"The only real mistake is the one from which we learn nothing."

- Henry Ford

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New strategies for the construction of heterocyclic systems through ring transformation of aziridines and azetidines

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Nieuwe strategieën voor de constructie van heterocyclische systemen door middel van ringtransformaties van aziridinen en azetidinen

Ghent, October 2017

The author,   The promoter,

ir. Jeroen Dolfen   Prof. dr. ir. Matthias D'hooghe

WOORD VOORAF

't Is gebeurd! Met deze welklikkende woorden van ene Erik Van Looy sluit ik een 9 jaar durend huzarenstukje aan het Boerekot met veel prettige (maar ook minder leuke) herinneringen af. We zeggen wel eens dat het leven als een trein voorbij raast en dat je het beste moet maken van elk moment. Zo'n zaken kan je natuurlijk niet alleen verwezenlijken en via deze weg wil ik dan ook iedereen een dankjewel zeggen die op de één of andere manier een steentje hebben bijgedragen tijdens de voorbije jaren.

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Jeroen Dolfen

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TABLE OF CONTENTS

LIST OF ABBREVIATONS

$AgBF_4$	silver tetrafluoroborate		EtOH	ethanol
$AgNO_3$	silver nitrate		eV	electronvolt
AIBN	azobisisobutyronitrile		$FeCl_3$	iron(III) chloride
$AlCl_3$	aluminium chloride		*gem*	geminal
AlH_2Cl	monochloroalane		H_2	hydrogen atmosphere
Ar	aryl or argon atmosphere		H_2O	water
Bn	benzyl		HCN	hydrogen cyanide
$BnNH_2$	benzylamine		HMBC	heteronuclear multiple-bond correlation
Boc_2O	di-*tert*-butyl dicarbonate			
Br_2	bromine		HMPA	hexamethylphosphoramide
BuLi	butyllithium		HPLC	high-performance liquid chromatography
c	concentration optical rotation			
CBz	carboxybenzyl		HRMS	high-resolution mass spectrometry
$CDCl_3$	deuterated chloroform			
CDI	carbonyldiimidazole		Hz	Hertz
CF_3	trifluoromethyl		I_2	iodine
CH_2Cl_2	dichloromethane		*i*Bu	isobutyl
CH_3CN	acetonitrile		$In(OTf)_3$	indium(III) trifluoromethane-sulfonate
$CHCl_3$	chloroform			
*c*Hex	cyclohexyl		*i*Pr	isopropyl
cm^{-1}	reciprocal centimeter		*i*PrOH	isopropanol
CsF	cesium fluoride		IR	infrared spectroscopy
d	doublet		*J*	coupling constant
DAST	diethylaminosulfur trifluoride		K_2CO_3	potassium carbonate
DCC	*N,N*-dicyclohexylcarbodiimide		KCN	potassium cyanide
DFT	density functional theory		KO*t*Bu	potassium *tert*-butoxide
DIBAL-H	diisobutylaluminium hydride		KSCN	potassium thiocyanate
DMAP	4-dimethylaminopyridine		kt	kamertemperatuur
DMF	*N,N*-dimethylformamide		LC	liquid chromatography
DMSO	dimethyl sulfoxide		LDA	lithium diisopropylamide
dr	diastereomeric ratio		$LiAlH_4$	lithium aluminium hydride
ee	enantiomeric excess		LiCl	lithium chloride
equiv	equivalents		LiHMDS	lithium hexamethyldisilazide
er	enantiomeric ratio		LR	Lawesson's reagent
Et	ethyl		m	multiplet
Et_2O	diethylether		*M*	mother ion
Et_3N	triethylamine		Me	methyl
Et_3SiH	triethylsilyl hydride		MeI	methyl iodide
EtI	ethyl iodide		MeOH	methanol
EtOAc	ethyl acetate		$MgSO_4$	magnesium sulfate

MHz	megaHertz		THF	tetrahydrofuran
Mp	melting point		TLC	thin layer chromatography
MS	mass spectrometry		TMSCF$_3$	trifluoromethyltrimethylsilane
MsCl	mesyl chloride		TOF	time-of-flight
MW	microwave		*t*Pent	*tert*-pentyl
m/*z*	mass number (*m*) over charge number (*z*)		TsCl	*para*-toluenesulfonyl chloride
			TS	transition state
N$_2$	nitrogen atmosphere		*vic*	vicinal
NaBH$_4$	sodium borohydride		ZnCl$_2$	zinc chloride
NaHCO$_3$	sodium bicarbonate		$[\alpha]_D^{25}$	specific optical rotation at 25 °C and 589 nm
NaIO$_4$	sodium periodate			
NaOAc	sodium acetate		δ	chemical shift
NaOH	sodium hydroxide		Δ	reflux
NaOMe	sodium methoxide		ΔG	Gibbs free energy
NBS	*N*-bromosuccinimide			
*n*Bu	*n*-butyl			
NMR	nuclear magnetic resonance			
NOE	nuclear Overhauser effect			
NOESY	nuclear Overhauser effect spectroscopy			
*n*Pr	*n*-propyl			
Pd	palladium			
Pd(OH)$_2$	palladium hydroxide			
Ph	phenyl			
p	pentet			
*p*TsOH·H$_2$O	*para*-toluenesulfonic acid monohydrate			
q	quadruplet			
R$_f$	retention factor			
rt	room temperature			
s	singlet			
*s*Bu	*sec*-butyl			
Sc(OTf)$_3$	scandium(III) trifluoromethane-sulfonate			
SiO$_2$	silicium dioxide			
Sn(OTf)$_2$	tin(II) trifluoromethane-sulfonate			
t	triplet			
TBACN	tetrabutylammonium cyanide			
*t*Bu	*tert*-butyl			
Tf$_2$O	triflic anhydride			
TFA	trifluoroacetic acid			

INTRODUCTION AND GOALS

1. Introduction

Azaheterocyclic systems comprise valuable substructures of biologically active compounds and, as a consequence, the design of novel synthetic approaches toward azaheterocyclic motifs represents an important aspect of modern organic chemistry. In particular, pyrrolidines and piperidines have acquired a pivotal position in medicinal chemistry, and many synthetic endeavors are devoted to the construction of these important scaffolds.[1] For example, the piperidine moiety is present in paroxetine **1** (Paxil®, Seroxat®),[2] which is known for its antidepressant activity (Figure 1). Methylphenidate **2**,[3] sold under Rilatin® as the most common trade name, stimulates the central nervous system, while loperamide **3** (Imodium®)[4] is known for its activity against diarrhea. Several pyrrolidines possess anticonvulsant properties, such as levetiracetam **4a** (Keppra®)[5] and brivaracetam **4b** (Briviact®).[6] Clindamycin **5** (Cleocin®) is an antibiotic used for the treatment of a number of bacterial infections.[7]

Paroxetine **1** Methylphenidate **2** Loperamide **3**

Levetiracetam **4a** (R = H) Clindamycin **5**
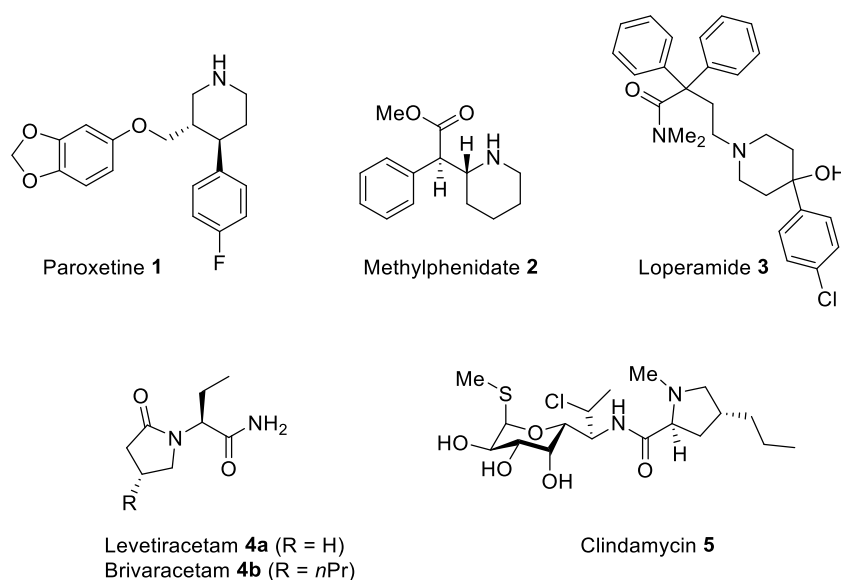Brivaracetam **4b** (R = *n*Pr)

Figure 1

A powerful strategy for the synthesis of stereodefined azaheterocycles is based on the ring rearrangement of small ring precursors, and aziridine and/or azetidine ring enlargements have been shown to be of particular importance in that respect.[8] Smaller ring systems have less conformational freedom, culminating in an enhanced reaction selectivity profile. Furthermore, due to their high ring strain, these small rings display a high reactivity toward nucleophilic attack,[9] often triggering a subsequent ring-expansion reaction. Moreover, judicious selection of nucleophiles enables the introduction of additional functional groups at specific sites with proper stereochemistry.[10]

The aziridine unit, being the smallest nitrogen-containing ring system, represents a prominent candidate susceptible to undergo reactions toward (a)cyclic target compounds because of its large ring strain energy (27 kcal/mol).[11] However, its ring opening is strictly dependent on the characteristics of the *N*-substituent present on the aziridine core.[12] Activated aziridines, bearing an electron-withdrawing group at nitrogen (such as *N*-sulfonylaziridines), are very prone to undergo ring-opening reactions. Moreover,

nucleophilic attack across these activated aziridines occurs mainly at the less-hindered carbon atom (steric effects), apart from some special cases with regard to 2-vinyl- and 2-phenyl-substituted aziridines (electronic reasons).[13] Aziridines with an electron-donating substituent at nitrogen, so-called non-activated aziridines (such as *N*-alkyl derivatives), are far more stable and activation of the ring system is often required to effect ring opening. As depicted in Scheme 1, the addition of an appropriate electrophile to aziridines **6** (R^1 = alkyl) leads to the formation of an aziridinium intermediate **7**, which is very compliant to undergo nucleophilic attack. More specifically, the external addition of Lewis acids, acyl or alkoxycarbonyl electrophiles, acids, alkyl halides, alkyl triflates, and silylation reagents has been proven to be successful in a broad range of ring-opening reactions.[14] Depending on the incoming nucleophile (Nu), the used electrophile (E) and the nature of the substituent (R^2) on the aziridine moiety, the envisioned ring-opening reaction can be controlled in a regio- and stereoselective manner.[15]
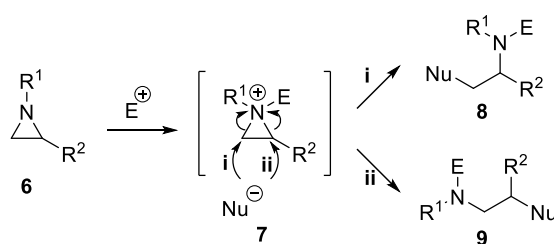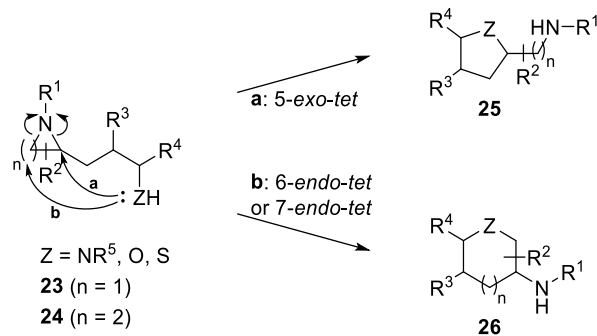

Scheme 1

Besides activation of the aziridine moiety via intermolecular *N*-alkylation/acylation/protonation (Scheme 2, equation 1, n = 1), implying the addition of external electrophiles, analogous aziridinium intermediates can be obtained in an intramolecular manner, leading to transient bicyclic aziridinium salts **13** (Scheme 2, equation 2, n = 1) which can act as a source for ring-expanded products. Depending on the distance between the nucleophilic aziridine nitrogen atom and the carbon atom attached to the leaving group, bicyclic aziridinium ions of different ring size can be generated. Due to their high ring strain energy, these bicyclic aziridinium salts, *i.e.* 1-azoniabicyclo[m.1.0]alkane intermediates **13** (n = 1), are consequently very prone to experience nucleophilic attack (often in a regioselective way), resulting in azaheterocycles of larger ring size. Analogous to aziridines, their higher, four-membered homologues are also characterized by a high ring strain energy (25.2 kcal/mol, parent *NH*-azetidine),[16] rendering them susceptible for ring-opening reactions toward a broad variety of (a)cyclic amines.[17] Ring enlargement of non-activated azetidines, as described above for non-activated aziridines, also represents a challenge in the chemical literature. As a consequence, non-activated azetidines should be equally considered as valuable building blocks in the synthesis of various functionalized heterocycles with the intention to provide new entries toward biologically interesting scaffolds. Activation of non-activated azetidines **10** (n = 2) and **12** (n = 2) can proceed either in an intermolecular or intramolecular fashion, providing access to monocyclic or bicyclic azetidinium salts **11** (n = 2) and **13** (n = 2), respectively (Scheme 2). These strained intermediates serve at their turn as starting points for analogous ring-expansion products.

Scheme 2

In previous studies at the Department of Sustainable Organic Chemistry and Technology (UGent), non-activated aziridines and azetidines have proven to be valuable synthons for the preparation of a broad variety of five- and six-membered azaheterocycles by exploitation of the nucleophilicity of the small-ring nitrogen atom in combination with an electrophilic carbon center at a remote position. As a representative example in the class of aziridines, diastereomerically pure 1-arylmethyl-2-(4-chloro-2-cyano-2-phenylbutyl)aziridines **14** have been subjected to microwave irradiation in CH_3CN (Scheme 3).[18] Displacement of the chloride leaving group, induced by the lone pair of the aziridine nitrogen, afforded 1-azoniabicyclo[4.1.0]heptanes **16**, which were immediately attacked by chloride to furnish 2-chloromethyl-4-phenylpiperidine-4-carbonitriles **17**. A complete overview dealing with the preparation and synthetic applications of bicyclic aziridinium intermediates in azaheterocyclic chemistry is highlighted in the next chapter (Literature Review).[19]

Scheme 3

Next to the deployment of bicyclic aziridinium intermediates toward the synthesis of stereodefined azaheterocycles, research at the Department of Sustainable Organic Chemistry and Technology (UGent) on the synthetic applicability of their higher homologues, *i.e.* bicyclic azetidinium salts, has also resulted in the efficient and diastereoselective preparation of a wide variety of functionalized piperidines.

In that respect, *cis*-azetidines **18**, easily accessible via monochloroalane (AlH$_2$Cl) reduction of the corresponding β-lactams, underwent a ring-expansion reaction toward diastereomerically pure piperidines **21** upon treatment with a broad variety of nucleophiles or heating in DMF or DMSO (Scheme 4).[20] Intramolecular displacement of the leaving group by the nitrogen nucleophilic lone pair of azetidines **19** resulted in bicyclic azetidinium intermediates **20**, which were regioselectively attacked by a nucleophile at the bridgehead carbon atom in an S$_N$2 fashion to afford the thermodynamically favored piperidines **21**. In case azetidines **18** were heated in DMSO, an extra proton abstraction step occurred toward the formation of piperidin-4-ones **22**.[20a]
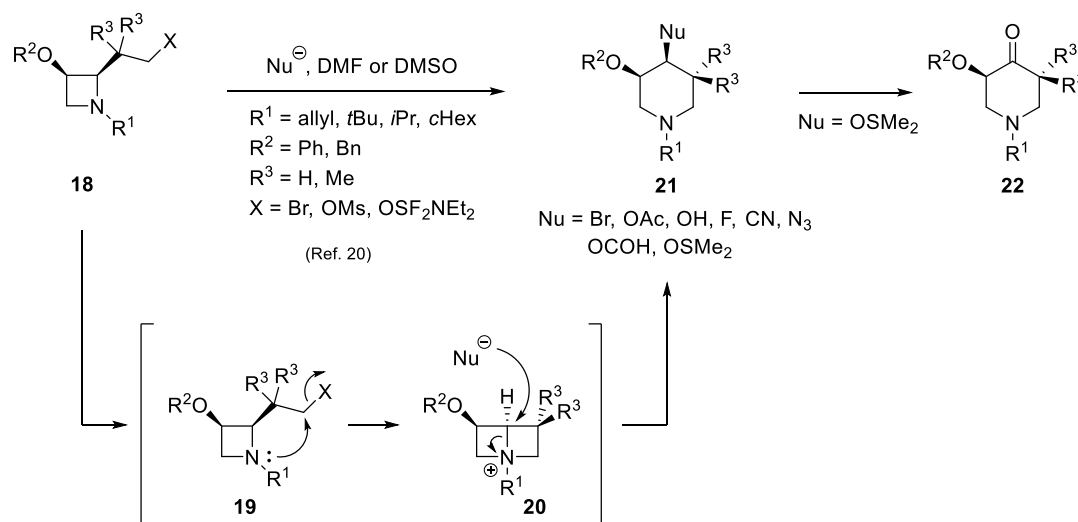
Scheme 4

In the literature, the nucleophilic interaction of the aziridine or azetidine nitrogen atom with an electrophilic moiety at a remote position toward the preparation of 1-azoniabicyclo[m.n.0]alkane scaffolds **13** has been well established (Scheme 2).[19] Consecutive intermolecular ring-opening reactions of these strained intermediates in a thermodynamically or kinetically controlled way[21] provide the formation of new medium-sized azaheterocycles in which the nitrogen atom originates from the aziridine/azetidine substrate. In contrast, the design of a general protocol for the selective conversion of non-activated aziridines **23** (n = 1) or azetidines **24** (n = 2) into five- to seven-membered heterocycles **25** and **26**, in which the aziridine or azetidine ring is deployed as an electrophilic moiety and subjected to intramolecular ring opening by a nucleophilic heteroatom at a remote position, still remains an underexplored field of research in heterocyclic synthesis (Scheme 5).[22]

Scheme 5

The regioselectivity of the ring-opening process can be directed more or less in a predictable manner by either the substitution pattern of the small-ring systems or by means of Baldwin's rules. According to these Baldwin's rules, a 5-*exo-tet* ring closure (route a) is favored whereas a 6-*endo-tet* (n = 1) or 7-*endo-tet* (n = 2) (route b) is disfavored.[23] On the other hand, the introduction of an aromatic ring (R^2 = Ar, vicinal substituted) might have a pronounced influence on the regiochemistry of the ring transformation, favoring the formation of heterocycles **26** instead of compounds **25**.[14b]

In recent research at the Department of Sustainable Organic Chemistry and Technology (UGent), a LiAlH₄-mediated ring rearrangement of 2-(4-chloro-2-cyano-2-phenylbutyl)aziridines **14** has been developed toward the selective preparation of stereodefined *endo-* and *exo-*1-azabicyclo[2.2.1]heptanes **30** (Scheme 6).[24] From a mechanistic point of view, LiAlH₄-promoted reduction of the cyano group afforded intermediates **27**, which underwent an iminyl anion-induced 5-*exo-tet* ring closure toward pyrrolines **28**. Consecutive hydride addition across the cyclic imine motif led to the formation of amides **29**, which finally opened the aziridine unit in a regioselective way to produce *endo-* and *exo-*1-azabicyclo[2.2.1]heptanes **30**. In the same way, 2-(2-cyano-2-phenylbutyl)aziridines **31** have been converted into 2-aminomethyl-4-ethyl-4-phenylpyrrolidines **34** via an iminyl anion-interceded regioselective ring opening of the aziridine ring.[25] Both ring transformations proceeded in a regioselective manner, *i.e.* ring opening of the aziridine core occurred at the more-hindered carbon atom, which is in accordance with Baldwin's rules.
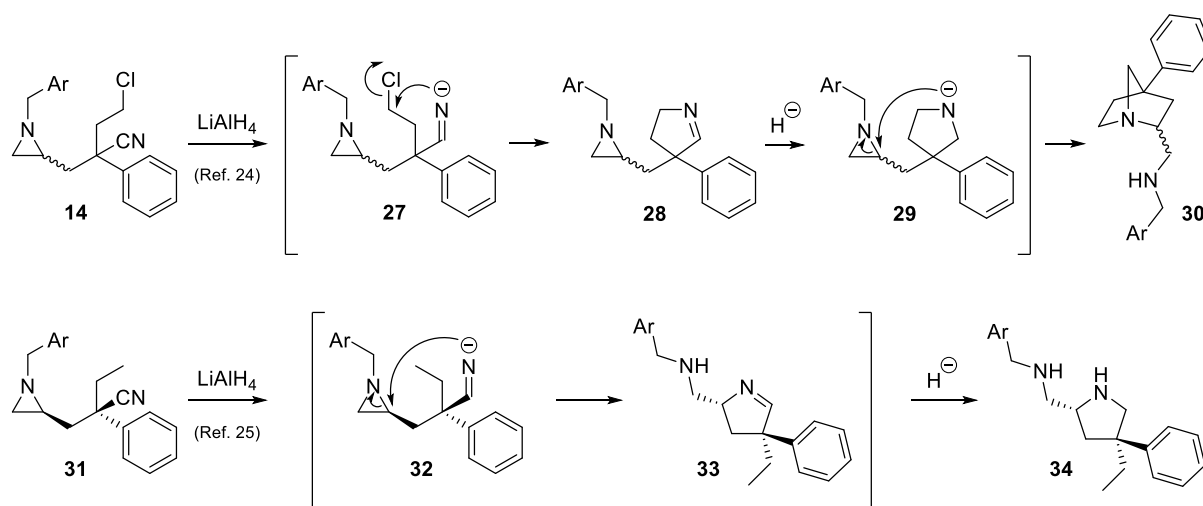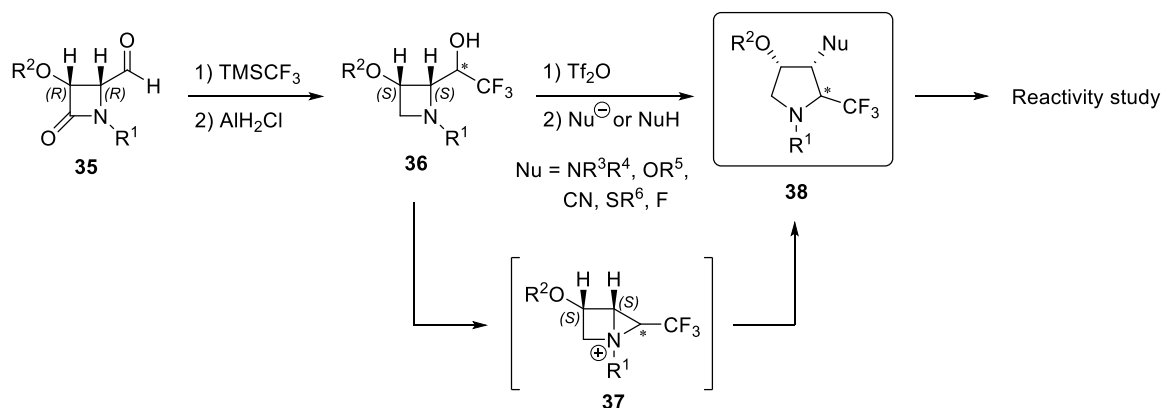
Scheme 6

In light of the emerging interest in efficient and reliable synthetic procedures toward medium-sized azaheterocyclic systems, many efforts will be devoted in this doctoral study to the evaluation of both ring-expansion methodologies on a series of small-ring substrates in order to provide access to the preparation of novel classes of functionalized representatives.

