $\text{C}_{16}\text{H}_{17}\text{NNaO}_4\text{S}^+$ $[\text{M}+\text{Na}]^+$: 342.0776; Found: 342.0785. **Note:** Rotamers present in ^1H NMR spectra for (NH and CHN) and OCH_3 peaks. Major peaks given in experimental.

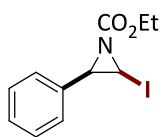


[(Phenyl-(4-tolylsulfonyl)-methyl)-ethylcarbamate (16b). Benzaldehyde (1.16 mL, 11.2 mmol, 1.50 equiv) was added to a stirred suspension of ethyl carbamate (1.00 g, 11.2 mmol, 1.00 equiv) and *p*-toluenesulfinate (2.00 g, 11.2 mmol, 2.0 equiv) in methanol and water (1:2, 15 mL). Formic acid (98%, 2.0 mL) was added dropwise and the resulting mixture was stirred for 72 h at rt. The reaction mixture was then filtered under reduced pressure, and the solid purified via trituration with a mixture of hexane:CH₂Cl₂ (10:1, 100 mL). Purification via drying under reduced pressure afforded imine-HSO₂Tol adduct **16b** (2.56 g, 67%) as a white solid: $\nu_{\max}$ (film)/ cm^{-1} 2991, 1710, 1512, 1483, 1316, 1304, 1237, 1197, 1145, 1083, 1050, 808; ^1H NMR (400 MHz, CDCl_3) δ 7.75 (d, J = 7.9 Hz, 2H, 2 $\times$ SO₂Tol-H), 7.47–7.38 (m, 5H, 5 $\times$ Ph-H), 7.33 (d, J = 7.9

Hz, 2H, 2 × SO₂Tol-H), 5.94 (d, *J* = 10.6 Hz, 1H, NH), 5.87 (d, *J* = 10.6 Hz, 1H, CHN), 4.00 (q, *J* = 7.0 Hz, 2H, CH₂), 2.46 (s, 3H, SO₂Tol-CH₃), 1.15 (t, *J* = 7.0 Hz, 3H, CH₃); ¹³C NMR (101 MHz, CDCl₃) δ 154.8 (C=O quat.), 145.3 (SO₂Tol-C quat), 133.4 (SO₂TolC-CH₃ quat.), 129.9 (2 × Ph-C), 129.8 (Ph-C), 129.7 (2 × SO₂Tol-C), 129.5 (2 × Ph-C), 129.0 (Ph-C quat.), 128.8 (2 × SO₂Tol-C), 74.3 (CHN), 62.0 (CH₂), 21.7 (SO₂Tol-CH₃), 14.4 (CH₃); HRMS (ESI⁺) *m/z* Calculated for C₁₇H₁₉NNaO₄S⁺ [M+Na]⁺: 356.0932; Found: 356.0935. Observed data consistent with that reported in the literature.^{232,233}

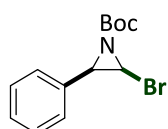


***cis*-(±)-2-iodo-3-phenyl-1-methoxycarbonylaziridine (17a).** Diiodomethane (150 μL, 1.88 mmol, 3.0 equiv) in THF (1.6 mL) was added dropwise to a solution of LiHMDS (1.0 M solution in THF, 1.63 mL, 1.63 mmol, 2.6 equiv) in THF (6.0 mL) and diethyl ether (3.0 mL) at –78 °C in the dark. After 20 minutes at –78 °C, a solution of imine–HSO₂Tol adduct **16a** (202 mg, 0.63 mmol, 1.0 equiv) in THF (2.0 mL) was added dropwise to the reaction mixture. After 10 minutes at –78 °C, the reaction flask was transferred to a water bath at rt for 10 minutes and then quenched by the addition of saturated aqueous sodium bicarbonate solution (30 mL). The aqueous mixture was extracted with CH₂Cl₂ (3 × 30 mL). The organic extracts were combined, dried (Na₂SO₄), filtered and solvent removed under reduced pressure. Purification by flash chromatography (10% diethyl ether/hexane) afforded *cis*-iodoaziridine **17a** (107 mg, 56%) as a colourless oil: *R_f* = 0.32 (20% EtOAc/hexane); ν_{max} (film)/cm^{–1} 2956, 1725 (C=O), 1508, 1437, 1403, 1319, 1301, 1270, 1225, 1196, 1015 (C-O), 963, 915, 813, 750, 698; ¹H NMR (400 MHz, CDCl₃) δ 7.41–7.34 (m, 5H, 5 × Ph-H), 4.77 (d, *J* = 5.4 Hz, 1H, CHI), 3.83 (s, 3H, OCH₃), 3.67 (d, *J* = 5.4 Hz, 1H, CHPh); ¹³C NMR (101 MHz, CDCl₃) δ 161.2 (C=O quat.), 134.2 (Ph-C quat.), 128.5 (Ph-C), 128.1 (2 × Ph-C), 127.4 (2 × Ph-C), 54.1 (OCH₃), 43.2 (PhCHN), 17.6 (CHI); HRMS (ESI⁺) *m/z* Calculated for C₁₀H₁₁INO₂⁺ [M+H]⁺: 303.9834; Found: 303.9848.



***cis*-(±)-2-iodo-3-phenyl-1-ethoxycarbonylaziridine (17b).** Diiodomethane (145 μL, 1.80 mmol, 3.0 equiv) in THF (1.6 mL) was added dropwise to a solution of LiHMDS (1.0 M solution in THF, 1.56 mL, 1.56 mmol, 2.6 equiv) in THF (6.0 mL) and diethyl ether (3.0 mL) at –78 °C in the dark. After 20 minutes at –78 °C, a solution of imine–HSO₂Tol adduct **16b** (200 mg, 0.60 mmol, 1.0 equiv) in THF (2.0 mL) was added dropwise to the reaction mixture. After 10 minutes at –78 °C, the reaction flask was transferred to a water bath at rt for 10 minutes and then quenched by the addition of saturated aqueous sodium bicarbonate solution (30 mL). The aqueous mixture was extracted with CH₂Cl₂ (3 × 30 mL). The organic extracts were combined, dried (Na₂SO₄), filtered and solvent removed under reduced pressure. Purification by flash chromatography (10% diethyl ether/hexane) afforded *cis*-iodoaziridine **17b** (114 mg, 60%) as a

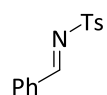
colourless oil: R_f = 0.32 (20% EtOAc/hexane); $\nu_{\max}$ (film)/ cm^{-1} 2989, 1727 (C=O), 1610, 1458, 1401, 1369, 1301, 1268, 1226, 1183, 1100, 1025 (C-O), 757, 698; ^1H NMR (400 MHz, CDCl_3) δ 7.43–7.34 (m, 5H, 5 $\times$ Ph-H), 4.76 (d, J = 5.4 Hz, 1H, CHI), 4.29 (q, J = 7.1 Hz, 2H, CH_2), 3.65 (d, J = 5.4 Hz, 1H, CHPh), 1.34 (t, J = 7.1 Hz, 3H, CH_3); ^{13}C NMR (101 MHz, CDCl_3) δ 160.8 (C=O quat.), 134.4 (Ph-C quat.), 128.5 (Ph-C), 128.1 (2 $\times$ Ph-C), 127.4 (2 $\times$ Ph-C), 63.4 (CH_2), 43.2 (PhCHN), 17.8 (CHI), 14.3 (CH_3); HRMS (ESI $^+$) m/z Calculated for $\text{C}_{11}\text{H}_{13}\text{INO}_2^+$ [M+H] $^+$: 317.9991; Found: 317.9998.



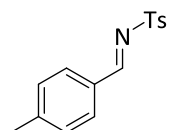
***cis*-($\pm$)-2-Bromo-3-phenyl-1-*tert*-butoxycarbonylaziridine (**18**):**

Dibromomethane (126 μL , 1.80 mmol, 3.0 equiv) in THF (1.6 mL) was added dropwise to a solution of LiHMDS (1.0 M solution in THF, 1.56 mL, 1.56 mmol, 2.6 equiv) in THF (6.0 mL) and diethyl ether (3.0 mL) at -78°C in the dark. After 20 minutes at -78°C , a solution of imine- HSO_2Tol adduct **9a** (217 mg, 0.60 mmol, 1.0 equiv) in THF (3.5 mL) was added dropwise to the reaction mixture. After 10 minutes at -78°C , the reaction was then transferred to a water bath at 30°C for 10 minutes and then was then quenched by the addition of saturated aqueous sodium bicarbonate solution (30 mL). The aqueous mixture was extracted with CH_2Cl_2 (3 $\times$ 30 mL). The organic extracts were combined, dried (Na_2SO_4), filtered and solvent removed under reduced pressure. Purification by flash chromatography (10% EtOAc/hexane) afforded *cis*-bromoaziridine **18** (53 mg, 30%) as a colourless oil: R_f = 0.25 (10% EtOAc/hexane); $\nu_{\max}$ (film)/ cm^{-1} 2982, 1726 (C=O), 1303, 1279, 1257, 1233, 1156, 907, 730, 698; ^1H NMR (400 MHz, CDCl_3) δ 7.43–7.35 (m, 5H, 5 $\times$ Ph-H), 4.87 (d, J = 5.1 Hz, 1H, CHBr), 3.75 (d, J = 5.1 Hz, 1H, CHPh), 1.52 (s, 9H, $\text{C}(\text{CH}_3)_3$); ^{13}C NMR (101 MHz, CDCl_3) δ 159.3 (C=O quat.), 133.2 (Ph-C quat.), 128.4 (Ph-C), 128.0 (2 $\times$ Ph-C), 127.8 (2 $\times$ Ph-C), 83.0 ($\text{C}(\text{CH}_3)_3$ quat.), 44.7 (CHBr), 44.1 (CHN), 27.9 ($\text{C}(\text{CH}_3)_3$); HRMS (CI) m/z Calculated for $\text{C}_{13}\text{H}_{17}\text{NO}_2^{79}\text{Br}^+$ [M+H] $^+$: 298.0443; Found: 298.0450.

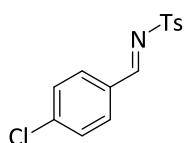
N-Ts Iodoaziridines (Section 2.2)



N-[(E)-Phenylmethylidene]-4-methylbenzenesulfonamide (19a). Prepared according to the method of Chemla and co-workers.¹⁰⁵ Benzaldehyde (1.02 mL, 10.0 mmol, 1.0 equiv) was added to a stirring solution of *p*-toluenesulfonamide (1.71 g, 10.0 mmol, 1.0 equiv) and sodium *p*-toluenesulfinate (1.96 g, 11.0 mmol, 1.1 equiv) in formic acid (98%) and water (1:1, 30 mL). After 24 h at rt, the reaction mixture was filtered under reduced pressure and then washed successively with water (50 mL) and hexane (50 mL). The resulting imine–HO₂STol adduct was dissolved in CH₂Cl₂ (100 mL) and saturated aqueous sodium bicarbonate solution (100 mL) was added. The resulting biphasic solution was vigorously stirred for 2 h at rt, after which the organic layer was separated, dried (Na₂SO₄) and solvent removed under reduced pressure to afford the crude imine. Purification by recrystallisation (EtOAc/hexane) afforded imine **19a** (2.06 g, 79%) as colourless crystals: mp = 106–108 °C (lit.²³⁴ mp = 107 °C); $\nu_{\max}$ (film)/cm⁻¹ 3360, 3263, 3067, 2925, 2259, 1599, 1319, 1155, 1088, 907, 781, 756, 729, 688, 672; ¹H NMR (400 MHz, CDCl₃) δ 8.99 (s, 1H, CHN), 7.88–7.82 (m, 4H, 2 $\times$ SO₂Tol-H and 2 $\times$ Ph-H), 7.53 (t, *J* = 7.4 Hz, 1H, Ph-H), 7.40 (t, *J* = 7.6 Hz, 2H, 2 $\times$ Ph-H), 7.28 (d, *J* = 8.1 Hz, 2H, 2 $\times$ SO₂Tol-H), 2.35 (s, 3H, SO₂Tol-CH₃); ¹³C NMR (101 MHz, CDCl₃) δ 169.9 (C=N), 144.4 (SO₂Tol-C quat.), 134.7 (SO₂TolC-CH₃ quat. and Ph-C), 131.9 (Ph-C quat.), 130.9 (2 $\times$ Ph-C), 129.5 (2 $\times$ SO₂Tol-C), 128.8 (2 $\times$ Ph-C), 127.7 (2 $\times$ SO₂Tol-C), 21.3 (SO₂Tol-CH₃). Observed data was consistent with that reported in the literature.²³⁵

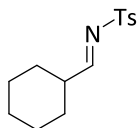


N-[(E)-4-Methylphenylmethylidene]-4-methylbenzenesulfonamide (19b). 4-Tolualdehyde (2.83 mL, 24.0 mmol, 1.2 equiv) was added to a stirred solution of *p*-toluenesulfonamide (3.42 g, 20.0 mmol, 1.0 equiv) in toluene (50 mL). The resulting mixture was heated under Dean-Stark conditions for 48 h, after which the solvent was removed under reduced pressure. The crude imine was washed with hexane (50 mL), diethyl ether (50 mL) and then washed with NaOH (1 M, 50 mL) to afford imine **19b** (1.75 g, 32%) as a brown solid: mp = 117–118 °C (lit.²³⁶ mp = 118–119 °C); $\nu_{\max}$ (film)/cm⁻¹ 2922, 1590, 1558, 1447, 1413, 1364, 1315, 1155, 1086, 1018, 871, 791, 760, 667; ¹H NMR (400 MHz, CDCl₃) δ 9.00 (s, 1H, CHN), 7.89 (d, *J* = 8.2 Hz, 2H, 2 $\times$ SO₂Tol-H), 7.82 (d, *J* = 8.1 Hz, 2H, 2 $\times$ Tol-H), 7.36 (d, *J* = 8.2 Hz, 2H, 2 $\times$ SO₂Tol-H), 7.30 (d, *J* = 8.1 Hz, 2H, 2 $\times$ Tol-H), 2.44 (s, 6H, SO₂Tol-CH₃ and Tol-CH₃); ¹³C NMR (101 MHz, CDCl₃) δ 169.9 (C=N), 146.3 (Tol-C quat.), 144.4 (SO₂Tol-C quat.), 135.2 (SO₂TolC-CH₃ quat.), 131.3 (2 $\times$ Tol-C), 129.8 (2 $\times$ SO₂Tol-C), 129.7 (2 $\times$ Tol-C and TolC-CH₃ quat.), 127.9 (2 $\times$ SO₂Tol-C), 21.9 (Tol-CH₃), 21.5 (SO₂Tol-CH₃). Observed data was consistent with that reported in the literature.²³⁷



***N*-[(*E*)-4-Chlorophenylmethylidene]-4-methylbenzenesulfonamide (**19f**).** Prepared

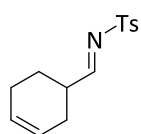
according to the method of Chemla and co-workers.¹⁰⁵ 4-Chlorobenzaldehyde (1.41 g, 10.0 mmol, 1.0 equiv) was added to a stirring solution of *p*-toluenesulfonamide (1.71 g, 10.0 mmol, 1.0 equiv) and sodium *p*-toluenesulfinate (1.96 g, 11.0 mmol, 1.1 equiv) in formic acid (98%) and water (1:1, 30 mL). After 48 h at rt, the reaction mixture was filtered under reduced pressure and then washed successively with water (50 mL) and hexane (50 mL). The resulting imine–HO₂STol adduct was dissolved in CH₂Cl₂ (100 mL) and saturated aqueous sodium bicarbonate solution (100 mL) was added. The resulting biphasic solution was vigorously stirred for 2 h at rt, after which the organic layer was separated, dried (Na₂SO₄) and the solvent was removed under reduced pressure affording the crude imine. Purification by recrystallisation (EtOAc/hexane) afforded imine **19f** as colourless crystals (700 mg, 24%): mp = 173–174 °C (lit.²³⁸ mp = 175–176 °C); $\nu_{\max}$ (film)/cm⁻¹ 3067, 2924, 1592, 1560, 1487, 1401, 1316, 1183, 1160, 1083, 1011, 869, 820, 786, 706, 692, 656; ¹H NMR (400 MHz, CDCl₃) δ 9.00 (s, 1H, CHN), 7.92–7.80 (m, 4H, 2 × ClAr-H and 2 × SO₂Tol-H), 7.47 (d, *J* = 8.5 Hz, 2H, 2 × ClAr-H), 7.36 (d, *J* = 8.1 Hz, 2H, 2 × SO₂Tol-H), 2.44 (s, 3H, SO₂Tol-CH₃); ¹³C NMR (101 MHz, CDCl₃) δ 168.6 (CHN), 144.8 (SO₂Tol-C quat.), 141.3 (C-ArCl quat.), 134.8 (SO₂TolC-CH₃ quat.), 132.3 (2 × ClAr-C), 130.7 (ClAr-C quat.), 129.8 (2 × SO₂Tol-C), 129.5 (2 × ClAr-C), 128.1 (2 × SO₂Tol-C), 21.6 (SO₂Tol-CH₃). Observed data was consistent with that reported in the literature.²³⁸



***N*-[(*E*)-Cyclohexylmethylidene]-4-methylbenzenesulfonamide (**19i**).** Prepared

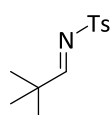
according to the method of Chemla and co-workers.¹⁰⁵ Cyclohexanecarboxaldehyde (5.45 mL, 45.0 mmol, 1.5 equiv) was added to a stirring solution of *p*-toluenesulfonamide (5.14 g, 30.0 mmol, 1.0 equiv) and sodium *p*-toluenesulfinate (6.41 g, 36.0 mmol, 1.2 equiv) in formic acid (98%) and water (1:1, 90 mL). After 24 h at rt, the reaction mixture was filtered under reduced pressure and then washed successively with water (100 mL) and hexane (100 mL). The resulting imine–HO₂STol adduct was dissolved in CH₂Cl₂ (300 mL) and saturated aqueous sodium bicarbonate solution (300 mL) was added. The resulting biphasic solution was vigorously stirred for 2 h at rt, after which the organic layer was separated, dried (Na₂SO₄) and the solvent was removed under reduced pressure to afford the crude imine. Purification by recrystallisation (EtOAc/hexane) afforded imine **19i** (6.39 g, 80%) as colourless crystals: mp = 109–110 °C (lit.¹⁰⁵ mp = 106 °C); $\nu_{\max}$ (film)/cm⁻¹ 3361, 3265, 2930, 2856, 1627, 1600, 1449, 1317, 1159, 1093, 901, 814, 676; ¹H NMR (400 MHz, CDCl₃) δ 8.48 (d, *J* = 4.4 Hz, 1H, CHN), 7.81 (d, *J* = 8.3 Hz, 2H, 2 × SO₂Tol-H), 7.34 (d, *J* = 8.3 Hz, 2H, 2 × SO₂Tol-H), 2.46–2.42 (m, 4H, Cy-H and SO₂Tol-CH₃), 1.92–1.63 (m, 5H, 5 × Cy-H), 1.40–1.18 (m, 5H, 5 × Cy-H); ¹³C NMR (101 MHz, CDCl₃) δ 181.0 (CHN), 144.5 (SO₂Tol-C quat.), 134.7 (SO₂TolC-CH₃ quat.), 129.7 (2 × SO₂Tol-C), 128.0 (2 × SO₂Tol-C), 43.6

(CH), 28.3 (2 × CH₂), 25.6 (CH₂), 25.0 (2 × CH₂), 21.6 (SO₂Tol-CH₃). Observed data was consistent with that reported in the literature.¹⁰⁵



***N*-[(*E*)-Cyclohex-3-en-1-ylmethylidene]-4-methylbenzenesulfonamide (19m).** 3-

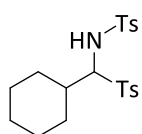
Cyclohexenecarboxaldehyde (1.76 mL, 15.0 mmol, 1.5 equiv.) was added to a stirred solution of *p*-toluenesulfonamide (1.71 g, 10.0 mmol, 1.0 equiv.) and sodium *p*-toluenesulfinate (2.14 g, 12.0 mmol, 1.2 equiv) in formic acid (98%) and water (1:1, 30 mL) at 0 °C. The reaction was then warmed to rt and stirred for 24 h. The reaction mixture was then filtered under reduced pressure and washed successively with water (50 mL) and hexane (50 mL). The solid was then dissolved in CH₂Cl₂ (50 mL) and washed rapidly with NaOH (1 M, 50 mL). The organic layer was separated, dried (Na₂SO₄), and the solvent was removed under reduced pressure affording imine **19m** (1.65 g, 63%) as a white solid: mp = 118–119 °C; $\nu_{\max}$ (film)/cm⁻¹ 3028, 2922, 1625, 1597, 1437, 1320, 1291, 1156, 1090, 786, 739, 670; ¹H NMR (400 MHz, CDCl₃) δ 8.58 (d, *J* = 4.3 Hz, 1H, CHN), 7.82 (d, *J* = 8.3 Hz, 2H, 2 × SO₂Tol-H), 7.35 (d, *J* = 8.3 Hz, 2H, 2 × SO₂Tol-H), 5.73–5.65 (m, 2H, HC=CH), 2.76–2.68 (m, 1H, CH), 2.45 (s, 3H, SO₂Tol-CH₃), 2.27–2.07 (m, 4H, 2 × CH₂), 2.00–1.93 (m, 1H, CH), 1.66–1.55 (m, 1H, CH); ¹³C NMR (101 MHz, CDCl₃) δ 180.6 (CHN), 144.6 (SO₂Tol-C quat.), 134.6 (SO₂TolC-CH₃ quat.), 129.7 (2 × SO₂Tol-C), 128.0 (2 × SO₂Tol-C), 127.0 (HC=CH), 124.4 (HC=CH), 40.0 (CH), 26.7 (CH₂), 24.5 (CH₂), 23.8 (CH₂), 21.6 (SO₂Tol-CH₃); HRMS (ESI⁺) *m/z* Calculated for C₁₄H₂₈NO₂S⁺ [M+H]⁺: 264.1053; Found: 264.1050.



***N*-[(*E*)-2,2-Dimethylpropylidene]-4-methylbenzenesulfonamide (19n).** A mixture of *p*-

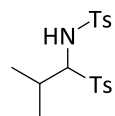
toluenesulfonamide (1.71 g, 10.0 mmol, 1.0 equiv), toluene (30 mL), pivaldehyde (1.14 mL, 10.5 mmol, 1.05 equiv) and boron trifluoride THF complex (89 μ L, 0.80 mmol, 8 mol%) was refluxed for 16 h. After cooling to rt the reaction mixture was quenched with NaOH (1 M, 20 mL) and extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine (50 mL), dried (Na₂SO₄), and the solvent was evaporated under reduced pressure. Excess sulfonamide was removed by precipitation (CH₂Cl₂/hexane) then filtration. The filtrate was concentrated under reduced pressure to afford imine **19n** (916 mg, 38%) as a white solid: mp = 90–94 °C (lit.²³⁹ mp = 84–86 °C, lit.²⁴⁰ mp = 102–103 °C); $\nu_{\max}$ (film)/cm⁻¹ 3359, 3261, 1741, 1530, 1389, 1305, 1157, 1098, 905, 816, 696; ¹H NMR (400 MHz, CDCl₃) δ 8.33 (s, 1H, CHN), 7.66 (d, *J* = 8.2 Hz, 2H, 2 × SO₂Tol-H), 7.19 (d, *J* = 8.2 Hz, 2H, 2 × SO₂Tol-H), 2.26 (s, 3H, SO₂Tol-CH₃), 0.99 (s, 9H, C(CH₃)₃); ¹³C NMR (101 MHz, CDCl₃) δ 183.4 (C=N), 144.1 (SO₂Tol-C quat.), 134.3 (SO₂TolC-CH₃ quat.), 129.3 (2 × SO₂Tol-C), 127.5 (2 × SO₂Tol-C), 37.3 (C(CH₃)₃ quat.), 25.3 (C(CH₃)₃), 21.1 (SO₂Tol-CH₃). Observed data was consistent with that reported in the literature.²⁴¹

Synthesis of Imine-HSO₂Tol Adducts, General Procedure 6: Prepared according to the method of Chemla and co-workers.¹⁰⁵ The relevant aldehyde (15.0 mmol, 1.5 equiv) was added to a stirred solution of *p*-toluenesulfonamide (1.71 g, 10.0 mmol, 1.0 equiv) and sodium *p*-toluenesulfinate (2.14 g, 12.0 mmol, 1.2 equiv) in formic acid (98%) and water (1:1, 30 mL) at 0 °C. The reaction was then warmed to rt and stirred at this temperature. After 3 days at rt, the reaction mixture was filtered under reduced pressure, washed successively with water (50 mL) and hexane (50 mL) affording the corresponding imine-HO₂STol adduct.



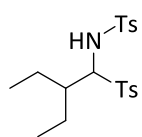
***N*-{2-Methyl-1-[(4-methylphenyl)sulfonyl]cyclohexyl}-4-tolylsulfonamide (24i).**

Prepared according to **General Procedure 6** described above, starting from cyclohexanecarboxaldehyde (1.21 mL, 10.0 mmol) afforded imine-HO₂STol adduct **24i** (2.52 g, 60%) as a white solid: mp = 99–102 °C (lit.²⁴² mp = 101–103 °C); $\nu_{\max}$ (film)/cm⁻¹ 3268, 2933, 2860, 1721, 1600, 1451, 1331, 1303, 1290, 1155, 1081, 906, 812, 731, 705, 661; ¹H NMR (400 MHz, CDCl₃) δ 7.65 (d, *J* = 8.2 Hz, 2H, 2 × SO₂Tol-H), 7.45 (d, *J* = 8.3 Hz, 2H, 2 × SO₂Tol-H), 7.23 (d, *J* = 8.2 Hz, 2H, 2 × SO₂Tol-H), 7.17 (d, *J* = 8.2 Hz, 2H, 2 × SO₂Tol-H), 5.17 (d, *J* = 10.7 Hz, 1H, NH), 4.47 (dd, *J* = 2.9, 10.7 Hz, 1H, HC-NH), 2.45 (s, 3H, SO₂Tol-CH₃), 2.42 (s, 3H, SO₂Tol-CH₃), 2.40–2.34 (m, 1H, Cy-H), 2.07–1.99 (m, 1H, Cy-H), 1.80–1.59 (m, 4H, 4 × Cy-H), 1.36–1.28 (m, 2H, 2 × Cy-H), 1.10–0.95 (m, 3H, 3 × Cy-H); ¹³C NMR (101 MHz, CDCl₃) δ 145.0 (SO₂Tol-C quat.), 143.5 (SO₂Tol-C quat.), 138.1 (SO₂TolC-CH₃ quat.), 134.1 (SO₂TolC-CH₃ quat.), 129.7 (2 × SO₂Tol-C), 129.5 (2 × SO₂Tol-C), 129.3 (2 × SO₂Tol-C), 126.6 (2 × SO₂Tol-C), 77.5 (CHN), 37.3 (CH), 31.0 (CH₂), 27.1 (CH₂), 26.2 (CH₂), 25.63 (CH₂), 25.61 (CH₂), 21.8 (SO₂Tol-CH₃), 21.6 (SO₂Tol-CH₃). Observed data was consistent with that reported in the literature.²⁴²



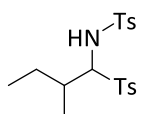
***N*-{2-Methyl-1-[(4-methylphenyl)sulfonyl]propyl}-4-tolylsulfonamide (24j).** Prepared according to the method of Chemla and co-workers.¹⁰⁵ Isobutyraldehyde (10.27 mL, 112.5 mmol, 1.5 equiv) was added to a stirred solution of *p*-toluenesulfonamide (13.36 g, 75.0 mmol, 1.0 equiv) and sodium *p*-toluenesulfinate (15.41 g, 90.0 mmol, 1.2 equiv) in formic acid (98%) and water (1:1, 200 mL) at 0 °C. The reaction was then warmed to rt and stirred at this temperature. After 3 days at rt, the reaction mixture was filtered under reduced pressure, washed successively with water (400 mL) and hexane (400 mL) affording the crude imine-HO₂STol adduct. The crude imine-HO₂STol adduct was dissolved in CH₂Cl₂ (300 mL), organic layer separated, dried (Na₂SO₄) and the solvent removed under reduced pressure affording imine-HO₂STol adduct **24j** (23.72 g, 83%) as a white solid: mp = 86–88 °C; $\nu_{\max}$ (film)/cm⁻¹ 3283 (NH), 2968, 1598, 1442, 1332, 1290, 1160, 1132, 1082, 890, 813, 779, 702, 670; ¹H NMR (400 MHz, CDCl₃) δ 7.70 (d, *J* = 8.0 Hz, 2H, 2 × SO₂Tol-H), 7.50

(d, J = 8.2 Hz, 2H, 2 $\times$ SO₂Tol-H), 7.26 (d, J = 8.0 Hz, 2H, 2 $\times$ SO₂Tol-H), 7.18 (d, J = 8.2 Hz, 2H, 2 $\times$ SO₂Tol-H), 5.38 (d, J = 10.6 Hz, 1H, NH), 4.52 (dd, J = 2.7, 10.6 Hz, 1H, HC-NH), 2.71 (dq, J = 2.7, 6.9, 6.9 Hz, 1H, CH), 2.45 (s, 3H, SO₂Tol-CH₃), 2.41 (s, 3H, SO₂Tol-CH₃), 1.05 (d, J = 6.9 Hz, 3H, CH₃), 0.87 (d, J = 6.9 Hz, 3H, CH₃); ¹³C NMR (101 MHz, CDCl₃) δ 145.0 (SO₂Tol-C quat.), 143.4 (SO₂Tol-C quat.), 138.0 (SO₂TolC-CH₃ quat.), 133.9 (SO₂TolC-CH₃ quat.), 129.6 (2 $\times$ SO₂Tol-C), 129.4 (2 $\times$ SO₂Tol-C), 129.2 (2 $\times$ SO₂Tol-C), 126.6 (2 $\times$ SO₂Tol-C), 77.5 (HC-NH), 27.6 (CH), 21.7 (SO₂Tol-CH₃), 21.5 (SO₂Tol-CH₃), 20.8 (CH₃), 16.5 (CH₃). The compound was previously reported without characterisation data.¹⁰⁵



***N*-{1-[(4-Methylphenyl)sulfonyl]pentan-2-yl}-4-tolylsulfonamide (24k).** Prepared according to **General Procedure 6** described above, starting from 2-ethylbutyraldehyde (1.85 mL, 15.0 mmol) afforded imine-HO₂Tol adduct **24k** (3.01 g, 73%) as a white

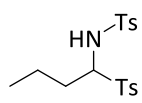
solid: mp = 63–64 °C (lit.²⁴² mp = 56–57 °C); $\nu_{\max}$ (film)/cm⁻¹ 3265 (NH), 2965, 2876, 1598, 1450, 1332, 1154, 1129, 1084, 1083, 1067, 885, 810, 703, 676; ¹H NMR (400 MHz, CDCl₃) δ 7.70 (d, J = 8.3 Hz, 2H, 2 $\times$ SO₂Tol-H), 7.52 (d, J = 8.3 Hz, 2H, 2 $\times$ SO₂Tol-H), 7.28 (d, J = 8.3 Hz, 2H, 2 $\times$ SO₂Tol-H), 7.20 (d, J = 8.3 Hz, 2H, 2 $\times$ SO₂Tol-H), 5.23 (d, J = 10.6 Hz, 1H, NH), 4.68 (dd, J = 2.0, 10.6 Hz, 1H, HC-NH), 2.46 (s, 3H, SO₂Tol-CH₃), 2.42 (s, 3H, SO₂Tol-CH₃), 2.10–2.01 (m, 1H, CH), 1.89–1.79 (m, 1H, CH₂), 1.57–1.47 (m, 1H, CH₂), 1.15–1.03 (m, 1H, CH₂), 0.97–0.90 (m, 4H, CH₂ and CH₃), 0.87 (t, J = 7.3 Hz, 3H, CH₃); ¹³C NMR (101 MHz, CDCl₃) δ 145.0 (SO₂Tol-C quat.), 143.5 (SO₂Tol-C quat.), 138.0 (SO₂TolC-CH₃ quat.), 134.1 (SO₂TolC-CH₃ quat.), 129.7 (2 $\times$ SO₂Tol-C), 129.4 (2 $\times$ SO₂Tol-C), 129.2 (2 $\times$ SO₂Tol-C), 126.5 (2 $\times$ SO₂Tol-C), 74.4 (HC-NH), 41.4 (CH), 22.7 (CH₂), 22.0 (CH₂), 21.7 (SO₂Tol-CH₃), 21.5 (SO₂Tol-CH₃), 11.9 (CH₃), 11.7 (CH₃). Observed data was consistent with that reported in the literature.²⁴²

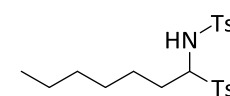


***N*-{1-[(4-Methylphenyl)sulfonyl]butan-2-yl}-4-tolylsulfonamide (24l).** Prepared according to **General Procedure 6** described above, starting from 2-methylbutyraldehyde (1.61 mL, 15.0 mmol) afforded imine-HO₂Tol adduct **24l** (2.38 g, 60%) as a white solid: mp = 86–87 °C; $\nu_{\max}$ (film)/cm⁻¹ 3227 (NH), 2929, 1599, 1454, 1334, 1292,

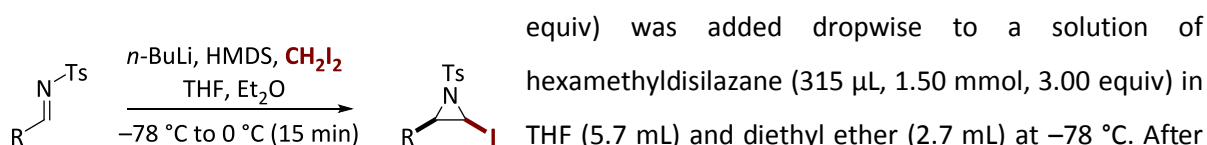
1131, 1083, 813, 763, 669; ¹H NMR (400 MHz, CDCl₃) δ 7.69 (d, J = 8.1 Hz, 2H, 2 $\times$ SO₂Tol-H), 7.50 (d, J = 8.3 Hz, 2H, 2 $\times$ SO₂Tol-H), 7.27 (d, J = 8.1 Hz, 2H, 2 $\times$ SO₂Tol-H), 7.19 (d, J = 8.3 Hz, 2H, 2 $\times$ SO₂Tol-H), 5.19 (d, J = 10.6 Hz, 1H, NH), 4.63 (dd, J = 2.0, 10.6 Hz, 1H, HC-NH), 2.46–2.42 (m, 1H, CH), 2.46 (s, 3H, SO₂Tol-CH₃), 2.42 (s, 3H, SO₂Tol-CH₃), 1.21–1.09 (m, 2H, CH₂), 1.05 (d, J = 6.8 Hz, 3H, CHCH₃), 0.87 (t, J = 7.3 Hz, 3H, CH₃); ¹³C NMR (101 MHz, CDCl₃) δ 145.0 (SO₂Tol-C quat.), 143.5 (SO₂Tol-C quat.), 138.0 (SO₂TolC-CH₃ quat.), 134.0 (SO₂TolC-CH₃ quat.), 129.7 (2 $\times$ SO₂Tol-C), 129.4 (2 $\times$ SO₂Tol-C), 129.2 (2 $\times$ SO₂Tol-C), 126.5 (2 $\times$ SO₂Tol-C), 75.8 (HC-NH), 33.9 (CH), 27.4 (CH₂), 21.8 (SO₂Tol-CH₃),

21.5 (SO₂Tol-CH₃), 14.1 (CHCH₃), 11.5 (CH₂CH₃); HRMS (ESI⁺) *m/z* Calculated for C₁₉H₂₄NO₄S₂⁺ [M-H]⁺: 394.1141; Found: 394.1137.

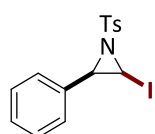
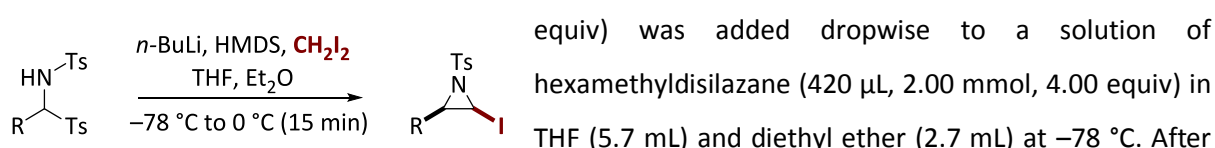
 ***N*-{1-[(4-Methylphenyl)sulfonyl]butyl}-4-tolylsulfonamide (24o).** Prepared according to **General Procedure 6** described above, starting from butyraldehyde (1.34 mL, 15.0 mmol) afforded imine-HO₂Tol adduct **24o** as a white solid (3.42 g, 90%): mp = 118–119 (lit.²⁴² mp = 119–120 °C); $\nu_{\max}$ (film)/cm⁻¹ 3214, 2932, 1597, 1460, 1441, 1334, 1291, 1210, 1166, 1127, 1078, 922, 815, 667; ¹H NMR (400 MHz, CDCl₃) δ 7.68 (d, *J* = 8.1 Hz, 2H, 2 × SO₂Tol-H), 7.54 (d, *J* = 8.1 Hz, 2H, 2 × SO₂Tol-H), 7.28 (d, *J* = 8.1 Hz, 2H, 2 × SO₂Tol-H), 7.21 (d, *J* = 8.1 Hz, 2H, 2 × SO₂Tol-H), 4.96 (d, *J* = 10.2 Hz, 1H, NH), 4.59 (dt, *J* = 3.8, 10.2 Hz, 1H, HC-NH), 2.45 (s, 3H, SO₂Tol-CH₃), 2.43 (s, 3H, SO₂Tol-CH₃), 2.17–2.08 (m, 1H, CH₂), 1.70–1.62 (m, 1H, CH₂), 1.45–1.38 (m, 1H, CH₂), 1.29–1.19 (m, 1H, CH₂), 0.87 (t, *J* = 7.3 Hz, 3H, CH₃); ¹³C NMR (101 MHz, CDCl₃) δ 145.2 (SO₂Tol-C quat.), 143.6 (SO₂Tol-C quat.), 137.8 (SO₂TolC-CH₃ quat.), 132.7 (SO₂TolC-CH₃ quat.), 129.7 (2 × SO₂Tol-C), 129.6 (2 × SO₂Tol-C), 129.5 (2 × SO₂Tol-C), 126.7 (2 × SO₂Tol-C), 73.6 (HC-NH), 27.6 (CH₂), 21.7 (SO₂Tol-CH₃), 21.5 (SO₂Tol-CH₃), 18.4 (CH₂), 13.5 (CH₃). Observed data was consistent with that reported in the literature.²⁴²

 ***N*-{1-[(4-Methylphenyl)sulfonyl]heptyl}-4-tolylsulfonamide (24p).** Prepared according to **General Procedure 6** described above, starting from 1-heptanal (2.09 mL, 15.0 mmol) afforded imine-HO₂Tol adduct **24p** as a white solid (2.67 g, 64%): mp = 76–77 °C; $\nu_{\max}$ (film)/cm⁻¹ 3261, 2925, 1597, 1451, 1334, 1301, 1161, 1129, 1081, 1038, 1010, 901, 813, 676; ¹H NMR (400 MHz, CDCl₃) δ 7.71 (d, *J* = 8.3 Hz, 2H, 2 × SO₂Tol-H), 7.55 (d, *J* = 8.3 Hz, 2H, 2 × SO₂Tol-H), 7.30 (d, *J* = 8.3 Hz, 2H, 2 × SO₂Tol-H), 7.22 (d, *J* = 8.3 Hz, 2H, 2 × SO₂Tol-H), 5.11 (d, *J* = 10.3 Hz, 1H, NH), 4.53 (dt, *J* = 3.6, 10.3 Hz, 1H, HC-NH), 2.45 (s, 3H, SO₂Tol-CH₃), 2.42 (s, 3H, SO₂Tol-CH₃), 2.19–2.01 (m, 1H, CH₂), 1.69–1.60 (m, 2H, 2 × CH₂), 1.22–1.07 (m, 7H, 7 × CH₂), 0.84 (t, *J* = 7.3 Hz, 3H, CH₃); ¹³C NMR (101 MHz, CDCl₃) δ 145.3 (SO₂Tol-C quat.), 143.6 (SO₂Tol-C quat.), 137.9 (SO₂TolC-CH₃ quat.), 132.6 (SO₂TolC-CH₃ quat.), 129.7 (4 × SO₂Tol-C), 129.5 (2 × SO₂Tol-C), 126.7 (2 × SO₂Tol-C), 73.8 (HC-NH), 31.3 (CH₂), 28.6 (CH₂), 28.0 (CH₂), 24.5 (CH₂), 22.3 (CH₂), 21.8 (SO₂Tol-CH₃), 21.5 (SO₂Tol-CH₃), 14.0 (CH₃). The above compound is previously reported without characterisation data.²⁴³

Synthesis of *cis*-*N*-Ts Iodoaziridines, General Procedure 7 (Method A): *n*-BuLi (1.50 mmol, 3.00



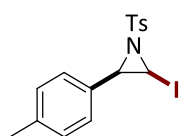
Synthesis of of *cis*-*N*-Ts Iodoaziridines: General Procedure 8 (Method C): *n*-BuLi (2.00 mmol, 4.00



***cis*-($\pm$)-2-Iodo-3-phenyl-1-(4-tolylsulfonyl)aziridine (20a).** Prepared according to **General Procedure 7** described above, starting from imine **19a** (130 mg, 0.50 mmol).

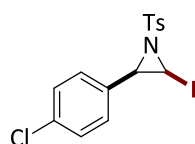
Purification by flash chromatography (10% EtOAc/hexane) on deactivated basic alumina (activity IV) afforded *cis*-iodoaziridine **20a** (152 mg, 76%) as a yellow oil: R_f = 0.24 (15% Et₂O/hexane); ν_{max} (film)/ cm^{-1} 3035, 2928, 1600, 1499, 1453, 1330, 1157, 1088, 902, 813, 763, 727, 696, 683, 666; ^1H NMR (400 MHz, CDCl_3) δ 7.92 (d, J = 8.5 Hz, 2H, $2 \times \text{SO}_2\text{Tol-H}$), 7.42–7.33 (m, 5H, 3

× Ph-H and 2 × SO₂Tol-H), 7.31–7.25 (m, 2H, 2 × Ph-H), 4.89 (d, *J* = 6.1 Hz, 1H, CHI), 3.89 (d, *J* = 6.1 Hz, 1H, CHPh), 2.47 (s, 3H, SO₂Tol-CH₃); ¹³C NMR (101 MHz, CDCl₃) δ 145.3 (SO₂C-Tol quat.), 134.1 (SO₂TolC-CH₃ quat.), 132.9 (Ph-C quat.), 129.9 (2 × SO₂Tol-C), 128.7 (Ph-C), 128.1 (2 × SO₂Tol-C), 127.8 (2 × Ph-C), 127.5 (2 × Ph-C), 44.9 (PhCN), 21.7 (SO₂Tol-CH₃), 16.4 (CHI); HRMS (ESI⁺) *m/z* Calculated for C₁₅H₁₅INO₂S⁺ [M+H]⁺ 399.9863; Found 399.9856.



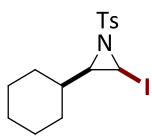
***cis*-(±)-2-iodo-3-(4-tolyl)-1-(4-tolylsulfonyl)aziridine (20b).** Prepared according to

General Procedure 7 described above, starting from imine **19b** (137 mg, 0.50 mmol). Purification by flash chromatography (5% EtOAc/hexane) on deactivated basic alumina (activity IV) afforded *cis*-iodoaziridine **20b** (100 mg, 48%) as a yellow oil: *R_f* = 0.16 (10% EtOAc/hexane); *v*_{max} (film)/cm⁻¹ 3022, 2923, 1616, 1598, 1517, 1329, 1292, 1242, 1158, 1089, 1037, 1019, 905, 842, 810, 766; ¹H NMR (400 MHz, CDCl₃) δ 7.90 (d, *J* = 8.2 Hz, 2H, 2 × SO₂Tol-H), 7.38 (d, *J* = 8.2 Hz, 2H, 2 × SO₂Tol-H), 7.18–7.14 (m, 4H, 4 × Tol-H), 4.87 (d, *J* = 6.1 Hz, 1H, CHI), 3.84 (d, *J* = 6.1 Hz, 1H, CHAr), 2.46 (s, 3H, SO₂Tol-CH₃), 2.35 (s, 3H, Tol-CH₃); ¹³C NMR (101 MHz, CDCl₃) δ 145.2 (SO₂Tol-C quat.), 138.6 (TolC quat.), 134.2 (SO₂TolC-CH₃ quat.), 129.9 (2 × SO₂Tol-C), 129.8 (Tol-C quat.), 128.9 (2 × Tol-C), 127.8 (2 × SO₂Tol-C), 127.4 (2 × Tol-C), 44.9 (CHN), 21.7 (SO₂Tol-CH₃), 21.2 (Tol-CH₃), 16.8 (CHI); HRMS (ESI⁺) *m/z* Calculated for C₁₆H₁₇INO₂S⁺ [M+H]⁺: 414.0019; Found: 414.0037.



***cis*-(±)-2-iodo-3-(4-chlorophenyl)-1-(4-tolylsulfonyl)aziridine (20f).** Prepared

according to **General Procedure 7** described above, starting from imine **19f** (147 mg, 0.50 mmol). Purification by flash chromatography (10% EtOAc/hexane) afforded *cis*-iodoaziridine **20f** (123 mg, 57%) as a yellow oil: *R_f* = 0.13 (10% EtOAc/hexane); *v*_{max} (film)/cm⁻¹ 3022, 2923, 1596, 1493, 1332, 1305, 1241, 1158, 1088, 1036, 1014, 903, 844, 805, 735, 688, 668; ¹H NMR (400 MHz, CDCl₃) δ 7.88 (d, *J* = 8.2 Hz, 2H, 2 × SO₂Tol-H), 7.38 (d, *J* = 8.2 Hz, 2H, 2 × SO₂Tol-H), 7.32 (d, *J* = 8.5 Hz, 2H, 2 × ClAr-H), 7.20 (d, *J* = 8.5 Hz, 2H, 2 × ClAr-H), 4.85 (d, *J* = 6.1 Hz, 1H, CHI), 3.83 (d, *J* = 6.1 Hz, 1H, CHAr), 2.46 (s, 3H, SO₂Tol-CH₃); ¹³C NMR (101 MHz, CDCl₃) δ 145.5 (SO₂Tol-C quat.), 134.7 (ClAr-C quat.), 133.9 (SO₂TolC-CH₃ quat.), 131.4 (ClAr-C quat.), 130.0 (2 × SO₂Tol-C), 128.8 (2 × ClAr-C), 128.4 (2 × ClAr-C), 127.8 (2 × SO₂Tol-C), 44.2 (CHN), 21.7 (SO₂Tol-CH₃), 16.1 (CHI); HRMS (ESI⁺) *m/z* Calculated for C₁₅H₁₅ClINO₂S⁺ [M+H]⁺: 433.9473; Found: 433.9467.



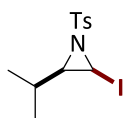
***cis*-(±)-2-Iodo-3-cyclohexyl-1-(4-tolylsulfonyl)aziridine (20i).** Prepared according to

General Procedure 7 described above, starting from imine **19i** (133 mg, 0.50 mmol).

Purification by flash chromatography (10% Et₂O/hexane) afforded *cis*-iodoaziridine

20i (137 mg, 68%) as a colourless oil: R_f = 0.18 (10% Et₂O/hexane); $\nu_{\max}$ (film)/cm⁻¹ 2926, 2851, 1598, 1450, 1330, 1242, 1158, 1090, 968, 900, 883, 814, 732, 669; ¹H NMR (400 MHz, CDCl₃) δ 7.82 (d, J = 8.2 Hz, 2H, 2 × SO₂Tol-H), 7.37 (d, J = 8.2 Hz, 2H, 2 × SO₂Tol-H), 4.53 (d, J = 6.0 Hz, 1H, CHI), 2.47 (s, 3H, SO₂Tol-CH₃), 2.26 (dd, J = 6.0, 9.4 Hz, 1H, CHCy), 1.84–1.71 (m, 2H, 2 × Cy-H), 1.70–1.62 (m, 2H, 2 × Cy-H), 1.60–1.53 (m, 1H, Cy-H), 1.33–0.99 (m, 6H, 6 × Cy-H); ¹³C NMR (101 MHz, CDCl₃) δ 145.0 (SO₂Tol-C quat.), 134.4 (2 × SO₂TolC-CH₃ quat.), 129.8 (2 × SO₂Tol-C), 128.0 (2 × SO₂Tol-C), 47.8 (Cy-CHN), 40.1 (CH), 30.3 (CH₂), 28.3 (CH₂), 25.9 (CH₂), 25.2 (CH₂), 25.1 (CH₂), 21.7 (SO₂Tol-CH₃), 13.5 (CHI); HRMS (ESI⁺) m/z Calculated for C₁₅H₂₁INO₂S⁺ [M+H]⁺: 406.0332; Found: 406.0328.

Alternative Protocol Using CIMgCHI₂: EtMgCl (2.0 M in THF, 4.50 mL, 9.00 mmol, 3.0 equiv) was added dropwise over 2 minutes to a solution of iodoform (3.54 g, 9.00 mmol, 3.0 equiv) in THF (34 mL) at –78 °C in the dark. After 10 minutes at –78 °C, a solution of imine **19i** (796 mg, 3.00 mmol, 1.0 equiv) in THF (8 mL) was added dropwise over 3 minutes. The reaction was left for 10 minutes at –78 °C and then warmed to 0 °C in an ice/water bath. After 15 minutes at 0 °C, the reaction was quenched by the addition of saturated aqueous sodium bicarbonate solution (100 mL). The aqueous solution was extracted with CH₂Cl₂ (3 × 100 mL) and the organic extracts were combined, dried (Na₂SO₄), filtered and solvent removed under reduced pressure. Purification by flash chromatography (silica, hexane to 10% EtOAc/hexane) afforded *cis*-iodoaziridine **20i** (999 mg, 82%) as a yellow solid. Data observed identical to that reported above.



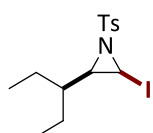
***cis*-(±)-2-Iodo-3-(propan-2-yl)-1-(4-tolylsulfonyl)aziridine (20j).** Prepared according to

General Procedure 8 described above, starting from imine–HO₂STol adduct **24j** (191 mg, 0.50 mmol). Purification by flash chromatography (5% EtOAc/hexane) on

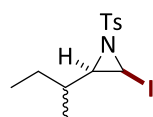
deactivated basic alumina (activity IV) afforded *cis*-iodoaziridine **20j** (114 mg, 63%) as a yellow oil: R_f = 0.21 (10% EtOAc/hexane); $\nu_{\max}$ (film)/cm⁻¹ 2963, 2931, 2874, 1597, 1466, 1403, 1329, 1244, 1156, 1089, 1026, 954, 885, 831, 813, 734, 684, 667; ¹H NMR (400 MHz, CDCl₃) δ 7.82 (d, J = 8.3 Hz, 2H, 2 × SO₂Tol-H), 7.36 (d, J = 8.3 Hz, 2H, 2 × SO₂Tol-H), 4.54 (d, J = 5.9 Hz, 1H, CHI), 2.46 (s, 3H, SO₂Tol-CH₃), 2.20 (dd, J = 5.9, 9.7 Hz, 1H, CHN), 1.92 (dq, J = 6.7, 6.7, 9.7 Hz, 1H, CH(CH₃)₂), 0.99 (d, J = 6.7 Hz, 3H, CH(CH₃)₂), 0.92 (d, J = 6.7 Hz, 3H, CH(CH₃)₂); ¹³C NMR (101 MHz, CDCl₃) δ 145.1 (SO₂Tol-C quat.), 134.3 (SO₂TolC-CH₃ quat.), 129.8 (2 × SO₂Tol-C), 128.0 (2 × SO₂Tol-C), 49.3 (CHN), 31.5 (CH(CH₃)₂),

21.7 (SO₂Tol-CH₃), 20.0 (CH₃), 17.9 (CH₃), 13.8 (CHI); HRMS (ESI⁺) *m/z* Calculated for C₁₂H₁₇INO₂S⁺ [M+H]⁺: 366.0019; Found: 366.0034.

Alternative Protocol Using CIMgCHI₂: EtMgCl (2.0 M in THF, 4.50 mL, 9.00 mmol, 3.0 equiv) was added dropwise over 2 minutes to a solution of iodoform (3.54 g, 9.00 mmol, 3.0 equiv) in THF (34 mL) at -78 °C in the dark. After 10 minutes at -78 °C, a solution of imine-HSO₂Tol adduct **24j** (1.14 g, 3.00 mmol, 1.0 equiv) in THF (8 mL) was added dropwise over 3 minutes. The reaction was left for 10 minutes at -78 °C and then warmed to 0 °C in an ice/water bath. After 15 minutes at 0 °C, the reaction was quenched by the addition of saturated aqueous sodium bicarbonate solution (100 mL). The aqueous solution was extracted with CH₂Cl₂ (3 × 100 mL) and the organic extracts were combined, dried (Na₂SO₄), filtered and solvent removed under reduced pressure. Purification by flash chromatography (silica, hexane to 10% EtOAc/hexane) afforded *cis*-iodoaziridine **20j** (930 mg, 85%) as a yellow solid. Data observed identical to that reported above.

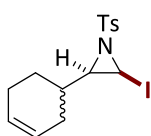


***cis*-(±)-2-iodo-3-(pentan-3-yl)-1-(4-tolylsulfonyl)aziridine (20k).** Prepared according to **General Procedure 8** described above, starting from imine-HO₂STol adduct **24k** (205 mg, 0.50 mmol). Purification by flash chromatography (5% EtOAc/hexane) on deactivated basic alumina (activity IV) afforded *cis*-iodoaziridine **20k** (123 mg, 63%) as a yellow oil: *R_f* = 0.31 (10% EtOAc/hexane); *v*_{max} (film)/cm⁻¹ 2963, 2930, 2877, 1597, 1458, 1330, 1244, 1157, 1089, 976, 887, 835, 813, 731, 667; ¹H NMR (400 MHz, CDCl₃) δ 7.82 (d, *J* = 8.3 Hz, 2H, 2 × SO₂Tol-H), 7.36 (d, *J* = 8.3 Hz, 2H, 2 × SO₂Tol-H), 4.55 (d, *J* = 5.9 Hz, 1H, CHI), 2.46 (s, 3H, SO₂Tol-CH₃), 2.39 (dd, *J* = 5.9, 9.6 Hz, 1H, CHN), 1.53–1.20 (m, 5H, 2 × CH₂ and CH), 0.97 (t, *J* = 7.4 Hz, 3H, CH₃), 0.84 (t, *J* = 7.4 Hz, 3H, CH₃); ¹³C NMR (101 MHz, CDCl₃) δ 145.0 (SO₂Tol-C quat.), 134.3 (SO₂TolC-CH₃ quat.), 129.8 (2 × SO₂Tol-C), 127.9 (2 × SO₂Tol-C), 47.1 (CHN), 42.1 (CH), 23.7 (CH₂), 22.3 (CH₂), 21.7 (SO₂Tol-CH₃), 15.0 (CHI), 10.6 (CH₃), 10.1 (CH₃); HRMS (ESI⁺) *m/z* Calculated for C₁₄H₂₁INO₂S⁺ [M+H]⁺: 394.0332; Found: 394.0332.