2. Goals

In continuation of the well-known deployment of 1-azoniabicyclo[m.n.0]alkane salts **13** as key intermediates toward the synthesis of a variety of functionalized azaheterocycles, this ring-expansion strategy will be evaluated in a first part of this PhD thesis starting from 4-formyl-β-lactams **35** (Scheme 7). The class of 4-formyl-β-lactams has amply proven to contain valuable synthons for the preparation of a wide variety of azaheterocycles and ring-opened products such as amino sugars, bi- and polycyclic β-lactams, γ-lactams and γ-lactones, amino acids and complex natural products.[26] Moreover, in light of the emerging interest in fluorinated compounds, the introduction of a trifluoromethyl group will be considered here, as the presence of this entity is known to provoke a pronounced impact on the physical and chemical properties of the resulting compounds.[27] Thus, trifluoromethylation of 4-formyl-β-lactams **35** will be pursued by means of the Ruppert-Prakash reagent (TMSCF₃) and subsequent AlH₂Cl-induced reduction of the β-lactam unit (without affecting the sensitive ring system) should afford the desired trifluoromethylated 2-(hydroxymethyl)azetidines **36**. Replacement of the hydroxyl moiety by a triflate leaving group is expected to render these scaffolds susceptible to intramolecular ring closure toward intermediate bicyclic aziridinium ions **37**. Subsequent ring opening by means of an appropriate nucleophile would then give rise to the formation of enantiopure trifluoromethylated pyrrolidines **38**, which can be further derivatized depending on the substitution pattern. The envisaged ring-expansion strategy of azetidines **36** is based on a ring-expansion protocol developed by the group of Cossy,[28]

although in that case trifluoromethylated pyrrolidines instead of their lower, four-membered homologues were deployed as substrates.

Scheme 7

In the major part of this PhD thesis, the 'reversed' ring-expansion strategy will be contemplated, involving the use of the aziridine unit as an electrophilic moiety toward the preparation of a variety of amino(methyl)-substituted heterocycles (Scheme 5). As an extension of previously reported aziridine-to-pyrrolidine ring transformations (Scheme 6), the synthesis of analogous azaheterocycles will be investigated starting from a variety of 2- and 3-(2-cyanoethyl)aziridines **41** (Scheme 8). These non-activated aziridines, bearing an interesting terminal functional group within the C2 side chain, are easily accessible via nucleophilic substitution of the corresponding 2-(bromomethyl)aziridines **39**[18,29] and 3-(tosyloxymethyl)aziridines **40**[30] upon treatment with α-lithiated (aryl)acetonitrile. Whereas the ring-expansion ability of 2-(2-cyanoethyl)aziridines **41** (R^1 = H) through the intermediacy of bicyclic aziridinium intermediates has been examined intensively, systematic studies dealing with the ring-transformation aptitude of these versatile building blocks in which the aziridine core is deployed as an electrophilic moiety have not been performed yet. Therefore, as a first objective of this approach, the development of a general methodology for the LiAlH$_4$-promoted ring rearrangement of different 2- and 3-(2-cyanoethyl)aziridines **41-43** toward 2-(aminomethyl)pyrrolidines **45** and 3-aminopiperidines **46** will be envisaged. The regioselectivity of the ring-opening process will be studied through variation of the substitution pattern on the aziridine core (R^1 = H, Ar) *en route* to the selective preparation of either 2-(aminomethyl)pyrrolidines **45** (route a) or 3-aminopiperidines **46** (route b). Furthermore, the introduction of alkyl and aryl substituents (R, R^2 and R^3) will be investigated to assess their steric and electronic effects on the premised ring transformation.
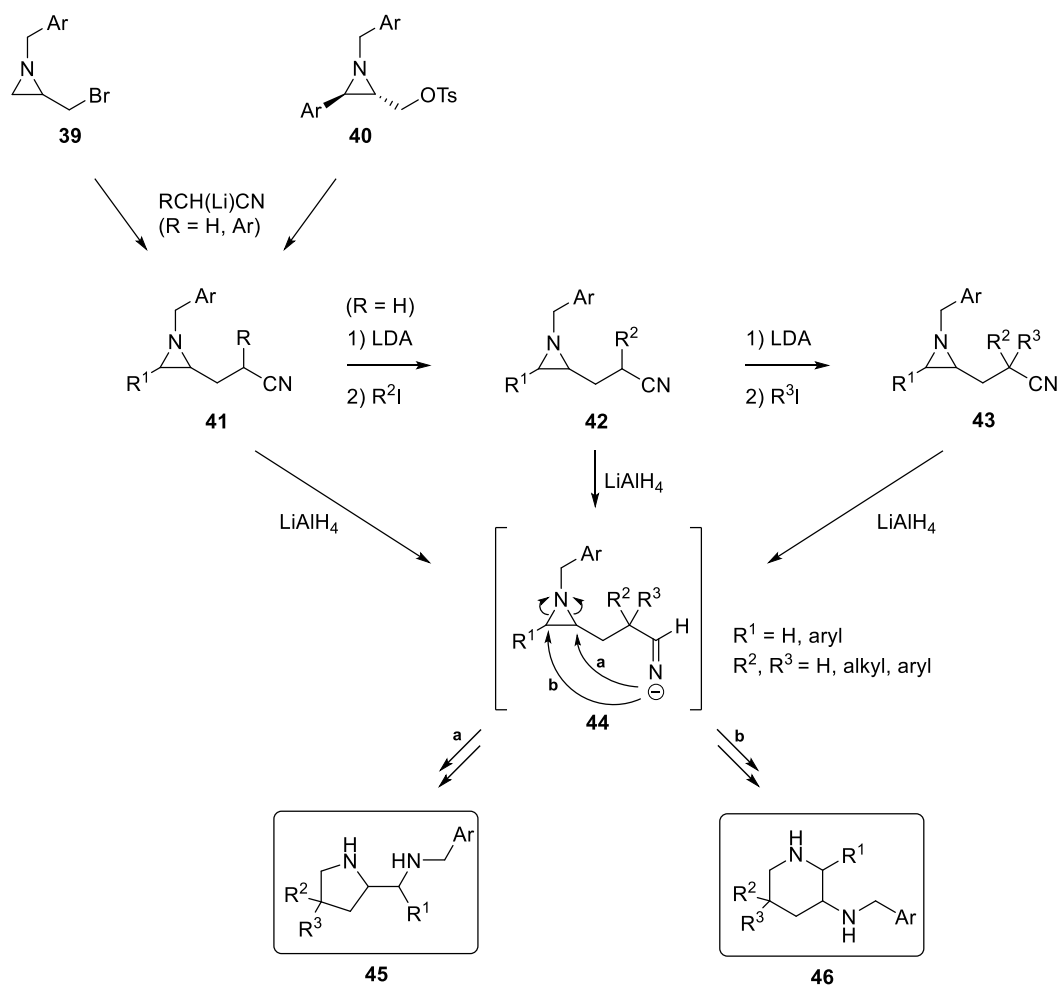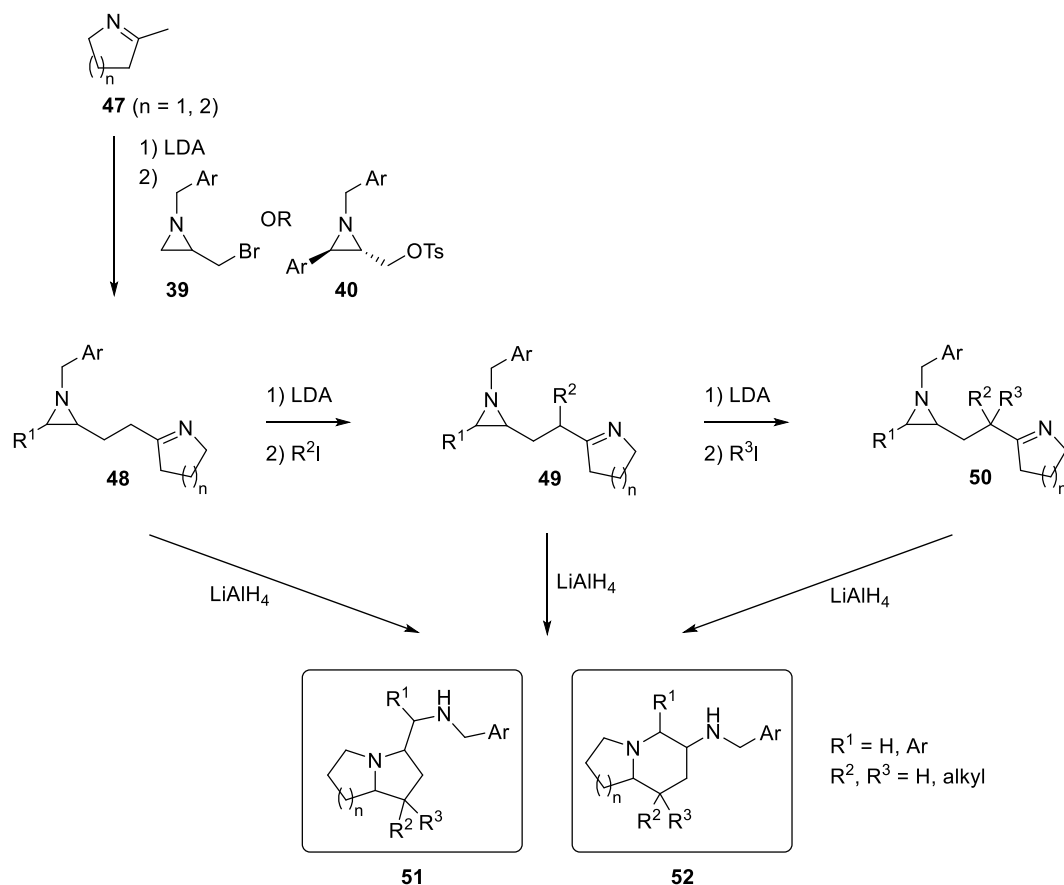
Scheme 8

The proposed scaffolds are endowed with a broad variety of biological activities. For example, platinum complexes of 2-(aminomethyl)pyrrolidines have been recognized as potent anticancer agents for more than two decades,[31] and 3-aminopiperidines have more recently emerged as valuable dipeptidyl peptidase IV inhibitors (treatment of type 2 diabetes).[32] The 2-(aminomethyl)pyrrolidine scaffold is also present in eticlopride, which acts as a dopamine antagonist.[33] Due to the presence of two secondary amino moieties, pyrrolidines **45** and piperidines **46** will be further evaluated as substrates for the synthesis of bicyclic imidazolidinones and diketopiperazines, bearing in mind the presence of these scaffolds in diverse compounds with pronounced biological properties.[34]

1-Azabicyclo[m.n.0]alkanes are present as core structures in a wide variety of amphibian skin alkaloids and are characterized by potent biological activities (anticancer, anti-HIV, antimicrobial, fungicidal, …).[35] For this reason, the search for reliable and efficient methods toward the construction of 1-azabicyclic scaffolds has attracted the attention of organic and medicinal chemists for many years. In that respect, aziridinyl pyrrolines **48** (n = 1) and aziridinyl piperideines **48** (n = 2) will be prepared and subjected to LiAlH$_4$ reduction in a third part of this thesis (Scheme 9). As selected examples, 2-methyl-1-pyrroline **47** (n = 1) and 2-methyl-1-piperideine **47** (n = 2) will be alkylated at the exocyclic position using 2-

(bromomethyl)aziridines **39** and 3-(tosyloxymethyl)aziridines **40** as the electrophiles. Treatment of the resulting compounds **48** with LiAlH$_4$ can provide a new pathway toward pyrrolizidines, indolizidines and quinolizidines **51/52** through initial reduction of the cyclic imine followed by intramolecular aziridine ring opening. Structural diversity will be introduced via α-alkylation with respect to the cyclic imine group (R^2, R^3), followed by ring transformation of the thus obtained aziridines **49** and **50** into 1-azabicyclo[m.n.0]alkanes **51** and **52**.

Scheme 9

In a final objective of this PhD thesis, the deployment of (thiocyanatomethyl)aziridines **56** will be explored as potential substrates for a premised LiAlH$_4$-induced ring rearrangement (Scheme 10). To that end, transformation of monosubstituted 2-(bromomethyl)aziridines **53**, *gem*-disubstituted 2-bromomethyl-2-methylaziridines **54** and *vic*-disubstituted *trans*-2-aryl-3-(tosyloxymethyl)aziridines **55** upon treatment with KSCN will lead to the corresponding (thiocyanatomethyl)aziridines **56**. As treatment of compounds bearing a terminal thiocyanatomethyl group with LiAlH$_4$ is known to result in the formation of the corresponding thiols after aqueous work-up,[36] it is suggested that addition of LiAlH$_4$ to a (thiocyanatomethyl)aziridine **56** will afford the *in situ* formation of sulfide anion **57**. Subsequent nucleophilic attack across the more-hindered carbon atom of the aziridine unit would give then rise to 2-(aminomethyl)thiiranes **58** via an unprecedented thia-aza-Payne rearrangement after aqueous work-up. In addition, the obtained 2-(aminomethyl)thiiranes **58** will be treated with triphosgene in order to provide

access to a series of 5-(chloromethyl)thiazolidin-2-ones **59**, which will be subjected to a final reactivity study. The employment of triphosgene to induce a ring expansion of thiiranes **58** is based on a method developed by Noh et al. who converted 2-(aminomethyl)aziridines to the corresponding 4-(chloromethyl)imidazolidin-2-ones in good to excellent yields (67-97%).[37] Importantly, special attention will be devoted to regio- and stereoselectivity issues within the above-described ring transformations.
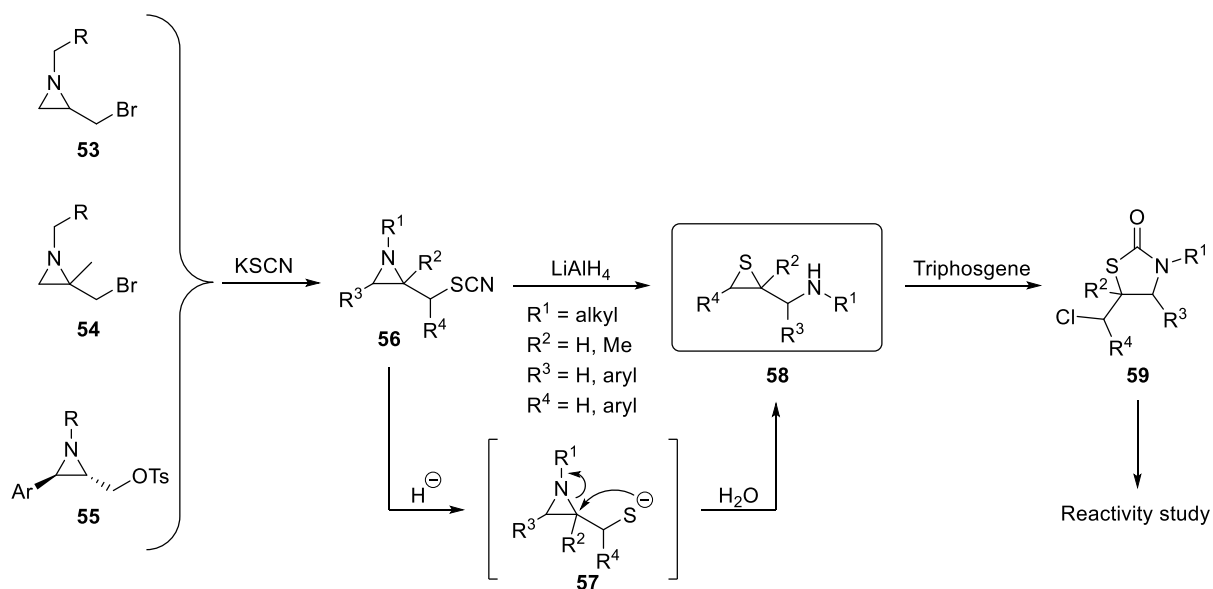
Scheme 10

LITERATURE REVIEW

Bicyclic aziridinium ions in azaheterocyclic chemistry – Preparation and synthetic application of 1-azoniabicyclo[n.1.0]alkanes

Abstract

Recent advances in the field of ring-expansion chemistry, involving 1-azoniabicyclo[n.1.0]alkane scaffolds (bicyclic aziridinium ions) as key transient intermediates, made it possible to efficiently construct a broad variety of medium- and large-sized functionalized nitrogen-containing heterocycles. In this tutorial review, a comprehensive survey of all pathways leading to the generation of 1-azoniabicyclo[n.1.0]alkanes is provided, as well as a discussion on their subsequent ring expansions to relevant azaheterocycles governed by ring size, substitution pattern, and/or nature of applied nucleophiles.

Graphical abstract
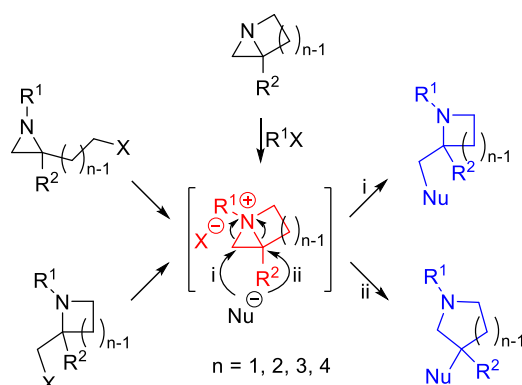
Reference

This chapter covers the preparation and synthetic utilization of various bicyclic aziridinium ions as polyvalent intermediates toward the synthesis of a variety of nitrogen-containing heterocycles. Herein, a classification will be adopted according to the size of the bicyclic intermediates, *i.e.* distinction will be made between 1-azoniabicyclo[1.1.0]butanes, 1-azoniabicyclo[2.1.0]pentanes, 1-azoniabicyclo[3.1.0]hexanes and 1-azoniabicyclo[4.1.0]heptanes as intermediates toward the formation of functionalized azetidines, pyrrolidines, piperidines and azepanes. Emphasis will be put on the relationship between the observed regioselectivity and inherent structural features, such as the nature of the substituents of the bicyclic aziridinium ion and the incoming nucleophile.