***cis*-(±)-2-iodo-3-(butan-2-yl)-1-(4-tolylsulfonyl)aziridine (20l).** Prepared according to **General Procedure 8** described above, starting from imine-HO₂STol adduct **24l** (198 mg, 0.50 mmol). Purification by flash chromatography (5% EtOAc/hexane) on deactivated basic alumina (activity IV) afforded a mixture of *cis*-iodoaziridines **20l** (1.9:1 major:minor) (115 mg, 61%) as a yellow oil: *R_f* = 0.24 (10% EtOAc/hexane); *v*_{max} (film)/cm⁻¹ 2963, 2926, 1597, 1459, 1402, 1330, 1243, 1157, 1089, 1019, 940, 871, 813, 733, 686; **major:** ¹H NMR (400 MHz, CDCl₃) δ 7.82 (d, *J* = 8.3 Hz, 2H, 2 × SO₂Tol-H), 7.36 (d, *J* = 8.3 Hz, 2H, 2 × SO₂Tol-H), 4.58 (d, *J* =

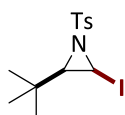
6.0 Hz, 1H, CHI), 2.46 (s, 3H, SO₂Tol-CH₃), 2.26 (d, *J* = 6.0, 9.7 Hz, 1H, CHN), 1.56–1.20 (m, 3H, CH and CH₂), 0.96 (t, *J* = 7.4 Hz, 3H, CH₂CH₃), 0.90 (d, *J* = 6.7 Hz, 3H, CHCH₃); ¹³C NMR (101 MHz, CDCl₃) δ 145.1 (SO₂Tol-C quat.), 134.3 (SO₂TolC-CH₃ quat.), 129.8 (2 × SO₂Tol-C), 128.0 (2 × SO₂Tol-C), 48.7 (CHN), 37.4 (CH), 25.8 (CH₂), 21.7 (SO₂Tol-CH₃), 17.0 (CH₂CH₃), 14.6 (CHI), 11.1 (CHCH₃); **minor**: ¹H NMR (400 MHz, CDCl₃) δ 7.82 (d, *J* = 8.3 Hz, 2H, 2 × SO₂Tol-H), 7.36 (d, *J* = 8.3 Hz, 2H, 2 × SO₂Tol-H), 4.50 (d, *J* = 6.0 Hz, 1H, CHI), 2.46 (s, 3H, SO₂Tol-CH₃), 2.29 (dd, *J* = 6.0, 10.3 Hz, 1H, CHN), 1.56–1.20 (m, 3H, CH and CH₂), 0.97 (d, *J* = 6.7 Hz, 3H, CH₂CH₃), 0.86 (t, *J* = 7.4 Hz, 3H, CHCH₃); ¹³C NMR (101 MHz, CDCl₃) δ 145.1 (SO₂Tol-C quat.), 134.3 (SO₂TolC-CH₃ quat.), 129.8 (2 × SO₂Tol-C), 127.9 (2 × SO₂Tol-C), 48.1 (CHN), 37.0 (CH), 27.6 (CH₂), 21.7 (SO₂Tol-CH₃), 14.5 (CHI), 13.9 (CH₂CH₃), 10.7 (CHCH₃); HRMS (ESI⁺) *m/z* Calculated for C₁₃H₁₉INO₂S⁺ [M+H]⁺: 380.0176; Found: 380.0186.



***cis*-(±)-2-Iodo-3-(cyclohex-3-en-1-yl)-1-(4-tolylsulfonyl)aziridine (20m).** Prepared

according to **General Procedure 7** described above, starting from imine **19m** (132 mg, 0.50 mmol). Purification by flash chromatography (5% EtOAc/hexane) on deactivated

basic alumina (activity IV) afforded a mixture of *cis*-iodoaziridines (1.5:1 major:minor) **20m** (105 mg, 52%) as a yellow oil: *R*_f = 0.33 (10% EtOAc/hexane); ν_{max} (film)/cm⁻¹ 3025, 2920, 1597, 1436, 1330, 1242, 1158, 1090, 1019, 957, 934, 893, 814, 732; **major**: ¹H NMR (400 MHz, CDCl₃) δ 7.84–7.81 (m, 2H, 2 × SO₂Tol-H), 7.39–7.36 (m, 2H, 2 × SO₂Tol-H), 5.73–5.56 (m, 2H, HC=CH), 4.57 (d, *J* = 6.0 Hz, 1H, CHI), 2.47 (s, 3H, SO₂Tol-CH₃), 2.38 (dd, *J* = 6.0, 9.7 Hz, 1H, CHN), 2.26–1.39 (m, 7H, 3 × CH₂ and CH); ¹³C NMR (101 MHz, CDCl₃) δ 145.1 (SO₂Tol-C quat.), 134.2 (SO₂TolC-CH₃ quat.), 129.8 (2 × SO₂Tol-C), 128.0 (2 × SO₂Tol-C), 127.0 (HC=CH), 125.2 (HC=CH), 47.0 (CHN), 36.2 (CH), 28.6 (CH₂), 24.0 (CH₂), 23.6 (CH₂), 21.7 (SO₂Tol-CH₃), 13.2 (CHI); **minor**: ¹H NMR (400 MHz, CDCl₃) δ 7.84–7.81 (m, 2H, 2 × SO₂Tol-H), 7.39–7.36 (m, 2H, 2 × SO₂Tol-H), 5.73–5.56 (m, 2H, HC=CH), 4.54 (d, *J* = 6.0 Hz, 1H, CHI), 2.47 (s, 3H, SO₂Tol-CH₃), 2.40 (dd, *J* = 6.0, 9.7 Hz, 1H, CHN), 2.26–1.39 (m, 7H, 3 × CH₂ and CH); ¹³C NMR (101 MHz, CDCl₃) δ 145.1 (SO₂Tol-C quat.), 134.2 (SO₂TolC-CH₃ quat.), 129.8 (2 × SO₂Tol-C), 128.0 (2 × SO₂Tol-C), 127.4 (HC=CH), 124.2 (HC=CH), 46.9 (CHN), 36.1 (CH), 26.6 (CH₂), 25.7 (CH₂), 23.6 (CH₂), 21.7 (SO₂Tol-CH₃), 13.7 (CHI); HRMS (ESI⁺) *m/z* Calculated for C₁₅H₁₉INO₂S⁺ [M+H]⁺: 404.0176; Found: 404.0183.

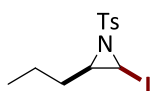


***cis*-(±)-2-Iodo-3-(tert-butyl)-1-(4-tolylsulfonyl)aziridine (20n).** EtMgCl (2.0 M in THF,

4.50 mL, 9.00 mmol, 3.0 equiv) was added dropwise over 2 minutes to a solution of iodoform (3.54 g, 9.00 mmol, 3.0 equiv) in THF (34 mL) at –78 °C in the dark. After 10

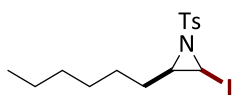
minutes at –78 °C, a solution of imine **19n** (718 mg, 3.00 mmol, 1.0 equiv) in THF (8 mL) was added dropwise over 3 minutes. The reaction was left for 10 minutes at –78 °C and then warmed to 0 °C in

an ice/water bath. After 15 minutes at 0 °C, the reaction was quenched by the addition of saturated aqueous sodium bicarbonate solution (100 mL). The aqueous solution was extracted with CH₂Cl₂ (3 × 100 mL) and the organic extracts were combined, dried (Na₂SO₄), filtered and solvent removed under reduced pressure. Purification by flash chromatography (hexane to 10% EtOAc/hexane) afforded *cis*-iodoaziridine **20n** (553 mg, 49%) as a yellow oil: R_f = 0.31 (10% EtOAc/hexane); $\nu_{\max}$ (film)/cm⁻¹ 2964, 2874, 1600, 1330, 1258, 1158, 1089, 953, 931, 852, 734, 677, 667; ¹H NMR (400 MHz, CDCl₃) δ 7.82 (d, J = 8.2 Hz, 2H, 2 × SO₂Tol-H), 7.36 (d, J = 8.2 Hz, 2H, 2 × SO₂Tol-H), 4.36 (d, J = 6.4 Hz, 1H, CHI), 2.45 (s, 3H, SO₂Tol-CH₃), 2.43 (d, J = 6.4, 1H, CHN), 0.98 (s, 9H, C(CH₃)₃); ¹³C NMR (101 MHz, CDCl₃) δ 145.0 (SO₂Tol-C quat.), 134.1 (SO₂TolC-CH₃ quat.), 129.7 (2 × SO₂Tol-C), 128.0 (2 × SO₂Tol-C), 50.2 (CHN), 31.4 (C(CH₃)₃ quat.), 27.0 (C(CH₃)₃), 21.7 (SO₂Tol-CH₃), 6.6 (CHI); HRMS (ESI⁺) m/z Calculated for C₁₃H₁₉INO₂S⁺ [M+H]⁺ 380.0176; Found 380.0203.

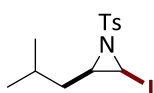


***cis*-(±)-2-iodo-3-propyl-1-(4-tolylsulfonyl)aziridine (20o).** Prepared according to **General Procedure 8** described above, starting from imine-HO₂STol adduct **24o** (191 mg, 0.50 mmol). Purification by flash chromatography (5% EtOAc/hexane) on deactivated basic alumina (activity IV) afforded *cis*-iodoaziridine **20o** (11 mg, 6%) as a yellow oil: R_f = 0.23 (10% EtOAc/hexane); $\nu_{\max}$ (film)/cm⁻¹ 2960, 2931, 2873, 1598, 1331, 1245, 1160, 1090, 902, 717; ¹H NMR (400 MHz, CDCl₃) δ 7.83 (d, J = 8.3 Hz, 2H, 2 × SO₂Tol-H), 7.37 (d, J = 8.3 Hz, 2H, 2 × SO₂Tol-H), 4.55 (d, J = 5.9 Hz, 1H, CHI), 2.58 (m, 1H, CHN), 2.47 (s, 3H, SO₂Tol-CH₃), 1.65–1.34 (m, 4H, CH₂CH₂), 0.95 (t, J = 7.3 Hz, 3H, CH₃); ¹³C NMR (101 MHz, CDCl₃) δ 145.1 (SO₂Tol-C quat.), 134.5 (SO₂TolC-CH₃ quat.), 129.8 (2 × SO₂Tol-C), 127.9 (2 × SO₂Tol-C), 43.7 (CHN), 33.5 (CH₂), 21.7 (SO₂Tol-CH₃), 19.7 (CH₂), 14.5 (CH₃), 13.7 (CHI); HRMS (ESI⁺) m/z Calculated for C₁₂H₁₇INO₂S⁺ [M+H]⁺: 366.0019; Found: 366.0031.

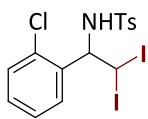
Alternative Protocol Using CIMgCHI₂: EtMgCl (2.0 M in THF, 0.75 mL, 1.50 mmol, 3.0 equiv) was added dropwise over 2 minutes to a solution of iodoform (591 mg, 1.50 mmol, 3.0 equiv) in THF (6 mL) at –78 °C in the dark. After 10 minutes at –78 °C, a solution of imine-HO₂STol adduct **24o** (191 mg, 0.50 mmol) in THF (2 mL) was added dropwise over 3 minutes. The reaction was left for 10 minutes at –78 °C and then warmed to 0 °C in an ice/water bath. After 15 minutes at 0 °C, the reaction was quenched by the addition of saturated aqueous sodium bicarbonate solution (20 mL). The aqueous solution was extracted with CH₂Cl₂ (3 × 30 mL) and the organic extracts were combined, dried (Na₂SO₄), filtered and solvent removed under reduced pressure. Purification by flash chromatography (hexane to 10% EtOAc/hexane) on deactivated basic alumina (activity IV) afforded *cis*-iodoaziridine **20o** (80 mg, 44%) as a yellow oil. Data observed identical to that reported above.



***cis*-(±)-2-iodo-3-hexyl-1-(4-tolylsulfonyl)aziridine (20p).** Prepared according to General Procedure 8 described above, starting from imine-HO₂Tol adduct **24p** (212 mg, 0.50 mmol). Purification by flash chromatography (5% EtOAc/hexane) on deactivated basic alumina (activity IV) afforded *cis*-iodoaziridine **20p** (9 mg, 4%) as a yellow oil: R_f = 0.24 (10% EtOAc/hexane); $\nu_{\max}$ (film)/cm⁻¹ 2955, 2927, 2858, 1597, 1458, 1402, 1334, 1246, 1161, 1091, 717. ¹H NMR (400 MHz, CDCl₃) δ 7.83 (d, J = 8.3 Hz, 2H, 2 × SO₂Tol-H), 7.37 (d, J = 8.3 Hz, 2H, 2 × SO₂Tol-H), 4.56 (d, J = 6.0 Hz, 1H, CHI), 2.54 (ddd, J = 6.0, 7.3, 7.3 Hz, 1H, CHN), 2.47 (s, 3H, SO₂Tol-CH₃), 1.65–1.46 (m, 2H, CH₂), 1.39–1.17 (m, 8H, 4 × CH₂), 0.88 (t, J = 7.1 Hz, 3H, CH₃); ¹³C NMR (101 MHz, CDCl₃) δ 145.1 (SO₂Tol-C quat.), 134.5 (SO₂TolC-CH₃ quat.), 129.8 (2 × SO₂Tol-C), 127.9 (2 × SO₂Tol-C), 43.9 (CHN), 31.6 (CH₂), 28.7 (CH₂), 26.2 (CH₂), 22.4 (CH₂), 21.7 (SO₂Tol-CH₃), 14.5 (CH₃), 14.0 (CHI); HRMS (ESI⁺) m/z Calculated for C₁₅H₂₃INO₂S⁺ [M+H]⁺: 408.0489; Found: 408.0509.

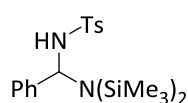


***cis*-(±)-2-iodo-3-(2-methylpropyl)-1-(4-tolylsulfonyl)aziridine (20q).** Isolated after sampling study. Data for iodoaziridine **20q**: orange solid; R_f = 0.31 (10% EtOAc/hexane); $\nu_{\max}$ (film)/cm⁻¹ 2956, 2872, 1597, 1467, 1329, 1246, 1158, 1089, 999, 904, 813, 714; ¹H NMR (400 MHz, CDCl₃) δ 7.82 (d, J = 8.3 Hz, 2H, 2 × SO₂Tol-H), 7.36 (d, J = 8.3 Hz, 2H, 2 × SO₂Tol-H), 4.54 (d, J = 5.9 Hz, 1H, CHI), 2.63 (ddd, J = 6.1, 7.0, 7.0 Hz, 1H, CHN), 2.46 (s, 3H, SO₂Tol-CH₃), 1.77–1.67 (m, 1H, CH), 1.51–1.42 (m, 2H, CH₂), 0.98 (t, J = 6.7 Hz, 3H, CH₃), 0.95 (t, J = 6.7 Hz, 3H, CH₃); ¹³C NMR (101 MHz, CDCl₃) δ 145.0 (SO₂Tol-C quat.), 134.5 (SO₂TolC-CH₃ quat.), 129.8 (2 × SO₂Tol-C), 127.8 (2 × SO₂Tol-C), 42.6 (CHN), 40.1 (CH₂), 26.3 (CH), 22.5 (CH₃), 22.3 (CH₃), 21.7 (SO₂Tol-CH₃), 14.9 (CHI); HRMS (ESI⁺) m/z Calculated for C₁₃H₁₉INO₂S⁺ [M+H]⁺: 380.0176; Found: 380.0195.



***N*-[1-(2-Chlorophenyl)-2,2-diiodoethyl]-4-methylbenzenesulfonamide (21h).** Diiodomethane (137 μ L, 1.70 mmol, 3.6 equiv) in THF (1.0 mL) was added dropwise to a solution of LiHMDS (1.0 M solution in THF, 1.50 mL, 1.50 mmol, 3.2 equiv) in THF (4.2 mL) and diethyl ether (2.7 mL) at –78 °C in the dark. After 20 minutes at –78 °C, a solution of imine **19h** (137 mg, 0.47 mmol, 1.0 equiv) in THF (2.0 mL) was added dropwise to the reaction mixture. After a further 10 minutes at –78 °C, the reaction was quenched by the addition of saturated aqueous sodium bicarbonate solution (40 mL). The aqueous solution was extracted with CH₂Cl₂ (3 × 30 mL), the organic layers were combined, dried (Na₂SO₄) and the solvent was removed under reduced pressure. Purification by flash chromatography (50% diethyl ether/hexane) afforded amino *gem*-diiodide **21h** (191 mg, 72%) as a white solid: mp = 210–211 °C; R_f = 0.20 (50% diethyl ether/hexane); $\nu_{\max}$ (film)/cm⁻¹ 3237 (NH), 1473, 1437, 1335, 1281, 1160, 1081, 1035, 910, 837, 815,

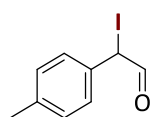
752; ^1H NMR (500 MHz, CDCl_3) δ 7.70 (d, J = 8.1 Hz, 2H, $2 \times \text{SO}_2\text{Tol-H}$), 7.37 (dd, J = 1.5, 7.8 Hz, 1H, ClAr-H), 7.30 (dd, J = 1.4, 8.0 Hz, 1H, ClAr-H), 7.26 (td, J = 1.5, 8.0 Hz, 1H, ClAr-H), 7.20 (d, J = 8.1 Hz, 2H, $2 \times \text{SO}_2\text{Tol-H}$), 7.15 (td, J = 1.4, 7.6 Hz, 1H, ClAr-H), 5.40 (d, J = 8.1 Hz, 1H, NH), 5.37 (d, J = 3.2 Hz, 1H, CH_2), 4.37 (dd, J = 3.2, 8.1 Hz, 1H, CHN), 2.37 (s, 3H, $\text{SO}_2\text{Tol-CH}_3$); ^{13}C NMR (125 MHz, CDCl_3) δ 143.8 ($\text{SO}_2\text{Tol-C quat.}$), 136.3 ($\text{SO}_2\text{TolC-CH}_3$ quat), 135.5 (ClAr-C quat.), 132.3 (ClAr-C quat.), 129.8 (ClAr-C), 129.6 (ClAr-C), 129.5 ($2 \times \text{SO}_2\text{Tol-C}$), 129.3 (ClAr-C), 127.5 ($2 \times \text{SO}_2\text{Tol-C}$), 126.7 (ClAr-C), 62.6 (CHN), 21.5 ($\text{SO}_2\text{Tol-CH}_3$), -22.1 (CH_2); HRMS (ESI $^+$) m/z Calculated for $\text{C}_{15}\text{H}_{15}\text{ClI}_2\text{NO}_2\text{S}^+$ $[\text{M}+\text{H}]^+$: 561.8596; Found: 561.8592.



***N*-{[Bis(trimethylsilyl)amino](phenyl)methyl}-4-methylbenzene-1-sulfonamide**

(22a). *n*-BuLi (1.60 M in hexane, 2.17 mL, 3.47 mmol, 3.00 equiv) was added dropwise to a solution of hexamethyldisilazane (730 μL , 3.47 mmol, 3.00 equiv) in THF (12 mL) and diethyl ether (5.5 mL) at -78°C . After 30 min, a solution of imine **19a** (300 mg, 1.16 mmol, 1.0 equiv) in THF (2.0 mL) was added dropwise over 5 minutes. The reaction mixture was then quenched by the addition of saturated aqueous sodium bicarbonate solution (40 mL). The aqueous solution was extracted with CH_2Cl_2 (3×30 mL) and the organic extracts were combined, dried (Na_2SO_4) and filtered. The solvent was then removed under reduced pressure to afford amina **22a** (490 mg, 99%) as a white solid: mp = $110\text{--}112^\circ\text{C}$; R_f = 0.36 (15% EtOAc/hexane); ν_{max} (film)/ cm^{-1} 3305, 2959, 1331, 1252, 1160, 965, 909, 869, 829, 813, 734, 698, 664; ^1H NMR (400 MHz, CDCl_3) δ 7.86 (d, J = 8.3 Hz, 2H, $2 \times \text{SO}_2\text{Tol-H}$), 7.35 (d, J = 8.3 Hz, 2H, $2 \times \text{SO}_2\text{Tol-H}$), 7.31–7.20 (m, 5H, $5 \times \text{Ph-H}$), 5.88 (d, J = 7.7 Hz, 1H, NH), 5.17 (d, J = 7.7 Hz, 1H, CHN), 2.46 (s, 3H, $\text{SO}_2\text{Tol-CH}_3$), 0.15 (s, 18H, $\text{N}[(\text{SiCH}_3)_3]_2$); ^{13}C NMR (101 MHz, CDCl_3) δ 143.3 ($\text{SO}_2\text{Tol-C quat.}$), 143.0 (Ph-C quat.), 136.2 ($\text{SO}_2\text{TolC-CH}_3$ quat.), 129.6 ($2 \times \text{SO}_2\text{Tol-C}$), 128.0 ($2 \times \text{SO}_2\text{Tol-C}$), 127.4 (Ph-C), 127.0 ($2 \times \text{Ph-C}$), 126.6 ($2 \times \text{Ph-C}$), 69.7 (PhCN), 21.5 ($\text{SO}_2\text{Tol-CH}_3$), 3.1 ($\text{N}[(\text{SiCH}_3)_3]_2$); HRMS (CI) m/z Calculated for $\text{C}_{20}\text{H}_{36}\text{N}_3\text{O}_2\text{SSi}_2^+$ $[\text{M}+\text{NH}_4]^+$ 438.2061; Found 438.2086.

Synthesis of Rearrangement Products 25 and 26b:

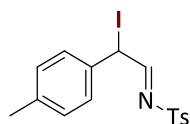


Iodo(4-tolyl)acetaldehyde (25). Following **General Procedure 7** starting from imine

19b (0.50 mmol): The crude *cis*-iodoaziridine was dissolved in CH_2Cl_2 (5 mL) and then added to a stirred suspension of silica (150 g) in a mixture of hexane/EtOAc (10:1, 300 mL). The resulting suspension was then stirred in the dark for 3 h, filtered, washed with CH_2Cl_2 (100 mL) and then the solvent was removed under reduced pressure. Purification by flash chromatography (5% EtOAc/hexane) afforded iodo-aldehyde **25** (70 mg, 54% over 2 steps) as a

yellow oil: R_f = 0.16 (5% EtOAc/hexane); $\nu_{\max}$ (film)/ cm^{-1} 3024, 2956, 1715, 1608, 1511, 1449, 1383, 1275, 1181, 1045, 1004, 813, 772, 715, 672; ^1H NMR (400 MHz, CDCl_3) δ 9.46 (d, J = 3.8 Hz, 1H, CHO), 7.38 (d, J = 8.0 Hz, 2H, 2 $\times$ Tol-H), 7.18 (d, J = 8.0 Hz, 2H, 2 $\times$ Tol-H), 5.58 (d, J = 3.8 Hz, 1H, CHI), 2.34 (s, 3H, Tol- CH_3); ^{13}C NMR (101 MHz, CDCl_3) δ 189.6 (C=O), 139.4 (Tol-C quat.), 131.0 (Tol-C quat.), 129.9 (2 $\times$ Tol-C), 129.2 (2 $\times$ Tol-C), 35.4 (CHI), 21.3 (Tol- CH_3); HRMS (CI) m/z Calculated for $\text{C}_9\text{H}_{13}\text{INO}^+$ $[\text{M}+\text{NH}_4]^+$: 278.0036; Found: 278.0049.

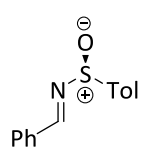
***N*-[(1*E*)-2-iodo-2-(4-methylphenyl)ethylidene]-4-methylbenzenesulfonamide**



(26b). Neat *cis*-iodoaziridine **20b** (95 mg, 0.23 mmol) in CDCl_3 (1.0 mL) was placed into a round bottom flask, and the solvent was removed under reduced pressure.

The resulting orange/red oil was heated at 35 °C under vacuum (2 mbar) for *c.a.* 1 h, where *cis*-iodoaziridine **20b** quantitatively rearranged to α -iodo-imine **26b** (93 mg, 99%): R_f = 0.15 (10% EtOAc/hexane); $\nu_{\max}$ (film)/ cm^{-1} 3031, 2921, 1611, 1512, 1449, 1320, 1157, 1088, 910, 812, 786, 731, 675; ^1H NMR (400 MHz, CDCl_3) δ 8.81 (d, J = 8.3 Hz, 1H, CHN), 7.82 (d, J = 8.2 Hz, 2H, $\text{SO}_2\text{Tol-H}$), 7.39–7.35 (m, 4H, 2 $\times$ $\text{SO}_2\text{Tol-H}$ and 2 $\times$ Tol-H), 7.16 (d, J = 7.9 Hz, 2H, 2 $\times$ Tol-H), 5.90 (d, J = 8.3 Hz, 1H, CHI), 2.45 (s, 3H, $\text{SO}_2\text{Tol-CH}_3$), 2.33 (s, 3H, Tol- CH_3); ^{13}C NMR (101 MHz, CDCl_3) δ 170.4 (C=N), 145.1 ($\text{SO}_2\text{Tol-C quat.}$), 139.7 (Tol-C quat.), 133.9 ($\text{SO}_2\text{TolC-CH}_3$ quat.), 132.1 (Tol-C quat.), 130.1 (2 $\times$ Tol-C), 129.9 (2 $\times$ $\text{SO}_2\text{Tol-C}$), 128.3 (2 $\times$ Tol-C), 128.2 (2 $\times$ $\text{SO}_2\text{Tol-C}$), 28.5 (CHI), 21.7 ($\text{SO}_2\text{Tol-CH}_3$), 21.3 (Tol- CH_3); HRMS (ES $^-$) m/z Calculated for $\text{C}_{16}\text{H}_{15}\text{INO}_2\text{S}^-$ $[\text{M-H}]^-$: 411.9874; Found: 411.9869.

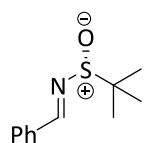
Preparation of Chiral Imines 27-28 and Chiral Iodoaziridines 29.