1. Preparation and synthetic utilization of bicyclic aziridinium ions

The most evident method toward the production of 1-azoniabicyclo[n.1.0]alkanes involves the intermolecular reaction between bicyclic azaheterocycles **1** (*in casu* 1-azabicyclo[n.1.0]alkanes) and suitable electrophiles (Scheme 1, route a), although these 1-azabicyclo[n.1.0]alkane substrates are rather difficult to access. Alternatively, bicyclic aziridinium ions can be prepared from monocyclic azaheterocycles in two different ways. On the one hand, intramolecular cyclization of aziridines **2**, bearing a terminal leaving group within the C2 side chain, results in the desired bicyclic intermediates **4** (Scheme 1, route b). On the other hand, intramolecular displacement of the leaving group in azaheterocycles **3** affords the same aziridinium salt intermediates **4** (Scheme 1, route c). Depending on the length of the tether between the leaving group and the C2 atom in aziridines **2,** or the number of carbon atoms in the ring in azaheterocycles **3**, the size of the obtained 1-azoniabicyclo[n.1.0]alkanes can be altered.
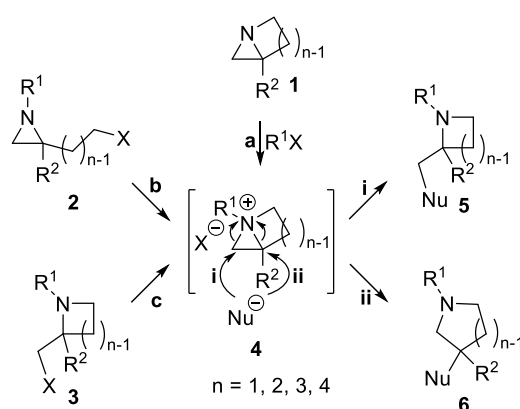
Scheme 1

The obtained cationic bicyclic intermediates **4** serve as a starting point for the generation of ring-expansion products by nucleophilic ring opening, either via pathway **i** at the less-substituted carbon atom or via pathway **ii** at the more-substituted carbon atom (Scheme 1). Although ring-expansion reactions starting from aziridines **2** or azaheterocycles **3** usually can be explained by the formation and

interception of transient 1-azoniabicyclo[n.1.0]alkane intermediates **4**, as supported by high-level computational analyses in several examples, a different reaction mechanism (e.g. dealing with the interference of monocyclic carbenium ion intermediates) cannot be completely excluded in some cases. Anyhow, recent advances in the field of ring-expansion chemistry, involving bicyclic aziridinium ions **4** as key transient intermediates, made it possible to construct a variety of medium- and large-size functionalized nitrogen-containing heterocycles in a regio- and stereoselective way.

Due to the high ring strain comprised in bicyclic intermediates **4**, attention has to be devoted to three possible monocyclic isomeric cations, including azacyclocarbenium ions **7**, primary methylium ions **8** and aziridinyl alkan-1-ylium ions **9**, as depicted in Scheme 2,[38] which may be equilibrated or contribute electronically, depending on the substitution pattern of the aziridinium intermediates. As a consequence, the outcome of the reactions stemming from bicyclic intermediates **4** are determined by the kinetics of the nucleophilic attack across **4** and/or its isomeric cations **7**, **8** and **9**. In most cases, formation of aziridinyl cations **9** from 1-azoniabicyclo[n.1.0]alkanes is very rare due to the strain of the three-membered ring and the highly unstable primary carbenium ion. Moreover, theoretical calculations showed that bicyclic intermediates **4** are generally the most stable cations. Although the intermediacy of 1-azoniabicyclo[n.1.0]alkanes **4** was not experimentally observable in most cases, their ring-expansion products are produced in high yields and with high stereoselectivity, rendering this ring-enlargement methodology to be unique and providing access to a broad library of elegant azaheterocycles with many substituents along the ring. Judging from the reaction kinetics and the high stereoselectivity, it is not always possible to exclude the intervention of a concerted reaction mechanism for the preparation of these azaheterocycles instead of a mechanism via cationic intermediates, although the formation and interception of transient 1-azoniabicyclo[n.1.0]alkanes is generally believed to represent the correct mechanistic interpretation in the majority of literature examples. Nonetheless, in the following sections, careful notice will be taken of the possible appearance of different ionic intermediates to gain a better understanding of the underlying processes for the formation of regio- and stereocontrolled end products.
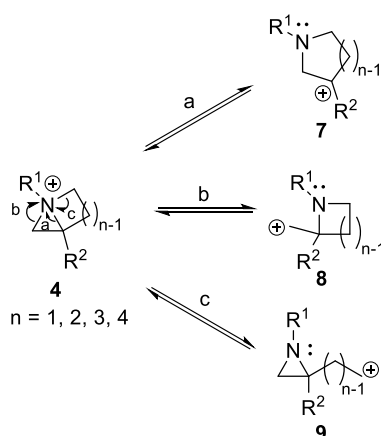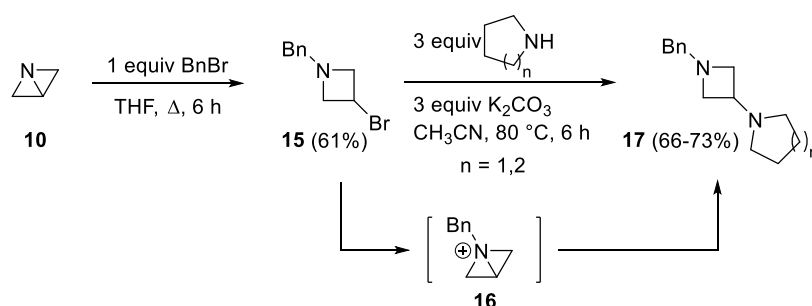

Scheme 2

2. Preparation and synthetic utility of 1-azoniabicyclo[1.1.0]butanes

The most basic strategy to prepare 1-azoniabicyclo[1.1.0]butanes involves the intermolecular reaction between 1-azabicyclo[1.1.0]butane and an appropriate electrophile. This intermolecular activation method has for example been used in the smooth reaction of 1-azabicyclo[1.1.0]butane **10** with aromatic thiols (Scheme 3).[39] Furthermore, ring opening of the *in situ* created aziridinium intermediate was also attained with a variety of aromatic nitrogen nucleophiles and dibenzylamine, however in the presence of Mg(ClO$_4$)$_2$. Direct reaction of azabicycle **10** with cyclic amines did not proceed, but this drawback was circumvented via nucleophilic substitution of *N*-benzyl-3-bromoazetidine **15**, acquired by treatment of 1-azabicyclo[1.1.0]butane **10** with benzyl bromide (Scheme 4). From a mechanistic point of view, direct substitution of the bromo atom in azetidine **15** could result in the desired azetidines **17**. However, an intramolecular expulsion of bromide followed by reaction with cyclic amines is more plausible. Due to the absence of stabilizing substituents at the C3-position, formation of the corresponding azetidine carbenium ion **7** (n = 1) can be excluded.
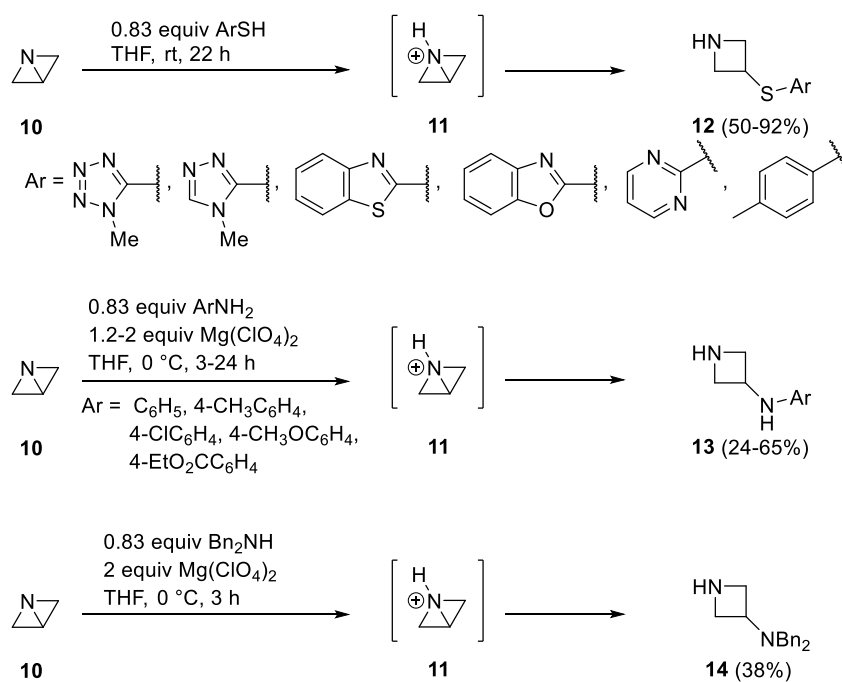
Scheme 3

Scheme 4

Starting from alkyl- and phenyl-substituted 1-azabicyclo[1.1.0]butanes **18**, a variety of 3-azido-azetidines **21** has been prepared using the same methodology (Scheme 5).[40] According to the regioselective formation of 3-azidoazetidines **21**, the formation of bicyclic aziridinium intermediates **19** is most acceptable. However, in case of 3-phenyl-substituted substrates **18** (R^2 = Ph), the *in situ* occurrence of carbenium intermediate **20** is more likely due to a higher stabilization of the carbenium ion in α-position with respect to the phenyl substituent. This benzylic stabilization has to be considered when the reactivity of 3-phenyl-1-azabicyclo[1.1.0]butanes toward halides is investigated, resulting in the regioselective synthesis of 3-halo-3-phenylazetidines.[41]
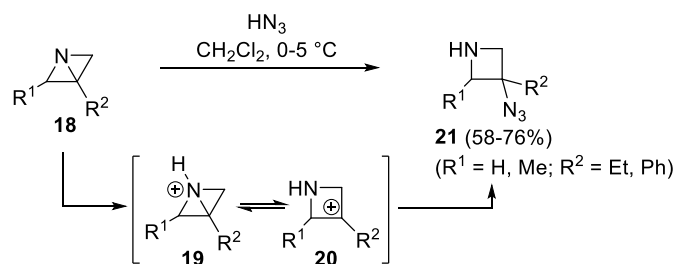
Scheme 5

Finally, in addition to the above-mentioned examples on the regioselective attack of nucleophiles across 1-azoniabicyclo[1.1.0]butanes, the stereocontrolled ring opening of 1-azoniabicyclo[1.1.0]butanes has also been reported by Hortmann et al.[42] Herein, reaction of bicyclic aziridine **22** with hydrogen chloride resulted in the stereoselective formation of azetidinium salt **23**. Analogously, treatment of bicyclic aziridine **24** using the same reaction conditions delivered the diastereomeric counterpart **25** (Scheme 6). Formation of 1-azoniabicyclo[1.1.0]butane **26** and its subsequent ring expansion in the reaction of 1-azabicyclo[1.1.0]butane with hydrochloric acid was found to yield the corresponding azetidine in a stereoselective manner, with cleavage of the C-N bond from concave attack by the chloride anion as a representative example of acid-assisted ring expansion.
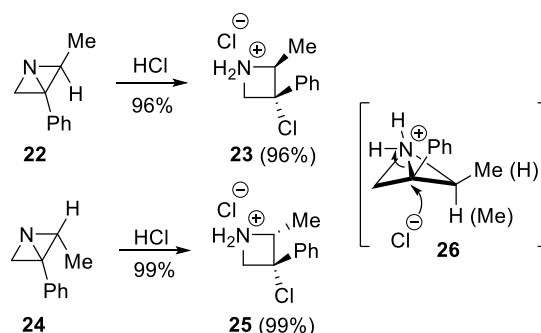
Scheme 6

Another strategy toward the preparation of 1-azoniabicyclo[1.1.0]butanes is related to the intramolecular expulsion of a good leaving group attached to the α-carbon in the tether of non-activated aziridines. Depending on the R-substituent present on the bridgehead carbon of the *in situ* created 1-azoniabicyclo[1.1.0]butanes, nucleophilic attack across these bicyclic intermediates resulted either in aziridines (pathway **i**, Scheme 1) or their higher homologues, azetidines (pathway **ii**, Scheme 1). This substituent-dependency has been observed during the reductive ring closure of *N*-(arylmethylidene)-2,3-dibromopropylamines **27**. When *N*-(arylmethylidene)-2,3-dibromopropylamines **27** (R^2 = H) were subjected to 3 molar equiv of $NaBH_4$ in methanol at reflux, 2-(bromomethyl)aziridines **28** were formed as the sole reaction products (Scheme 7).[43] However, an additional methyl group (R^2 = Me in **27**) changed the reactivity completely, *i.e.* treatment of *N*-(alkylmethylidene)-2,3-dibromo-2-methylpropylamines **27** (R^2 = Me) applying the same reaction conditions afforded 3-methoxy-3-methylazetidines **32** in a clean and selective way.[44] Treatment of this starting material **27** with a smaller amount of $NaBH_4$ (2 molar equiv) at room temperature, however, yielded 2-methyl-2-(bromomethyl)aziridines **29** as the major products, which were then converted to 3-methoxy-3-methylazetidines **32** using 3 molar equiv of $NaBH_4$ under reflux. 3-Methoxyazetidines **32** were also obtained by reaction of *N*-(2,3-dibromo-2-methylpropylidene)arylmethylamines **33** (R^1 = Ar) with 3 molar equiv of $NaBH_4$ under reflux. This result supported the presumption that 2-methyl-2-(bromomethyl)aziridines **29** are the kinetically controlled products, which are transformed into the thermodynamically more stable 3-methoxy-3-methylazetidines **32** via transient 1-azoniabicyclo[1.1.0]butane intermediates **30** in methanol.
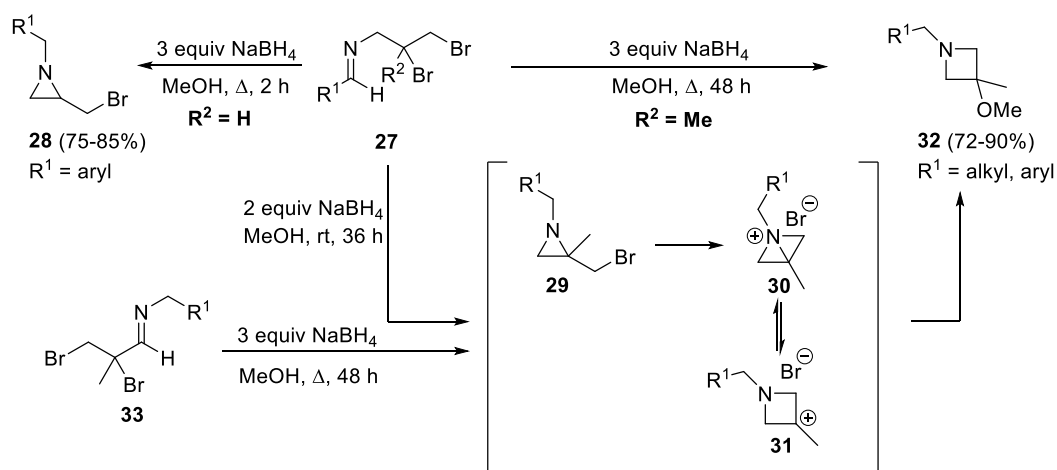
Scheme 7

From a mechanistic point of view, the formation of 3-methoxy-3-methylazetidines **32** is reasonable considering the different isomeric cations involved during this ring transformation. Despite the presence of an extra methyl group at C3, enabling a higher stabilization of the carbenium ion in isomer **31**, the equilibrium is shifted toward the bicyclic cation **30** based on computational analysis.[44] Subsequent solvolysis in methanol finally resulted in 3-methoxy-3-methylazetidines **32**. As a consequence of these observations, nucleophilic substitution reactions of 2-alkyl-2-(bromomethyl)aziridines are temperature

sensitive to yield either 2-substituted 2-alkylaziridines or 3-substituted-3-alkylazetidines. Furthermore, it was found that these transformations were remarkably influenced by the choice of the solvent.[45] Whereas the use of dimethylformamide (DMF) resulted in direct displacement of bromide in 2-bromomethyl-2-methylaziridines **29**, the deployment of acetonitrile (CH_3CN) as a solvent favored the selective preparation of 3-methylazetidines **35** (Scheme 8). These experimental observations have been supported by means of DFT calculations, which revealed a better coordination and stabilization of the nucleophiles in CH_3CN, hence allowing the formation of 1-azoniabicyclo[1.1.0]butanes **30** in CH_3CN to afford the corresponding azetidines. It is worth mentioning that the formation of substituted 2-methylaziridines **34** in DMF is more complicated due to two possible routes, including a simple direct displacement of bromide by an appropriate nucleophile with retention of the aziridine core, or nucleophilic attack at the less-hindered site of the *in situ* created 1-azoniabicyclo[1.1.0]butanes **30**.
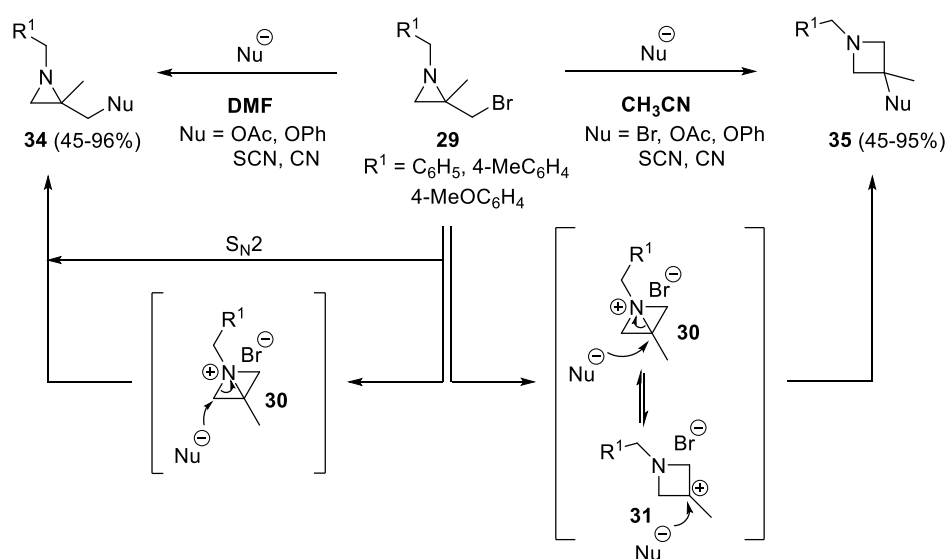
Scheme 8

Additional support for the occurrence of different isomeric cations has been provided by the ring expansion of 2-(bromomethyl)aziridines **36** toward the corresponding 3-substituted azetidines **40**.[46] In that study, the isomerization reaction of alkyl aziridine-2-carboxylates **36** toward alkyl azetidine-3-carboxylates **39** has been investigated (Scheme 9). Heating of 2-(bromomethyl)aziridines **36** in DMSO during 5 to 48 hours resulted in the ring-expanded target compounds **39**. The addition of external nucleophiles could not effect the desired ring expansion [apart from a small amount (4-5%) in case of phenoxide as the nucleophile], but afforded the corresponding 2,2-disubstituted aziridines **37** instead. However, treatment of the obtained alkyl 3-bromoazetidine-3-carboxylates **39** with the same nucleophiles seemed successful, furnishing a variety of 3-substituted azetidine-3-carboxylates **40** in good yields.
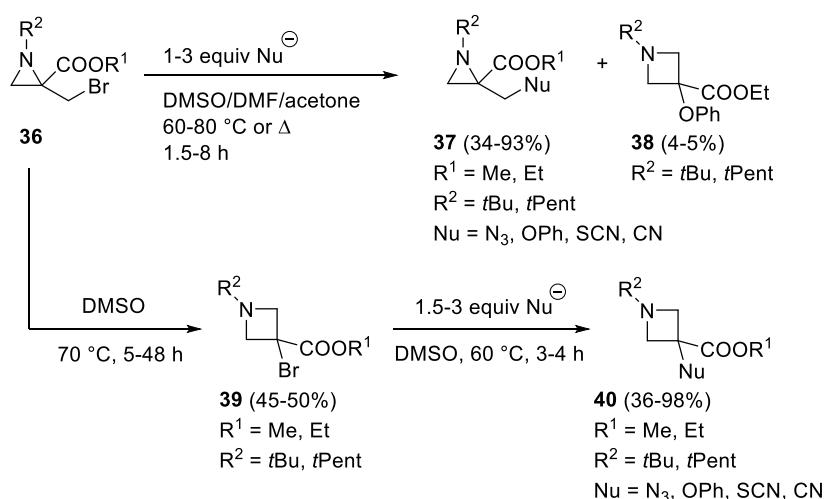
Scheme 9

The intervention of a 1-azoniabicyclo[1.1.0]butane intermediate is also highlighted in the synthesis of 3-substituted azetidines **43** starting from 3-bromo-3-methylazetidines **41** (Scheme 10),[47] in which treatment of azetidines **41** with a variety of nucleophiles afforded 3-substituted azetidines **43** in high yields (63-96%) via bicyclic aziridinium intermediates **42**.
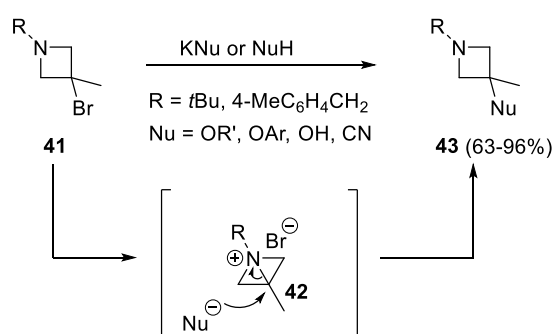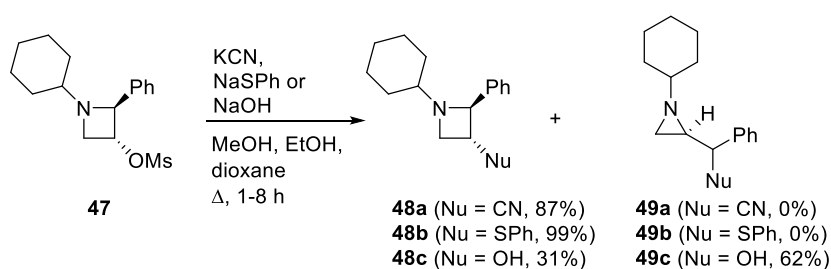

Scheme 10

Formation of a 1-azoniabicyclo[1.1.0]butane intermediate has also been suggested in the substitution reaction of 3-chloroazetidines **44** by a variety of nucleophiles toward the preparation of 3-substituted azetidines **46** (Scheme 11).[48] Because of the retention of configuration, a double S_N2-reaction can be assumed. The initial displacement of the chloride atom by nitrogen results in the corresponding bicyclic intermediate **45**, followed by regio- and stereoselective attack by a suitable nucleophile.
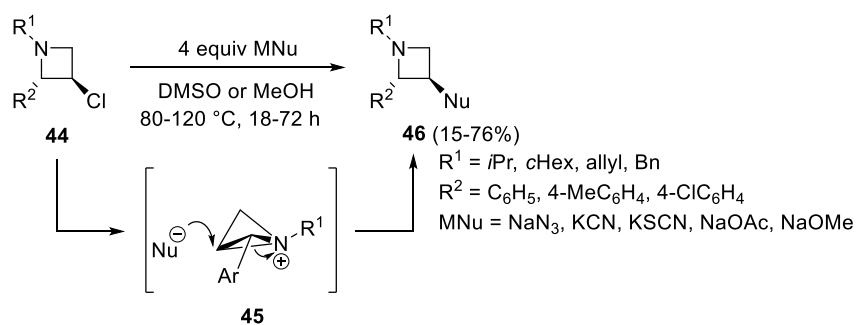
Scheme 11

The synthesis of 3-substituted azetidines from properly decorated 3-halo- or 3-sulfonyloxyazetidines has been covered in 2009, although without a systematic analysis to elucidate the influencing parameters on these transformations and the intervention of transient 1-azoniabicyclo[1.1.0]butane cations.[49]

In some cases, analogous reactions have also provided ring-contraction products, as exemplified by Okutani and Masuda.[50] When *trans*-azetidine **47** was treated with various nucleophiles including KCN and NaSPh, substituted azetidines **48a,b** were obtained as the sole products (Scheme 12). On the other hand, the reaction with NaOH in 50% aqueous dioxane furnished a major amount of 2-substituted aziridine **49c** (62%), in contrast to the expected azetidine scaffold according to thermodynamic principles. Depending on the selection of the nucleophile, the reaction outcome could thus be regiocontrolled. Whereas carbon and sulfur nucleophiles afforded the thermodynamically stable products **48a** and **48b**, the deployment of the oxygen nucleophile (hydroxide) delivered the kinetically stable aziridine **49c** as the major isomer.

Scheme 12

Analogous to the depicted azetidine-to-aziridine ring contraction in Scheme 12, ring contractions have also been observed for 2-aryl-3,3-dichloroazetidines **50**.[51] When these 3,3-dichloroazetidines **50** were treated with a large excess of NaOMe in MeOH at reflux, 2-(dimethoxymethyl)aziridines **55** were obtained in high yields via elusive 2-azetine intermediates **51** (Scheme 13). From a mechanistic point of view, the formation of the kinetic products **49c** and **55** is reasonable considering the *in situ* created aziridin-2-ylmethylcarbenium ions **8** (n = 1) or **9** (n = 1). As depicted in Scheme 13 for the formation of aziridines **55**, the expulsion of the second chloride atom results in bicyclic aziridinium intermediates **53**,

which are in equilibrium with aziridin-2-ylmethylcarbenium ions **54** due to stabilization of the positive charge by means of the phenyl substituent in α-position. Finally, trapping of these intermediates **54** by a second methoxide affords aziridines **55**.
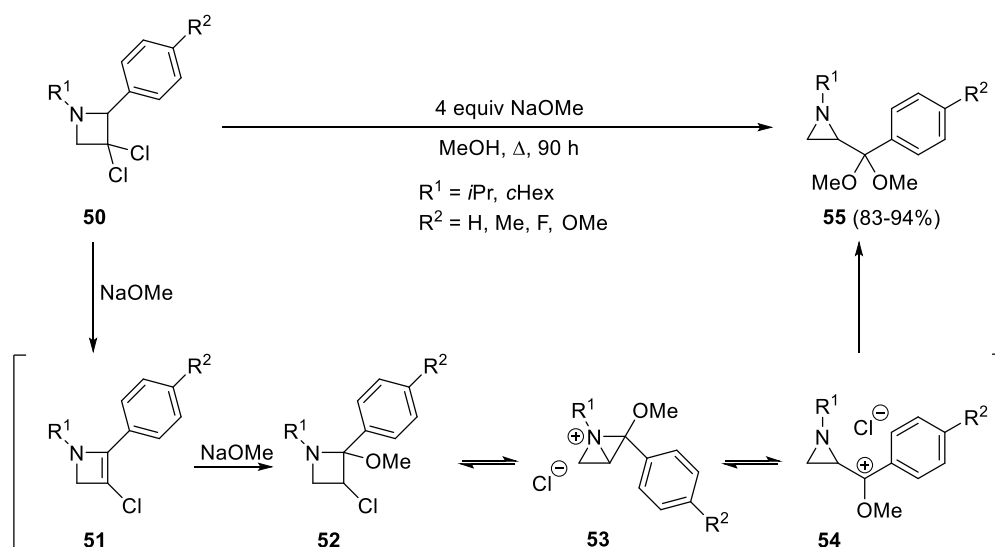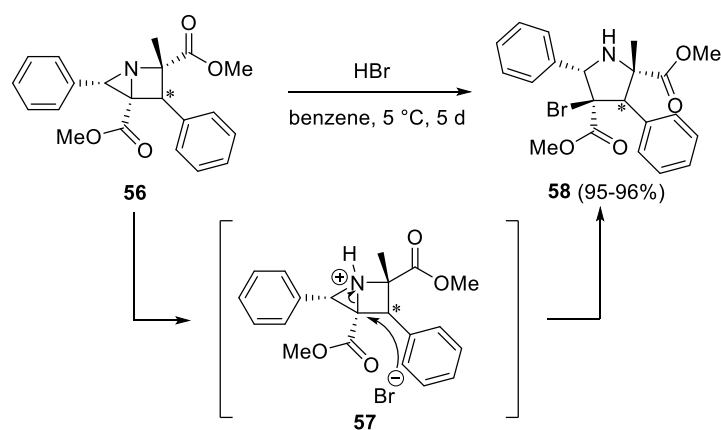

Scheme 13

The abovementioned results clearly demonstrated the formation of 1-azoniabicyclo[1.1.0]butane intermediates from either 2-(bromomethyl)aziridines or 3-(halo/sulfonyloxy)azetidines upon intramolecular leaving group displacement by the nitrogen atom of the aziridine or azetidine ring. Once the 1-azoniabicyclo[1.1.0]butane intermediate **4** (n = 1) is generated, it can be transformed into either a 3-azetidinecarbenium ion **7** (n = 1) or an aziridin-2-ylmethylcarbenium ion **8** (n = 1) or **9** (n = 1) (Scheme 2). Among three isomeric cations, the 3-azetidinecarbenium ion **7** (n = 1) dominates when the reaction is governed by thermodynamic control due to the lowest ring-strain energy. However, when there are substituents along the ring system which influence the stability of and the equilibrium between the different possible isomeric cations, the aziridin-2-ylmethylcarbenium ion **8** (n = 1) or **9** (n = 1) can occur as well in particular cases, resulting in a kinetically-controlled product outcome. As a consequence, the ring expansion pattern is adjustable taking into account the design of the substrate and the selection of the nucleophile.

3. Preparation and synthetic utility of 1-azoniabicyclo[2.1.0]pentanes

In the literature, only one report has been published so far dealing with the synthesis of 1-azoniabicyclo[2.1.0]pentanes via intermolecular reaction between 1-azabicyclo[2.1.0]pentanes and an activating agent.[52] Therein, treatment of 1-azabicyclo[2.1.0]pentanes **56** with hydrogen bromide led to the *in situ* formation of bicyclic intermediates **57**, which were regioselectively opened toward 4-bromopyrrolidines **58** in excellent yields (95-96%, Scheme 14).

Scheme 14

Among two other methods for the preparation of 1-azoniabicyclo[2.1.0]pentanes from properly substituted azetidines or aziridines, mainly the deployment of decorated azetidine substrates with a leaving group attached to the α-carbon of the C2 side chain has been reported. Furthermore, the subsequent ring-opening reactions always proceed following pathway **ii** (Scheme 1), resulting in pyrrolidines regardless of the substituents. Reactions according to pathway **i** (Scheme 1) would afford a more constrained azetidine structure, which explains the selectivity. Furthermore, pathway **ii** is both kinetically and thermodynamically favorable due to the large difference of ring strain energy (about 20 kcal mol^{-1}).[53]

One of the few reactions related to the generation of 1-azoniabicyclo[2.1.0]pentane intermediates from aziridines has been employed in a route from a β-lactam over an aziridine to a pyrrolidine.[20d] Reduction of β-lactams **59** with LiAlH$_4$ afforded 2-(2-hydroxyethyl)aziridines **60**, which were consecutively subjected to Mitsunobu conditions in the presence of NBS (Scheme 15). After 18 hours stirring at room temperature, *cis*-3-bromopyrrolidines **62** were finally produced in a stereoselective way via bromide interception of bicyclic aziridinium intermediates **61**.
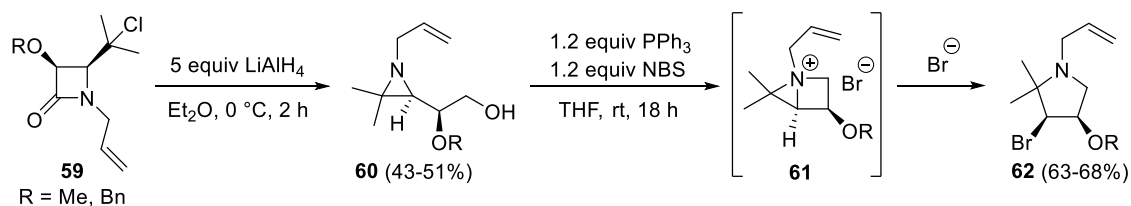
Scheme 15

This aziridine-to-pyrrolidine ring transformation has also been deployed by the same group for the synthesis of 3-bromo-2-methylpyrrolidines **65** and **66** starting from 2-(2-hydroxyethyl)-3-methylaziridines **63** (Scheme 16).[54] Thus, 2-(2-hydroxyethyl)aziridines **63** were analogously treated with PPh$_3$ and NBS, resulting in bicyclic aziridinium intermediates **64**. Consecutive ring opening by the bromide anion afforded the thermodynamically favored *cis*- and *trans*-pyrrolidines **65** and **66**, which could be separated by means of column chromatography.
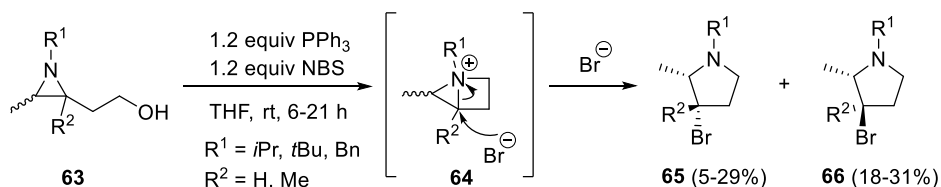
Scheme 16

Generation and utilization of 1-azoniabicyclo[2.1.0]pentane intermediates has also been shown to be synthetically valuable for the preparation of ring-expanded and multi-substituted pyrrolidines **68** and **69**, as exemplified in Scheme 17.[55] The reactions of 2-chloromethyl- and 2-(methanesulfonyloxymethyl)azetidines **67** with a variety of nucleophiles afforded 3-substituted pyrrolidines **68** and **69** through regioselective ring opening of the *in situ* created 1-azoniabicyclo[2.1.0]pentanes **70** at the bridgehead carbon atom, which is fully consistent with the mechanism of the production of azetidines from 1-azoniabicyclo[1.1.0]butanes (*vide supra*).
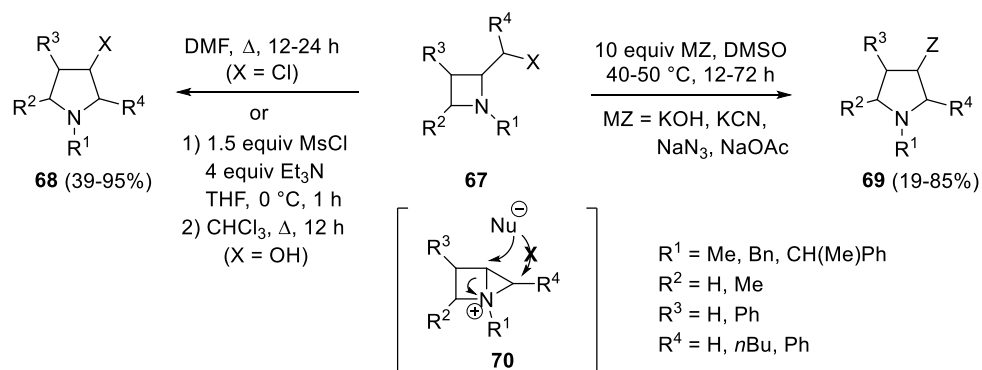
Scheme 17

The same group has also investigated the fluoride-induced ring expansion of 2-(hydroxymethyl)azetidines **71** upon treatment with DAST, resulting in the synthesis of the corresponding 3-fluoropyrrolidines **72** (Scheme 18).[56] However, for one example (R^1, R^2 = Me, R^3 = Ph, R^4 = nBu), an overall hydroxyl-by-fluoride substitution occurred. Furthermore, retention of configuration indicated that the mechanism was based on the intermediacy of a bicyclic aziridinium intermediate, which was not attacked at the bridgehead carbon atom but at C5. When an additional substituent was present in α-position of the hydroxyl group in azetidines **71** (resulting in the development of a quaternary center, e.g. a *gem*-di-methyl unit), no rearrangement product was observed which might be explainable by the fact that bicyclic azetidinium ion **70** formation could not be realized as a result of steric hindrance. Thus, depending on the selected nucleophile, the ring opening of bicyclic aziridinium intermediates **70** can be regiocontrolled to a certain extent, although these transformations predominantly proceeded at the bridgehead carbon atom in a regioselective manner to produce pyrrolidines **72**.
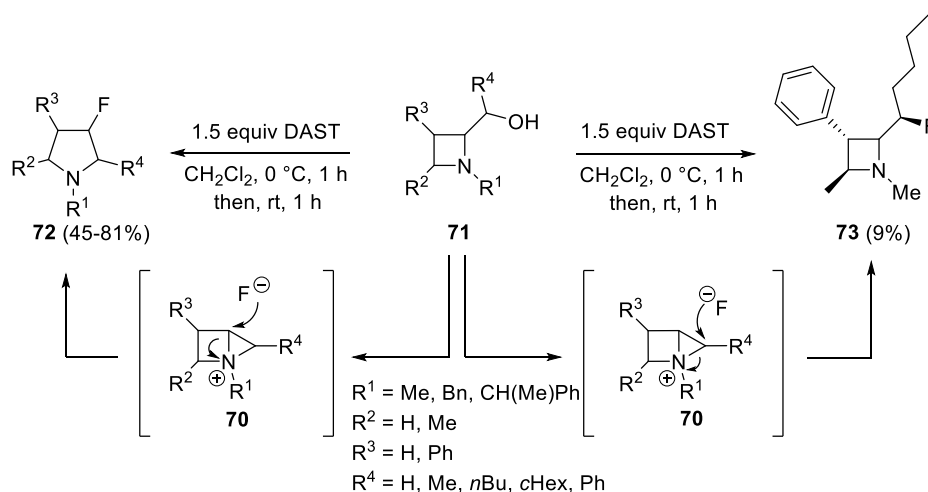
Scheme 18

A DAST-promoted azetidine-to-pyrrolidine transformation has also been described by the group of Cossy.[57] In that regard, treatment of chiral azetidine **74** with 1.4 equiv of DAST in dichloromethane resulted in the regioselective formation of pyrrolidine **75** with excellent enantioselectivity (Scheme 19).
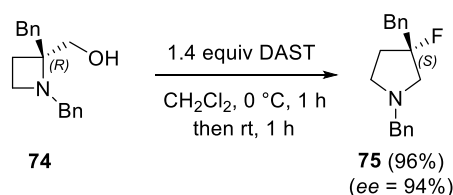
Scheme 19

In analogy, ring-expansion reactions have been elaborated starting from enantiopure 2-(chloromethyl)azetidines **76** (Scheme 20). In that work, chloride-induced ring opening of *in situ* formed bicyclic aziridinium intermediates **77** led smoothly to 3-chloropyrrolidines **78** in reasonable yields with high stereoselectivity.[58]
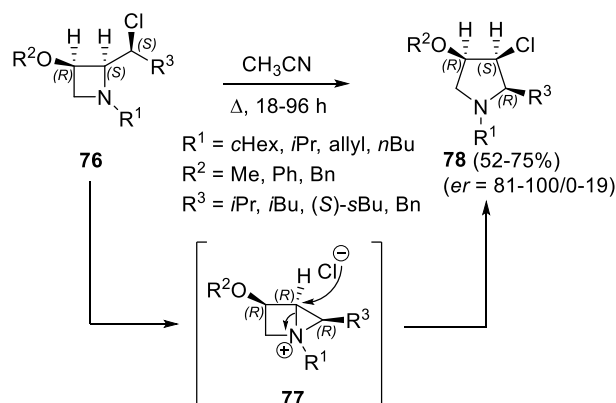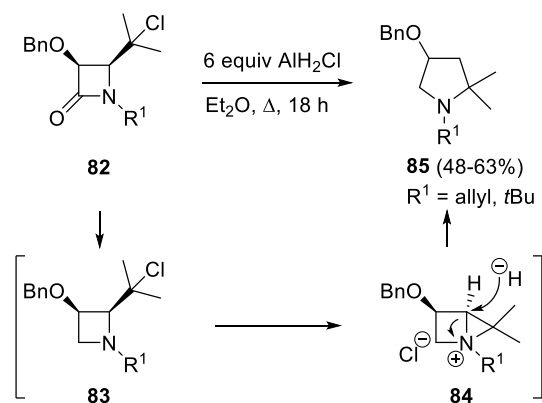

Scheme 20

The high stereoselective ring rearrangement of analogous 2-(chloromethyl)azetidines **79** into the corresponding 3-chloropyrrolidines **80** without intervention of an external nucleophile has been described (Scheme 21).[20d] Furthermore, the introduction of different nucleophiles (hydroxide, cyanide, azide and hydride) was established, furnishing 3-substituted pyrrolidines **81** (Scheme 21) and **85** (Scheme 22). In the case of β-lactams **82**, an initial reduction toward azetidines **83** with monochloroalane in diethyl ether under reflux took place, followed by a rearrangement to pyrrolidines **85** via bicyclic aziridinium ions **84**.
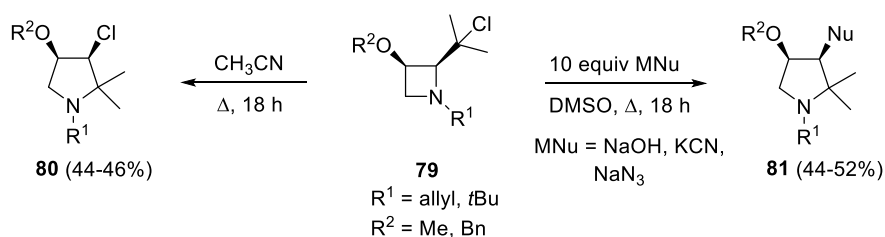
Scheme 21

Scheme 22

Ring-expansion reactions of 2-(halomethyl)azetidines toward 3-substituted pyrrolidines have also been reported by Feula et al.[59] In that respect, iodocyclization of homoallylamines **86** yielded 2-(iodomethyl)azetidines **87** through a 4-*exo*-trig cyclization, the appearance of which was confirmed by NMR analysis (Scheme 23). Heating of azetidines **87** in CH_3CN at 60 °C resulted in preparation of *cis*-4-iodopyrrolidines **89**. In the same way, azetidine-to-pyrrolidine transformations have been performed upon treatment of azetidines **87** with *O*- and *N*-nucleophiles, affording *cis*-4-hydroxy- and *cis*-4-aminopyrrolidines **88** and **91**, respectively. The retention of configuration is attributed to the formation of bicyclic aziridinium intermediates **93** (via intramolecular expulsion of iodide), which underwent ring opening upon nucleophilic attack in a regio- and stereoselective manner. Reaction of *cis*-4-iodopyrrolidines **89** with *N*-nucleophiles (azide and amines) furnished *trans*-pyrrolidines **90** and **92**. In contrast to the substitution reactions of 3-haloazetidines, involving the *in situ* creation of 1-azoniabicyclo[1.1.0]butanes (*vide supra*), 1-azoniabicyclo[2.1.0]pentanes are not formed in these substitution reactions (**89** to **90/92**), resulting in the inversion of configuration by direct displacement of the iodide atom by the nucleophile.
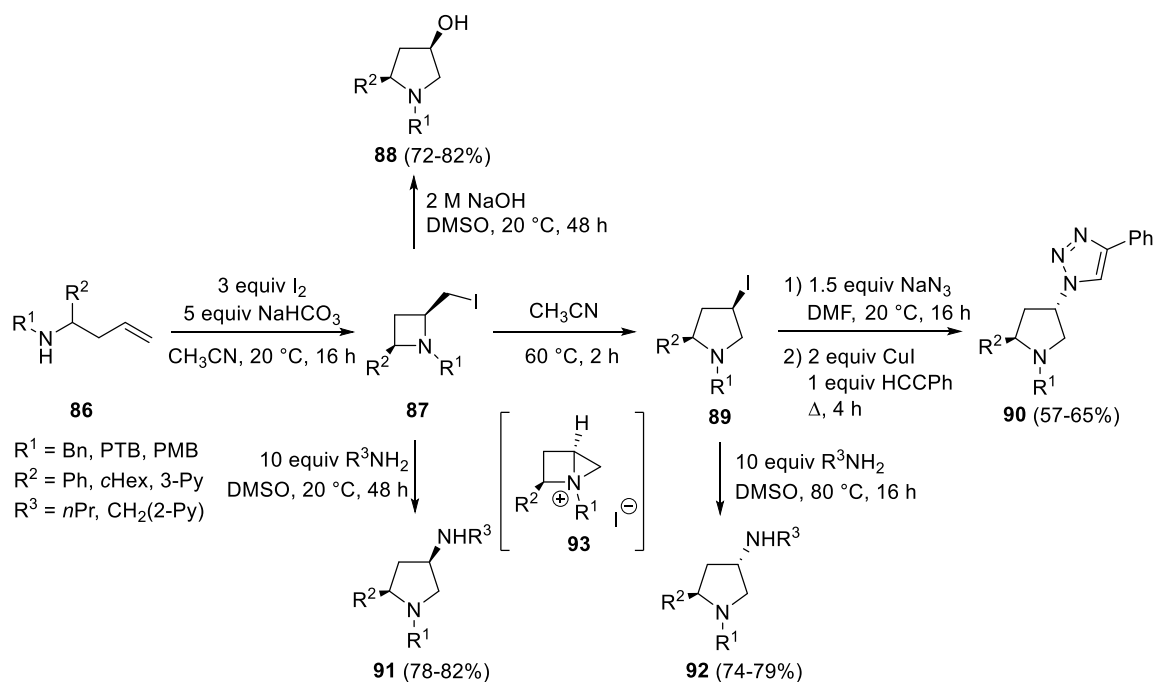
Scheme 23

Although 1-azoniabicyclo[2.1.0]pentane intermediates have never been isolated and characterized, theoretical calculations have indicated that the strained 1-azoniabicyclo[2.1.0]pentane structure is a viable intermediate in the ring expansion of 2-chloromethyl-1-isopropylazetidine toward 3-chloro-1-isopropylpyrrolidine.[60] As is clear from previously mentioned examples involving nucleophilic attack at the bridgehead carbon atom of *in situ* generated 1-azoniabicyclo[2.1.0]pentanes **4** (n = 2), pyrrolidin-3-ylium cations **7** (n = 2) should also be taken into consideration as possible intermediates in azetidine-to-pyrrolidine ring transformations, in contrast to the two other possible isomers **8** (n = 2) and **9** (n = 2) (Scheme 2). Because of the large difference in ring strain energies between the azetidine and pyrrolidine ring system, release of ring strain in 1-azoniabicyclo[2.1.0]pentanes preferentially gives rise to isomers **7** (n = 2) among four possible isomeric cations.