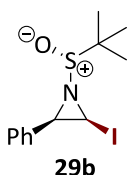
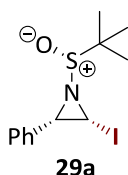
(*S*)-(+)-*N*-(Phenylmethylidene)-4-tolylsulfonamide (27). $\text{Ti}(\text{OEt})_4$ (1.71 g, 7.50 mmol, 5.0 equiv), benzaldehyde (152 μL , 1.50 mmol, 1.0 equiv) and (*S*)-(+)-toluenesulfonamide (234 mg, 1.50 mmol, 1.0 equiv) were sequentially added to CH_2Cl_2 (20 mL). The

reaction was refluxed for 5 h, after which the reaction was cooled to 0 °C, water (20 mL) was added, whilst stirring vigorously. The resulting suspension was filtered through Celite and the filter cake was washed with CH_2Cl_2 (100 mL). The filtrate was transferred to a separating funnel, water was added (10 mL) and the aqueous layer was extracted with CH_2Cl_2 (2 $\times$ 40 mL). The organic layers were washed with brine, dried (Na_2SO_4) and the solvent was removed under reduced pressure affording sulfinylimine **27** (278 mg, 76%) as a colorless oil, which was used without further purification: R_f = 0.25 (25% EtOAc/hexane); ^1H NMR (400 MHz, CDCl_3) δ 8.77 (s, 1H, CHN), 7.87–7.84 (m, 2H, 2 $\times$ SOTol-H), 7.65 (d, J = 8.2 Hz, 2H, 2 $\times$ Ph-H), 7.53–7.43 (m, 3H, 3 $\times$ Ph-H), 7.32 (d, J = 8.2 Hz, 2H, 2 $\times$ SOTol-H), 2.40 (s, 3H, Tol- CH_3); ^{13}C NMR (101 MHz, CDCl_3) δ 160.6 (C=N), 141.7 (SOTol-C quat.), 141.6

(SOTol-C quat.), 133.8 (Ph-C quat.), 132.5 (Ph-C), 129.8 (2 × SOTol-C), 129.5 (2 × Ph-C), 128.8 (2 × SOTol-C), 124.7 (2 × Ph-C), 21.4 (CH₃). Observed data was consistent with that reported in the literature.²⁴⁴



(R)-(+)-2-Methyl-N-(phenylmethyldiene)propane-2-sulfinamide (28). Ti(OEt)₄ (2.05 g, 9.0 mmol, 3.0 equiv.), benzaldehyde (306 μL, 3.0 mmol, 1.0 equiv) and (R)-(+)-2-methyl-2-propanesulfinamide (364 mg, 3.0 mmol, 1.0 equiv) were sequentially added to THF (6 mL). The reaction was stirred at rt for 24 h, after which brine (6 mL) was added, whilst stirring vigorously. The resulting suspension was filtered through Celite and the filter cake was washed with EtOAc (100 mL). The filtrate was transferred to a separating funnel, water (10 mL) was added and the aqueous layer was extracted with EtOAc (3 × 30 mL). The organic layers were washed with brine (50 mL), dried (Na₂SO₄) and the solvent was removed under reduced pressure affording sulfinylimine **28** (625 mg, 99%) as a colorless oil, which was used without further purification: *R_f* = 0.29 (25% EtOAc/hexane); *v*_{max} (film)/cm⁻¹ 3063, 2961, 2925, 2868, 1606, 1573, 1450, 1363, 1216, 1171, 1084, 1026, 855, 759, 729, 691; ¹H NMR (400 MHz, CDCl₃) δ 8.60 (s, 1H, CHN), 7.89–7.84 (m, 2H, 2 × Ph-H), 7.56–7.45 (m, 3H, 3 × Ph-H), 1.28 (s, 9H, C(CH₃)₃); ¹³C NMR (101 MHz, CDCl₃) δ 162.7 (C=N), 134.0 (Ph-C quat.), 132.4 (Ph-C), 129.4 (2 × Ph-C), 128.9 (2 × Ph-C), 57.8 (C(CH₃)₃ quat.), 22.6 (C(CH₃)₃). Observed data was consistent with that reported in the literature.²⁴⁵



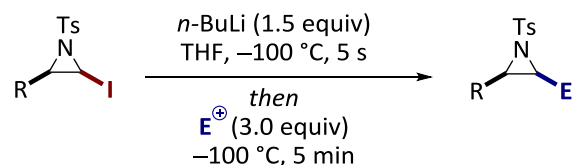
(2R,3S)-2-Iodo-1-[(R)-2-methylpropane-2-sulfinyl]-3-phenylaziridine (major, 29a) and (2S,3R)-2-Iodo-1-[(R)-2-methylpropane-2-sulfinyl]-3-phenylaziridine (minor, 29b). EtMgCl (2.0 M in THF, 0.75 mL, 1.50 mmol, 3.0 equiv) was added dropwise over 2 minutes to a solution of iodoform

(591 mg, 1.50 mmol, 3.0 equiv) in THF (6 mL) at –78 °C in the dark. After 10 minutes at –78 °C, a solution of imine **28** (175 mg, 0.50 mmol, 1.0 equiv) in THF (1.5 mL) was added dropwise over 3 minutes. The reaction was left for 10 minutes at –78 °C and then warmed to 0 °C in an ice/water bath. After 15 minutes at 0 °C, the reaction was quenched by the addition of saturated aqueous sodium bicarbonate solution (20 mL). The aqueous solution was extracted with CH₂Cl₂ (3 × 30 mL) and the organic extracts were combined, dried (Na₂SO₄), filtered and solvent removed under reduced pressure. Purification by flash chromatography (silica, hexane to 10% EtOAc/hexane) afforded a mixture of *cis*-iodoaziridines (71:29 major:minor) **29a** and **29b** (101 mg, 58%) as a yellow oil: *R_f* = 0.36 (25% EtOAc/hexane); *v*_{max} (film)/cm⁻¹ 2960, 2867, 1605, 1495, 1475, 1454, 1363, 1312, 1238, 1170, 1080, 1026, 906, 847, 817, 791, 758, 699, 676; **major:** ¹H NMR (400 MHz, CDCl₃) δ 7.43–7.33 (m, 5H, 5 × Ph-H), 4.54 (d, *J* = 6.0 Hz, 1H, CHI), 3.71 (d, *J* = 6.0 Hz, 1H, CHPh), 1.20 (s, 9H,

$C(CH_3)_3$; ^{13}C NMR (101 MHz, $CDCl_3$) δ 133.8 (Ph-C quat.), 128.5 (Ph-C), 128.2 (2 $\times$ Ph-C), 128.1 (2 $\times$ Ph-C), 57.5 (CHPh), 35.4 ($C(CH_3)_3$), 22.6 ($C(CH_3)_3$), 17.8 (CHI); minor: 1H NMR (400 MHz, $CDCl_3$) δ 7.43–7.33 (m, 5H, 5 $\times$ Ph-H), 4.83 (d, J = 5.9 Hz, 1H, CHI), 3.30 (d, J = 5.9 Hz, 1H, CHPh), 1.41 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 134.7 (Ph-C quat.), 128.4 (Ph-C), 128.0 (2 $\times$ Ph-C), 127.7 (2 $\times$ Ph-C), 58.6 (CHPh), 38.6 ($C(CH_3)_3$), 23.3 ($C(CH_3)_3$), 15.4 (CHI); HRMS (ESI $^+$) m/z Calculated for $C_{12}H_{17}INOS^+$ [M+H] $^+$ 350.0070; Found 350.0078.

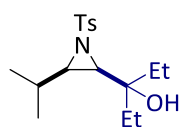
Functionalisation of the Intact Iodoaziridine – Iodine–Lithium Exchange (Section 2.3)

General Procedure For Iodine–Lithium Exchange & Trapping, General Procedure 9: Separate



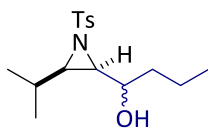
syringes containing the appropriate iodoaziridine (0.27 mmol, 1.0 equiv) in THF (0.5 mL) and electrophile (0.81 mmol, 3.0 equiv) were inserted into a 25 mL round bottom flask containing THF

(6.0 mL) at rt. The flask was cooled to $-100\text{ }^{\circ}\text{C}$ in a liquid $\text{N}_2/\text{Et}_2\text{O}$ bath (**external bath temperature**), and then $n\text{-BuLi}$ (0.41 mmol, 1.5 equiv) was added in one portion. The resulting solution was further cooled to $-102\text{ }^{\circ}\text{C}$ (**external bath temperature**) for a further 3 minutes. The aziridine solution was then added dropwise down the side of the flask over 30 s, maintaining the **external** bath temperature at $-102\text{ }^{\circ}\text{C}$. After 5 s, the electrophile was added in one portion and the bath was warmed to $-100\text{ }^{\circ}\text{C}$. After 5 minutes at $-100\text{ }^{\circ}\text{C}$, the reaction was quenched by the addition of saturated aqueous sodium bicarbonate solution (10 mL), then removed from the bath. Once at rt, the aqueous solution was extracted with CH_2Cl_2 ($3 \times 20\text{ mL}$) and the organic extracts were combined, dried (Na_2SO_4), filtered and solvent was removed under reduced pressure. Purification by flash chromatography afforded the appropriate *cis*-aziridine.



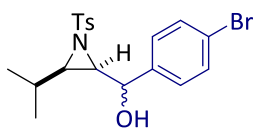
3-[*cis*-(±)-1-(4-Tolylsulfonyl)-3-(propan-2-yl)aziridin-2-yl]pentan-3-ol (**35a**).

Prepared according to **General Procedure 9** described above, starting from iodoaziridine **20j** (100 mg, 0.27 mmol) and 3-pentanone (86 μL , 0.81 mmol, 3.0 equiv). Purification by flash chromatography (30% diethyl ether/hexane) afforded *cis*-aziridine **35a** (71 mg, 81%) as a white solid: mp = $80\text{--}81\text{ }^{\circ}\text{C}$; R_f = 0.17 (30% diethyl ether/hexane); ν_{max} (film)/ cm^{-1} 3528 (br, OH), 2968, 2882, 1599, 1461, 1322, 1157, 1090, 949, 877, 776, 719, 669; ^1H NMR (400 MHz, CDCl_3) δ 7.84 (d, J = 8.3 Hz, 2H, $2 \times \text{SO}_2\text{Tol-H}$), 7.35 (d, J = 8.1 Hz, 2H, $2 \times \text{SO}_2\text{Tol-H}$), 2.88 (d, J = 7.2 Hz, 1H, CHCOH), 2.46 (s, 3H, $\text{SO}_2\text{Tol-CH}_3$), 2.43 (dd, J = 7.2, 10.2 Hz, 1H, CHN), 2.22–2.12 (m, 1H, CHH), 1.73–1.61 (m, 2H, CHH and OH), 1.58–1.46 (m, 3H, CH_2 and CH), 0.99–0.91 (m, 6H, CHCH_3 and CH_2CH_3), 0.87 (t, J = 7.5 Hz, 3H, CH_2CH_3), 0.63 (d, J = 6.7 Hz, 3H, CHCH_3); ^{13}C NMR (101 MHz, CDCl_3) δ 144.7 ($\text{SO}_2\text{Tol-C quat.}$), 134.6 ($\text{SO}_2\text{TolC-CH}_3\text{ quat.}$), 129.6 ($2 \times \text{SO}_2\text{Tol-C}$), 128.4 ($2 \times \text{SO}_2\text{Tol-C}$), 72.5 (C-OH quat.), 52.7 (NCHCOH), 50.4 (CHN), 32.1 (CH), 27.6 (CH_2), 25.1 (CH_2), 21.7 ($\text{SO}_2\text{Tol-CH}_3$), 21.3 (CHCH_3), 20.3 (CHCH_3), 7.8 (CH_2CH_3), 7.4 (CH_2CH_3); HRMS (ESI^+) m/z Calculated for $\text{C}_{17}\text{H}_{28}\text{NO}_3\text{S}^+$ $[\text{M}+\text{H}]^+$ 326.1784; Found: 326.1790.



1-[*cis*-(±)-1-(4-Tolylsulfonyl)-3-(propan-2-yl)aziridin-2-yl]butan-1-ol (35b).

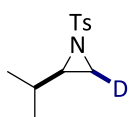
Prepared according to **General Procedure 9** described above, starting from iodoaziridine **20j** (100 mg, 0.27 mmol) and butyraldehyde (73 μ L, 0.81 mmol, 3.0 equiv). Purification by flash chromatography (30% diethyl ether/hexane) afforded a mixture of *cis*-aziridines **35b** (71 mg, 85%) as colourless oils (major = 54 mg, minor: major (3.2:1) = 17 mg): **major**: R_f = 0.14 (40% diethyl ether/hexane); $\nu_{\max}$ (film)/ cm^{-1} 3520 (br, OH), 2961, 2932, 2873, 1599, 1466, 1323, 1244, 1157 1091, 966, 949, 887, 812, 757, 675; ^1H NMR (400 MHz, CDCl_3) δ 7.85 (d, J = 8.3 Hz, 2H, 2 $\times$ $\text{SO}_2\text{Tol-H}$), 7.35 (d, J = 8.3 Hz, 2H, 2 $\times$ $\text{SO}_2\text{Tol-H}$), 3.48 (ddd, J = 3.5, 8.2, 8.2 Hz, 1H, CHOH), 2.85 (dd, J = 7.3, 7.3 Hz, 1H, NCHCHOH), 2.57 (dd, J = 7.3, 10.2 Hz, 1H, CHN), 2.45 (s, 3H, $\text{SO}_2\text{Tol-CH}_3$), 1.64 (br s, 1H, OH), 1.61–1.34 (m, 5H, 2 $\times$ CH_2 and CH), 0.95 (d, J = 6.7 Hz, 3H, CH_3), 0.92 (t, J = 7.1 Hz, 3H, CH_3), 0.84 (d, J = 6.7 Hz, 3H, CH_3); ^{13}C NMR (101 MHz, CDCl_3) δ 144.7 ($\text{SO}_2\text{Tol-C quat.}$), 134.5 ($\text{SO}_2\text{TolC-CH}_3$ quat.), 129.7 (2 $\times$ $\text{SO}_2\text{Tol-C}$), 128.3 (2 $\times$ $\text{SO}_2\text{Tol-C}$), 67.9 (CHOH), 52.0 (CHN), 50.0 (NCHCOH), 37.1 (CH_2), 26.8 (CH), 21.7 ($\text{SO}_2\text{Tol-CH}_3$), 21.2 (CH_3), 19.6 (CH_3), 18.4 (CH_2), 13.9 (CH_2CH_3); **minor**: R_f = 0.11 (40% diethyl ether/hexane); $\nu_{\max}$ (film)/ cm^{-1} 3509 (br, OH), 2961, 2932, 2873, 1599, 1466, 1323, 1159, 1091, 1004, 961, 813, 755, 674; ^1H NMR (400 MHz, CDCl_3) δ 7.83 (d, J = 8.3 Hz, 2H, 2 $\times$ $\text{SO}_2\text{Tol-H}$), 7.34 (d, J = 8.3 Hz, 2H, 2 $\times$ $\text{SO}_2\text{Tol-H}$), 3.52–3.45 (m, 1H, CHOH), 2.77 (dd, J = 7.2, 7.3 Hz, 1H, NCHCHOH), 2.52 (dd, J = 7.2, 10.1 Hz, 1H, CHN), 2.45 (s, 3H, $\text{SO}_2\text{Tol-CH}_3$), 1.60 (br s, 1H, OH), 1.65–1.25 (m, 5H, 2 $\times$ CH_2 and CH), 1.03 (d, J = 6.8 Hz, 3H, CH_3), 0.85 (t, J = 7.2 Hz, 3H, CH_3), 0.81 (d, J = 6.7 Hz, 3H, CH_3); ^{13}C NMR (101 MHz, CDCl_3) δ 144.6 ($\text{SO}_2\text{Tol-C quat.}$), 134.7 ($\text{SO}_2\text{TolC-CH}_3$ quat.), 129.5 (2 $\times$ $\text{SO}_2\text{Tol-C}$), 128.4 (2 $\times$ $\text{SO}_2\text{Tol-C}$), 68.8 (CHOH), 51.6 (CHN), 47.8 (NCHCOH), 37.9 (CH_2), 26.6 (CH), 21.6 ($\text{SO}_2\text{Tol-CH}_3$), 21.1 (CH_3), 19.7 (CH_3), 18.3 (CH_2), 13.9 (CH_2CH_3); HRMS (ESI^+) m/z Calculated for $\text{C}_{16}\text{H}_{26}\text{NO}_3\text{S}^+$ $[\text{M}+\text{H}]^+$ 312.1628; Found: 312.1636.



(4-Bromophenyl)[*cis*-(±)-1-(4-tolylsulfonyl)-3-(propan-2-yl)aziridin-2-yl]

methanol (35c). Prepared according to **General Procedure 9** described above, starting from iodoaziridine **20j** (100 mg, 0.27 mmol) and 4-bromobenzaldehyde (150 mg, 0.81 mmol, 3.0 equiv). 4-Bromobenzaldehyde dissolved in THF (0.5 mL) prior to addition. Purification by flash chromatography (40% diethyl ether/hexane) afforded a mixture of *cis*-aziridines (1.1:1 major:minor) **35c** (96 mg, 83%) as a white solid: mp = 39–40 $^{\circ}\text{C}$; $\nu_{\max}$ (film)/ cm^{-1} 3479 (br, OH), 2963, 2928, 2871, 1598, 1488, 1467, 1405, 1321, 1248, 1157, 1090, 1042, 1010, 969, 888, 812, 731, 673; **major**: R_f = 0.14 (40% diethyl ether/hexane); ^1H NMR (400 MHz, CDCl_3) δ 7.40 (d, J = 8.3 Hz, 2H, 2 $\times$ $\text{SO}_2\text{Tol-H}$), 7.17 (d, J = 8.3 Hz, 2H, 2 $\times$ BrAr-H), 7.09 (d, J = 8.2 Hz, 2H, 2 $\times$ $\text{SO}_2\text{Tol-H}$), 6.98 (d, J = 8.3 Hz, 2H, 2 $\times$ BrAr-H), 4.37 (d, J = 8.7 Hz, 1H, CHOH), 2.92 (dd, J = 7.0, 8.7 Hz, 1H, NCHCHOH), 2.74 (dd, J = 7.0, 10.0 Hz, 1H, CHN), 2.46 (s, 3H, $\text{SO}_2\text{Tol-CH}_3$), 2.10 (br s, 1H,

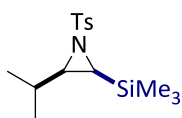
OH), 1.79–1.70 (m, 1H, CH), 1.13–1.10 (m, 6H, 2 × CH₃); ¹³C NMR (101 MHz, CDCl₃) δ 144.4 (SO₂Tol-C quat.), 140.6 (BrAr-C quat.), 134.4 (SO₂TolC-CH₃ quat.), 131.2 (2 × BrAr-C), 129.3 (2 × SO₂Tol-C), 127.7 (2 × SO₂Tol-C), 127.5 (2 × BrAr-C), 121.8 (BrAr-C quat.), 70.5 (CHOH), 50.3 (NCHCHOH), 50.2 (CHN), 26.9 (CH), 21.8 (SO₂Tol-CH₃), 21.3 (CH₃), 19.5 (CH₃); **minor**: *R*_f = 0.11 (40% diethyl ether/hexane); ¹H NMR (400 MHz, CDCl₃) δ 7.84 (d, *J* = 8.3 Hz, 2H, 2 × SO₂Tol-H), 7.49 (d, *J* = 8.4 Hz, 2H, 2 × BrAr-H), 7.35 (d, *J* = 8.1 Hz, 2H, 2 × SO₂Tol-H), 7.23 (d, *J* = 8.4 Hz, 2H, 2 × BrAr-H), 4.49 (d, *J* = 7.8 Hz, 1H, CHOH), 3.14 (dd, *J* = 7.5, 7.5 Hz, 1H, NCHCHOH), 2.55 (dd, *J* = 7.3, 10.2 Hz, 1H, CHN), 2.47 (s, 3H, SO₂Tol-CH₃), 2.47–2.36 (br s, 1H, OH), 1.71–1.61 (m, 1H, CH), 0.82–0.78 (m, 6H, 2 × CH₃); ¹³C NMR (101 MHz, CDCl₃) δ 144.9 (SO₂Tol-C quat.), 139.0 (BrAr-C quat.), 134.1 (SO₂TolC-CH₃ quat.), 131.8 (2 × BrAr-C), 129.7 (2 × SO₂Tol-C), 128.3 (2 × SO₂Tol-C and 2 × BrAr-C), 122.4 (BrAr-C quat.), 70.3 (CHOH), 52.0 (CHN), 50.0 (NCHCHOH), 26.9 (CH), 21.7 (SO₂Tol-CH₃), 21.0 (CH₃), 19.6 (CH₃); HRMS (ESI⁺) *m/z* Calculated for C₁₉H₂₃NO₃S⁷⁹Br⁺ [M+H]⁺ 424.0577; Found: 424.0585.



***cis*-(±)-1-(4-Tolylsulfonyl)-2-(propan-2-yl)-3-deutero-aziridine (35d).**

Prepared

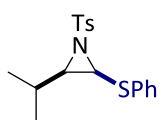
according to **General Procedure 9** described above, starting from iodoaziridine **20j** (100 mg, 0.27 mmol) and *d*₄-MeOD (55 μL, 1.35 mmol, 5.0 equiv). Purification by flash chromatography (20% diethyl ether/hexane) afforded *cis*-aziridine **35d** (60 mg, 92%, 95% D incorporation) as a white solid: mp = 60–62 °C; *R*_f = 0.26 (20% diethyl ether/hexane); *v*_{max} (film)/cm⁻¹ 2963, 2930, 2876, 1598, 1465, 1406, 1319, 1225, 1156, 1091, 1053, 970, 888, 814, 710, 690, 661; ¹H NMR (400 MHz, CDCl₃) δ 7.83 (d, *J* = 8.3 Hz, 2H, 2 × SO₂Tol-H), 7.33 (d, *J* = 8.2 Hz, 2H, 2 × SO₂Tol-H), 2.60 (d, *J* = 7.0 Hz, 1H, CHD), 2.50 (dd, *J* = 7.3, 7.3 Hz, CHN), 2.44 (s, 3H, SO₂Tol-CH₃), 1.45–1.36 (m, 1H, CH), 0.90 (d, *J* = 6.9 Hz, 3H, CH₃), 0.79 (d, *J* = 6.8 Hz, 3H, CH₃); ¹³C NMR (101 MHz, CDCl₃) δ 144.4 (SO₂Tol-C quat.), 135.1 (SO₂TolC-CH₃ quat.), 129.5 (2 × SO₂Tol-C), 128.0 (2 × SO₂Tol-C), 46.2 (CHN), 32.4 (t, *J* = 27.1 Hz, CHD), 30.1 (CH), 21.6 (SO₂Tol-CH₃), 19.5 (CH₃), 19.0 (CH₃); HRMS (ESI⁺) *m/z* Calculated for C₁₂H₁₇DNO₂S⁺ [M+H]⁺ 241.1116; Found: 241.1126.



***cis*-(±)-1-(4-Tolylsulfonyl)-2-(propan-2-yl)-3-(trimethylsilyl)aziridine (35e).**

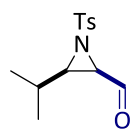
Prepared according to **General Procedure 9** described above, starting from iodoaziridine **20j** (100 mg, 0.27 mmol) and trimethylsilyl chloride (103 μL, 0.81 mmol, 3.0 equiv). Purification by flash chromatography (10% diethyl ether/hexane) afforded *cis*-aziridine **35e** (63 mg, 75%) as a colourless oil: *R*_f = 0.26 (20% diethyl ether/hexane); *v*_{max} (film)/cm⁻¹ 2961, 1599, 1324, 1251, 1157, 1091, 896, 842, 769, 730, 684, 665; ¹H NMR (400 MHz, CDCl₃) δ 7.82 (d, *J* = 8.3 Hz, 2H, 2 × SO₂Tol-H), 7.32 (d, *J* = 8.2 Hz, 2H, 2 × SO₂Tol-H), 2.53 (dd, *J* = 8.3, 10.0 Hz, 1H, CHN), 2.44 (s, 3H, SO₂Tol-CH₃), 1.94 (d, *J* = 8.3 Hz, 1H, CHSiMe₃), 1.36–1.26 (m, 1H, CH), 0.96 (d, *J* =

6.8 Hz, 3H, CH₃), 0.83 (d, *J* = 6.6 Hz, 3H, CH₃), -0.01 (s, 9H, SiMe₃); ¹³C NMR (101 MHz, CDCl₃) δ 144.1 (SO₂Tol-C quat.), 135.3 (SO₂TolC-CH₃ quat.), 129.4 (2 × SO₂Tol-C), 128.3 (2 × SO₂Tol-C), 51.5 (CHN), 36.6 (CHSiMe₃), 29.4 (CH), 21.6 (SO₂Tol-CH₃), 21.2 (CH₃), 19.7 (CH₃), -1.7 (SiCH₃)₃; HRMS (ESI⁺) *m/z* Calculated for C₁₅H₂₆NO₂SSi⁺ [M+H]⁺ 312.1448; Found: 312.1463.



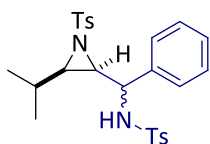
***cis*-(±)-1-(4-Tolylsulfonyl)-2-(phenylsulfonyl)-3-(propan-2-yl)aziridine (35f).** Prepared according to **General Procedure 9** described above, starting from iodoaziridine **20j** (100 mg, 0.27 mmol) and diphenyl disulfide (177 mg, 0.81 mmol, 3.0 equiv). Diphenyl

disulfide dissolved in THF (0.5 mL) prior to addition. Purification by flash chromatography (20% diethyl ether/hexane) afforded *cis*-aziridine **35f** (77 mg, 82%) as a colourless oil: *R_f* = 0.21 (20% diethyl ether/hexane); *v*_{max} (film)/cm⁻¹ 2963, 2874, 1598, 1482, 1441, 1402, 1327, 1292, 1232, 1159, 1090, 1025, 942, 896, 819, 766, 666; ¹H NMR (400 MHz, CDCl₃) δ 7.77 (d, *J* = 8.3 Hz, 2H, 2 × SO₂Tol-H), 7.42–7.38 (m, 2H, 2 × Ph-H), 7.29–7.27 (m, 5H, 2 × SO₂Tol-H and 3 × Ph-H), 4.20 (d, *J* = 7.0 Hz, 1H, CHSPh), 2.76 (dd, *J* = 7.0, 10.0 Hz, 1H, CHN), 2.45 (s, 3H, SO₂Tol-CH₃), 1.79–1.69 (m, 1H, CH), 1.03 (d, *J* = 6.8 Hz, 3H, CH₃), 0.89 (d, *J* = 6.7 Hz, 3H, CH₃); ¹³C NMR (101 MHz, CDCl₃) δ 144.6 (SO₂Tol-C quat.), 134.6 (SO₂TolC-CH₃ quat.), 132.6 (Ph-C quat.), 131.3 (2 × Ph-C), 129.6 (2 × SO₂Tol-C), 129.1 (2 × Ph-C), 128.2 (2 × SO₂Tol-C), 127.5 (Ph-C), 51.8 (CHSPh), 50.8 (CHN), 28.2 (CH), 21.6 (SO₂Tol-CH₃), 20.6 (CH₃), 19.3 (CH₃); HRMS (ESI⁺) *m/z* Calculated for C₁₈H₂₂NO₂S₂⁺ [M+H]⁺ 348.1086; Found: 348.1098.



***cis*-(±)-1-(4-Tolylsulfonyl)-3-(propan-2-yl)aziridine-2-carbaldehyde (35g).** Prepared according to **General Procedure 9** described above, starting from iodoaziridine **20j** (100 mg, 0.27 mmol) and dimethylformamide (62 μL, 0.81 mmol, 3.0 equiv). Purification by

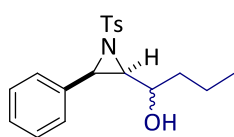
flash chromatography (40% diethyl ether/hexane) afforded *cis*-aziridine **35g** (52 mg, 73%) as a white solid: mp = 99–100 °C (lit.²⁴⁶ = 88–92 °C); *R_f* = 0.09 (40% diethyl ether/hexane); *v*_{max} (film)/cm⁻¹ 2964, 2875, 1720 (C=O), 1598, 1468, 1330, 1160, 1091, 1003, 942, 878, 815, 733, 674; ¹H NMR (400 MHz, CDCl₃) δ 9.31 (d, *J* = 5.1 Hz, 1H, CHO), 7.85 (d, *J* = 8.3 Hz, 2H, 2 × SO₂Tol-H), 7.37 (d, *J* = 8.1 Hz, 2H, 2 × SO₂Tol-H), 3.30 (dd, *J* = 5.1, 7.6 Hz, 1H, NCHCHO), 2.76 (dd, *J* = 7.6, 10.1 Hz, 1H, CHN), 2.46 (s, 3H, SO₂Tol-CH₃), 1.65–1.56 (m, 1H, CH), 0.92 (d, *J* = 6.9 Hz, 3H, CH₃), 0.89 (d, *J* = 6.6 Hz, 3H, CH₃); ¹³C NMR (101 MHz, CDCl₃) δ 195.5 (CHO), 145.3 (SO₂Tol-C quat.), 134.8 (SO₂TolC-CH₃ quat.), 129.9 (2 × SO₂Tol-C), 128.3 (2 × SO₂Tol-C), 52.0 (CHN), 46.9 (NCHCHO), 27.8 (CH), 21.7 (SO₂Tol-CH₃), 20.9 (CH₃), 19.0 (CH₃); HRMS (ESI⁺) *m/z* Calculated for C₁₃H₁₈NO₃S⁺ [M+H]⁺ 268.1002; Found: 268.1017. Observed data was consistent with that found in the literature.²⁴⁶



***N*-{[(*cis*-±)-1-(4-tolylsulfonyl)-3-(propan-2-yl)aziridin-2-yl](phenyl)methyl}-(4-methylbenzene)-1-sulfonamide (**35h**).** Prepared according to **General**

Procedure 9 described above, starting from iodoaziridine **20j** (100 mg, 0.27

mmol) and imine **19a** (70 mg, 0.27 mmol, 1.0 equiv). Imine **19a** dissolved in THF (0.5 mL) prior to addition. Purification by flash chromatography (50% diethyl ether/hexane) afforded a mixture of *cis*-aziridines **35h** (108 mg, 80%) as white solids: **minor**: (25 mg, 18%); mp = 153–155 °C; R_f = 0.14 (50% diethyl ether/hexane); $\nu_{\max}$ (film)/cm⁻¹ 3295 (br, NH), 2963, 2932, 2876, 1599, 1496, 1456, 1325, 1247, 1158, 1091, 1056, 970, 915, 814, 746, 701, 675; ¹H NMR (400 MHz, CDCl₃) δ 7.83 (d, J = 8.3 Hz, 2H, 2 × SO₂Tol-H), 7.40–7.37 (m, 4H, 4 × SO₂Tol-H), 7.20–7.11 (m, 5H, 5 × Ph-H), 7.06 (d, J = 8.1 Hz, 2H, 2 × SO₂Tol-H), 5.03 (d, J = 3.3 Hz, NH), 4.19 (dd, J = 3.3, 8.5 Hz, 1H, CHPh), 3.05 (dd, J = 7.2, 8.5 Hz, 1H, NCHCHPh), 2.50 (s, 3H, SO₂Tol-CH₃), 2.47 (dd, J = 7.2, 10.3 Hz, 1H, CHN), 2.34 (s, 3H, SO₂Tol-CH₃), 1.54–1.47 (m, 1H, CH), 0.70 (d, J = 6.7 Hz, 3H, CH₃), 0.67 (d, J = 6.6 Hz, 3H, CH₃); ¹³C NMR (101 MHz, CDCl₃) δ 145.2 (SO₂Tol-C quat.), 142.9 (SO₂Tol-C quat.), 137.4 (SO₂TolC-CH₃ quat.), 137.2 (Ph-C quat.), 134.0 (SO₂TolC-CH₃ quat.), 129.8 (2 × SO₂Tol-C), 129.0 (2 × SO₂Tol-C), 128.5 (2 × SO₂Tol-C), 128.3 (2 × SO₂Tol-C), 128.2 (Ph-C), 127.7 (2 × Ph-C), 127.2 (2 × Ph-C), 55.9 (CHPh), 53.2 (CHN), 47.2 (NCHCHPh), 26.6 (CH), 21.7 (SO₂Tol-CH₃), 21.4 (SO₂Tol-CH₃), 20.9 (CH₃), 19.4 (CH₃); HRMS (ESI⁺) m/z Calculated for C₂₆H₃₁N₂O₄S₂⁺ [M+H]⁺ 499.1720; Found: 499.1721. **major**: (83 mg, 62%); mp = 159–160 °C; R_f = 0.22 (70% diethyl ether/hexane); $\nu_{\max}$ (film)/cm⁻¹ 3278 (br, NH), 3033, 2964, 2928, 2871, 1599, 1496, 1457, 1326, 1158, 1090, 974, 914, 886, 839, 809, 765, 743, 699, 675; ¹H NMR (400 MHz, CDCl₃) δ 7.34–7.31 (m, 4H, 4 × Ar-H), 6.95–6.92 (m, 5H, 5 × Ar-H), 6.82–6.78 (m, 2H, 2 × Ar-H), 6.73–6.71 (m, 2H, 2 × Ar-H), 5.71 (d, J = 8.8 Hz, 1H, NH), 4.13 (dd, J = 9.1, 9.1 Hz, CHPh), 2.99 (dd, J = 6.9, 9.1 Hz, 1H, NCHCHPh), 2.70 (dd, J = 6.9, 10.1 Hz, 1H, CHN), 2.31 (s, 3H, SO₂Tol-CH₃), 2.26 (s, 3H, SO₂Tol-CH₃), 1.79–1.70 (m, 1H, CH), 1.15 (d, J = 6.6 Hz, 3H, CH₃), 1.07 (d, J = 6.6 Hz, 3H, CH₃); ¹³C NMR (101 MHz, CDCl₃) δ 143.8 (SO₂Tol-C quat.), 143.0 (SO₂Tol-C quat.), 137.7 (Ph-C quat.), 137.0 (SO₂TolC-CH₃ quat.), 134.2 (SO₂TolC-CH₃ quat.), 129.2 (2 × SO₂Tol-C), 129.0 (2 × SO₂Tol-C), 128.1 (2 × SO₂Tol-C), 127.6 (2 × Ph-C), 127.0 (Ph-C), 126.8 (2 × Ph-C), 126.6 (2 × SO₂Tol-C), 56.1 (CHPh), 50.7 (CHN), 50.0 (NCHCHPh), 26.5 (CH), 21.5 (SO₂Tol-CH₃), 21.29 (CH₃), 21.26 (SO₂Tol-CH₃), 20.1 (CH₃); HRMS (ESI⁺) m/z Calculated for C₂₆H₃₁N₂O₄S₂⁺ [M+H]⁺ 499.1720; Found: 499.1732.