4. Preparation and synthetic utility of 1-azoniabicyclo[3.1.0]hexanes

In contrast to their lower homologues, the synthesis of 1-azoniabicyclo[3.1.0]hexanes via intermolecular reaction between polysubstituted 1-azabicyclo[3.1.0]hexanes and electrophiles has been well documented. Furthermore, isolation and characterization of 1-ethyl-1-azoniabicyclo[3.1.0]hexane perchlorate **95** has been realized, pointing to the higher stability of these larger ring intermediates (Scheme 24).[61] In that study, the feasibility of all possible routes toward the formation of 1-azoniabicyclo[3.1.0]hexane skeleton **95** was demonstrated as well.
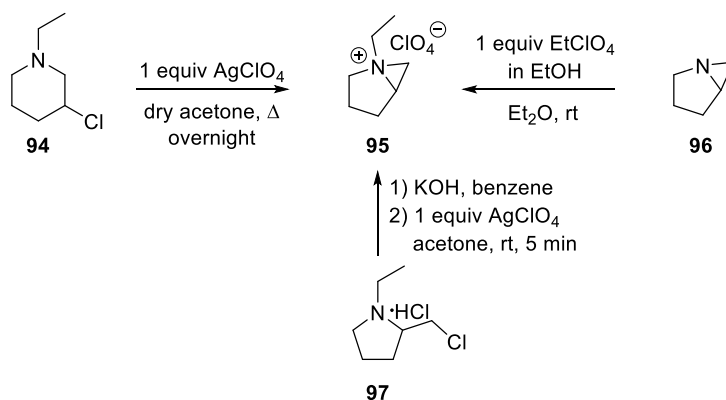
Scheme 24

1-Azabicyclo[3.1.0]hexane **96** has also been deployed as a starting material toward the synthesis of a variety of 2-(halomethyl)pyrrolidines **98/100** and 3-halopiperidines **99/101** (Scheme 25).[62] Reaction of azabicycle **96** with acyl halides resulted mainly in the formation of the corresponding pyrrolidines **98**, whereas treatment of the same starting material with a range of alkyl halides afforded piperidines **101** as the major compounds, apart from the reaction with bromoacetonitrile (R^2 = CN) yielding the corresponding pyrrolidine **100** as the main constituent. Activation of bicyclic azaheterocycle **96** with an electrophile resulted in bicyclic aziridinium intermediates **103**, which were then attacked at the least hindered side, affording 2-(halomethyl)pyrrolidines **102** as the kinetic products. Depending on the nature of the *N*-substituent, recyclization toward intermediates **103** can occur, followed by nucleophilic attack across the bridgehead carbon atom toward the thermodynamically stable 3-halopiperidines **104** (thermodynamic control). Because of the fact that *N*-acylation decreases the nucleophilicity of the nitrogen atom, these equilibrium reactions are considerably less favored as compared to *N*-alkyl-induced ring transformations. As a result, 2-(halomethyl)pyrrolidines **102** are considered to be the kinetically controlled products, whereas the isomeric 3-halopiperidines **104** are the thermodynamic products.
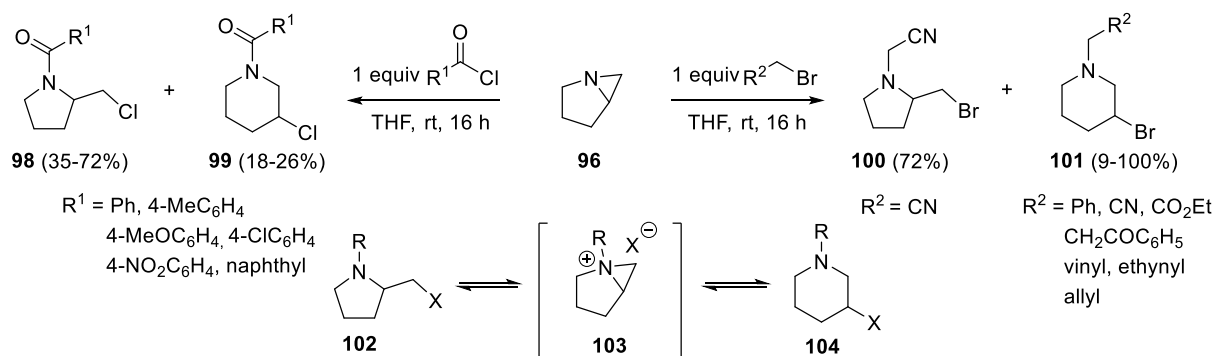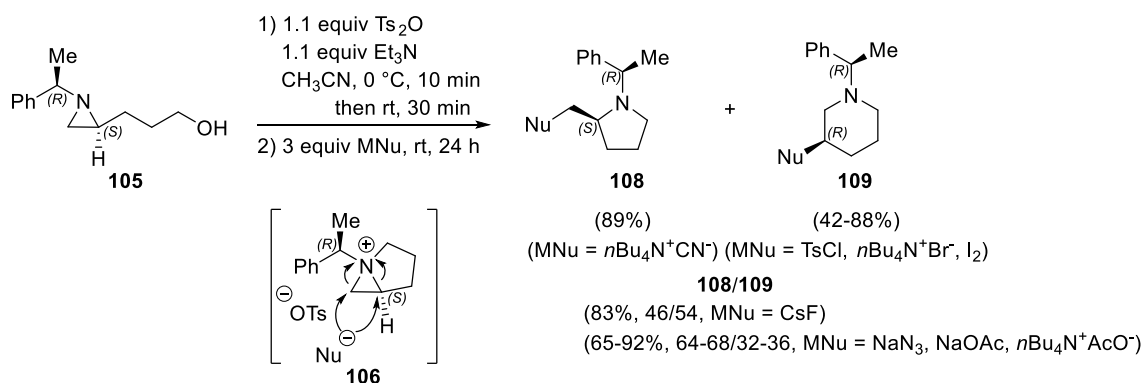
Scheme 25

Besides the production of 1-azoniabicyclo[3.1.0]hexanes via intermolecular activation procedures, the preparation of these bicyclic intermediates via intramolecular reactions are ubiquitous as well, starting either from 2-propylaziridines with a terminal leaving group in the side chain, or from 2-(halomethyl/sulfonyloxymethyl)pyrrolidines.

The employment of 2-(3-hydroxypropyl)aziridine **105** for the synthesis of a variety of 3-substituted piperidines and their regioisomeric pyrrolidines has extensively been investigated by Ha et al. (Scheme 26).[63] Furthermore, the structure of the decisive 1-azoniabicyclo[3.1.0]hexane tosylate **106** in this study was identified by means of NMR analysis. This product unexpectedly proved to remain stable in CH_3CN upon storage for 5 days at room temperature. Dissolving this bicyclic intermediate in CH_2Cl_2, however, resulted in 3-tosyloxypipiderine **107** formation, indicating a major solvent issue with respect to the stability and reactivity of bicyclic aziridinium salt **106**.
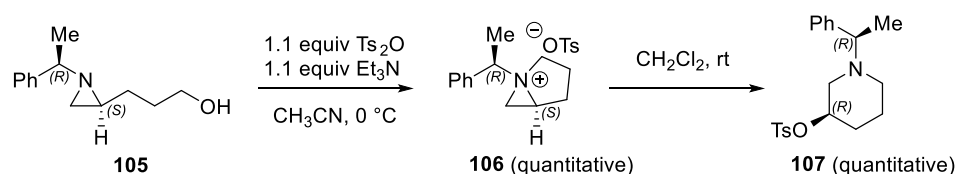
Scheme 26

This stable 1-azoniabicyclo[3.1.0]hexane tosylate **106** was also treated with various nucleophiles in CH_3CN. As shown in Scheme 27, the proposed ring-opening reactions can proceed through two different pathways to yield either pyrrolidines (pathway **i**, Scheme 1) or piperidines (pathway **ii**, Scheme 1), depending on the nature of the selected nucleophile. Addition of CsF, NaN_3, NaOAc and nBu$_4$NOAc afforded a mixture of those two regioisomers within the ratio 1:1 – 2:1 in 65-92% yield. Reaction of the bicyclic intermediate **106** with halides as nucleophile (TsCl, nBu$_4$NBr) and iodine (I_2), however, selectively furnished piperidines **109**, whereas nBu$_4$NCN only afforded the five-membered ring product **108**. Furthermore, these regioselective nucleophile-dependent ring transformations were also supported by DFT-calculations to rationalize the observed reactivities.

1) 1.1 equiv Ts₂O
1.1 equiv Et₃N
CH₃CN, 0 °C, 10 min
then rt, 30 min
2) 3 equiv MNu, rt, 24 h

(89%)   (42-88%)
(MNu = *n*Bu₄N⁺CN⁻) (MNu = TsCl, *n*Bu₄N⁺Br⁻, I₂)
108/109
(83%, 46/54, MNu = CsF)
(65-92%, 64-68/32-36, MNu = NaN₃, NaOAc, *n*Bu₄N⁺AcO⁻)

Scheme 27

In another study, an equilibration between the pyrrolidine ring and the corresponding piperidine has not been observed, affording the five-membered ring **112** as the sole regioisomer (Scheme 28). Treatment of enantiopure aziridine **110** with mesyl chloride, triethylamine and DMAP resulted in an *in situ* produced 1-azoniabicyclo[3.1.0]hexane intermediate **111**, followed by regioselective ring opening by chloride to furnish the kinetically favored end product **112**. Additional factors (such as steric interactions) might come in play in this particular transformation, accounting for the opposite reactivity as observed for the formation of 3-chloropiperidine **109** (Nu = Cl). This type of ring expansion with 1-azoniabicyclo[3.1.0]hexane as an intermediate was further utilized for the synthesis of the hydroxylated alkaloid hyacinthacin.[64]

MsCl, DMAP, Et₃N
CH₂Cl₂, 0 °C to Δ, 2 h

(+)-7a-epi-
hyacinthacin A₁
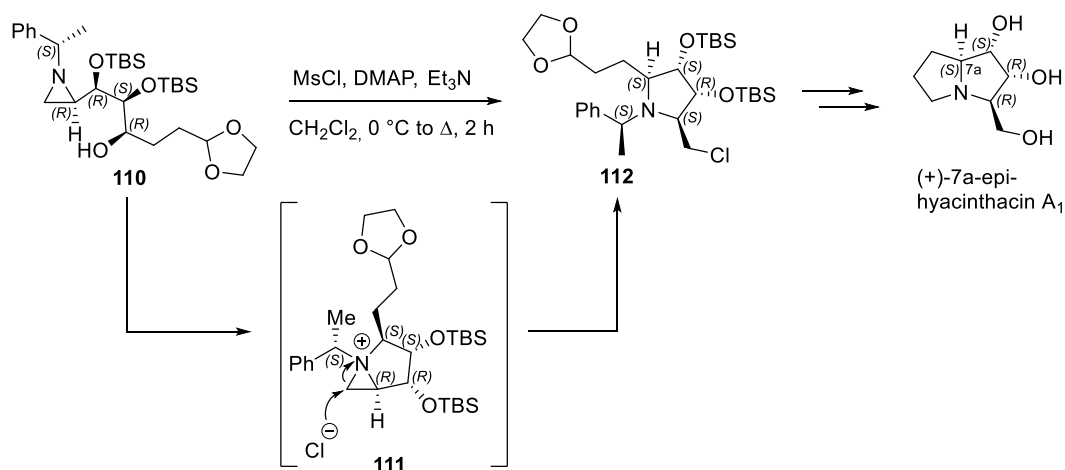
Scheme 28

Another powerful method to provide access to 1-azoniabicyclo[3.1.0]hexanes starts from 2-(halomethyl/hydroxymethyl)pyrrolidines. Due to the fact that a more stable piperidine scaffold can be obtained from these pyrrolidines, expulsion of the β-carbon-attached leaving group within these pyrrolidines occurs, resulting in a bicyclic intermediate. Subsequent nucleophile-induced ring opening across the bridgehead carbon atom finally affords the thermodynamically controlled piperidine. A first

example of this ring transformation involved (2*S*)-1-alkyl-2-(chloromethyl)pyrrolidines **113**, which were converted to (3*R*)-1-alkyl-3-chloropiperidines **115** as the sole products at a high reaction temperature (Scheme 29).[65] These conversions implied that the reaction proceeded via 1-azoniabicyclo[3.1.0]hexane intermediates **114**, followed by chloride attack at the bridgehead carbon atom rather than at the less-substituted site. This regiochemical outcome to yield (3*R*)-1-alkyl-3-chloropiperidines **115** stems from the kinetic and thermodynamic behavior of chloride attack, *i.e.* (3*R*)-1-alkyl-3-chloropiperidines **115** are the thermodynamic products, while their kinetic products, (2*S*)-1-alkyl-2-(chloromethyl)pyrrolidines **113** are in equilibrium with the corresponding 1-azoniabicyclo[3.1.0]hexanes **114**.
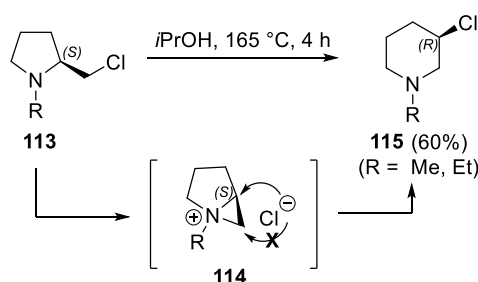
Scheme 29

Although a similar pyrrolidine-to-piperidine transformation has been observed by Brain et al., treatment of substrate **113** (R = Et) with various nucleophiles resulted in a mixture of pyrrolidines, obtained via an apparent direct chloride-by-nucleophile displacement, and the desired piperidines.[61] Extensive studies have also been carried out on the ring expansion of prolinols and their derivatives toward the synthesis of optically active 3-substituted piperidines, which has been well documented by Cossy and co-workers.[66] Besides the nucleophile dependency of these ring transformations, related to a thermodynamically or kinetically controlled reaction pathway, the nature of the substituents on the nitrogen atom and along the ring comprises a determining factor as well. As a representative example, the influence of the substitution pattern on the fluoride-induced ring transformation of prolinols **116** will be illustrated here (Scheme 30).[67] Upon altering the R^2 and R^3 substituents, only the replacement of R^2 with larger groups culminated in a higher ratio of the two regioisomers in favor of the piperidine structure. The presence of a more bulky *N*-protecting group (R^1) was also shown to improve the selectivity of the reaction toward piperidine formation (in the order: $CH_2tBu < CHPh_2 < CPh_3$). Finally, when an extra alkyl group was introduced at C2 (R^4 = Et, allyl, Bn), resulting in a quaternary carbon center, the rearrangement proceeded selectively toward piperidines **120**. As a consequence, these bicyclic aziridinium ion-interceded ring transformations could be controlled in a regioselective manner depending on the substitution pattern on the ring of prolinols **116**. Because of a more steric *N*-substituent, the C5-N bond in aziridinium intermediates **118** increased and the equilibrium was shifted more toward piperidin-3-ylium cations **119**, improving the selectivity in favor of a ring expansion. Also, the development of a quaternary center due to an extra alkyl group at C2 in prolinols **116** (R^4) led to a higher

stability of the produced cations **118** and, as a result, prolinols **116** were completely converted toward their higher homologues **120**.
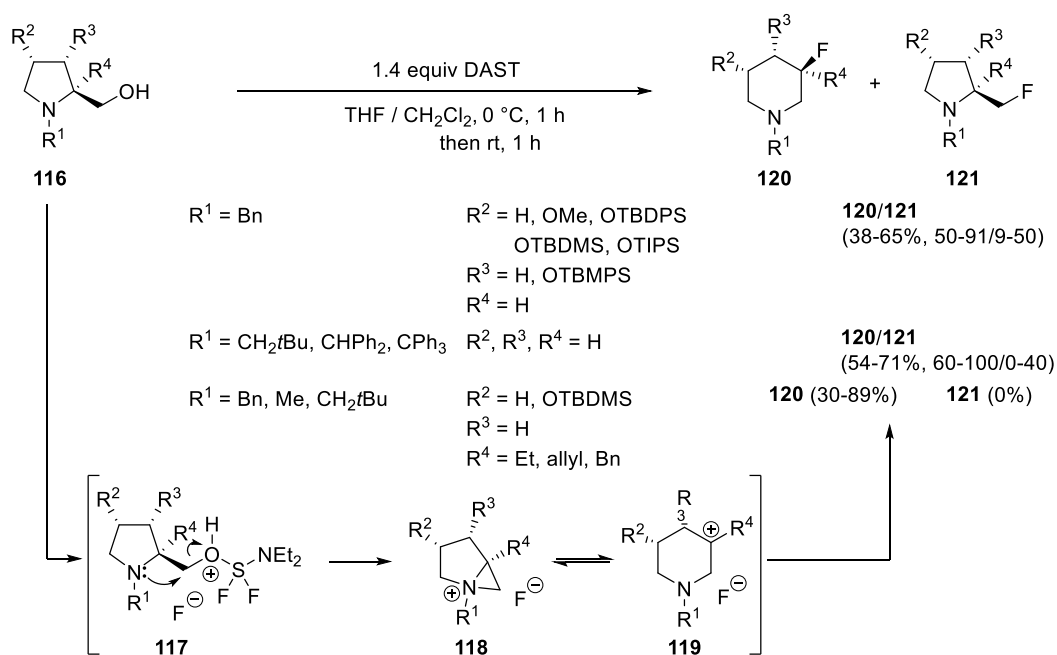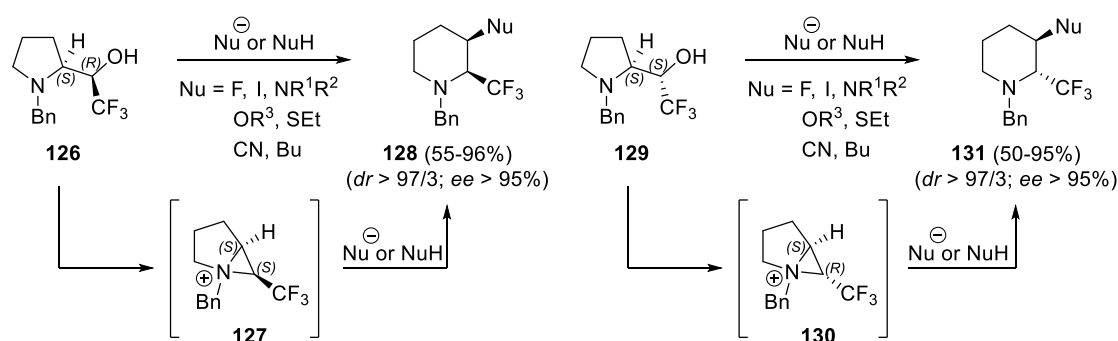

Scheme 30

In another study, the influence of a quaternary center in α-position with respect to the nitrogen atom has also been evaluated employing cyclic amino alcohols **122** and **124** as substrates, resulting in complete regioselective ring-transformation reactions in favor of piperidine formation (Scheme 31).[57] Moreover, DAST-induced ring expansion of β-amino alcohols **124** proceeded with excellent enantioselectivity (*ee* = 98-99%). Depending on the type of nucleophile, the reaction proceeds under thermodynamic or kinetic control. The regioselective attack of the nucleophiles across the aziridinium intermediate is affected by the nature of the substituents on the nitrogen atom and the C2 position of the starting prolinols.
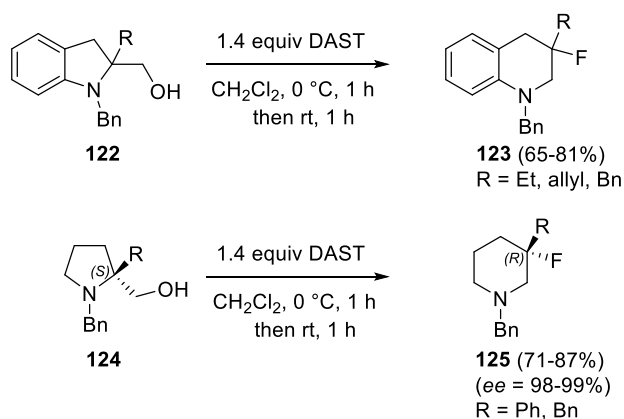
Scheme 31

All these observations can be interpreted and rationalized by comparing the possible contribution of four isomeric cations including **4**, **7**, **8** and **9** (n = 3, Scheme 2), which each could be generated from a 1-azoniabicyclo[3.1.0]hexane intermediate. The relative stability of the piperidin-3-ylium cation **7** (n = 3) can account for the formation of the piperidine ring as the major end product.

In accordance with these results, the reactivity of trifluoromethylated prolinols **126** and **129** toward a variety of nucleophiles has recently been elucidated (Scheme 32).[28] Due to the presence of a trifluoromethyl substituent, the proposed ring-transformation reactions proceeded with complete regioselectivity. Furthermore, these aziridinium-interceded ring expansions occurred with excellent diastereoselectivity.

Scheme 32

A similar pyrrolidine-to-piperidine rearrangement protocol has been developed by Davies et al. as a key step in the synthesis of polyhydroxylated piperidines.[68] This ring-expansion chemistry has also been deployed by Bilke et al. in the synthesis of the neurokinin-1-receptor antagonist (+)-L-733,060.[69]

Besides the overwhelming number of examples dealing with 1-azoniabicyclo[3.1.0]hexane-interceded pyrrolidine-to-piperidine transformations, ring-contraction reactions from 3-substituted piperidines toward 2-substituted pyrrolidines, involving analogous bicyclic intermediates, are known in the literature as well. Recently, Cossy and co-workers have developed a general protocol for the ring contraction of 3-hydroxy-3-(trifluoromethyl)piperidines **132** into a broad library of 2-substituted 2-(trifluoromethyl)pyrrolidines **134**, using a variety of halogen, nitrogen, oxygen, carbon and sulfur nucleophiles to trigger this ring transformation (Scheme 33).[70] Herein, treatment of 3-hydroxypiperidines **132** with 1.5 equiv of triflic anhydride (Tf$_2$O) and 2 equiv of proton sponge resulted in the production of 5-trifluoromethyl-1-azoniabicyclo[3.1.0]hexane **133**. Subsequent addition of two equiv of a suitable nucleophile afforded 2-(trifluoromethyl)pyrrolidines **134**. Due to the presence of a trifluoromethyl group, exerting electronic repulsion and steric hindrance toward an incoming nucleophile at C5, nucleophilic attack proceeded at C6, resulting in the kinetically controlled pyrrolidine scaffolds **134**. In addition, a more favorable methylium ion **8** (n = 3, R^2 = CF$_3$) as compared to its isomeric azacyclocarbenium ion **7** (n = 3, R^2 = CF$_3$) possibly accounts for the pyrrolidine formation as well due to the electron-withdrawing character of the trifluoromethyl group.
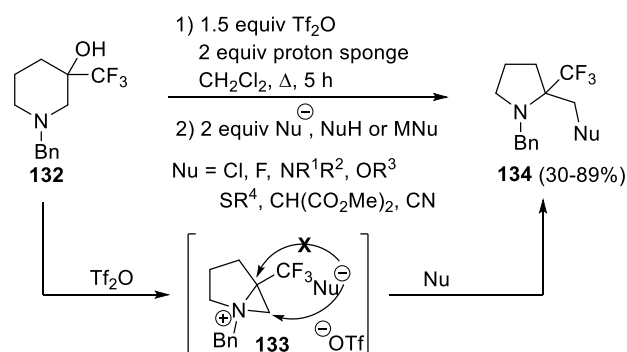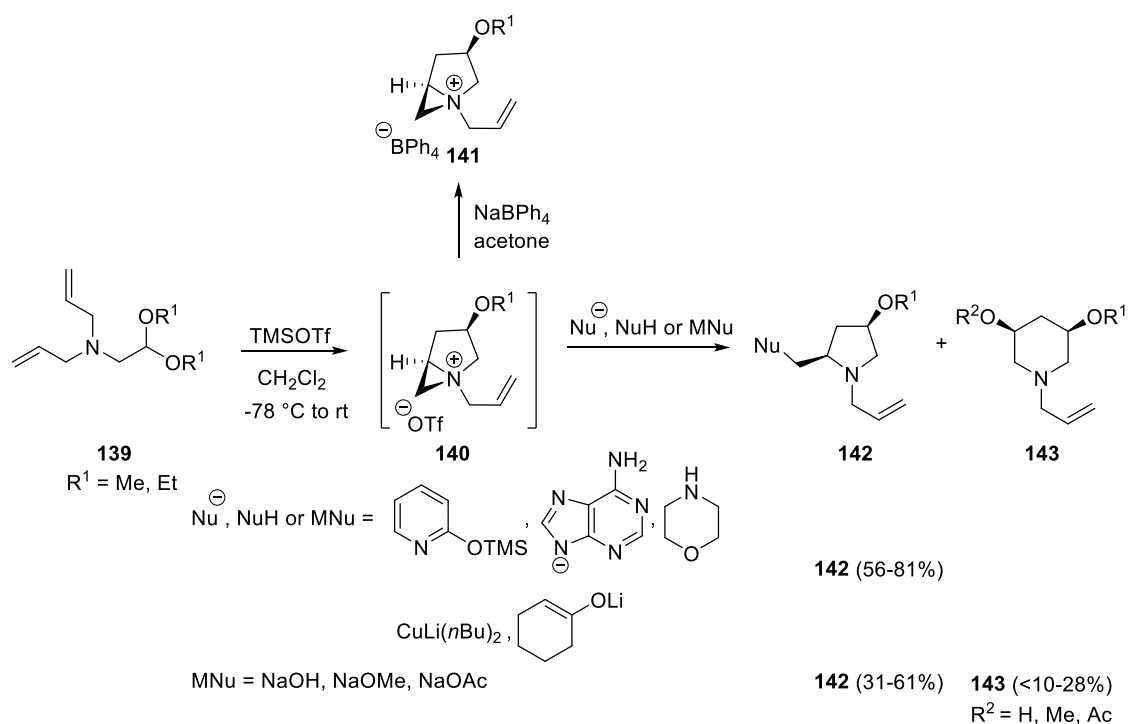
Scheme 33

A piperidine-to-pyrrolidine ring contraction has also been observed in the preparation of 2-(bromomethyl)pyrrolidines **138** (Scheme 34).[71] Reaction of 3-methoxypiperidines **135** with BBr$_3$ in dichloromethane and subsequent treatment with aqueous NaOH afforded 2-(bromomethyl)pyrrolidines **138**. Formation of the kinetically favored pyrrolidines **138** could be attributed to the use of an apolar solvent (CH$_2$Cl$_2$), as more polar solvents favored the production of the corresponding piperidines.
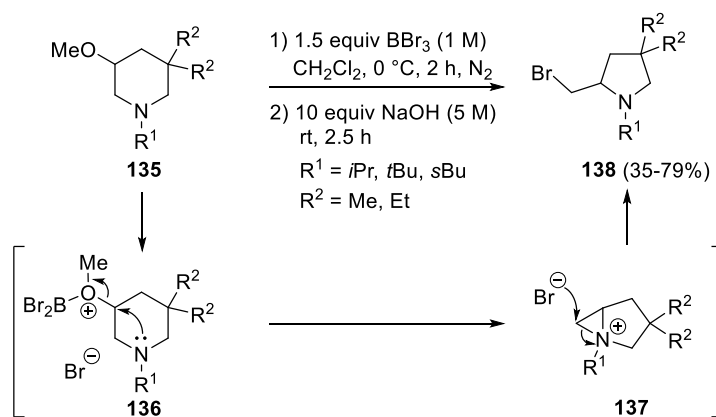
Scheme 34

Apart from the well-documented formation of 1-azoniabicyclo[3.1.0]hexanes via an intramolecular S$_N$2-mediated expulsion of a terminal leaving group in cyclic substrates, an analogous bicyclic intermediate has also been produced from an acyclic precursor, further supporting the stability and feasibility of 1-azoniabicyclo[3.1.0]hexane formation.[72] In that respect, treatment of β-(*N,N*-diallylamino)acetals **139** with TMSOTf produced diastereomerically pure 1-azoniabicyclo[3.1.0]hexanes **140** via a cationic cyclization reaction (Scheme 35). The 1-azoniabicyclo[3.1.0]hexanes **140** were isolated and characterized as the corresponding tetraphenylborate salts **141**. The subsequent ring-opening reactions, induced by the addition of an appropriate nucleophile, showed to be mainly regioselective affording 1,2,4-trisubstituted pyrrolidines **142**. However, treatment of intermediates **140** with oxygen nucleophiles also delivered a small amount of the isomeric piperidine structures **143**.

Scheme 35

1-Azoniabicyclo[3.1.0]hexanes have also been involved in the preparation of functionalized pyrrolidines **148** and piperidines **149** (Scheme 36).[73] Bromination of γ,δ-unsaturated aldimines **144** with bromine resulted in 5-bromomethyl-1-pyrrolinium bromides **145** via an electrophile-induced cyclization. Immediate reaction of these reactive intermediates **145** with hydride or alkoxides as nucleophiles afforded pyrrolidines **146**, which underwent intramolecular ring closure toward bicyclic intermediates **147**. Finally, ring opening of aziridinium ions **147** furnished the corresponding pyrrolidines **148** or piperidines **149**. The presence of two methyl substituents at C6 in azabicycles **147** clearly has a profound effect on the regioselectivity of the ring-opening process, resulting in either the thermodynamically favored piperidines **149** (R^3 = H, route ii) or the kinetically controlled pyrrolidines **148** (R^3 = Me, route i).
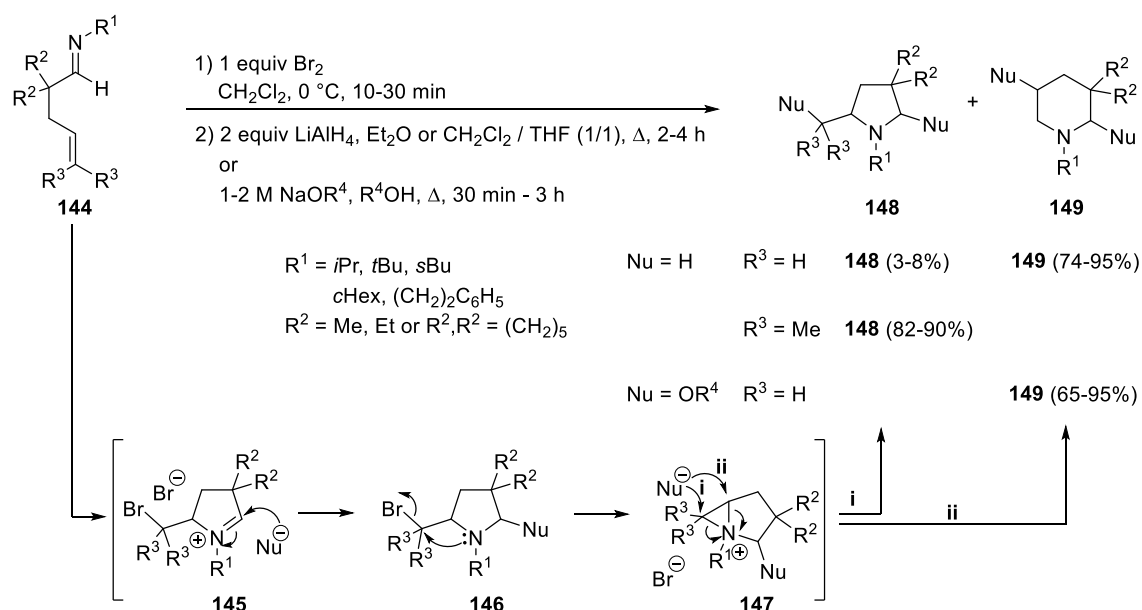
Scheme 36

Hydride-promoted ring opening of 1-azoniabicyclo[3.1.0]hexanes has also been investigated toward the synthesis of (—)-nitramine.[74] Analogous to the bromine-induced cyclization of aldimines **144** (Scheme 36), aldimines **150** were treated with bromine under the same reaction conditions (Scheme 37). Subsequent addition of two equiv of LiAlH$_4$ resulted in a higher production of the corresponding pyrrolidines **152** as compared to their six-membered regioisomers **153**. Finally, debenzylation of benzyl-protected piperidine **153** (PG = Bn) afforded the desired (—)-nitramine.
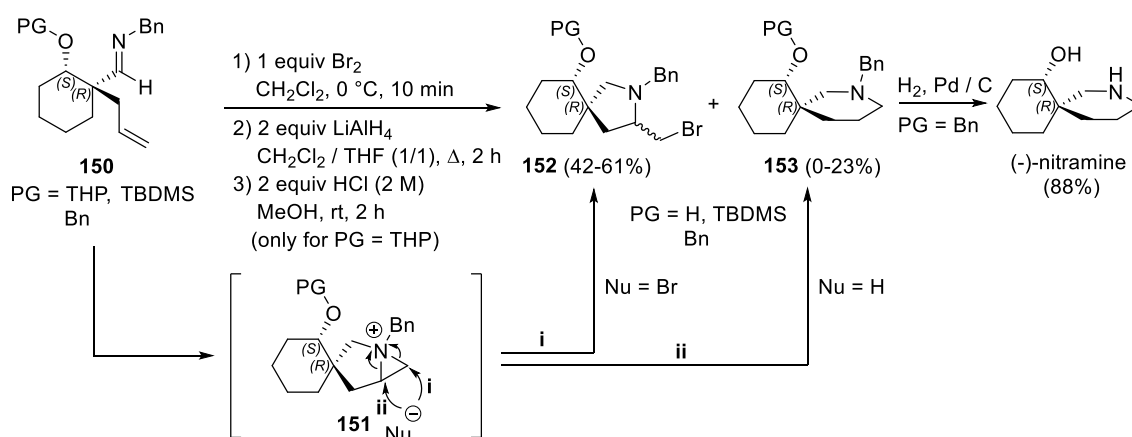
Scheme 37

As illustrated by several examples, the regioselectivity of the ring-opening process of 1-azoniabicyclo[3.1.0]hexanes is dependent upon the nature of the applied nucleophile, yielding either a pyrrolidine ring or a piperidine scaffold. The outcome of the premised ring transformation is also

influenced by the starting substrate, which is predictable to a certain extent by comparison of the stabilities among four possible cationic isomers (**4**, **7**, **8** and **9**, n = 3, Scheme 2).

5. Preparation and synthetic utility of 1-azoniabicyclo[4.1.0]heptanes

The intermolecular preparation of 1-azoniabicyclo[4.1.0]heptanes and their subsequent ring-opening reactions have been scarcely described in the literature so far. To illustrate this methodology, the synthesis of benzo-fused six- and seven-membered heterocycles will be discussed here as an example (Scheme 38).[75] Activation of the starting material **154** was accomplished upon heating with HBr, resulting in tricyclic aziridinium intermediates **155**. Whereas benzo-fused morpholine **154a** (Y = O) was regioselectively ring opened affording new morpholine **156a** as the sole reaction product, bromide-promoted ring opening of benzo-fused thiomorpholine **154b** (Y = S) afforded mainly the analogous thiomorpholine **156b** together with a small amount (5%) of its ring-expanded product **158b** after hydrolysis. The production of this seven-membered thiazepine derivative **158b** is reasonable considering the resonance stabilization of the developing benzylic carbenium ion in the corresponding azepin-3-ylium cation **7** (n = 4, R^2 = Ph), which is in equilibrium with aziridinium cation **155**.
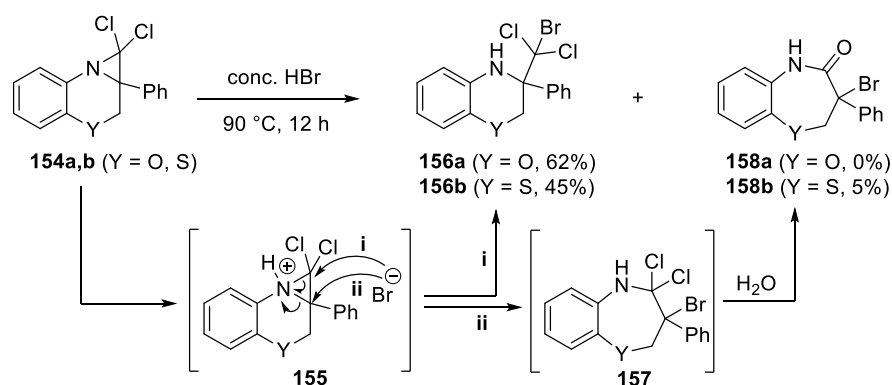
Scheme 38

In contrast to the small number of studies regarding the preparation of 1-azoniabicyclo[4.1.0]heptanes via intermolecular activation, more research has been performed dealing with the synthesis of these bicyclic intermediates via intramolecular reactions. Analogous to the previous sections, these intramolecular methods can again be subdivided into two approaches, depending on whether the starting material involves an aziridine scaffold or a piperidine skeleton. Both methodologies have been applied in a study on the preparation of stereodefined piperidines and azepanes starting from diastereomerically pure aziridines.[18] Microwave-assisted intramolecular cyclization of 2-(2-cyanoethyl)aziridines **159** resulted in 1-azoniabicyclo[4.1.0]heptanes **160**, which subsequently underwent a regioselective ring opening toward 2-chloromethyl-4-phenylpiperidine-4-carbonitriles **161** (Scheme 39). Taking advantage of the chloride leaving group in piperidines **161**, the latter piperidines were heated to regenerate bicyclic intermediates **160**. Upon addition of KCN in DMSO, the latter salts

were regioselectively opened at the less-substituted carbon atom, affording 2-cyanomethyl-4-phenylpiperidine-4-carbonitriles **162** in high yields (88-92%). However, reaction with NaOAc in EtOH also furnished the regioisomeric azepanes **163**. Surprisingly, the regioselectivity of these ring-opening reactions was strongly influenced by the relative stereochemistry of the substrates and could presumably be attributed to π-π interactions between the phenyl substituent on the piperidine core and the *N*-aryl substituent.
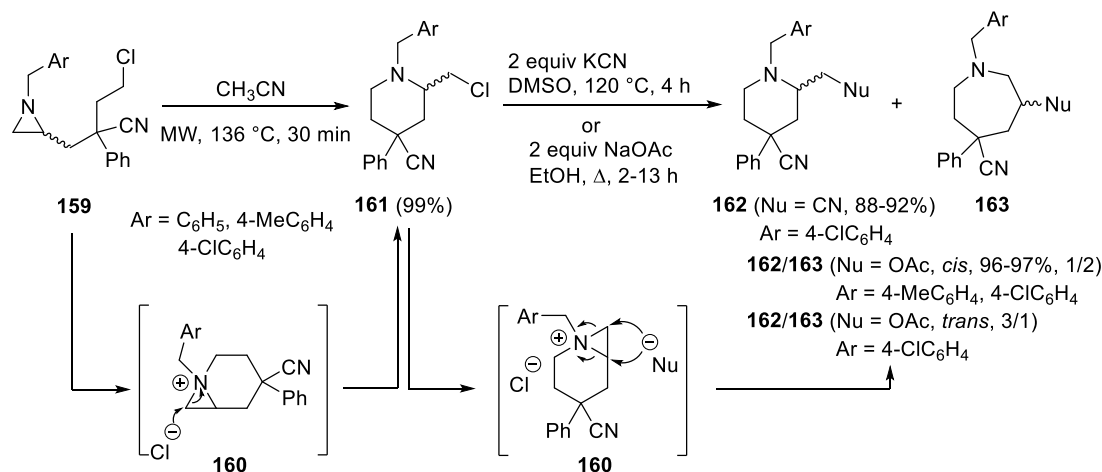
Scheme 39