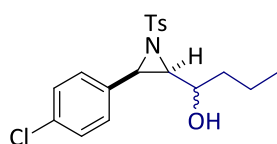


1-[(*cis*-±)-1-(4-Tolylsulfonyl)-3-phenylaziridin-2-yl]butan-1-ol (37**).** Prepared

according to **General Procedure 9** described above, starting from iodoaziridine **20a** (108 mg, 0.27 mmol) and butyraldehyde (73 μ L, 0.81 mmol, 3.0 equiv).

Purification by flash chromatography (40% diethyl ether/hexane) afforded a mixture of *cis*-aziridines **37** (69 mg, 74%) (major: 51 mg, minor: 18 mg) as colourless oils: **major**: R_f = 0.16 (50%

diethyl ether/hexane); $\nu_{\max}$ (film)/ cm^{-1} 3513 (br, OH), 2960, 2931, 2872, 1598, 1530, 1497, 1454, 1326, 1160, 1092, 911, 804, 772, 701, 677; ^1H NMR (400 MHz, CDCl_3) δ 7.91 (d, J = 8.3 Hz, 2H, 2 $\times$ $\text{SO}_2\text{Tol-H}$), 7.35 (d, J = 8.2 Hz, 2H, 2 $\times$ $\text{SO}_2\text{Tol-H}$), 7.31–7.23 (m, 5H, 5 $\times$ Ph-H), 4.04 (d, J = 6.9 Hz, CHPh), 3.13–3.03 (m, 2H, NCHCHOH and NCHCHOH), 2.44 (s, 3H, $\text{SO}_2\text{Tol-CH}_3$), 1.60 (br s, 1H, OH), 1.47–1.37 (m, 1H, CHH), 1.28–1.06 (m, 3H, CHH and CH_2), 0.63 (t, J = 7.2 Hz, 3H, CH_3); ^{13}C NMR (101 MHz, CDCl_3) δ 144.9 ($\text{SO}_2\text{Tol-C quat.}$), 134.4 ($\text{SO}_2\text{TolC-CH}_3$ quat.), 132.2 (Ph-C quat.), 129.8 (2 $\times$ $\text{SO}_2\text{Tol-C}$), 128.4 (2 $\times$ Ph-C), 128.07 (2 $\times$ $\text{SO}_2\text{Tol-C}$), 128.06 (Ph-C), 127.1 (2 $\times$ Ph-C), 67.9 (CHOH), 50.8 (NCHCHOH), 45.7 (CHPh), 35.6 (CH_2), 21.7 ($\text{SO}_2\text{Tol-CH}_3$), 17.8 (CH_2), 13.6 (CH_3). **minor:** R_f = 0.14 (50% diethyl ether/hexane); $\nu_{\max}$ (film)/ cm^{-1} 3511 (br, OH), 2959, 2931, 2872, 1598, 1453, 1326, 1159, 1091, 1006, 916, 813, 768, 700, 676; ^1H NMR (400 MHz, CDCl_3) δ 7.90 (d, J = 8.3 Hz, 2H, 2 $\times$ $\text{SO}_2\text{Tol-H}$), 7.36 (d, J = 8.2 Hz, 2H, 2 $\times$ $\text{SO}_2\text{Tol-H}$), 7.33–7.23 (m, 5H, 5 $\times$ Ph-H), 4.02 (d, J = 7.0 Hz, CHPh), 3.13–2.98 (m, 2H, NCHCHOH and NCHCHOH), 2.46 (s, 3H, $\text{SO}_2\text{Tol-CH}_3$), 1.57 (br s, 1H, OH), 1.42–1.12 (m, 4H, 2 $\times$ CH_2), 0.79 (t, J = 6.9 Hz, 3H, CH_3); ^{13}C NMR (101 MHz, CDCl_3) δ 144.8 ($\text{SO}_2\text{Tol-C quat.}$), 134.5 ($\text{SO}_2\text{TolC-CH}_3$ quat.), 132.4 (Ph-C quat.), 129.7 (2 $\times$ $\text{SO}_2\text{Tol-C}$), 128.6 (2 $\times$ Ph-C), 128.2 (2 $\times$ $\text{SO}_2\text{Tol-C}$), 128.1 (Ph-C), 127.3 (2 $\times$ Ph-C), 68.1 (CHOH), 48.6 (NCHCHOH), 45.2 (CHPh), 37.2 (CH_2), 21.7 ($\text{SO}_2\text{Tol-CH}_3$), 18.1 (CH_2), 13.9 (CH_3); HRMS (ESI $^+$) m/z Calculated for $\text{C}_{19}\text{H}_{24}\text{NO}_3\text{S}^+$ $[\text{M}+\text{H}]^+$ 346.1471; Found: 346.1460.

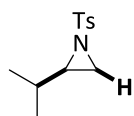


1-[cis-(±)-1-(4-Tolylsulfonyl)-3-(4-chlorobenzene)aziridin-2-yl]butan-1-ol

(38). Prepared according to **General Procedure 9** described above, starting

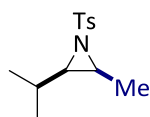
from iodoaziridine **20f** (117 mg, 0.27 mmol) and butyraldehyde (73 μL , 0.81 mmol, 3.0 equiv). Purification by flash chromatography (40% diethyl ether/hexane) afforded a mixture of *cis*-aziridines **38** (70 mg, 68%) (major: 51 mg, minor: 19 mg) as colourless oils: **major:** R_f = 0.17 (50% diethyl ether/hexane); $\nu_{\max}$ (film)/ cm^{-1} 3518 (br, OH), 2960, 2932, 2872, 1598, 1494, 1325, 1160, 1090, 1014, 913, 834, 795, 763, 679; ^1H NMR (400 MHz, CDCl_3) δ 7.91 (d, J = 8.3 Hz, 2H, 2 $\times$ $\text{SO}_2\text{Tol-H}$), 7.36 (d, J = 8.2 Hz, 2H, 2 $\times$ $\text{SO}_2\text{Tol-H}$), 7.27 (d, J = 8.4 Hz, 2H, 2 $\times$ ClAr-H), 7.19 (d, J = 8.4 Hz, 2H, 2 $\times$ ClAr-H), 4.00 (d, J = 6.6 Hz, 1H, CHAr), 3.10–3.03 (m, 2H, NCHCHOH and NCHCHOH), 2.45 (s, 3H, $\text{SO}_2\text{Tol-CH}_3$), 1.63 (br s, 1H, OH), 1.47–1.38 (m, 1H, CHH), 1.28–1.09 (m, 3H, CHH and CH_2), 0.68 (t, J = 7.2 Hz, 3H, CH_3); ^{13}C NMR (101 MHz, CDCl_3) δ 145.1 ($\text{SO}_2\text{Tol-C quat.}$), 134.3 ($\text{SO}_2\text{TolC-CH}_3$ quat.), 134.0 (ClAr-C quat.), 130.9 (ClAr-C quat.), 129.9 (2 $\times$ $\text{SO}_2\text{Tol-C}$), 128.6 (2 $\times$ ClAr-C), 128.5 (2 $\times$ ClAr-C), 128.1 (2 $\times$ $\text{SO}_2\text{Tol-C}$), 67.9 (CHOH), 50.8 (NCHCHOH), 45.0 (CHAr), 35.7 (CH_2), 21.7 ($\text{SO}_2\text{Tol-CH}_3$), 17.9 (CH_2), 13.6 (CH_3); **minor:** R_f = 0.13 (50% diethyl ether/hexane); $\nu_{\max}$ (film)/ cm^{-1} 3517 (br, OH), 2959, 2873, 1598, 1494, 1328, 1161, 1090, 1009, 919, 803, 759, 686; ^1H NMR (400 MHz, CDCl_3) δ 7.88 (d, J = 8.3 Hz, 2H, 2 $\times$ $\text{SO}_2\text{Tol-H}$), 7.36 (d, J = 8.2 Hz, 2H, 2 $\times$ $\text{SO}_2\text{Tol-H}$),

7.30–7.27 (m, 2H, 2 × ClAr-H), 7.23 (d, J = 8.5 Hz, 2H, 2 × ClAr-H), 3.97 (d, J = 6.9 Hz, 1H, CHAr), 3.09–2.97 (m, 2H, NCHCHOH and NCHCHOH), 2.46 (s, 3H, SO₂Tol-CH₃), 1.58 (br s, 1H, OH), 1.40–1.32 (m, 2H, CH₂), 1.26–1.18 (m, 2H, CH₂), 0.79 (t, J = 6.9 Hz, 3H, CH₃); ¹³C NMR (101 MHz, CDCl₃) δ 145.0 (SO₂Tol-C quat.), 134.3 (SO₂TolC-CH₃ quat.), 134.1 (ClAr-C quat.), 131.0 (ClAr-C quat.), 129.8 (2 × SO₂Tol-C), 128.8 (4 × ClAr-C), 128.2 (2 × SO₂Tol-C), 68.0 (CHOH), 48.6 (NCHCHOH), 44.5 (CHAr), 37.3 (CH₂), 21.7 (SO₂Tol-CH₃), 18.0 (CH₂), 13.8 (CH₃); HRMS (ESI⁺) m/z Calculated for C₁₉H₂₃ClNO₃S⁺ [M+H]⁺ 380.1082; Found: 380.1063.



1-(4-Tolylsulfonyl)-2-(propan-2-yl)aziridine (36). A syringe containing iodoaziridine **20j**

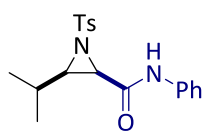
(100 mg, 0.27 mmol, 1.0 equiv) in THF (0.5 mL) was inserted into a 25 mL round bottom flask containing THF (3.0 mL) at rt. The flask was cooled to –100 °C in a liquid N₂/Et₂O bath (external bath temperature), and then *n*-BuLi (0.41 mmol, 1.5 equiv) was added in one portion. The resulting solution was further cooled to –102 °C (external bath temperature) for a further 3 minutes. The aziridine solution was then added dropwise down the side of the flask over 30 s, maintaining the external bath temperature at –102 °C, and then the bath was warmed to –100 °C. After 5 minutes at –100 °C, the reaction was quenched by the addition of saturated aqueous sodium bicarbonate solution (10 mL), then removed from the bath. Once at rt, the aqueous solution was extracted with CH₂Cl₂ (3 × 20 mL) and the organic extracts were combined, dried (Na₂SO₄), filtered and solvent removed under reduced pressure. Purification by flash chromatography (30% diethyl ether/hexane) afforded aziridine **36** (56 mg, 86%) as a white solid: mp = 66–68 °C (lit.²⁴⁷ = 85–86 °C); R_f = 0.24 (30% diethyl ether/hexane); $\nu_{\max}$ (film)/cm^{–1} 2965, 1598, 1467, 1323, 1161, 1091, 940, 890, 816, 723, 671; ¹H NMR (400 MHz, CDCl₃) δ 7.84 (d, J = 8.3 Hz, 2H, 2 × SO₂Tol-H), 7.34 (d, J = 8.1 Hz, 2H, 2 × SO₂Tol-H), 2.63 (d, J = 7.1 Hz, 1H, CHH), 2.55–2.49 (m, 1H, CHN), 2.45 (s, 3H, SO₂Tol-CH₃), 2.12 (d, J = 4.6 Hz, 1H, CHH), 1.46–1.36 (m, 1H, CH), 0.91 (d, J = 6.8 Hz, 3H, CH₃), 0.80 (d, J = 6.7 Hz, 3H, CH₃); ¹³C NMR (101 MHz, CDCl₃) δ 144.4 (SO₂Tol-C quat.), 135.1 (SO₂TolC-CH₃ quat.), 129.6 (2 × SO₂Tol-C), 128.1 (2 × SO₂Tol-C), 46.3 (CHN), 32.7 (CHH), 30.1 (CH), 21.6 (SO₂Tol-CH₃), 19.6 (CH₃), 19.0 (CH₃). Observed data (¹H NMR and ¹³C NMR) consistent with that found in the literature.²⁴⁷



***cis*-(±)-2-Methyl-1-(4-tolylsulfonyl)-3-(propan-2-yl)aziridine (39).** Prepared according

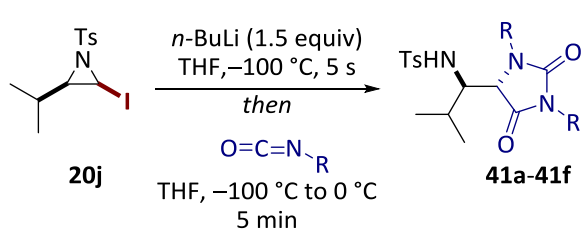
to a modification of **General Procedure 9** described above: Separate syringes containing iodoaziridine **20j** (100 mg, 0.27 mmol, 1.0 equiv) in THF (0.5 mL) and MeI (84 μL, 1.35 mmol, 5.0 equiv) were inserted into a 25 mL round bottom flask containing THF (6.0 mL) at rt. The flask was cooled to –100 °C in a liquid N₂/Et₂O bath (external bath temperature), and then *n*-BuLi (0.41 mmol, 1.5 equiv) was added in one portion. The resulting solution was further cooled to

–102 °C (external bath temperature) for a further 3 minutes. The aziridine solution was then added dropwise down the side of the flask over 30 s, maintaining the external bath temperature at –102 °C. After 5 s, MeI was added in one portion and the bath was warmed to –90 °C (external bath temperature), stirring the bath until it reached this temperature. After 5 minutes at –90 °C, the reaction was quenched by the addition of saturated aqueous sodium bicarbonate solution (10 mL), then removed from the bath. Once at rt, the aqueous solution was extracted with CH₂Cl₂ (3 × 20 mL) and the organic extracts were combined, dried (Na₂SO₄), filtered and solvent removed under reduced pressure. Purification by flash chromatography (10% diethyl ether/hexane) afforded a 5.1:1 mixture of *cis*-aziridine **39** (43 mg, 63%) and unsubstituted aziridine **36** (8 mg, 13%) as a white solid: mp = 74–75 °C (lit.²⁴⁸ = 78 °C); *R*_f = 0.15 (20% diethyl ether/hexane); *v*_{max} (film)/cm^{–1} 2962, 2932, 2874, 1598, 1469, 1321, 1305, 1250, 1155, 1091, 1045, 986, 943, 867, 813; ¹H NMR (400 MHz, CDCl₃) δ 7.82 (d, *J* = 8.2 Hz, 2H, 2 × SO₂Tol-H), 7.33 (d, *J* = 8.1 Hz, 2H, 2 × SO₂Tol-H), 2.97–2.91 (m, 1H, NCHCH₃), 2.44 (s, 3H, SO₂Tol-CH₃), 2.42 (dd, *J* = 7.4, 10.1 Hz, 1H, CHN), 1.49–1.38 (m, 1H, CH), 1.23 (d, *J* = 5.9 Hz, 3H, NCHCH₃), 0.92 (d, *J* = 6.8 Hz, 3H, CH₃), 0.78 (d, *J* = 6.6 Hz, 3H, CH₃); ¹³C NMR (101 MHz, CDCl₃) δ 144.1 (SO₂Tol-C quat.), 135.4 (SO₂TolC-CH₃ quat.), 129.5 (2 × SO₂Tol-C), 128.0 (2 × SO₂Tol-C), 51.5 (CHN), 40.3 (NCHCH₃), 26.4 (CH), 21.6 (SO₂Tol-CH₃), 20.8 (CH₃), 19.2 (CH₃), 12.0 (NCHCH₃); HRMS (ESI⁺) *m/z* Calculated for C₁₃H₂₀NO₂S⁺ [M+H]⁺ 254.1209; Found: 254.1212. Observed data was consistent with that found in the literature.²⁴⁸



***cis*-(±)-1-(4-Tolylsulfonyl)-*N*-phenyl-3-(propan-2-yl)aziridine-2-carboxamide**

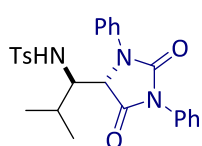
(40a). Prepared according to **General Procedure 9** described above, starting from iodoaziridine **20j** (100 mg, 0.27 mmol) and phenyl isocyanate (81 μL, 0.81 mmol, 3.0 equiv). Purification by flash chromatography (30% diethyl ether/hexane) afforded *cis*-aziridine **40a** (63 mg, 65%) as a white solid: mp = 132–134 °C; *R*_f = 0.17 (40% diethyl ether/hexane); *v*_{max} (film)/cm^{–1} 3329 (br, NH), 2964, 2873, 1679 (C=O), 1598, 1528, 1444, 1328, 1253, 1159, 1090, 1040, 948, 909, 885, 834, 815, 753, 679; ¹H NMR (400 MHz, CDCl₃) δ 7.89–7.87 (m, 3H, 2 × SO₂Tol-H and NH), 7.45 (d, *J* = 8.1 Hz, 2H, 2 × Ph-H), 7.41 (d, *J* = 8.1 Hz, 2H, 2 × SO₂Tol-H), 7.34–7.30 (m, 2H, 2 × Ph-H), 7.14 (t, *J* = 7.4 Hz, 1H, Ph-H), 3.52 (d, *J* = 7.8 Hz, 1H, CHCO), 2.70 (dd, *J* = 7.8, 10.1 Hz, 1H, CHN), 2.48 (s, 3H, SO₂Tol-CH₃), 1.48–1.39 (m, 1H, CH), 0.98 (d, *J* = 6.8 Hz, 3H, CH₃), 0.87 (d, *J* = 6.6 Hz, 3H, CH₃); ¹³C NMR (101 MHz, CDCl₃) δ 162.7 (C=O quat.), 145.6 (SO₂Tol-C quat.), 136.4 (Ph-C quat.), 133.3 (SO₂TolC-CH₃ quat.), 130.0 (2 × SO₂Tol-C), 129.0 (2 × Ph-C), 128.3 (2 × SO₂Tol-C), 124.5 (Ph-C), 119.9 (2 × Ph-C), 52.1 (CHN), 44.3 (CHCO), 27.9 (CH), 21.7 (SO₂Tol-CH₃), 20.7 (CH₃), 18.9 (CH₃); HRMS (ESI⁺) *m/z* Calculated for C₁₉H₂₃N₂O₃S⁺ [M+H]⁺ 359.1424; Found: 359.1429.



Synthesis of 1,3,5-Trisubstituted Hydantoins,

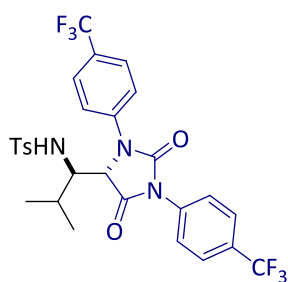
General Procedure 10: Separate syringes containing iodoaziridine **20j** (100 mg, 0.27 mmol, 1.0 equiv) in THF (0.5 mL) and the appropriate isocyanate (0.81 mmol, 3.0 equiv) were inserted

into a 25 mL round bottom flask containing THF (6.0 mL) at rt. The flask was cooled to $-100\text{ }^{\circ}\text{C}$ in a liquid $\text{N}_2/\text{Et}_2\text{O}$ bath (external bath temperature), and then $n\text{-BuLi}$ (0.41 mmol, 1.5 equiv) was added in one portion. The resulting solution was further cooled to $-102\text{ }^{\circ}\text{C}$ (external bath temperature) for a further 3 minutes. The aziridine solution was then added dropwise down the side of the flask over 30 s, maintaining the external bath temperature at $-102\text{ }^{\circ}\text{C}$. After 5 s, the isocyanate was added in one portion and the bath was warmed to $0\text{ }^{\circ}\text{C}$ in an ice/water bath. After 5 minutes at $0\text{ }^{\circ}\text{C}$, the reaction was quenched by the addition of saturated aqueous sodium bicarbonate solution (10 mL). Once at rt, the aqueous solution was extracted with CH_2Cl_2 ($3 \times 20\text{ mL}$) and the organic extracts were combined, dried (Na_2SO_4), filtered and solvent removed under reduced pressure. Purification by flash chromatography afforded the appropriate 1,3,5-trisubstituted hydantoin.



(±)-N-[(1R)-1-[(4S)-2,5-Dioxo-1,3-diphenylimidazolidin-4-yl]-2-methylpropyl]-4-tolyl-1-sulfonamide (41a). Prepared according to **General Procedure 10** described above, starting from iodoaziridine **20j** (100 mg, 0.27 mmol) and phenyl

isocyanate (81 μL , 0.81 mmol, 3.0 equiv). Purification by flash chromatography (40% diethyl ether/hexane) afforded 1,3,5-trisubstituted hydantoin **41a** (110 mg, 85%) as a white solid: mp = $85\text{--}87\text{ }^{\circ}\text{C}$; R_f = 0.14 (50% diethyl ether/hexane); ν_{max} (film)/ cm^{-1} 3295 (br, NH), 2967, 1774 (C=O), 1714 (C=O), 1598, 1497, 1406, 1331, 1296, 1157, 1093, 911, 816, 759, 733, 692, 664; ^1H NMR (400 MHz, CDCl_3) δ 7.83 (d, J = 8.3 Hz, 2H, $2 \times \text{SO}_2\text{Tol-H}$), 7.51–7.27 (m, 12H, $2 \times \text{SO}_2\text{Tol-H}$ and $10 \times \text{Ph-H}$), 5.89 (d, J = 10.5 Hz, 1H, NH), 4.63 (d, J = 4.7 Hz, 1H, CHCO), 3.60 (ddd, J = 4.7, 9.4, 10.5 Hz, CHN), 2.46 (s, 3H, $\text{SO}_2\text{Tol-CH}_3$), 1.86–1.78 (m, 1H, CH), 0.79 (d, J = 6.8 Hz, 3H, CH_3), 0.73 (d, J = 6.8 Hz, 3H, CH_3); ^{13}C NMR (101 MHz, CDCl_3) δ 170.3 (C=O quat.), 152.9 (C=O quat.), 144.0 ($\text{SO}_2\text{Tol-C}$ quat.), 137.4 (Ph-C quat.), 134.4 ($\text{SO}_2\text{TolC-CH}_3$ quat.), 130.9 (Ph-C quat.), 129.8 ($2 \times \text{Ph-C}$), 129.5 ($2 \times \text{SO}_2\text{Tol-C}$), 129.2 ($2 \times \text{Ph-C}$), 128.7 (Ph-C), 127.3 ($2 \times \text{SO}_2\text{Tol-C}$), 126.2 (Ph-C), 126.9 ($2 \times \text{Ph-C}$), 122.0 ($2 \times \text{Ph-C}$), 59.6 (CHCO), 56.2 (CHN), 27.8 (CH), 21.6 ($\text{SO}_2\text{Tol-CH}_3$), 20.8 (CH_3), 17.7 (CH_3); HRMS (ESI $^+$) m/z Calculated for $\text{C}_{26}\text{H}_{28}\text{N}_3\text{O}_4\text{S}^+$ $[\text{M}+\text{H}]^+$ 478.1795; Found: 478.1788.

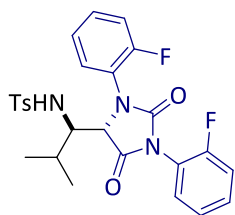


(±)-N-[(1R)-1-[(4S)-2,5-Dioxo-1,3-bis[4-(trifluoromethyl)phenyl]

imidazolidin-4-yl]-2-methylpropyl]-4-tolyl-1-sulfonamide (41b). Prepared

according to **General Procedure 10** described above, starting from iodoaziridine **20j** (100 mg, 0.27 mmol) and 4-(trifluoromethyl)phenyl isocyanate (116 μ L, 0.81 mmol, 3.0 equiv). Purification by flash chromatography (1% acetonitrile/dichloromethane) afforded 1,3,5-

trisubstituted hydantoin **41b** (123 mg, 74%) as a white solid: mp = 99–101 °C; R_f = 0.37 (1% acetonitrile/dichloromethane); $\nu_{\max}$ (film)/cm⁻¹ 3297 (br, NH), 2974, 1781 (C=O), 1719 (C=O), 1616, 1520, 1404, 1321, 1158, 1123, 1066, 1018, 908, 838, 730, 661; ¹H NMR (400 MHz, CDCl₃) δ 7.80 (d, J = 8.3 Hz, 2H, 2 $\times$ SO₂Tol-H), 7.77–7.73 (m, 4H, 4 $\times$ F₃CAr-H), 7.62–7.60 (m, 4H, 4 $\times$ F₃CAr-H), 7.33 (d, J = 8.2 Hz, 2H, 2 $\times$ SO₂Tol-H), 5.75 (d, J = 10.3 Hz, 1H, NH), 4.99 (d, J = 4.3 Hz, 1H, CHCO), 3.58 (ddd, J = 4.3, 5.3, 10.3 Hz, CHN), 2.44 (s, 3H, SO₂Tol-CH₃), 1.76 (dq, J = 6.7, 13.3 Hz, 1H, CH), 0.71 (d, J = 6.7 Hz, 3H, CH₃), 0.68 (d, J = 6.8 Hz, 3H, CH₃); ¹³C NMR (101 MHz, CDCl₃) δ 169.4 (C=O quat.), 152.3 (C=O quat.), 144.3 (SO₂Tol-C quat.), 137.7 (F₃CAr-C quat.), 136.9 (F₃CAr-C quat.), 133.8 (SO₂TolC-CH₃ quat.), 130.6 (q, J = 33.6 Hz, F₃C-CAr quat.), 129.9 (2 $\times$ SO₂Tol-C), 128.0 (q, J = 33.2 Hz, F₃C-CAr quat.), 127.3 (2 $\times$ SO₂Tol-C), 126.8 (q, J = 3.5 Hz, 2 $\times$ F₃CAr-C), 126.4 (q, J = 3.5 Hz, 2 $\times$ F₃CAr-C), 126.1 (4 $\times$ F₃CAr-C), 123.7 (q, J = 271.7 Hz, F₃C-CAr quat.), 123.5 (q, J = 271.7 Hz, F₃C-CAr quat.), 60.2 (CHCO), 56.4 (CHN), 28.3 (CH), 21.6 (SO₂Tol-CH₃), 20.6 (CH₃), 18.2 (CH₃); ¹⁹F NMR (377 MHz, CDCl₃) δ -62.4 (CF₃), -62.8 (CF₃); HRMS (ESI⁺) m/z Calculated for C₂₈H₂₆F₆N₃O₄S⁺ [M+H]⁺ 614.1543; Found: 614.1552.