A 1-azoniabicyclo[4.1.0]heptane intermediate was also involved in the transformation of aziridine **164** upon treatment with MsCl and Et₃N in acetonitrile (Scheme 40). The resulting tricyclic intermediate **165** was consecutively subjected to regioselective ring opening toward 1,2,3,4-tetrahydroisoquinolines **166** upon reaction with acetate and azide as nucleophiles.[76]
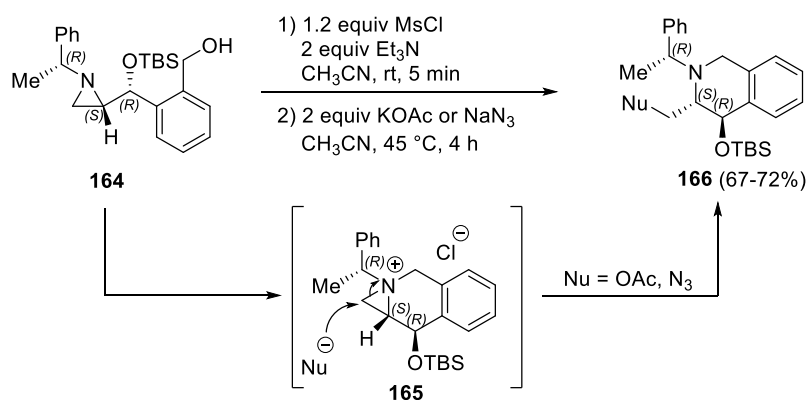
Scheme 40

In comparison to their lower homologues (especially bicyclic butanes and pentanes), the formation of a 1-azoniabicyclo[4.1.0]heptane skeleton is energetically more favored because of associated ring strain

energy differences. As a consequence, also activated aziridines, bearing a less nucleophilic nitrogen atom than their non-activated counterparts, can be converted into 1-azoniabicyclo[4.1.0]heptanes. In that respect, treatment of Boc-protected aziridines **167** with NBS and NsNH$_2$ in ethyl acetate afforded 3-nosylazepanes **169** in excellent enantioselectivity (Scheme 41). From a mechanistic point of view, aziridines **167** were transformed into bicyclic intermediates **168** upon reaction with NBS, followed by NsNH$_2$-induced nucleophilic ring opening.[77]
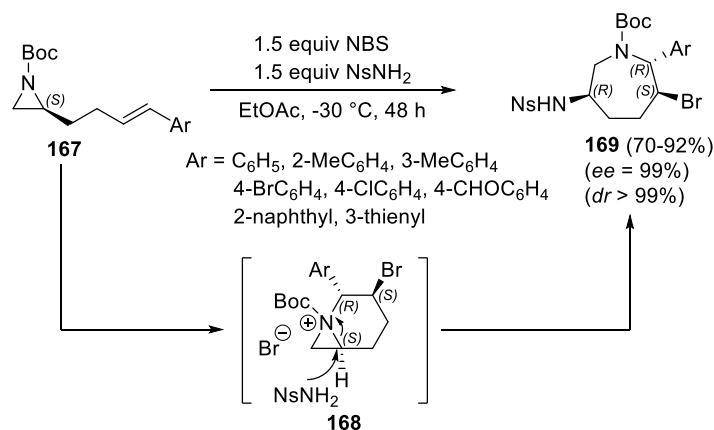
Scheme 41

A similar ring expansion has also been applied as a key step in the synthetic pathway toward the alkaloid (+)-castanospermine.[78] As depicted in Scheme 42, treatment of methyl hydroxamates **170** with [bis(trifluoroacetoxy)iodo]benzene (PIFA) generated 1-azoniabicyclo[4.1.0]heptanes **171**, which underwent nucleophilic attack across the less-hindered carbon atom upon reaction with trifluoroacetic acid (TFA).
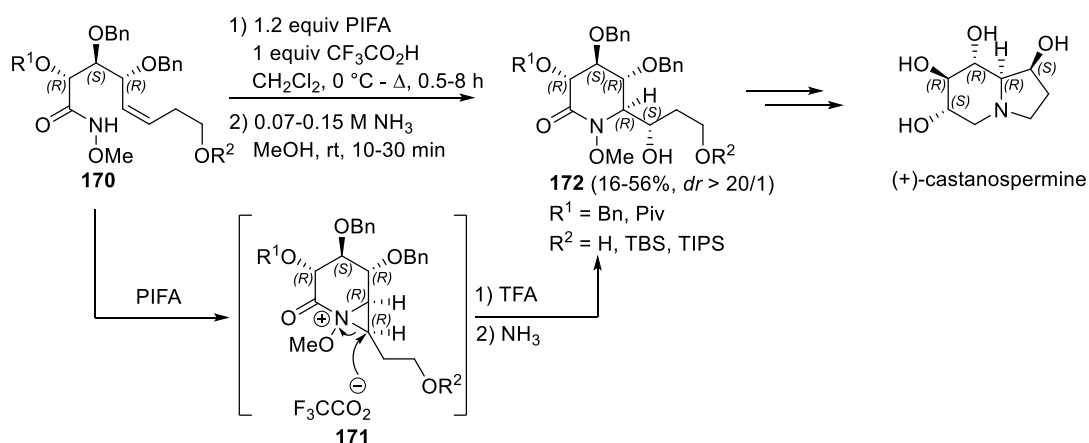
Scheme 42

The influence of the nitrogen-protecting group on the premised bicyclic aziridinium ion-interceded reactions has also been studied by Chong et al.[79] To that end, *cis*-2,6-di(chloromethyl)piperidines **173** bearing different protecting groups (R = Bn, CBz, Ts) were treated with an excess of NaN$_3$ in DMSO, furnishing either ring-expanded *cis*-azepanes **175** or chloride-by-azide substituted diazido piperidine **176** (Scheme 43). As anticipated, reaction of benzyl-protected piperidine **173** (R = Bn, X = Cl) with an excess of NaN$_3$ resulted in the regioselective formation of the corresponding azepane **175** (R = Bn). Although the CBz-protecting group rendered the nitrogen atom less nucleophilic for intramolecular expulsion of the leaving group in piperidine **173** (R = CBz, X = OTs), the corresponding azepane **175** (R = CBz) could be produced, probably due to the small amount of energy needed to create the 1-azoniabicyclo[4.1.0]heptane intermediate **174** (R = CBz). Furthermore, the piperidine-to-azepane transformations proceeded with complete stereoselectivity, again pointing to the occurrence of a bicyclic aziridinium intermediate. In case of tosyl-protected piperidine **173** (R = Ts, X = OTs), no azepane derivatives were observed after application of the same reaction conditions. Due to the strong electron-withdrawing character of the tosyl group, it seemed impossible to create a bicyclic aziridinium intermediate, affording piperidine **176** via direct substitution of the tosyloxy groups. Finally, the effect of the deployed nucleophile was also studied by heating up the benzyl-protected starting material **173** (R = Bn, X = Cl). After 4 hours in DMSO at 90 °C, a mixture of the corresponding piperidine and azepane in a 2.3:1 ratio was acquired, pointing to the influence of the applied nucleophile (*in casu* chloride) as well.
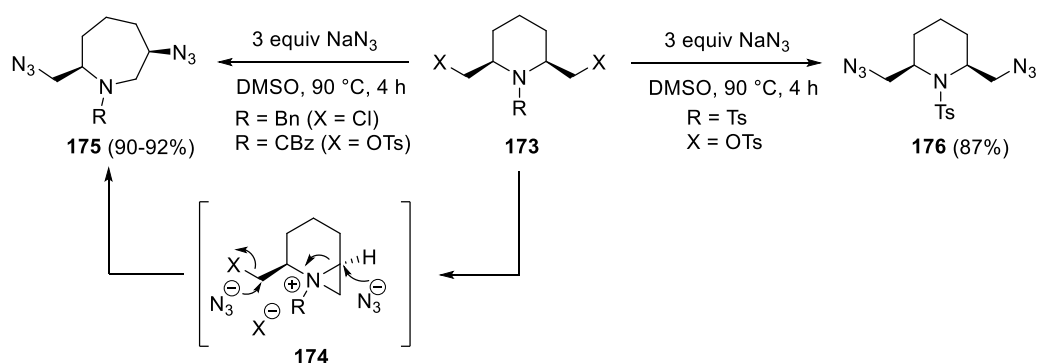
Scheme 43

As an extension of the DAST-induced ring enlargement of prolinols with a quaternary center in α-position with respect to the nitrogen atom, the ring expansion of their higher homologues, 2-(hydroxymethyl)piperazines/morpholines **177**, has also been investigated by Anxionnat et al.[57] As exemplified in Scheme 44, six-membered substrates **177** underwent a ring expansion toward diazepanes/oxazepanes **180** without any trace of a six-membered product. Due to the presence of a quaternary center in the corresponding bicyclic aziridinium intermediates **178**, the positive charge of their isomeric azepan-3-ylium cations **179** is extra stabilized, favoring the regioselective fluoride attack toward seven-membered ring formation.
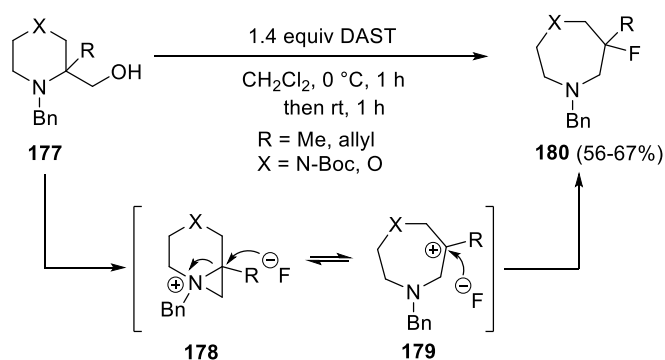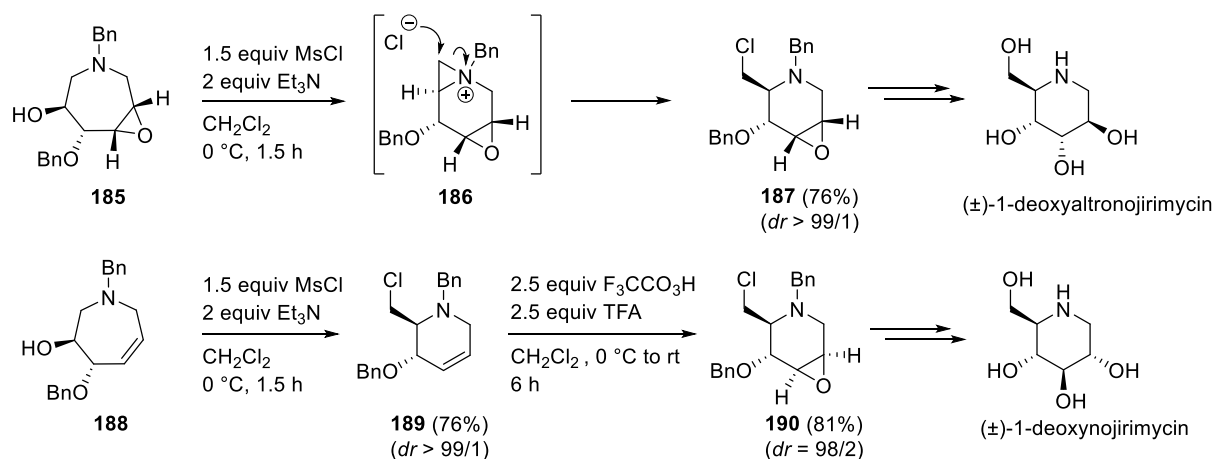
Scheme 44

In addition, the same reaction conditions have also been applied to (*S*)-piperidine **181a** (Scheme 45). Although the anticipated (*R*)-azepane **184a** was obtained, the enantioselectivity of this reaction was decreased compared to the ring expansion of (*S*)-pyrrolidine **124** to the corresponding (*R*)-piperidine **125** (see Scheme 31). This phenomenon is attributed to the structure of the involved bicyclic aziridinium intermediates. Because of the larger ring of 1-azoniabicyclo[4.1.0]heptane **182a** compared to its lower homologue, the C6-N bond is longer, causing a higher incidence of the azepan-3-yl cation **183a**. This hypothesis was further confirmed by reaction of (*S*)-azepane **181b** with DAST, yielding the corresponding (*R*)-azocane **184b** in an enantiomeric excess of only 52%.
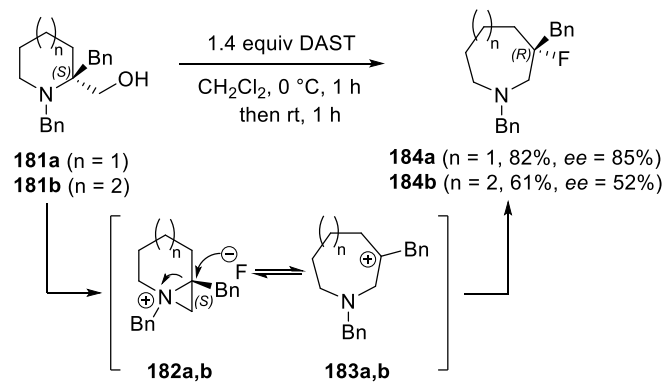
Scheme 45

Besides the involvement of 1-azoniabicyclo[4.1.0]heptane intermediates in ring-expansion reactions, these intermediates have also been deployed in ring-contraction reactions for the conversion of azepanes toward the corresponding piperidine scaffolds, for example as a key step in the synthesis of (±)-1-deoxynojirimycin and (±)-1-deoxyaltronojirimycin.[80] Treatment of azepane **185** with mesylchloride resulted in aziridinium salt **186**, which was immediately converted into the kinetically controlled piperidine **187** in an excellent diastereoselecitivity (Scheme 46). The same procedure was performed starting from tetrahydroazepine **188**, affording the corresponding piperidine structure **189**, whereas an additional step was required to obtain the diastereomeric counterpart of **187**.

Scheme 46

As elucidated by a selection of examples, the 1-azoniabicyclo[4.1.0]heptane intermediates are able to be converted into 2-substituted piperidines and/or 3-substituted azepanes, whether or not with high enantioselectivity. The ratio of piperidine versus azepane formation is dependent on the structural features of the substrate and the applied nucleophile. Furthermore, 1-azoniabicyclo[4.1.0]heptanes can be produced bearing a less nucleophilic nitrogen atom as well, which is reasonable from the lower energy input needed to create this intermediate in contrast to their lower homologues. Comparison of the stability among all possible isomeric cationic intermediates (**4**, **7**, **8** and **9**, n = 4, Scheme 2) should provide the reader the possibility to predict the regiochemical outcome of the aimed transformations to a large extent.

6. Conclusion

Although there is still some debate concerning the exact details of the involved mechanistic aspects, a broad diversity of useful synthetic applications of ring expansions involving 1-azoniabicyclo[n.1.0]alkane intermediates has been exploited to date. This methodology, implying the incorporation of the nitrogen atom of the small ring system into the newly formed ring-expansion product, will be covered in a first part of this PhD thesis toward the preparation of enantiopure trifluoromethylated pyrrolidines. However, strategies for the selective conversion of non-activated aziridines into pyrrolidines, piperidines, and other heterocycles, in which the aziridine unit is deployed as an electrophilic moiety and subjected to ring opening by an (*in situ* created) nucleophilic heteroatom at a remote position, still remain a scarcely investigated research field. In the main part of this PhD thesis, the latter strategy will be evaluated on a variety of aziridine substrates with the intention to provide new entries toward the construction of heterocyclic systems.

RESULTS AND DISCUSSION

This chapter is partly based on the following SCI-papers:

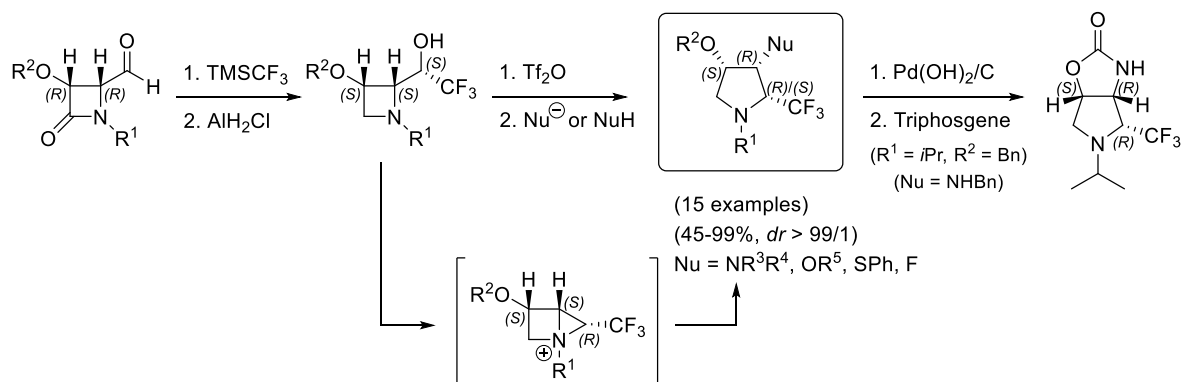PART I. **Dolfen, J.**; Boydas E. B.; Van Speybroeck, V.; Catak, S.; Van Hecke, K.; D'hooghe, M. "Asymmetric synthesis of 3,4-disubstituted 2-(trifluoromethyl)pyrrolidines through rearrangement of chiral 2-(2,2,2-trifluoro-1-hydroxyethyl)azetidines". *J. Org. Chem.* **2017**, DOI: 10.1021/acs.joc.7b01241 (I.F. 4.85).

PART II. **Dolfen, J.**; Vervisch, K.; De Kimpe, N.; D'hooghe, M. "LiAlH$_4$-induced selective ring rearrangement of 2-(2-cyanoethyl)aziridines toward 2-(aminomethyl)pyrrolidines and 3-aminopiperidines as eligible heterocyclic building blocks". *Chem. Eur. J.* **2016**, *22*, 4945-4951 (I.F. 5.77).

PART III. **Dolfen, J.**; D'hooghe, M. "Concise synthesis of 3-(aminomethyl)pyrrolizidines via an In(OTf)$_3$-mediated ring rearrangement of 2-[2-(1-pyrrolin-2-yl)alkyl]aziridines". *Synthesis* **2017**, 49, 2215-2222 (I.F. 2.65).

PART IV. **Dolfen, J.**; Van Hecke, K.; D'hooghe, M. "LiAlH$_4$-induced thia-aza-Payne rearrangement of functionalized 2-(thiocyanatomethyl)aziridines into 2-(aminomethyl)thiiranes as an entry to 5-(chloromethyl)thiazolidin-2-ones". *Eur. J. Org. Chem.* **2017**, 3229-3233 (I.F. 3.07).

PART I

Asymmetric synthesis of 3,4-disubstituted 2-(trifluoromethyl)pyrrolidines through rearrangement of chiral 2-(2,2,2-trifluoro-1-hydroxyethyl)azetidines

Abstract

Enantiopure 4-formyl-β-lactams were deployed as synthons for the diastereoselective formation of chiral 2-(2,2,2-trifluoro-1-hydroxyethyl)azetidines via trifluoromethylation through aldehyde modification followed by reductive removal of the β-lactam carbonyl moiety. Subsequent treatment of the (*in situ*) activated 2-trifluoroethylated azetidines with a variety of nitrogen, oxygen, sulfur and fluorine nucleophiles afforded chiral 3,4-disubstituted 2-(trifluoromethyl)pyrrolidines in good to excellent yields (45-99%) and high diastereoselectivities (*dr* > 99/1, ¹H NMR) via interception of bicyclic aziridinium intermediates. Furthermore, representative pyrrolidines were *N,O*-debenzylated in a selective way and used for further synthetic elaboration to produce e.g. a CF₃-substituted 2-oxa-4,7-diazabicyclo[3.3.0]octan-3-one system.

Graphical abstract

Reference

Dolfen, J.; Boydas, E. B.; Van Speybroeck, V.; Catak, S.; Van Hecke, K.; D'hooghe, M. "Asymmetric synthesis of 3,4-disubstituted 2-(trifluoromethyl)pyrrolidines through rearrangement of chiral 2-(2,2,2-trifluoro-1-hydroxyethyl)azetidines". *J. Org. Chem.* **2017**, DOI: 10.1021/acs.joc.7b01241 (I.F. 4.85).