(±)-N-[(1R)-1-[(4S)-1,3-Bis(2-fluorophenyl)-2,5-dioxoimidazolidin-4-yl]-2-

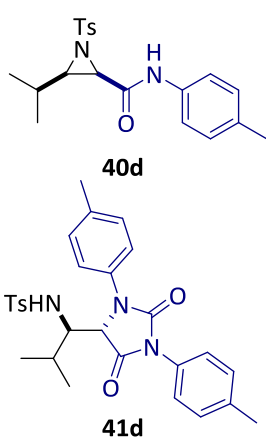
methylpropyl]-4-tolyl-1-sulfonamide (41c). Prepared according to **General**

Procedure 10 described above, starting from iodoaziridine **20j** (100 mg, 0.27 mmol) and 2-fluorophenyl isocyanate (91 μ L, 0.81 mmol, 3.0 equiv).

Purification by flash chromatography (1% acetonitrile/dichloromethane)

afforded 1,3,5-trisubstituted hydantoin **41c** (119 mg, 86%) as a white solid: mp = 70–72 °C; R_f = 0.22 (1% acetonitrile/dichloromethane); $\nu_{\max}$ (film)/cm⁻¹ 3301 (br, NH), 2969, 1785 (C=O), 1724 (C=O), 1597, 1505, 1463, 1409, 1332, 1161, 1092, 907, 870, 846, 758, 728, 662; ¹H NMR (400 MHz, CDCl₃) δ 7.74 (d, J = 8.2 Hz, 2H, 2 $\times$ SO₂Tol-H), 7.49–7.38 (m, 3H, 3 $\times$ FAr-H), 7.34–7.23 (m, 7H, 5 $\times$ FAr-H and 2 $\times$ SO₂Tol-H), 5.57 (br s, 1H, NH), 4.52 (br s, CHO), 3.53–3.45 (br m, 1H, CHN), 2.45 (s, 3H, SO₂Tol-CH₃), 1.89 (br s, 1H, CH), 0.85 (d, J = 6.6 Hz, 6H, 2 $\times$ CH₃); ¹³C NMR (101 MHz, CDCl₃) δ 169.9 (C=O quat.), 157.5 (d, J = 253.1 Hz, F-CAr quat.), 157.4 (d, J = 253.2 Hz, F-CAr quat.), 152.7 (C=O quat.), 143.8 (SO₂Tol-C quat.), 137.5 (SO₂TolC-CH₃ quat.), 131.2 (d, J = 8.1 Hz, FAr-C), 129.9 (d, J = 8.2 Hz, FAr-C),

129.8 (2 × SO₂Tol-C), 129.3 (FAr-C), 128.4 (FAr-C), 127.0 (2 × SO₂Tol-C), 125.1 (d, *J* = 3.3 Hz, FAr-C), 124.7 (d, *J* = 3.4 Hz, FAr-C), 121.8 (d, *J* = 12.6 Hz, FAr-C quat.), 118.5 (d, *J* = 12.9 Hz, FAr-C quat.), 117.0 (d, *J* = 31.1 Hz, FAr-C), 116.8 (d, *J* = 31.1 Hz, FAr-C), 61.4 (CHCO), 57.6 (CHN), 28.0 (CH), 21.5 (SO₂Tol-CH₃), 20.9 (CH₃), 17.5 (CH₃); ¹⁹F NMR (377 MHz, CDCl₃) δ -118.6 (C-F), -119.5 (C-F); HRMS (ESI⁺) *m/z* Calculated for C₂₆H₂₆F₂N₃O₄S⁺ [M+H]⁺ 514.1607; Found: 514.1629.

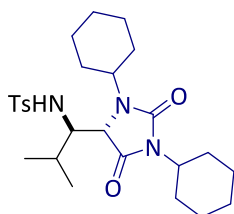


***cis*-(±)-1-(4-Tolylsulfonyl)-N-(4-tolyl)-3-(propan-2-yl)aziridine-2-carboxamide (40d) and (±)-N-[(1R)-1-[(4S)-1,3-Bis(4-tolyl)-2,5-dioxoimidazolidin-4-yl]-2-methylpropyl]-4-tolyl-1-sulfonamide (41d)**

Prepared according to **General Procedure 10** described above, starting from iodoaziridine **20j** (100 mg, 0.27 mmol) and 4-methylphenyl isocyanate (102 μL, 0.81 mmol, 3.0 equiv). Purification by flash chromatography (30% diethyl ether/hexane) afforded *cis*-aziridine **40d** (44 mg, 44%) and 1,3,5-trisubstituted hydantoin **41d** (50 mg, 37%): ***cis*-aziridine 40d**: white solid; mp = 97–99 °C; *R_f* = 0.18 (40% diethyl ether/hexane); *v*_{max} (film)/cm⁻¹ 3330 (br,

NH), 2964, 2928, 2873, 1674 (C=O), 1597, 1521, 1469, 1407, 1330, 1252, 1160, 1091, 1039, 949, 886, 813, 732, 677; ¹H NMR (400 MHz, CDCl₃) δ 7.88 (d, *J* = 8.3 Hz, 2H, 2 × SO₂Tol-H), 7.81 (br s, 1H, NH), 7.40 (d, *J* = 8.3 Hz, 2H, 2 × SO₂Tol-H), 7.33 (d, *J* = 8.4 Hz, 2H, 2 × Tol-H), 7.12 (d, *J* = 8.4 Hz, 2H, 2 × Tol-H), 3.51 (d, *J* = 7.8 Hz, 1H, CHCO), 2.69 (dd, *J* = 7.8, 10.0 Hz, 1H, CHN), 2.48 (s, 3H, SO₂Tol-CH₃), 2.31 (s, 3H, Tol-CH₃), 1.47–1.38 (m, 1H, CH), 0.98 (d, *J* = 6.8 Hz, 3H, CH₃), 0.86 (d, *J* = 6.7 Hz, 3H, CH₃); ¹³C NMR (101 MHz, CDCl₃) δ 162.5 (C=O quat.), 145.6 (SO₂Tol-C quat.), 134.7 (Tol-C quat.), 133.8 (SO₂TolC-CH₃ quat.), 133.3 (Tol-C quat.), 130.0 (2 × SO₂Tol-C), 129.5 (2 × Tol-C), 128.3 (2 × SO₂Tol-C), 119.9 (2 × Tol-C), 52.1 (CHN), 44.3 (CHCO), 27.9 (CH), 21.7 (SO₂Tol-CH₃), 20.9 (Tol-CH₃), 20.7 (CH₃), 18.9 (CH₃); HRMS (ESI⁺) *m/z* Calculated for C₂₀H₂₅N₂O₃S⁺ [M+H]⁺ 373.1580; Found: 373.1588. **1,3,5-trisubstituted hydantoin 41d**: white solid; mp = 69–71 °C; *R_f* = 0.13 (40% diethyl ether/hexane); *v*_{max} (film)/cm⁻¹ 3298 (br, NH), 2965, 2924, 1774 (C=O), 1712 (C=O), 1513, 1405, 1381, 1332, 1295, 1156, 1092, 910, 812, 729, 661; ¹H NMR (400 MHz, CDCl₃) δ 7.83 (d, *J* = 8.3 Hz, 2H, 2 × SO₂Tol-H), 7.36 (d, *J* = 8.3 Hz, 2H, 2 × SO₂Tol-H), 7.29–7.23 (m, 6H, 6 × Tol-H), 7.15 (d, *J* = 8.5 Hz, 2H, 2 × Tol-H), 5.90 (d, *J* = 10.5 Hz, 1H, NH), 4.48 (d, *J* = 4.9 Hz, 1H, CHCO), 3.58 (ddd, *J* = 4.7, 9.2, 10.5 Hz, CHN), 2.46 (s, 3H, SO₂Tol-CH₃), 2.39 (s, 6H, 2 × Tol-CH₃), 1.86–1.78 (m, 1H, CH), 0.79 (d, *J* = 6.7 Hz, 3H, CH₃), 0.75 (d, *J* = 6.8 Hz, 3H, CH₃); ¹³C NMR (101 MHz, CDCl₃) δ 170.5 (C=O quat.), 153.1 (C=O quat.), 144.0 (SO₂Tol-C quat.), 138.7 (Tol-C quat.), 137.6 (Tol-C quat.), 136.1 (SO₂TolC-CH₃ quat.), 131.7 (Tol-C quat.), 130.1 (2 × SO₂Tol-C), 129.84 (2 × Tol-C), 129.80 (2 × Tol-C), 128.2 (Tol-C quat.), 127.3 (2 × SO₂Tol-C), 125.7 (2 × Tol-C), 122.1 (2 × Tol-C), 59.5 (CHCO), 56.2 (CHN), 27.7 (CH), 21.6 (SO₂Tol-CH₃), 21.1 (Tol-CH₃),

21.0 (CH₃), 20.8 (Tol-CH₃), 17.7 (CH₃); HRMS (ESI⁺) *m/z* Calculated for C₂₈H₃₂N₃O₄S⁺ [M+H]⁺ 506.2108; Found: 506.2109.

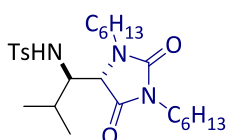


(±)-N-[(1R)-1-[(4S)-1,3-Dicyclohexyl-2,5-dioxoimidazolidin-4-yl]-2-

methylpropyl]-4-tolyl-1-sulfonamide (41e). Prepared according to **General**

Procedure 10 described above, starting from iodoaziridine **20j** (100 mg, 0.27 mmol) and cyclohexyl isocyanate (104 μL, 0.81 mmol, 3.0 equiv). Purification by flash chromatography (20% diethyl ether/hexane) afforded 1,3,5-

trisubstituted hydantoin **41e** (70 mg, 53%) as a colourless oil: *R_f* = 0.15 (30% diethyl ether/hexane); *v*_{max} (film)/cm⁻¹ 3293 (br, NH), 2933, 2857, 1756 (C=O), 1695 (C=O), 1427, 1337, 1163, 1093, 912, 816, 732, 662; ¹H NMR (400 MHz, CDCl₃) δ 7.84 (d, *J* = 8.3 Hz, 2H, 2 × SO₂Tol-H), 7.33 (d, *J* = 8.2 Hz, 2H, 2 × SO₂Tol-H), 6.12 (d, *J* = 10.1 Hz, 1H, NH), 3.82 (tt, *J* = 4.0, 12.4 Hz, 1H, NCHCH₂), 3.62–3.51 (m, 2H, CHN and NCHCH₂), 3.48 (d, *J* = 5.2 Hz, 1H, CHCO), 2.43 (s, 3H, SO₂Tol-CH₃), 2.08–1.99 (m, 2H, 2 × Cy-H), 1.90–1.61 (m, 9H, 8 × Cy-H and CH), 1.48–1.46 (m, 1H, Cy-H), 1.32–1.09 (m, 9H, 9 × Cy-H), 0.87 (d, *J* = 6.9 Hz, 3H, CH₃), 0.75 (d, *J* = 6.7 Hz, 3H, CH₃); ¹³C NMR (101 MHz, CDCl₃) δ 172.7 (C=O quat.), 156.1 (C=O quat.), 143.7 (SO₂Tol-C quat.), 138.0 (SO₂TolC-CH₃ quat.), 129.8 (2 × SO₂Tol-C), 127.2 (2 × SO₂Tol-C), 58.1 (CHCO), 57.6 (CHN), 53.6 (NCHCH₂), 51.7 (NCHCH₂), 32.0 (CH₂), 30.0 (CH₂), 29.13 (CH₂), 29.05 (CH₂), 26.6 (CH), 25.8 (CH₂), 25.72 (2 × CH₂), 25.68 (CH₂), 25.2 (CH₂), 24.9 (CH₂), 21.6 (CH₃), 21.5 (SO₂Tol-CH₃), 17.1 (CH₃); HRMS (ESI⁺) *m/z* Calculated for C₂₆H₄₀N₃O₄S⁺ [M+H]⁺ 490.2734; Found: 490.2744.



(±)-N-[(1R)-1-[(4S)-1,3-Dihexyl-2,5-dioxoimidazolidin-4-yl]-2-

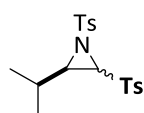
tolyl-1-sulfonamide (41f). Prepared according to **General Procedure 10**

described above, starting from iodoaziridine **20j** (100 mg, 0.27 mmol) and hexyl

isocyanate (118 μL, 0.81 mmol, 3.0 equiv). Purification by flash chromatography (30% diethyl ether/hexane) afforded 1,3,5-trisubstituted hydantoin **41f** (25 mg, 19%) as a colourless oil: *R_f* = 0.10 (30% diethyl ether/hexane); *v*_{max} (film)/cm⁻¹ 3288 (br, NH), 2957, 2930, 2859, 1768 (C=O), 1699 (C=O), 1425, 1339, 1162, 1093, 904, 815, 664; ¹H NMR (400 MHz, CDCl₃) δ 7.82 (d, *J* = 8.3 Hz, 2H, 2 × SO₂Tol-H), 7.32 (d, *J* = 8.2 Hz, 2H, 2 × SO₂Tol-H), 5.96 (d, *J* = 9.6 Hz, 1H, NH), 3.66–3.62 (m, 1H, NCHH), 3.55–3.34 (m, 4H, CHCO, CHN and NCH₂), 2.80–2.75 (m, 1H, NCHH), 2.43 (s, 3H, SO₂Tol-CH₃), 1.77–1.69 (m, 1H, CH*i*Pr), 1.53–1.58 (m, 2H, CH₂), 1.32–1.14 (m, 14H, 7 × CH₂), 0.92–0.86 (m, 9H, 3 × CH₃), 0.74 (d, *J* = 6.8 Hz, 3H, CH₃); ¹³C NMR (101 MHz, CDCl₃) δ 172.5 (C=O quat.), 156.1 (C=O quat.), 143.7 (SO₂Tol-C quat.), 138.1 (SO₂TolC-CH₃ quat.), 129.9 (2 × SO₂Tol-C), 127.0 (2 × SO₂Tol-C), 58.2 (CHCO), 56.6 (CHN), 40.5 (NCH₂), 39.0 (NCH₂), 31.3 (CH₂), 31.2 (CH₂), 27.7 (CH₂), 27.5 (CH), 27.2 (CH₂),

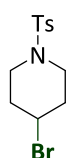
26.3 (CH₂), 26.2 (CH₂), 22.5 (2 × CH₂), 21.5 (SO₂Tol-CH₃), 21.1 (CH₃), 17.3 (CH₃), 14.0 (2 × CH₃); HRMS (ESI⁺) *m/z* Calculated for C₂₆H₄₄N₃O₄S⁺ [M+H]⁺ 494.3047; Found: 494.3041.

Iodoaziridine Cross-Coupling (Section 2.4)

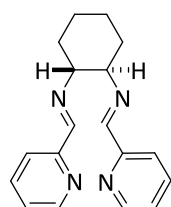


***cis*-(±)-1,2-Bis(4-tolylsulfonyl)-3-(propan-2-yl)aziridine and *trans*-(±)-1,2-Bis(4-tolylsulfonyl)-3-(propan-2-yl)aziridine (43).** ¹H NMR and HRMS data given for **43**: *cis*:

¹H NMR (400 MHz, CDCl₃) δ 7.64–7.58 (m, 4H, 4 × SO₂Tol-H), 7.23–7.16 (m, 4H, 4 × SO₂Tol-H), 3.84 (d, *J* = 6.8 Hz, 1H, CHTs), 2.82 (dd, *J* = 6.8, 10.3 Hz, 1H, CHN), 2.44 (s, 3H, SO₂Tol-CH₃), 2.42 (s, 3H, SO₂Tol-CH₃), 2.46–2.37 (m, 1H, CH(CH₃)₂), 1.14 (d, *J* = 6.8 Hz, 3H, CHCH₃), 0.94 (d, *J* = 6.8 Hz, 3H, CHCH₃). *trans*: ¹H NMR (400 MHz, CDCl₃) δ 7.52 (d, *J* = 8.2 Hz, 2H, 2 × SO₂Tol-H), 7.43 (d, *J* = 8.2 Hz, 2H, 2 × SO₂Tol-H), 7.12 (d, *J* = 8.1 Hz, 2H, 2 × SO₂Tol-H), 7.03 (d, *J* = 8.1 Hz, 2H, 2 × SO₂Tol-H), 4.05 (d, *J* = 3.8 Hz, 1H, CHTs), 3.10 (dd, *J* = 3.8 Hz, 10.2 Hz, 1H, CHN), 2.43 (s, 3H, SO₂Tol-CH₃), 2.38 (s, 3H, SO₂Tol-CH₃), 2.46–2.37 (m, 1H, CH(CH₃)₂), 1.33 (d, *J* = 6.8 Hz, 3H, CHCH₃), 1.14 (d, *J* = 6.8 Hz, 3H, CHCH₃); HRMS (ESI⁺) *m/z* Calculated for C₁₉H₂₄NO₄S₂⁺ [M+H]⁺: 394.1141; Found: 394.1149.



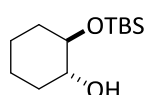
4-Bromo-1-tosylpiperidine (45). Prepared according to the procedure of Fu and co-workers.¹⁴³ *p*-Toluenesulfonyl chloride (580 mg, 3.05 mmol, 1.3 equiv) was added to a stirred suspension of 4-bromopiperidine hydrobromide salt (575 mg, 2.35 mmol, 1.0 equiv) in pyridine (5 mL). After 24 h at rt, the resulting mixture was poured into a separating funnel containing CH₂Cl₂ (50 mL) and HCl (1 N, 50 mL). The aqueous layer was extracted with CH₂Cl₂ (3 × 30 mL), washed with HCl (1 N, 50 mL), brine (50 mL) and dried (Na₂SO₄). Filtration and removal of the solvent under reduced pressure afforded bromopiperidine **45** (672 mg, 90%) as a white solid, which was used without further purification: *v*_{max} (film)/cm⁻¹ 2926, 1342, 1300, 1243, 1160, 1093, 1009, 927, 860, 814, 745, 714, 699; ¹H NMR (400 MHz, CDCl₃) δ 7.66 (d, *J* = 8.3 Hz, 2H, 2 × SO₂Tol-H), 7.35 (d, *J* = 8.3 Hz, 2H, 2 × SO₂Tol-H), 4.28–4.23 (m, 1H, CHBr), 3.23–3.17 (m, 2H, CH₂), 3.13–3.08 (m, 2H, CH₂), 2.46 (s, 3H, SO₂Tol-CH₃), 2.24–2.16 (m, 2H, CH₂), 2.10–2.02 (m, 2H, CH₂); ¹³C NMR (101 MHz, CDCl₃) δ 143.7 (SO₂Tol-C quat.), 133.2 (SO₂TolC-CH₃ quat.), 129.7 (2 × SO₂Tol-C), 127.6 (2 × SO₂Tol-C), 47.8 (CHBr), 43.8 (2 × CH₂), 34.7 (2 × CH₂), 21.5 (SO₂Tol-CH₃). The observed data is consistent with that previously reported in the literature.²⁴⁹



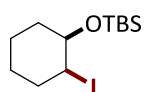
(±)-(N,N'-Bis(pyridin-2-ylmethylene)cyclohexane-1,2-diamine (47). Prepared

according to the procedure of Taillefer and co-workers.¹⁹⁰ *trans*-(±)-1,2-Diaminocyclohexane (0.48 mL, 4.4 mmol, 1.0 equiv) was dissolved in MeOH (20 mL) over 3 Å MS (~1 g) and cooled to 0 °C in an ice/water bath. 2-Pyridinecarboxaldehyde (0.84 mL, 8.8 mmol, 2.0 equiv) was dissolved in MeOH (20 mL) and added to the reaction mixture dropwise at 0 °C. The reaction was then warmed to rt over 16 h, filtered through Celite®, washed through with CH₂Cl₂ (50 mL) and solvent removed under reduced pressure

to afford the crude diamine. Recrystallisation (EtOAc) afforded diamine **47** (535 mg, 42%) as yellow crystals: mp = 136–137 °C (lit.¹⁹⁰ = 140–141 °C); ¹H NMR (400 MHz, CDCl₃) 8.57–8.55 (m, 2H, 2 × Ar-H), 8.32 (br s, 2H, 2 × HC=N), 7.99 (d, *J* = 8.0 Hz, 2H, 2 × Ar-H), 7.65 (dt, *J* = 1.6, 7.7 Hz, 2H, 2 × Ar-H), 7.23 (ddd, *J* = 1.2, 4.9, 7.7 Hz, 2H, 2 × Ar-H), 3.58–3.51 (m, 2H, 2 × CH), 1.90–1.79 (m, 6H, 3 × CH₂), 1.55–1.49 (m, 2H, CH₂); ¹³C NMR (101 MHz, CDCl₃) δ 161.3 (2 × C=N), 154.5 (2 × Ar-C quat.), 149.1 (2 × Ar-C), 136.3 (2 × Ar-C), 124.3 (2 × Ar-C), 121.2 (2 × Ar-C), 73.5 (2 × CyCHN), 32.6 (2 × CH₂), 24.3 (2 × CH₂). The observed data is consistent with that previously reported in the literature.¹⁹⁰

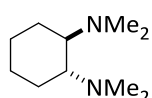


tert-Butyl(cyclohexyl)oxydimethylsilane (49). Imidazole (511 mg, 7.50 mmol, 1.5 equiv) was added to stirred solution of *trans*-1,2-cyclohexanediol (580 mg, 5.00 mmol, 1.0 equiv) in CH₂Cl₂ (20 mL) at 0 °C. After 5 mins at 0 °C, TBSCl (1.13 g, 7.50 mmol, 1.5 equiv) was added portionwise. The resulting suspension was then heated to reflux at 45 °C for 3 h, monitoring reaction progress via thin layer chromatography. On completion, the reaction was cooled to rt and water (20 mL) was added. The aqueous solution was extracted with CH₂Cl₂ (3 × 30 mL) and the organic extracts were combined, dried (Na₂SO₄), filtered and solvent removed under reduced pressure. Purification by flash chromatography (5% EtOAc/hexane) afforded protected alcohol **49** (920 mg, 80%) as a colourless oil: *R*_f = 0.32 (15% EtOAc/hexane); *v*_{max} (film)/cm⁻¹ 3449 (OH), 2930, 2858, 1473, 1251, 1092, 946, 876, 834, 775, 668; ¹H NMR (400 MHz, CDCl₃) δ 3.39–3.30 (m, 2H, 2 × CH), 2.46 (br s, 1H, OH), 2.02–1.95 (m, 1H, CH₂), 1.89–1.82 (m, 1H, CH₂), 1.72–1.64 (m, 2H, CH₂), 1.31–1.22 (m, 4H, 2 × CH₂), 0.91 (s, 9H, Si[C(CH₃)₃]), 0.11 (s, 3H, SiCH₃), 0.10 (s, 3H, SiCH₃); ¹³C NMR (101 MHz, CDCl₃) δ 77.2 (CH), 75.5 (CH), 33.5 (CH₂), 31.5 (CH₂), 25.8 (C(CH₃)₃), 24.4 (CH₂), 24.1 (CH₂), 18.0 (C(CH₃)₃ quat.), -4.1 (SiCH₃), -4.7 (SiCH₃). The observed data is consistent with that previously reported in the literature.²⁵⁰



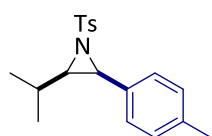
tert-Butyl((2-iodocyclohexyl)oxy)dimethylsilane (50). Prepared according to a modified procedure of Lange and co-workers.²⁵¹ Imidazole (355 mg, 5.22 mmol, 3.0 equiv) was added to a stirred solution of the protected alcohol **49** (400 mg, 1.74 mmol, 1.0 equiv), iodine (889 mg, 3.48 mmol, 2.0 equiv) and triphenylphosphine (1.37 g, 5.22 mmol, 3.0 equiv) in THF (17 mL) at rt. The reaction was then heated to 80 °C, monitoring reaction progress via thin layer chromatography. After 90 min, the reaction was cooled to rt and quenched with saturated ammonium chloride solution (50 mL). The aqueous solution was extracted with EtOAc (3 × 30 mL) and the organic extracts were combined, washed with 5% w/v sodium thiosulfate solution (50 mL), dried (Na₂SO₄), filtered and solvent removed under reduced pressure. Purification by flash chromatography (hexane) afforded cycloalkyl iodide **50** (540 mg, 91%) as a colourless oil: *R*_f = 0.72

(15% EtOAc/hexane); ν_{max} (film)/ cm^{-1} 2933, 2885, 2856, 1472, 1462, 1445, 1361, 1251, 1196, 1167, 1100, 1029, 984, 836, 834, 775, 670; ^1H NMR (400 MHz, CDCl_3) δ 4.49–4.43 (m, 1H, CHI), 3.42–3.28 (m, 1H, CH), 2.31–2.20 (m, 1H, CH_2), 1.94–1.86 (m, 1H, CH_2), 1.77–1.53 (m, 4H, $2 \times \text{CH}_2$), 1.47–1.34 (m, 2H, CH_2), 0.94 (s, 9H, $\text{Si}[\text{C}(\text{CH}_3)_3]$), 0.14 (s, 3H, SiCH_3), 0.08 (s, 3H, SiCH_3); ^{13}C NMR (101 MHz, CDCl_3) δ 71.7 (CH), 42.3 (CHI) 34.1 (CH_2), 33.4 (CH_2), 25.9 ($\text{C}(\text{CH}_3)_3$), 25.3 (CH_2), 21.4 (CH_2), 18.2 ($\text{C}(\text{CH}_3)_3$ quat.), –4.1 (SiCH_3), –4.7 (SiCH_3). The observed data is consistent with that previously reported in the literature.¹⁹³



***N,N,N,N*-Tetramethylcyclohexane-1,2-diamine (53).** Prepared according to the procedure of Snyder and co-workers.¹⁹⁸ Formic acid (98%, 7.55 mL, 200 mmol, 10.0 equiv) was added to a mixture of *trans*-($\pm$)-1,2-diaminocyclohexane (2.40 mL, 20.0

mmol, 1.0 equiv) in formaldehyde (37% aq. solution, 16.38 mL, 200 mmol, 10.0 equiv) and was heated under reflux at 95 °C for 17 h. After this time period, the reaction mixture was cooled to rt and made basic to pH = 10 with NaOH (1 M, 200 mL). The aqueous layer was then separated and further made basic to pH = 14 with NaOH (1 M, 100 mL), extracted with CH_2Cl_2 (2×200 mL), organic extracts combined, dried (Na_2SO_4), filtered and solvent removed under reduced pressure to give protected diamine **53** (2.97 g, 87%) as a pale yellow oil: ν_{max} (film)/ cm^{-1} 2926, 2856, 2820, 2774, 1451, 1273, 1172, 1065, 1047, 1026; ^1H NMR (400 MHz, CDCl_3) δ 2.40–2.36 (m, 2H, $2 \times \text{CH}$), 2.28 (s, 12H, $4 \times \text{CH}_3$), 1.85–1.82 (m, 2H, CH_2), 1.74–1.72 (m, 2H, CH_2), 1.04–1.19 (m, 4H, $2 \times \text{CH}_2$); ^{13}C NMR (101 MHz, CDCl_3) δ 63.9 ($2 \times \text{CHN}$), 40.1 ($4 \times \text{CH}_3$), 25.6 ($2 \times \text{CH}_2$), 22.9 ($2 \times \text{CH}_2$). The observed data is consistent with that previously reported in the literature.¹⁹⁸

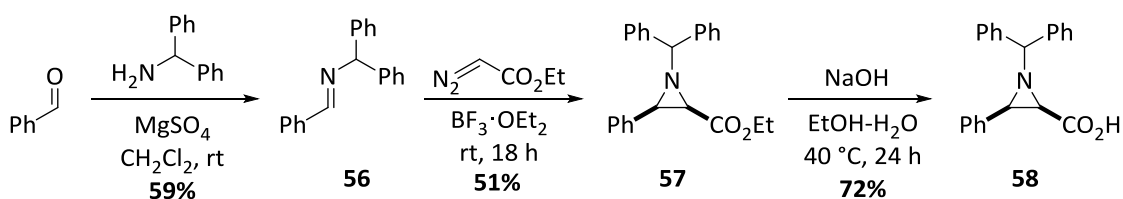


***cis*-($\pm$)-1-(4-Tolylsulfonyl)-2-(4-tolyl)-3-(propan-2-yl)aziridine (54).** In a N_2 filled glove box, CoCl_2 (3.2 mg, 0.025 mmol, 5 mol%) was added to a flame dried vial and sealed. The CoCl_2 was flame dried under reduced pressure with a heat gun

for 2 min until dark blue and cooled under reduced pressure. THF (0.5 mL) and a mixture of *N,N,N,N*-tetramethylcyclohexane-1,2-diamine **53** (6 μL , 0.030 mmol, 6 mol%) in THF (0.5 mL) were sequentially added. *N*-Ts iodoaziridine **20j** (183 mg, 0.50 mmol, 1.0 equiv) was dissolved in THF (0.5 mL) and was added to the CoCl_2 /**53** mixture at 0 °C. At 0 °C, tolylmagnesium bromide (0.95 mL, 0.60 mmol, 1.2 equiv) was added over 5 s to the reaction mixture (during which an instant colour change occurred from blue to green) and then warmed to rt. After 2 h at rt, the reaction mixture was poured into an aqueous ammonium chloride solution (30 mL), extracted with EtOAc (3×30 mL), dried (Na_2SO_4), filtered and solvent removed under reduced pressure which afforded a mixture of aziridines (89:11, *cis:trans*). Purification by flash chromatography (10% diethyl ether/hexane)

afforded *cis*-aziridine **54** (17 mg, 10%) as a colourless oil: R_f = 0.27 (20% diethyl ether/hexane); $\nu_{\max}$ (film)/ cm^{-1} 2963, 2928, 2871, 1599, 1467, 1327, 1161, 1092, 1037, 966, 896, 814, 773, 672; ^1H NMR (400 MHz, CDCl_3) δ 7.90 (d, J = 8.3 Hz, 2H, 2 $\times$ $\text{SO}_2\text{Tol-H}$), 7.33 (d, J = 8.3 Hz, 2H, 2 $\times$ $\text{SO}_2\text{Tol-H}$), 7.14 (d, J = 8.1 Hz, 2H, 2 $\times$ Tol-H), 7.09 (d, J = 8.1 Hz, 2H, 2 $\times$ Tol-H), 3.96 (d, J = 7.2 Hz, 1H, CHTol), 2.71 (dd, J = 7.2, 9.9 Hz, 1H, CHN), 2.44 (s, 3H, $\text{SO}_2\text{Tol-CH}_3$), 2.32 (s, 3H, Tol- CH_3), 1.21–1.14 (m, 1H, CH), 0.83 (d, J = 6.7 Hz, 3H, CHCH_3), 0.71 (d, J = 6.7 Hz, 3H, CHCH_3); ^{13}C NMR (101 MHz, CDCl_3) δ 144.4 ($\text{SO}_2\text{Tol-C}$ quat.), 137.4 (Tol-C quat.), 135.2 ($\text{SO}_2\text{TolC-CH}_3$ quat.), 129.9 (Tol-C quat.), 129.6 (2 $\times$ $\text{SO}_2\text{Tol-C}$), 128.9 (2 $\times$ Tol-C), 128.1 (2 $\times$ $\text{SO}_2\text{Tol-C}$), 127.2 (2 $\times$ Tol-C), 52.7 (CHN), 46.1 (CHTol), 25.8 (CH), 21.7 ($\text{SO}_2\text{Tol-CH}_3$), 21.1 (Tol- CH_3), 20.6 (CHCH_3), 18.6 (CHCH_3); HRMS (ESI $^+$) m/z Calculated for $\text{C}_{19}\text{H}_{24}\text{NO}_2\text{S}^+$ [$\text{M}+\text{H}$] $^+$ 330.1522; Found: 330.1539.

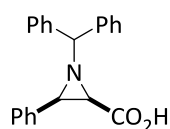
Synthesis of Selenoaziridine 60



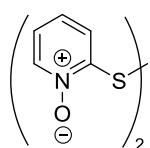
(E)-(Diphenylmethyl)(phenylmethyldene)amine (56). Prepared according to the procedure of Cainelli and co-workers.²⁵² Benzhydramine (3.44 mL, 20.0 mmol, 1.0 equiv) was added to a stirred suspension of magnesium sulfate (8.0 g) in CH_2Cl_2 (40 mL). After 5 minutes at rt, benzaldehyde (2.02 mL, 20.0 mmol, 1.0 equiv) was added portionwise and the resulting suspension was stirred at rt for 14 h. The suspension was filtered through Celite®, washed with CH_2Cl_2 (2 × 50 mL) and the filtrate concentrated under reduced pressure. The resulting solid was then recrystallised (EtOAc) affording imine **56** (3.20 g, 59%) as an off-white solid: mp = 100–101 °C (lit.²⁵² = 98–100 °C); ν_{max} (film)/ cm^{-1} 3088, 3066, 3029, 2850, 1647, 1579, 1495, 1455, 1381, 1310, 1025, 756, 694; ^1H NMR (400 MHz, CDCl_3) δ 8.47 (s, 1H, CHN), 7.90–7.87 (m, 2H, 2 × Ph-H), 7.46–7.44 (m, 7H, 7 × Ph-H), 7.38–7.34 (m, 4H, 4 × Ph-H), 7.29–7.25 (m, 2H, 2 × Ph-H), 5.64 (s, 1H, CHPh_2); ^{13}C NMR (101 MHz, CDCl_3) δ 160.7 (CHN), 143.9 (2 × Ph-C quat.), 136.3 (Ph-C quat.), 130.7 (Ph-C), 128.5 (2 × Ph-C), 128.42 (2 × Ph-C), 128.40 (4 × Ph-C), 127.6 (4 × Ph-C), 126.9 (2 × Ph-C), 77.9 (CH). Observed data was consistent with that found in the literature.²⁵²

cis-(±)-Ethyl-1-(diphenylmethyl)-3-phenylaziridine-2-carboxylate (57). Prepared according to the procedure of Templeton and co-workers.²⁵³ $\text{BF}_3\cdot\text{Et}_2\text{O}$ (45 μL , 0.37 mmol, 10 mol%) was added to a solution of ethyl diazoacetate (0.79 mL, 7.44 mmol, 2.0 equiv) in diethyl ether (10 mL). A solution of imine **56** (1.00 g, 3.72 mmol, 1.0 equiv) in diethyl ether (15 mL) was then added dropwise to the reaction mixture over 45 minutes at rt. The resulting solution was left to stir at rt for 18 h. The reaction was then diluted with diethyl ether (50 mL), washed with brine (3 × 20 mL), dried (MgSO_4), filtered and solvent removed under reduced pressure. Purification by flash chromatography afforded aziridine carboxylate **57** (683 mg, 51%) as a white solid: mp = 124–126 °C (lit.²⁵⁴ = 128–129 °C); R_f = 0.15 (10% diethyl ether/hexane); ν_{max} (film)/ cm^{-1} 3071, 3033, 2980, 2252, 1737, 1606, 1452, 1372, 1304, 1191, 1095, 1067, 1034, 906, 697, 728; ^1H NMR (400 MHz, CDCl_3) δ 7.61–7.60 (m, 2H, 2 × Ph-H), 7.50–7.48 (m, 2H, 2 × Ph-H), 7.41–7.39 (m, 2H, 2 × Ph-H), 7.36–7.32 (m, 2H, 2 × Ph-H), 7.28–7.18 (m, 7H, 7 × Ph-H), 3.95 (s, 1H, CHPh_2), 3.95 (s, 1H, CHPh_2), 3.94 (q, J = 7.1 Hz, 2H, CH_2), 3.22 (d, J = 6.8 Hz, 1H, CHCO_2Et), 2.67 (d, J = 6.8 Hz, 1H, CHPh), 0.98 (t, J = 7.1 Hz, 3H, CH_3); ^{13}C NMR (101 MHz, CDCl_3) δ 167.7 (C=O quat.), 142.5 (Ph-C quat.), 142.3

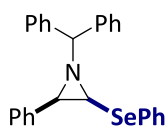
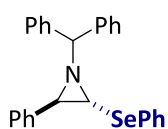
(Ph-C quat.), 135.0 (Ph-C quat.), 128.4 (4 × Ph-C), 127.72 (2 × Ph-C), 127.70 (2 × Ph-C), 127.5 (2 × Ph-C), 127.34 (Ph-C), 127.26 (Ph-C), 127.1 (3 × Ph-C), 77.6 (CHPh₂), 60.5 (CH₂), 48.6 (CHCO₂Et), 46.3 (CHPh), 13.9 (CH₃). Observed data was consistent with that found in the literature.²⁰⁵



***cis*-(±)-1-(Diphenylmethyl)-3-phenylaziridine-2-carboxylic acid (58).** NaOH (200 mg, 5.00 mmol, 1.05 equiv) was added to a suspension of aziridine ester **57** (1.70 g, 4.76 mmol, 1.0 equiv) in a mixture of ethanol: water (9:1, 50 mL). The resulting mixture was heated to 40 °C and after 24 h, the solvent was removed under reduced pressure. The remaining residue was suspended in water and EtOAc (1:1, 200 mL) and the aqueous layer was then acidified to pH = 3 via the addition of aqueous 1 N HCl. The aqueous layer was then extracted with EtOAc (5 × 20 mL), organic extracts combined, dried (Na₂SO₄), filtered and solvent removed under reduced pressure affording aziridine acid **58** (1.13 g, 72%) as a white solid, which was used without further purification: mp = 155–156 °C (lit.²⁰⁵ = 143–145 °C); ν_{max} (film)/cm⁻¹ 3033, 2831, 1697, 1603, 1499, 1449, 1308, 1246, 1065, 889, 735, 705, 694; ¹H NMR (400 MHz, DMSO-*d*₆) δ 12.23 (br s, 1H, OH), 7.60 (d, *J* = 7.3 Hz, 2H, 2 × Ph-H), 7.49 (d, *J* = 7.3 Hz, 2H, 2 × Ph-H), 7.40 (d, *J* = 7.2 Hz, 2H, 2 × Ph-H), 7.34 (t, *J* = 7.3 Hz, 2H, 2 × Ph-H), 7.27–7.14 (m, 7H, 7 × Ph-H), 4.16 (s, 1H, CHPh₂), 3.32 (d, *J* = 7.0 Hz, 1H, CHPh), 2.76 (d, *J* = 7.0 Hz, 1H, CHCO₂H); ¹³C NMR (101 MHz, DMSO-*d*₆) δ 169.0 (C=O quat.), 143.5 (Ph-C quat.), 143.3 (Ph-C quat.), 135.9 (Ph-C quat.), 128.7 (4 × Ph-C), 128.0 (2 × Ph-C), 127.9 (2 × Ph-C), 127.5 (2 × Ph-C), 127.4 (2 × Ph-C), 127.3 (Ph-C), 127.2 (2 × Ph-C), 75.6 (CHPh₂), 47.5 (CHCO₂H), 46.6 (CHPh); HRMS (ESI⁺) *m/z* Calculated for C₂₂H₂₀NO₂⁺ [M+H]⁺: 330.1494; Found: 330.1478. Observed data was consistent with that found in the literature.²⁵⁵

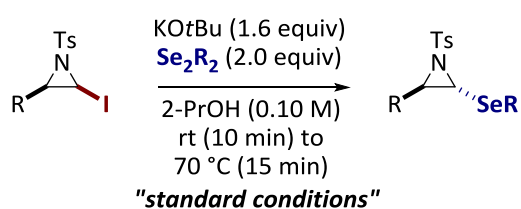


2,2'-Dithiobispyridine-1,1'-dioxide (59). Prepared according to a modified procedure of Barton and co-workers.²⁰⁶ Conc. HCl (2.64 mL, 26.8 mmol, 1.0 equiv) was added dropwise to 2-mercaptopyridine sodium salt solution (40%, 10.0 mL, 26.8 mmol, 1.0 equiv) at 0 °C. The resulting mixture was warmed to rt and water (22 mL) was added followed by the dropwise addition of hydrogen peroxide (6.4%, 12.47 mL, 28.1 mmol, 1.0 equiv). The mixture was stirred at 45 °C for 1 h, and the grey solid formed was collected via suction filtration. Purification via recrystallisation (MeOH) afforded dimer **59** (1.16 g, 34%) as white crystals: mp = 215–216 °C (lit.²⁰⁶ = 205–206 °C); ν_{max} (film)/cm⁻¹ 3440, 3092, 1464, 1421, 1255, 1223, 1139, 838, 760, 676; ¹H NMR (400 MHz, CDCl₃) δ 8.30–8.28 (m, 1H, Ar-H), 7.60 (dd, *J* = 1.7, 8.3 Hz, 1H, Ar-H), 7.27 (dt, *J* = 1.3, 7.7 Hz, 1H, Ar-H), 7.20–7.16 (m, 1H, Ar-H); ¹³C NMR (101 MHz, CDCl₃) δ 149.2 (Ar-C quat.), 138.7 (Ar-C), 126.5 (Ar-C), 122.5 (Ar-C), 121.9 (Ar-C). Compound previously reported without full characterisation data.²⁰⁶



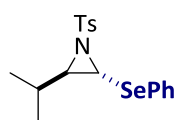
***trans*-(±)-1-(Diphenylmethyl)-2-phenyl-3-(phenylselanyl)aziridine and *cis*-(±)-1-(Diphenylmethyl)-2-phenyl-3-(phenylselanyl)aziridine (60).** In a pyrex tube aziridine carboxylic acid **58** (50 mg, 0.15 mmol, 1.0 equiv) and dimer **59** (49 mg, 0.195 mmol, 1.3 equiv) were dissolved in degassed CH₂Cl₂ (5 mL). The mixture was cooled to 0 °C and covered with aluminium foil. Tributylphosphine (49 µL, 0.195 mmol, 1.3 equiv) was added rapidly and the reaction stirred at rt in the dark for 30 min. After 30 min, diphenyl diselenide (94 mg, 0.30 mmol, 2.0 equiv) was then added to the reaction mixture. The aluminium foil was removed from the reaction set up and the tube was placed in an ice bath so the reaction mixture was half immersed. The reaction mixture was then irradiated for 40 min using a 150 W tungsten bulb. After 40 min at 0 °C, the crude mixture was filtered through a pad of silica gel, washed through with CH₂Cl₂ (30 mL) and the solvent was removed under reduced pressure. Purification by flash chromatography (2.5% diethyl ether/hexane) afforded *trans*-selenoaziridine (5 mg, 7%) and *cis*-selenoaziridine **60** (40 mg, 60%): ***trans*-diastereoisomer:** ¹H NMR (400 MHz, CDCl₃) δ 7.64–7.56 (m, 2H, 2 × Ph-H), 7.46–7.42 (m, 2H, 2 × Ph-H), 7.31–7.09 (m, 12H, 12 × Ph-H), 7.05–7.02 (m, 4H, 4 × Ph-H), 4.77 (br s, 1H, CHPh₂), 3.84 (d, *J* = 3.0 Hz, 1H, CHSePh), 2.62 (br s, 1H, CHPh). ***cis*-diastereoisomer 60:** off white solid; mp = 116–120 °C; *R*_f = 0.34 (10% diethyl ether/hexane); ν_{max} (film)/cm⁻¹ 3061, 3028, 1601, 1578, 1493, 1477, 1454, 1391, 1269, 1068, 1028, 739, 700; ¹H NMR (400 MHz, CDCl₃) δ 7.59 (d, *J* = 7.8 Hz, 2H, 2 × Ph-H), 7.54–7.49 (m, 4H, 4 × Ph-H), 7.39–7.27 (m, 8H, 8 × Ph-H), 7.23–7.15 (m, 2H, 2 × Ph-H), 7.11–7.04 (m, 4H, 4 × Ph-H), 4.01 (s, 1H, CHPh₂), 3.69 (d, *J* = 6.1 Hz, 1H, CHSePh), 3.11 (d, *J* = 6.1 Hz, 1H, CHPh); ¹³C NMR (101 MHz, CDCl₃) δ 142.5 (Ph-C quat.), 142.4 (Ph-C quat.), 136.5 (Ph-C quat.), 133.2 (2 × Ph-C), 128.7 (2 × Ph-C), 128.5 (2 × Ph-C), 128.4 (2 × Ph-C), 127.9 (4 × Ph-C), 127.5 (Ph-C), 127.4 (Ph-C), 127.3 (Ph-C), 127.2 (2 × Ph-C), 127.1 (Ph-C), 126.8 (Ph-C), 78.8 (CHPh₂), 48.8 (CHSePh), 46.4 (CHPh); HRMS (ESI⁺) *m/z* Calculated for C₂₇H₂₄N⁸⁰Se⁺ [M+H]⁺: 442.1074; Found: 442.1071.

KOtBu Mediated Aziridinyl Radical Formation & Trapping, General Procedure 11: To a flame dried



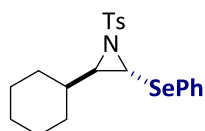
10 mL vial was added the appropriate iodoaziridine (0.27 mmol, 1.0 equiv) and diselenide (0.54 mmol, 2.0 equiv), which was taken into a N₂ filled glove box. KOtBu (49.2 mg, 0.44 mmol, 1.6 equiv) was added and the reaction vial was sealed under nitrogen with a

teflon cap. The vial was then taken outside of the glove box and degassed 2-propanol (2.7 mL) was added. The reaction was then stirred at rt for 10 minutes and transferred to an oil bath at 70 °C. After 15 minutes, the reaction mixture was cooled to 0 °C, filtered through a pad of silica (3 cm × 1 cm) eluting with EtOAc (4 × 10 mL) and solvent removed under reduced pressure. Purification by flash chromatography on deactivated basic alumina (activity IV) afforded the appropriate selenoaziridine.



***trans*-(±)-1-(4-Tolylsulfonyl)-2-(phenylselanyl)-3-(propan-2-yl)aziridine (62a).**

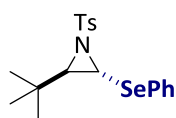
Prepared according to **General Procedure 11** described above, starting from iodoaziridine **20j** (100 mg, 0.27 mmol) and diphenyl diselenide (170 mg, 0.54 mmol). Purification by flash chromatography (10% diethyl ether/hexane) on deactivated basic alumina (activity IV) afforded selenoaziridine **62a** (56 mg, 52%) (*dr* = 5.4:1, *trans*:*cis*) as a colourless oil: ***trans*-selenoaziridine**: *R_f* = 0.25 (20% diethyl ether/hexane); *v*_{max} (film)/cm⁻¹ 3058, 2963, 2874, 1598, 1578, 1478, 1439, 1402, 1326, 1241, 1157, 1088. 964, 908, 815, 742, 688; ¹H NMR (400 MHz, CDCl₃) δ 7.87 (d, *J* = 8.3 Hz, 2H, 2 × SO₂Tol-H), 7.56–7.53 (m, 2H, 2 × SePh-H), 7.33–7.20 (m, 5H, 2 × SO₂Tol-H and 3 × SePh-H), 3.86 (d, *J* = 4.6 Hz, 1H, CHSePh), 2.78 (dd, *J* = 4.6, 8.1 Hz, 1H, CHN), 2.44 (s, 3H, SO₂Tol-CH₃), 1.69–1.61 (m, 1H, CH), 0.92 (d, *J* = 6.8 Hz, 3H, CHCH₃), 0.87 (d, *J* = 6.7 Hz, 3H, CHCH₃); ¹³C NMR (101 MHz, CDCl₃) δ 144.2 (SO₂Tol-C quat.), 136.6 (SO₂TolC-CH₃ quat.), 134.1 (2 × SePh-C), 129.5 (2 × SO₂Tol-C), 129.2 (2 × SePh-C), 129.1 (SePh-C quat.), 128.1 (2 × SO₂Tol-C and SePh-C), 53.8 (CHN), 43.9 (CHSePh), 30.2 (CH), 21.6 (SO₂Tol-CH₃), 19.9 (CHCH₃), 19.5 (CHCH₃); HRMS (ESI⁺) *m/z* Calculated for C₁₈H₂₂NO₂S⁸⁰Se⁺ [M+H]⁺: 396.0531; Found: 396.0555.



***trans*-(±)-1-(4-Tolylsulfonyl)-2-(phenylselanyl)-3-cyclohexylaziridine (62b).**

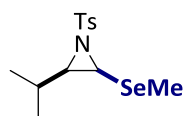
Prepared according to **General Procedure 11** described above, starting from iodoaziridine **20i** (111 mg, 0.27 mmol) and diphenyl diselenide (170 mg, 0.27 mmol). Purification by flash chromatography (10% diethyl ether/hexane) on deactivated basic alumina (activity IV) afforded selenoaziridine **62b** (65 mg, 54%) (*dr* = 6.2:1, *trans*:*cis*) as a colourless oil: ***trans*-selenoaziridine**: *R_f* = 0.22 (20% diethyl ether/hexane); *v*_{max} (film)/cm⁻¹ 2952, 2925, 1598,

1579, 1478, 1449, 1439, 1327, 1160, 1087, 930, 913, 887, 815, 742, 689; ^1H NMR (400 MHz, CDCl_3) δ 7.87 (d, J = 8.3 Hz, 2H, $2 \times \text{SO}_2\text{Tol-H}$), 7.53–7.51 (m, 2H, $2 \times \text{Ph-H}$), 7.32–7.19 (m, 5H, $2 \times \text{SO}_2\text{Tol-H}$ and $3 \times \text{Ph-H}$), 3.86 (d, J = 4.6 Hz, 1H, CHSePh), 2.79 (dd, J = 4.6, 8.3 Hz, 1H, CHN), 2.44 (s, 3H, $\text{SO}_2\text{Tol-CH}_3$), 1.77–1.59 (m, 5H, $2 \times \text{Cy-H}$), 1.34–0.94 (m, 6H, $6 \times \text{Cy-H}$); ^{13}C NMR (101 MHz, CDCl_3) δ 144.2 ($\text{SO}_2\text{Tol-C quat.}$), 136.5 ($\text{SO}_2\text{TolC-CH}_3 \text{ quat.}$), 134.1 ($2 \times \text{SePh-C}$), 129.5 ($2 \times \text{SO}_2\text{Tol-C}$), 129.2 ($2 \times \text{SePh-C}$), 129.1 (SePh-C quat.), 128.1 ($2 \times \text{SO}_2\text{Tol-C}$), 128.0 (SePh-C), 52.6 (CHN), 43.9 (CHSePh), 39.3 (CH), 30.5 (CH_2), 29.9 (CH_2), 25.9 (CH_2), 25.4 (CH_2), 25.2 (CH_2), 21.6 ($\text{SO}_2\text{Tol-CH}_3$); HRMS (ESI^+) m/z Calculated for $\text{C}_{21}\text{H}_{26}\text{NO}_2\text{S}^{80}\text{Se}^+$ $[\text{M}+\text{H}]^+$ 436.0849; Found: 436.0866.



***trans*-(±)-1-(4-Tolylsulfonyl)-2-(phenylselanyl)-3-*tert*-butylaziridine (62c).** Prepared

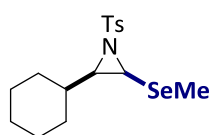
according to **General Procedure 11** described above, starting from iodoaziridine **20n** (104 mg, 0.27 mmol) and diphenyl diselenide (170 mg, 0.54 mmol). Purification by flash chromatography (10% diethyl ether/hexane) on deactivated basic alumina (activity IV) afforded *trans*-selenoaziridine **62c** (75 mg, 67%) as a colourless oil: R_f = 0.25 (20% diethyl ether/hexane); ν_{max} (film)/ cm^{-1} 2959, 1598, 1478, 1328, 1227, 1160, 1089, 931, 898, 743, 687; ^1H NMR (400 MHz, CDCl_3) δ 7.91 (d, J = 8.3 Hz, 2H, $2 \times \text{SO}_2\text{Tol-H}$), 7.62–7.60 (m, 2H, $2 \times \text{SePh-H}$), 7.32–7.28 (m, 5H, $2 \times \text{SO}_2\text{Tol-H}$ and $3 \times \text{SePh-H}$), 3.84 (d, J = 4.7 Hz, 1H, CHSePh), 2.90 (d, J = 4.7 Hz, 1H, CHN), 2.44 (s, 3H, $\text{SO}_2\text{Tol-CH}_3$), 0.77 (s, 9H, $\text{C}(\text{CH}_3)_3$); ^{13}C NMR (101 MHz, CDCl_3) δ 144.2 ($\text{SO}_2\text{Tol-C quat.}$), 136.5 ($\text{SO}_2\text{TolC-CH}_3 \text{ quat.}$), 133.9 ($2 \times \text{SePh-C}$), 129.8 ($2 \times \text{SO}_2\text{Tol-C}$), 129.4 (SePh-C quat.), 129.2 ($2 \times \text{SePh-C}$), 128.3 ($2 \times \text{SO}_2\text{Tol-C}$), 127.9 (SePh-C), 55.3 (CHN), 41.9 (CHSe), 30.9 ($\text{C}(\text{CH}_3)_3 \text{ quat.}$), 26.2 ($\text{C}(\text{CH}_3)_3$), 21.6 ($\text{SO}_2\text{Tol-CH}_3$); HRMS (ESI^+) m/z Calculated for $\text{C}_{19}\text{H}_{24}\text{NO}_2\text{S}^{80}\text{Se}^+$ $[\text{M}+\text{H}]^+$ 410.0693; Found: 410.0707.



***cis*-(±)-1-(4-Tolylsulfonyl)-2-(methylselanyl)-3-(propan-2-yl)aziridine (67a).**

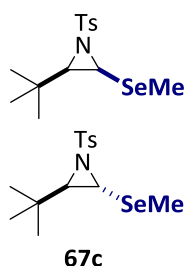
Prepared according to **General Procedure 11** described above, starting from iodoaziridine **20j** (100 mg, 0.27 mmol) and dimethyl diselenide (52 μL , 0.54 mmol). Purification by flash chromatography (10% diethyl ether/hexane) on deactivated basic alumina (activity IV) afforded *cis*-selenoaziridine **67a** (45 mg, 49%) as a colourless oil: R_f = 0.28 (20% diethyl ether/hexane); ν_{max} (film)/ cm^{-1} 2963, 1598, 1467, 1327, 1264, 1159, 1090, 1020, 950, 888, 818, 747, 692, 672; ^1H NMR (400 MHz, CDCl_3) δ 7.85 (d, J = 8.3 Hz, 2H, $2 \times \text{SO}_2\text{Tol-H}$), 7.35 (d, J = 8.2 Hz, 2H, $2 \times \text{SO}_2\text{Tol-H}$), 4.02 (d, J = 6.8 Hz, 1H, CHSeMe), 2.78 (dd, J = 6.8, 9.8 Hz, 1H, CHN), 2.45 (s, 3H, $\text{SO}_2\text{Tol-CH}_3$), 2.02 (s, 3H, SeCH_3), 1.64–1.54 (m, 1H, CH), 0.97 (d, J = 6.8 Hz, 3H, CHCH_3), 0.82 (d, J = 6.7 Hz, 3H, CHCH_3); ^{13}C NMR (101 MHz, CDCl_3) δ 144.7 ($\text{SO}_2\text{Tol-C quat.}$), 134.6 ($\text{SO}_2\text{TolC-CH}_3 \text{ quat.}$), 129.6 ($2 \times \text{SO}_2\text{Tol-C}$), 128.3 ($2 \times \text{SO}_2\text{Tol-C}$), 52.1 (CHN), 41.6 (CHSeMe), 29.3 (CH), 21.7 ($\text{SO}_2\text{Tol-CH}_3$), 20.5

(CHCH₃), 19.3 (CHCH₃), 5.0 (SeCH₃); HRMS (ESI⁺) *m/z* Calculated for C₁₃H₂₀NO₂S⁸⁰Se⁺ [M+H]⁺: 334.0388; Found: 334.0380.



***cis*-(±)-1-(4-Tolylsulfonyl)-2-(methylselanyl)-3-cyclohexylaziridine (67b).**

Prepared according to **General Procedure 11** described above, starting from iodoaziridine **20i** (111 mg, 0.27 mmol) and dimethyl diselenide (52 μL, 0.54 mmol). Purification by flash chromatography (10% diethyl ether/hexane) on deactivated basic alumina (activity IV) afforded *cis*-selenoaziridine **67b** (53 mg, 52%) as a colourless oil: *R_f* = 0.22 (20% diethyl ether/hexane); *v*_{max} (film)/cm⁻¹ 2925, 2851, 1597, 1449, 1325, 1260, 1157, 1090, 1018, 963, 902, 881, 811, 800, 734, 667; ¹H NMR (400 MHz, CDCl₃) δ 7.84 (d, *J* = 8.3 Hz, 2H, 2 × SO₂Tol-H), 7.34 (d, *J* = 8.2 Hz, 2H, 2 × SO₂Tol-H), 4.00 (d, *J* = 6.9 Hz, 1H, CHSeMe), 2.66 (dd, *J* = 6.9, 9.7 Hz, 1H, CHN), 2.45 (s, 3H, SO₂Tol-CH₃), 2.00 (s, 3H, SeCH₃), 1.73–1.61 (m, 3H, 3 × Cy-H), 1.51–1.48 (m, 1H, 3 × Cy-H), 1.28–1.09 (m, 7H, 7 × Cy-H); ¹³C NMR (101 MHz, CDCl₃) δ 144.7 (SO₂Tol-C quat.), 134.6 (SO₂TolC-CH₃ quat.), 129.6 (2 × SO₂Tol-C), 128.3 (2 × SO₂Tol-C), 50.7 (CHN), 41.2 (CHSeMe), 38.1 (CH), 30.8 (CH₂), 29.8 (CH₂), 25.9 (CH₂), 25.3 (CH₂), 25.2 (CH₂), 21.7 (SO₂Tol-CH₃), 4.9 (SeCH₃); HRMS (ESI⁺) *m/z* Calculated for C₂₆H₂₄NO₂S⁸⁰Se⁺ [M+H]⁺ 374.0693; Found: 374.0695.

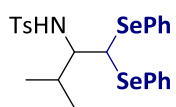


***cis*-(±)-1-(4-Tolylsulfonyl)-2-(methylselanyl)-3-*tert*-butylaziridine and *trans*-(±)-1-**

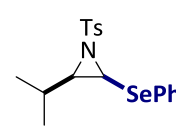
(4-Tolylsulfonyl)-2-(methylselanyl)-3-*tert*-butylaziridine (67c).

Prepared according to **General Procedure 11** described above, starting from iodoaziridine **20n** (104 mg, 0.27 mmol) and dimethyl diselenide (52 μL, 0.54 mmol). Purification by flash chromatography (10% diethyl ether/hexane) on deactivated basic alumina (activity IV) afforded a mixture of selenoaziridines **67c** (53 mg, 55%) as colourless oils (*cis* = 26 mg, *trans*:*cis* (1.9:1) = 27 mg): ***cis*-selenoaziridine**: *R_f* = 0.26 (20% diethyl ether/hexane); *v*_{max} (film)/cm⁻¹ 2959, 2929, 2870, 1598, 1478, 1325, 1290, 1224, 1157, 1089, 1019, 927, 877, 813, 747, 708, 680; ¹H NMR (400 MHz, CDCl₃) δ 7.86 (d, *J* = 8.3 Hz, 2H, 2 × SO₂Tol-H), 7.35 (d, *J* = 8.2 Hz, 2H, 2 × SO₂Tol-H), 3.85 (d, *J* = 7.4 Hz, 1H, CHSeMe), 2.71 (d, *J* = 7.4 Hz, 1H, CHN), 2.46 (s, 3H, SO₂Tol-CH₃), 2.05 (s, 3H, SeCH₃), 0.91 (s, 9H, C(CH₃)₃); ¹³C NMR (101 MHz, CDCl₃) δ 144.6 (SO₂Tol-C quat.), 134.7 (SO₂TolC-CH₃ quat.), 129.6 (2 × SO₂Tol-C), 128.2 (2 × SO₂Tol-C), 53.8 (CHN), 41.4 (CHSe), 31.6 (C(CH₃)₃ quat.), 27.6 (C(CH₃)₃), 21.7 (SO₂Tol-CH₃), 7.2 (SeCH₃); ***trans*-selenoaziridine**: *R_f* = 0.23 (20% diethyl ether/hexane); *v*_{max} (film)/cm⁻¹ 2958, 2870, 1598, 1404, 1366, 1325, 1226, 1156, 1089, 1019, 929, 814, 746, 707, 686; ¹H NMR (400 MHz, CDCl₃) δ 7.88 (d, *J* = 8.3 Hz, 2H, 2 × SO₂Tol-H), 7.32 (d, *J* = 8.2 Hz, 2H, 2 × SO₂Tol-H), 3.71 (d, *J* = 4.8 Hz, 1H, CHSeMe), 2.85 (d, *J* = 4.8 Hz, 1H, CHN), 2.44 (s, 3H, SO₂Tol-CH₃), 2.28 (s, 3H, SeCH₃), 0.77 (s, 9H, C(CH₃)₃); ¹³C NMR (101 MHz, CDCl₃) δ 144.0 (SO₂Tol-C

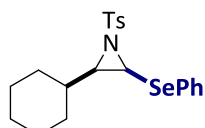
quat.), 137.1 (SO₂TolC-CH₃ quat.), 129.4 (2 × SO₂Tol-C), 128.0 (2 × SO₂Tol-C), 55.9 (CHN), 38.6 (CHSe), 30.8 (C(CH₃)₃ quat.), 26.2 (C(CH₃)₃), 21.6 (SO₂Tol-CH₃), 7.2 (SeCH₃); HRMS (ESI⁺) *m/z* Calculated for C₁₄H₂₂NO₂S⁸⁰Se⁺ [M+H]⁺ 348.0536; Found: 348.0554.

 **4-Tolyl-N-[3-methyl-1,1-bis(phenylselanyl)butan-2-yl]-1-sulfonamide (64).** Diphenyl diselenide (169 mg, 0.54 mmol, 2.0 equiv) and KOtBu (49 mg, 0.43 mmol, 1.6 equiv) were sealed in a 5 mL vial under an inert atmosphere in a N₂ filled glove box. *s*-BuOH (1.6 mL) was then added and the resulting suspension stirred for 10 minutes at rt. Iodoaziridine **20j** (100 mg, 0.27 mmol, 1.0 equiv) was dissolved in *s*-BuOH (0.8 mL) and added dropwise at rt to the reaction mixture. The reaction was then heated to 60 °C in an oil bath for 2 h. The suspension was then filtered through a pad of silica, eluting with hexane:EtOAc (1:1, 50 mL) and the solvent was then removed under reduced pressure. Purification by flash chromatography (10% EtOAc/hexane) afforded amino *gem*-diselenide **64** (12 mg, 11%) as a colourless oil: *R*_f = 0.08 (10% EtOAc/hexane); *v*_{max} (film)/cm⁻¹ 3280, 3056, 2963, 1598, 1578, 1475, 1438, 1415, 1331, 1162, 1093, 1022, 906, 814, 740, 691, 664; ¹H NMR (400 MHz, CDCl₃) δ 7.45–7.22 (m, 12 H, 10 × SePh-H and 2 × SO₂Tol-H), 7.04 (d, *J* = 8.1 Hz, 2H, 2 × SO₂Tol-H), 5.03 (d, *J* = 10.3 Hz, 1H, NH), 4.22 (d, *J* = 3.8 Hz, 1H, CHSePh), 3.44 (td, *J* = 3.8, 4.2, 10.3 Hz, 1H, CHN), 2.40–2.35 (m, 4H, SO₂Tol-CH₃ and CH), 0.90 (d, *J* = 6.8 Hz, 3H, CH₃), 0.82 (d, *J* = 6.8 Hz, 3H, CH₃); ¹³C NMR (101 MHz, CDCl₃) δ 143.0 (SO₂Tol-C quat.), 137.7 (SO₂TolC-CH₃ quat.), 134.9 (2 × SePh-C), 133.8 (2 × SePh-C), 130.4 (SePh-C quat.), 130.0 (SePh-C quat.), 129.4 (2 × SO₂Tol-C), 129.2 (4 × SePh-C), 128.5 (SePh-C), 128.2 (SePh-C), 126.9 (2 × SO₂Tol-C), 61.4 (CHN), 50.9 (CHSePh), 29.9 (CH), 21.5 (SO₂Tol-CH₃), 21.3 (CH₃), 17.9 (CH₃); HRMS (ESI) *m/z* Calculated for C₂₄H₂₇NO₂S⁸⁰Se₂⁻ [M-H]⁻: 552.0020; Found: 552.0042.

Iodine–Lithium Exchange and Trapping with Diselenides (General Procedure 9): Identical to **General Procedure 9** (*vide supra*), but 1.0 equiv diselenide used as electrophile instead of 3.0 equiv.

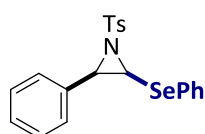
 ***cis*-(±)-1-(4-Tolylsulfonyl)-2-(phenylselanyl)-3-(propan-2-yl)aziridine (63a).** Prepared according to **General Procedure 9** described above, starting from iodoaziridine **20j** (100 mg, 0.27 mmol) and diphenyl diselenide (84 mg, 0.27 mmol). Diphenyl diselenide dissolved in THF (0.5 mL) prior to addition. Purification by flash chromatography (10% diethyl ether/hexane) afforded *cis*-selenoaziridine **63a** (86 mg, 80%) as a colourless oil: *R*_f = 0.25 (20% diethyl ether/hexane); *v*_{max} (film)/cm⁻¹ 2962, 2873, 1598, 1478, 1439, 1327, 1158, 1090, 1021, 946, 887, 822, 743, 691, 671; ¹H NMR (400 MHz, CDCl₃) δ 7.75 (d, *J* = 8.3 Hz, 2H, 2 × SO₂Tol-H), 7.50–7.47 (m, 2H, 2 × SePh-H), 7.32–7.20 (m, 5H, 2 × SO₂Tol-H and 3 × SePh-H), 4.26 (d, *J* = 6.8 Hz,

1H, CHSePh), 2.69 (dd, $J = 6.8, 9.9$ Hz, 1H, CHN), 2.45 (s, 3H, SO₂Tol-CH₃), 1.68–1.56 (m, 1H, CH), 1.04 (d, $J = 6.8$ Hz, 3H, CHCH₃), 0.91 (d, $J = 6.7$ Hz, 3H, CHCH₃); ¹³C NMR (101 MHz, CDCl₃) δ 144.5 (SO₂Tol-C quat.), 134.6 (SO₂TolC-CH₃ quat.), 134.0 (2 $\times$ SePh-C), 129.6 (2 $\times$ SO₂Tol-C), 129.3 (2 $\times$ SePh-C), 128.2 (2 $\times$ SO₂Tol-C), 128.0 (SePh-C), 127.5 (SePh-C quat.), 50.7 (CHN), 45.7 (CHSePh), 29.6 (CH), 21.7 (SO₂Tol-CH₃), 20.6 (CHCH₃), 19.3 (CHCH₃); HRMS (ESI⁺) m/z Calculated for C₁₈H₂₂NO₂S⁸⁰Se⁺ [M+H]⁺ 396.0536; Found: 396.0543.



***cis*-(±)-1-(4-Tolylsulfonyl)-2-(phenylselanyl)-3-cyclohexylaziridine (63b).**

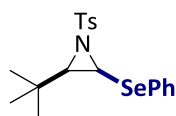
Prepared according to **General Procedure 9** described above, starting from iodoaziridine **20i** (109 mg, 0.27 mmol) and diphenyl diselenide (84 mg, 0.27 mmol). Diphenyl diselenide dissolved in THF (0.5 mL) prior to addition. Purification by flash chromatography (10% diethyl ether/hexane) afforded *cis*-selenoaziridine **63b** (82 mg, 70%) as a colourless oil: $R_f = 0.22$ (20% diethyl ether/hexane); $\nu_{\max}$ (film)/cm⁻¹ 2925, 2851, 1597, 1579, 1478, 1327, 1159, 1091, 1021, 960, 901, 883, 818, 741, 691, 669; ¹H NMR (400 MHz, CDCl₃) δ 7.74 (d, $J = 8.2$ Hz, 2H, 2 $\times$ SO₂Tol-H), 7.47 (d, $J = 8.1$ Hz, 2H, 2 $\times$ Ph-H), 7.31–7.20 (m, 5H, 2 $\times$ SO₂Tol-H and 3 $\times$ Ph-H), 4.24 (d, $J = 6.8$ Hz, 1H, CHSePh), 2.74 (dd, $J = 6.8, 9.7$ Hz, 1H, CHN), 2.45 (s, 3H, SO₂Tol-CH₃), 1.79–1.71 (m, 2H, 2 $\times$ Cy-H), 1.69–1.60 (m, 3H, 3 $\times$ Cy-H), 1.35–1.05 (m, 6H, 6 $\times$ Cy-H); ¹³C NMR (101 MHz, CDCl₃) δ 144.5 (SO₂Tol-C quat.), 134.6 (SO₂TolC-CH₃ quat.), 134.0 (2 $\times$ SePh-C), 129.6 (2 $\times$ SO₂Tol-C), 129.2 (2 $\times$ SePh-C), 128.1 (2 $\times$ SO₂Tol-C), 127.9 (SePh-C), 127.5 (SePh-C quat.), 49.1 (CHN), 45.4 (CHSePh), 38.4 (CH), 30.9 (CH₂), 29.8 (CH₂), 25.9 (CH₂), 25.3 (CH₂), 25.2 (CH₂), 21.7 (SO₂Tol-CH₃); HRMS (ESI⁺) m/z Calculated for C₂₁H₂₆NO₂S⁸⁰Se⁺ [M+H]⁺ 436.0849; Found: 436.0851.



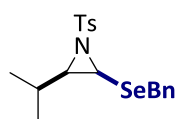
***cis*-(±)-1-(4-Tolylsulfonyl)-2-(phenylselanyl)-3-phenylaziridine (63c).**

Prepared according to **General Procedure 9** described above, starting from iodoaziridine **20a** (108 mg, 0.27 mmol) and diphenyl diselenide (84 mg, 0.27 mmol). Diphenyl diselenide dissolved in THF (0.5 mL) prior to addition. Purification by flash chromatography (10% diethyl ether/hexane) afforded *cis*-selenoaziridine **63c** (78 mg, 67%) as a white solid: mp = 98–99 °C; $R_f = 0.23$ (20% diethyl ether/hexane); $\nu_{\max}$ (film)/cm⁻¹ 3060, 1597, 1326, 1260, 1156, 1089, 1021, 895, 733, 690, 658; ¹H NMR (400 MHz, CDCl₃) δ 7.84 (d, $J = 8.3$ Hz, 2H, 2 $\times$ SO₂Tol-H), 7.41–7.18 (m, 12H, 5 $\times$ SePh-H, 5 $\times$ Ph-H and 2 $\times$ SO₂Tol-H), 4.51 (d, $J = 7.0$ Hz, 1H, CHSePh), 4.18 (d, $J = 7.0$ Hz, 1H, CHN), 2.46 (s, 3H, SO₂Tol-CH₃); ¹³C NMR (101 MHz, CDCl₃) δ 144.8 (SO₂Tol-C quat.), 134.5 (SO₂TolC-CH₃ quat.), 134.1 (2 $\times$ SePh-C), 132.5 (Ph-C quat.), 129.8 (2 $\times$ SO₂Tol-C), 129.2 (2 $\times$ SePh-C), 128.5 (Ph-C), 128.3 (2 $\times$ Ph-C), 128.1 (2 $\times$ SO₂Tol-C), 128.0 (SePh-C), 127.9 (SePh-C quat.), 127.4 (2 $\times$ Ph-C), 47.3

(CHSePh), 45.3 (CHN), 21.7 (SO₂Tol-CH₃); HRMS (ESI⁺) *m/z* Calculated for C₂₁H₂₀NO₂S⁸⁰Se⁺ [M+H]⁺ 430.0380; Found: 430.0385.

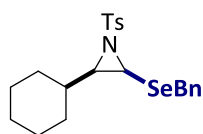


***cis*-(±)-1-(4-Tolylsulfonyl)-2-(phenylselanyl)-3-*tert*-butylaziridine (63d).** Prepared according to **General Procedure 9** described above, starting from iodoaziridine **20n** (102 mg, 0.27 mmol) and diphenyl diselenide (84 mg, 0.27 mmol). Diphenyl diselenide dissolved in THF (0.5 mL) prior to addition. Purification by flash chromatography (10% diethyl ether/hexane) afforded *cis*-selenoaziridine **63d** (81 mg, 74%) as a colourless oil: *R_f* = 0.29 (20% diethyl ether/hexane); *v*_{max} (film)/cm⁻¹ 3055, 2961, 2870, 1598, 1579, 1478, 1326, 1158, 1090, 925, 874, 834, 814, 743, 679; ¹H NMR (400 MHz, CDCl₃) δ 7.76 (d, *J* = 8.3 Hz, 2H, 2 × SO₂Tol-H), 7.51–7.48 (m, 2H, 2 × SePh-H), 7.34–7.23 (m, 5H, 2 × SO₂Tol-H and 3 × SePh-H), 4.08 (d, *J* = 7.3 Hz, 1H, CHSePh), 2.76 (d, *J* = 7.3 Hz, 1H, CHN), 2.46 (s, 3H, SO₂Tol-CH₃), 0.99 (s, 9H, C(CH₃)₃); ¹³C NMR (101 MHz, CDCl₃) δ 144.5 (SO₂Tol-C quat.), 134.6 (SO₂TolC-CH₃ quat.), 134.1 (2 × SePh-C), 129.6 (2 × SO₂Tol-C), 129.4 (SePh-C quat.), 129.3 (2 × SePh-C), 128.2 (2 × SO₂Tol-C), 128.1 (SePh-C), 52.9 (CHN), 45.5 (CHSe), 31.7 (C(CH₃)₃ quat.), 27.5 (C(CH₃)₃), 21.7 (SO₂Tol-CH₃); HRMS (ESI⁺) *m/z* Calculated for C₁₉H₂₄NO₂S⁸⁰Se⁺ [M+H]⁺ 410.0693; Found: 410.0704.

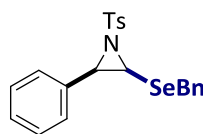


***cis*-(±)-1-(4-Tolylsulfonyl)-2-(benzylselanyl)-3-(propan-2-yl)aziridine (68a).**

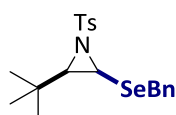
Prepared according to **General Procedure 9** described above, starting from iodoaziridine **20j** (100 mg, 0.27 mmol) and dibenzyl diselenide (92 mg, 0.27 mmol). Dibenzyl diselenide dissolved in THF (0.5 mL) prior to addition. Purification by flash chromatography (10% diethyl ether/hexane) afforded *cis*-selenoaziridine **68a** (75 mg, 68%) as a colourless oil: *R_f* = 0.23 (20% diethyl ether/hexane); *v*_{max} (film)/cm⁻¹ 3030, 2961, 2872, 1598, 1495, 1326, 1185, 1158, 1090, 947, 888, 818, 747, 697; ¹H NMR (400 MHz, CDCl₃) δ 7.85 (d, *J* = 8.3 Hz, 2H, 2 × SO₂Tol-H), 7.36–7.29 (m, 6H, 2 × SO₂Tol-H and 4 × Ph-H), 7.26–7.22 (m, 1H, Ph-H), 4.07 (d, *J* = 6.9 Hz, 1H, CHSePh), 3.94 (d, *J* = 11.8 Hz, 1H, CH₂), 3.87 (d, *J* = 11.8 Hz, 1H, CH₂), 2.57 (dd, *J* = 6.9, 9.9 Hz, 1H, CHN), 2.45 (s, 3H, SO₂Tol-CH₃), 1.59–1.51 (m, 1H, CH), 0.89 (d, *J* = 6.8 Hz, 3H, CHCH₃), 0.77 (d, *J* = 6.7 Hz, 3H, CHCH₃); ¹³C NMR (101 MHz, CDCl₃) δ 144.7 (SO₂Tol-C quat.), 138.2 (Ph-C quat.), 134.6 (SO₂TolC-CH₃ quat.), 129.6 (2 × SO₂Tol-C), 128.9 (2 × Ph-C), 128.7 (2 × Ph-C), 128.3 (2 × SO₂Tol-C), 127.1 (Ph-C), 52.1 (CHN), 41.5 (CHSePh), 29.5 (CH), 28.7 (PhCH₂), 21.7 (SO₂Tol-CH₃), 20.5 (CHCH₃), 19.2 (CHCH₃); HRMS (ESI⁺) *m/z* Calculated for C₁₉H₂₄NO₂S⁸⁰Se⁺ [M+H]⁺ 410.0693; Found: 410.0690.



***cis*-(±)-1-(4-Tolylsulfonyl)-2-(benzylselanyl)-3-cyclohexylaziridine (68b).** Prepared according to **General Procedure 9** described above, starting from iodoaziridine **20i** (109 mg, 0.27 mmol) and dibenzyl diselenide (92 mg, 0.27 mmol). Dibenzyl diselenide dissolved in THF (0.5 mL) prior to addition. Purification by flash chromatography (10% diethyl ether/hexane) afforded *cis*-selenoaziridine **68b** (87 mg, 72%) as a colourless oil: R_f = 0.22 (20% diethyl ether/hexane); $\nu_{\max}$ (film)/ cm^{-1} 2924, 2851, 1598, 1495, 1451, 1325, 1223, 1158, 1091, 961, 902, 885, 817, 742, 697, 669; ^1H NMR (400 MHz, CDCl_3) δ 7.84 (d, J = 8.2 Hz, 2H, 2 $\times$ $\text{SO}_2\text{Tol-H}$), 7.36–7.22 (m, 7H, 2 $\times$ $\text{SO}_2\text{Tol-H}$ and 5 $\times$ Ph-H), 4.06 (d, J = 6.9 Hz, 1H, CHSeBn), 3.93 (d, J = 11.8 Hz, 1H, PhCH₂), 3.85 (d, J = 11.8 Hz, 1H, PhCH₂), 2.62 (dd, J = 6.9, 9.8 Hz, 1H, CHN), 2.45 (s, 3H, $\text{SO}_2\text{Tol-CH}_3$), 1.69–1.52 (m, 3H, 3 $\times$ Cy-H), 1.46–1.40 (m, 1H, Cy-H), 1.32–0.85 (m, 7H, 7 $\times$ Cy-H); ^{13}C NMR (101 MHz, CDCl_3) δ 144.7 ($\text{SO}_2\text{Tol-C quat.}$), 138.2 (Ph-C quat.), 134.6 ($\text{SO}_2\text{TolC-CH}_3$ quat.), 129.6 (2 $\times$ $\text{SO}_2\text{Tol-C}$), 128.9 (2 $\times$ Ph-C), 128.6 (2 $\times$ Ph-C), 128.3 (2 $\times$ $\text{SO}_2\text{Tol-C}$), 127.1 (Ph-C), 50.9 (CHN), 41.1 (CHSeBn), 38.3 (CH), 30.8 (CH_2), 29.7 (CH_2), 28.7 (PhCH₂), 25.9 (CH_2), 25.19 (CH_2), 25.15 (CH_2), 21.7 ($\text{SO}_2\text{Tol-CH}_3$); HRMS (ESI⁺) m/z Calculated for $\text{C}_{22}\text{H}_{28}\text{NO}_2\text{S}^{80}\text{Se}^+$ [M+H]⁺ 450.1006; Found: 450.1005.



***cis*-(±)-1-(4-Tolylsulfonyl)-2-(benzylselanyl)-3-phenylaziridine (68c).** Prepared according to **General Procedure 9** described above, starting from iodoaziridine **20a** (108 mg, 0.27 mmol) and dibenzyl diselenide (92 mg, 0.27 mmol). Dibenzyl diselenide dissolved in THF (0.5 mL) prior to addition. Purification by flash chromatography (10% diethyl ether/hexane) afforded *cis*-selenoaziridine **68c** (89 mg, 74%) as a colourless oil: R_f = 0.22 (20% diethyl ether/hexane); $\nu_{\max}$ (film)/ cm^{-1} 3030, 1598, 1495, 1453, 1326, 1156, 1090, 1025, 899, 758, 736, 696, 659; ^1H NMR (400 MHz, CDCl_3) δ 7.93 (d, J = 8.1 Hz, 2H, 2 $\times$ $\text{SO}_2\text{Tol-H}$), 7.39–7.24 (m, 12H, 10 $\times$ Ph-H and 2 $\times$ $\text{SO}_2\text{Tol-H}$), 4.31 (d, J = 7.0 Hz, 1H, CHSeBn), 4.08 (d, J = 7.0 Hz, 1H, CHN), 3.90 (d, J = 11.8 Hz, 1H, PhCH₂), 3.80 (d, J = 11.8 Hz, 1H, PhCH₂), 2.48 (s, 3H, $\text{SO}_2\text{Tol-CH}_3$); ^{13}C NMR (101 MHz, CDCl_3) δ 144.8 ($\text{SO}_2\text{Tol-C quat.}$), 138.0 (Ph-C quat.), 134.6 ($\text{SO}_2\text{TolC-CH}_3$ quat.), 132.6 (Ph-C quat.), 129.8 (2 $\times$ $\text{SO}_2\text{Tol-C}$), 128.9 (2 $\times$ Ph-C), 128.6 (2 $\times$ Ph-C), 128.4 (2 $\times$ Ph-C), 128.1 (2 $\times$ $\text{SO}_2\text{Tol-C}$), 128.0 (2 $\times$ Ph-C), 127.3 (2 $\times$ Ph-C), 127.1 (Ph-C), 46.3 (CHN), 43.1 (CHSeBn), 28.4 (PhCH₂), 21.7 ($\text{SO}_2\text{Tol-CH}_3$); HRMS (ESI⁺) m/z Calculated for $\text{C}_{22}\text{H}_{22}\text{NO}_2\text{S}^{80}\text{Se}^+$ [M+H]⁺ 444.0536; Found: 444.0540.



***cis*-(±)-1-(4-Tolylsulfonyl)-2-(benzylselanyl)-3-tert-butylaziridine (68d).** Prepared according to **General Procedure 9** described above, starting from iodoaziridine **20n** (102 mg, 0.27 mmol) and dibenzyl diselenide (92 mg, 0.27 mmol). Dibenzyl diselenide dissolved in THF (0.5 mL) prior to addition. Purification by flash chromatography (10% diethyl ether/hexane) afforded *cis*-selenoaziridine **68d** (82 mg, 72%) as a colourless oil: R_f = 0.33

(20% diethyl ether/hexane); $\nu_{\max}$ (film)/ cm^{-1} 2961, 1598, 1366, 1325, 1288, 1158, 1090, 926, 878, 815, 748, 698, 681; ^1H NMR (400 MHz, CDCl_3) δ 7.86 (d, J = 8.3 Hz, 2H, 2 $\times$ $\text{SO}_2\text{Tol-H}$), 7.36–7.22 (m, 7H, 2 $\times$ $\text{SO}_2\text{Tol-H}$ and 5 $\times$ Ph-H), 3.94–3.84 (m, 3H, PhCH_2 and CHSeBn), 2.67 (d, J = 7.5 Hz, 1H, CHN), 2.46 (s, 3H, $\text{SO}_2\text{Tol-CH}_3$), 0.87 (s, 9H, $\text{C}(\text{CH}_3)_3$); ^{13}C NMR (101 MHz, CDCl_3) δ 144.6 ($\text{SO}_2\text{Tol-C quat.}$), 137.8 (Ph-C quat.), 134.7 ($\text{SO}_2\text{TolC-CH}_3$ quat.), 129.6 (2 $\times$ $\text{SO}_2\text{Tol-C}$), 129.1 (2 $\times$ Ph-C), 128.7 (2 $\times$ Ph-C), 128.2 (2 $\times$ $\text{SO}_2\text{Tol-C}$), 127.1 (Ph-C), 54.0 (CHN), 40.5 (CHSeBn), 31.6 ($\text{C}(\text{CH}_3)_3$ quat.), 30.4 (PhCH_2), 27.6 ($\text{C}(\text{CH}_3)_3$), 21.7 ($\text{SO}_2\text{Tol-CH}_3$); HRMS (ESI^+) m/z Calculated for $\text{C}_{20}\text{H}_{26}\text{NO}_2\text{S}^{80}\text{Se}^+$ $[\text{M}+\text{H}]^+$ 424.0849; Found: 424.0862.

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