1. Introduction

In recent years, the search for synthetic strategies enabling the incorporation of a trifluoromethyl group in organic molecules has been expanded considerably, as the presence of this entity is known to provoke a pronounced impact on the physical and chemical properties of the resulting compounds.[27] In particular, hydrogen-by-fluorine replacement has been shown to induce an enhancement of the metabolic stability and a change in lipophilicity of the involved molecules.[81] Furthermore, the introduction of fluorine can have a significant effect on the acidity or basicity of proximal functional groups.[82] As a consequence, fluorine chemistry plays a pivotal role in pharmaceutical research nowadays, which is reflected in the fact that nearly 25% of new drugs contains at least one fluorine atom in their structure.[82-83]

Although many protocols toward fluorinated target compounds have been developed in the chemical literature, the preparation of enantiopure representatives still remains an important challenge and, as a consequence, novel routes toward these products are highly desirable.[84] Within the range of methods to access enantioenriched fluorinated azaheterocycles, ring enlargements of smaller-ring homologs cover very useful reactions because they can provide a straightforward and efficient access to different nitrogen-containing target molecules in a stereoselective way. Among them, ring-expansion reactions associated with strained bicyclic aziridinium intermediates have attracted considerable attention bearing in mind the extent and scope of the involved transformations.[19,66] In that respect, Cossy et al. have studied the ring enlargement of enantiopure trifluoromethylated prolinols toward 3-substituted 2-(trifluoromethyl)piperidines **IV** via bicyclic aziridinium intermediates **III** (Scheme 1).[28] It was shown that enantiopure piperidines **IV** could be prepared via regioselective ring expansion of 2-(hydroxymethyl)pyrrolidines **I** bearing a CF_3 group at the C1' position. Analogously, the synthesis of enantiopure 2-(trifluoromethyl)pyrrolidines **VIII** via ring enlargement of azetidines **V** is pursued in the present chapter. Activation of the hydroxyl motif in azetidines **V** and subsequent heating might lead to the formation of bicyclic aziridinium intermediates **VII**, and interception by an appropriate nucleophile at the bridgehead carbon atom is then expected to afford pyrrolidine scaffolds **VIII** in a selective way.
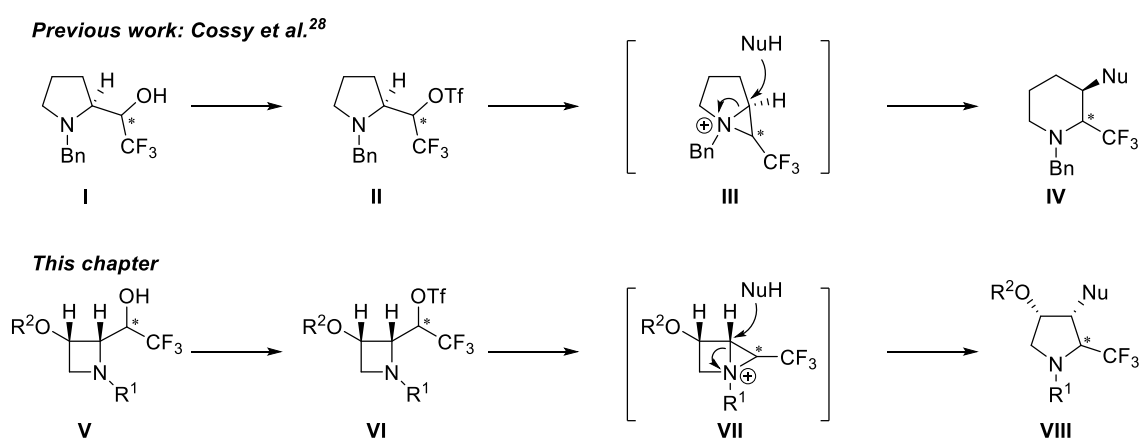
Scheme 1

From a retrosynthetic point of view, enantiopure pyrrolidines **VIII** will thus be prepared via ring expansion of trifluoromethylated 2-(hydroxymethyl)azetidines **V** through the intermediacy of bicyclic aziridinium ions **VII**. The synthesis of azetidines **V** will be performed starting from 4-formyl-β-lactams **IX** (Figure 1), relying on a trifluoromethylation of the aldehyde moiety by the Ruppert-Prakash reagent (TMSCF₃)[85] and subsequent reduction of the β-lactam unit by *in situ* prepared monochloroalane (AlH₂Cl). It is worth mentioning that the class of 4-formyl-β-lactams has already proven to include versatile synthetic intermediates toward a broad range of substances of biological interest, which is reflected by the large amount of reactivity studies concerning the deployment of these synthons in the preparation of amino sugars, bi- and polycyclic β-lactams, γ-lactams and γ-lactones, amino acids and complex natural products.[26]
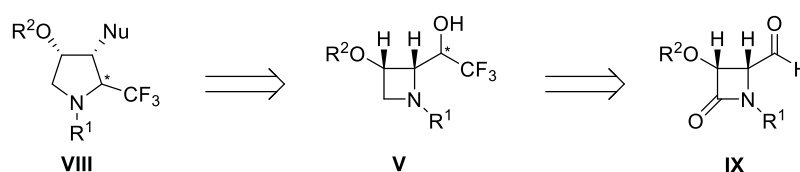
Figure 1

2. Synthesis of 4-oxo-azetidine-2-carbaldehydes

The synthesis of 4-formyl-β-lactams **4** was performed according to a well-known four-step protocol[26e,26f,86] and was initiated by the imination of (*R*)-glyceraldehyde acetonide **1** upon treatment with a variety of alkylamines in the presence of MgSO₄ (Scheme 2, Table 1). The corresponding chiral imines were immediately and as such treated with phenoxy- or benzyloxyacetyl chloride in the presence of triethylamine in CH₂Cl₂, affording *cis*-β-lactams **2** in an overall yield of 73-87% after column chromatography or recrystallization. Furthermore, it should be mentioned that these azetidin-2-ones **2** were obtained with high *cis*-diastereoselectivity (diastereomeric ratios of 91-99/1-9, determined by NMR, CDCl₃). This *cis*-diastereoselectivity could be determined by means of ¹H NMR spectroscopy, as typical coupling constants of 5.0-5.2 Hz (CDCl₃) between the 3H and 4H protons on the β-lactam ring indicate a *cis*-configuration according to the literature.[86] Subsequently, acetal hydrolysis in the latter compounds **2** was performed in THF/H₂O (1/1) upon stirring with an equimolar amount of *p*-toluenesulfonic acid during four hours under reflux and afforded 4-(1,2-dihydroxyethyl)-β-lactams **3** in good to excellent yields (67-99%). A final NaIO₄-mediated Malaprade-type oxidation of the 1,2-dihydroxy moiety in β-lactams **3** furnished the desired 4-formyl-β-lactams **4** in 57-97% yield.
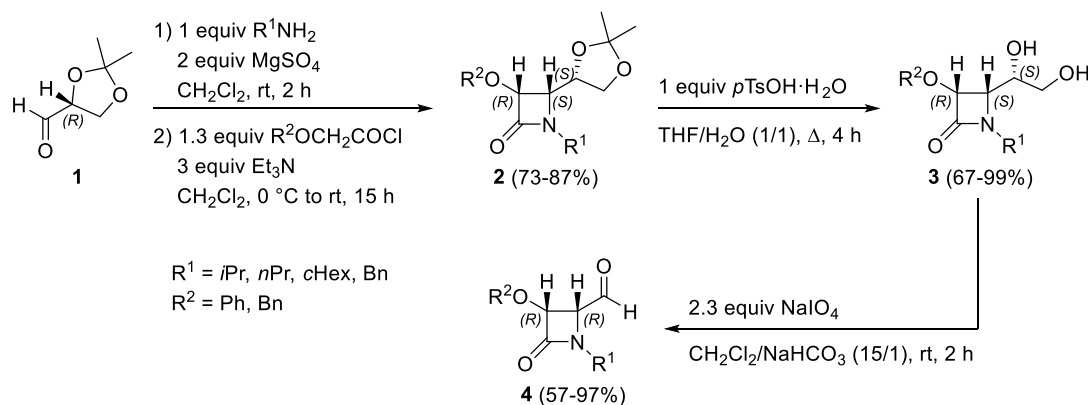
Scheme 2

Table 1. Synthesis of 4-(2,2-dimethyl-1,3-dioxolanyl)-β-lactams 2, 4-(1,2-dihydroxyethyl)-β-lactams 3 and 4-formyl-β-lactams 4.

Entry	R[1]	R[2]	Compound 2 (yield [%])[a]	dr (2)[b]	Compound 3 (yield [%])	Compound 4 (yield [%])
1	iPr	Ph	2a (73)	93/7	3a (99)	4a (94)
2	nPr	Ph	2b (81)	95/5	3b (95)	4b (80)
3	cHex	Ph	2c (87)	99/1	3c (99)	4c (78)
4	Bn	Ph	2d (74)	91/9	3d (99)	4d (81)
5	iPr	Bn	2e (80)	93/7	3e (67)	4e (86)
6	nPr	Bn	2f (87)	94/6	3f (76)	4f (97)
7	Bn	Bn	2g (74)	91/9	3g (98)	4g (57)[c]

[a] After purification by column chromatography (SiO$_2$) or recrystallization from EtOH.

[b] Determined by ^{1}H NMR spectroscopy (CDCl$_3$) of the crude reaction mixture.

[c] After recrystallization from EtOAc/hexane (15/1).

3. Synthesis of 2-(2,2,2-trifluoro-1-hydroxyethyl)azetidines

Due to the presence of the aldehyde moiety in 4-formyl-β-lactams **4**, the introduction of the trifluoromethyl group could take place upon reaction with a nucleophilic CF$_3$ source (Scheme 3). To that end, 4-formyl-β-lactams **4a,b** were converted into the corresponding 4-(2,2,2-trifluoro-1-hydroxyethyl)azetidin-2-ones **5a,b** and **6a,b** in a diastereomeric ratio of 72-74/26-28 using slightly adapted reaction conditions as compared to those employed for the synthesis of prolinols **I**,[28] *i.e.* a reduced amount of TMSCF$_3$ (1.1 instead of 1.5 equiv) and CsF (3 instead of 5.3 equiv) was used in this study to obtain the adducts **5a,b** and **6a,b** in 88-95% yield after 2 hours at room temperature (Table 2, Entries 1 and 3). Importantly, lowering the reaction temperature at which the reagents are added, from room temperature to -78 °C, resulted in an improvement of the diastereomeric ratio in favor of β-lactams **5** (diastereomeric ratio of 90-93/7-10, Table 2, Entries 2 and 4). Having the optimal reaction conditions for the diastereoselective introduction of the CF$_3$ group across the aldehyde moiety in hand, the other

4-formyl-β-lactams **4c-g** were also deployed as substrates, affording diastereomers **5c-g** and **6c-g** in a 64-77/23-36 ratio (Table 2, Entries 5-9) and in 63-93% yield after work-up. The preferential formation of (3*R*,4*S*,1'*S*)-diastereomers **5** above (3*R*,4*S*,1'*R*)-isomers **6** can be rationalized by the Felkin-Ahn model, through an anti-Felkin addition in which Cs⁺ acts a chelating agent. The isolation of enantiomers out of the diastereomeric mixtures **5/6** appeared to be highly dependent on the substitution pattern of the obtained 4-(trifluoroethyl)azetidin-2-ones. In particular, purification of derivatives **a-c**,**e** via either recrystallization or column chromatography furnished the major isomers **5a-c,e** exclusively in variable yields of 16-74% (Table 2, Entries 1-5,7). For compounds **5d,f** and **6f**, only minor amounts (< 2%) could be obtained for spectroscopic analysis and, as a consequence, the involved diastereomeric mixtures **5/6d,f** were used as such in the next step. Fortunately, column chromatographic purification of **5g** and **6g** afforded the pure enantiomers in a yield of 35% and 23%, respectively.
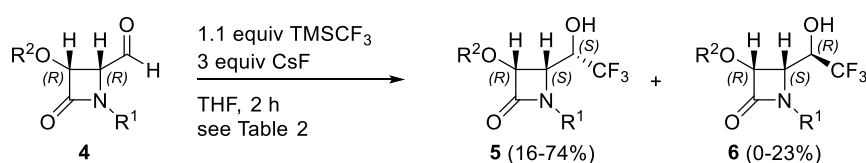
Scheme 3

Table 2. Synthesis of 4-(2,2,2-trifluoro-1-hydroxyethyl)azetidin-2-ones 5 and 6.

Entry	R¹	R²	Reaction temp.	Compound **5 + 6** (yield [%])[a]	dr (**5/6**)[b]	Compound **5** (yield [%])[c]	Compound **6** (yield [%])[c]
1	*i*Pr	Ph	rt	95	74/26	**5a** (65)	**6a** (-)
2	*i*Pr	Ph	-78 °C – rt	92	93/7	**5a** (74)	**6a** (-)
3	*n*Pr	Ph	rt	88	72/28	**5b** (18)	**6b** (-)
4	*n*Pr	Ph	-78 °C – rt	64	90/10	**5b** (29)	**6b** (-)
5	*c*Hex	Ph	-78 °C – rt	63	77/23	**5c** (16)	**6c** (-)
6	Bn	Ph	-78 °C – rt	93	70/30	**5d** (-)[d]	**6d** (-)
7	*i*Pr	Bn	-78 °C – rt	93	67/33	**5e** (50)	**6e** (-)
8	*n*Pr	Bn	-78 °C – rt	92	71/29	**5f** (-)[d]	**6f** (-)[d]
9	Bn	Bn	-78 °C – rt	91	64/36	**5g** (35)	**6g** (23)

[a] After work-up.

[b] Determined by ¹H NMR spectroscopy (CDCl₃) of the crude reaction mixture.

[c] After purification by column chromatography (SiO₂) or recrystallization from EtOAc/hexane (5-15/1).

[d] Only minor amounts (< 2%) could be obtained for spectroscopic analysis.

The absolute stereochemistry of the major 4-(2,2,2-trifluoro-1-hydroxyethyl)azetidin-2-ones **5** was unequivocally established by means of a single crystal X-ray analysis of compounds **5a** (Figure 2) and **5e**. Although 4-formyl-β-lactams **4** are known to provoke a diastereoselective control upon reaction with a nucleophile,[26a,26c] the number of literature procedures involving a catalyst-free enantioselective

introduction of a CF$_3$ group across carbonyl moieties is rather limited,[84a] and for that reason, the above-described trifluoromethylation procedure should be considered as relevant.
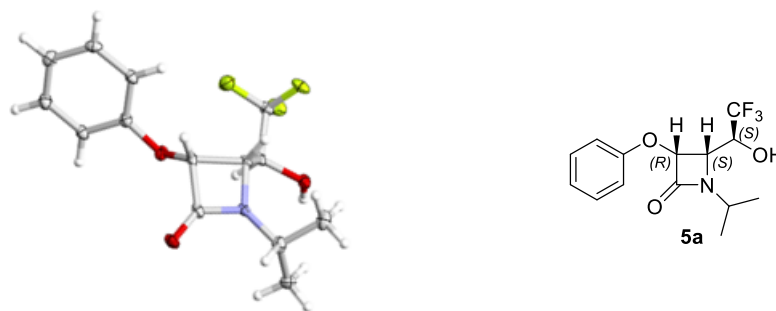
Figure 2

In the next step, the obtained 4-(2,2,2-trifluoro-1-hydroxyethyl)azetidin-2-ones **5** and **6** were reduced toward the corresponding azetidines through selective carbonyl removal without affecting the sensitive ring system. To that end, azetidin-2-ones (3*R*,4*S*,1'*S*)-**5a-c,e,g** were subjected to 1.5 equiv of monochloroalane (*in situ* prepared from AlCl$_3$ and LiAlH$_4$)[87] and stirred during 2 hours at 0 °C, affording the corresponding azetidines **7** in good to excellent yields (71-94%, Scheme 4a).[88] Azetidine **7e** appeared to be unstable upon purification on silica gel and, as a consequence, was used as such in the next step. The same reaction conditions were applied for the selective reduction of the carbonyl moiety in diastereomeric β-lactam mixtures **5/6d,f**, and, fortunately, subsequent column chromatographic purification enabled the separation of the major azetidines **7d,f** from the minor isomers **8a,b**, although in the case of minor compound **8a**, no pure azetidine could be obtained (Scheme 4b). Finally, treatment of (3*R*,4*S*,1'*R*)-azetidin-2-one **6g** with 1.5 equiv of AlH$_2$Cl afforded the corresponding azetidine **8c** in 79% yield (Scheme 4c). The isolation of azetidines **8b,c** as the 1'-epimers of azetidines **7** is important in order to be able to assess the influence of this stereocenter on their further ring-rearrangement aptitude. Also in this stage of the reaction sequence, the absolute stereochemistry of azetidines **7** was confirmed by means of a single crystal X-ray analysis of compounds **7a** and **7b** (Figure 3, asymmetric unit contains two molecules).
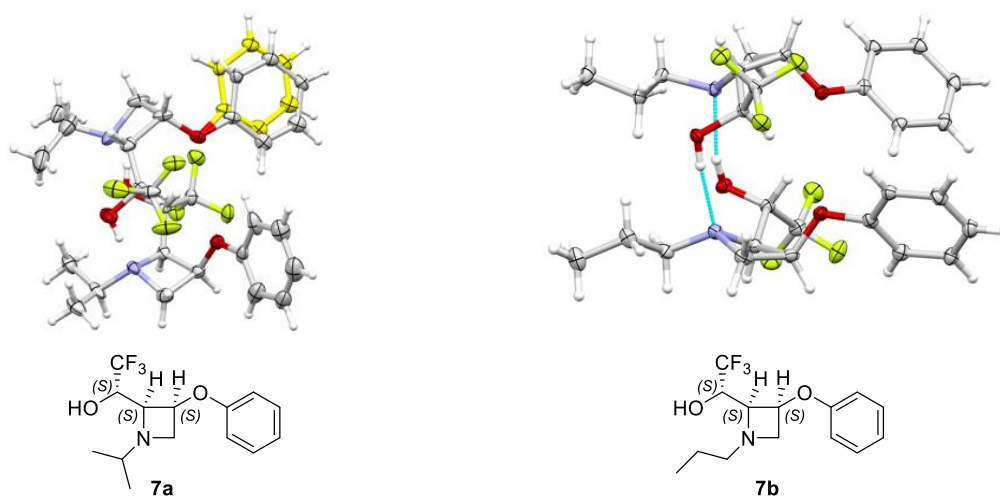
Figure 3
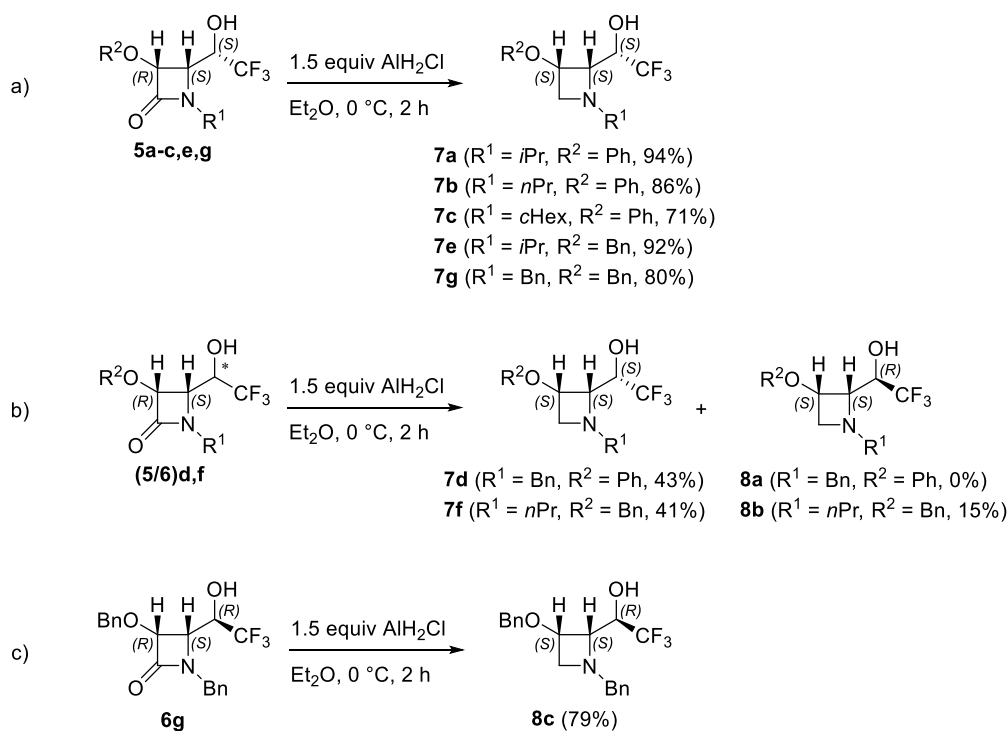
Scheme 4

4. Ring rearrangement of 2-(2,2,2-trifluoro-1-hydroxyethyl)azetidines toward enantiopure 3,4-disubstituted 2-(trifluoromethyl)pyrrolidines

In accordance with the work performed on the ring expansion of prolinols **I** as the higher homologs of azetidines **7** (Scheme 1),[28] azetidine **7a** was treated with N,N,N',N'-tetramethylnaphthalene-1,8-diamine (proton sponge, 2 equiv) and triflic anhydride (Tf$_2$O, 1.1 equiv) at 0 °C in CH$_2$Cl$_2$. Surprisingly, no ring-expansion product was detected after addition of benzylamine and, instead, triflate **9a** was isolated from the reaction mixture in 61% yield (Scheme 5).
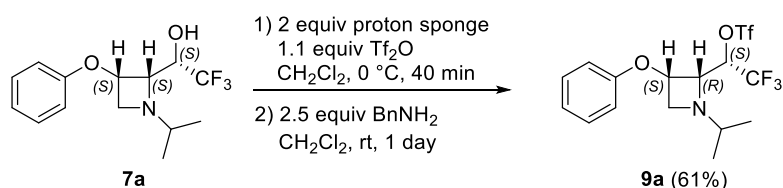
Scheme 5

In order to effect the premised azetidine-to-pyrrolidine ring transformation, the reaction temperature was increased and finally, after 3 days stirring at reflux conditions, the desired 3,4-disubstituted pyrrolidine **10a** was produced in a good yield (67%) and with excellent diastereoselectivity (dr > 99/1, determined by NMR, CDCl$_3$) (Scheme 6). The requirement of applying a higher temperature and a prolonged reaction time to realize the formation of the bicyclic aziridinium intermediates **VII** can be explained by

the fact that generation of 1-azoniabicyclo[2.1.0]pentanes might energetically be more difficult as compared to the production of less-constrained 1-azoniabicyclo[3.1.0]hexanes.[19] Extension of the scope of the observed diastereoselective azetidine-to-pyrrolidine rearrangement was then accomplished through variation of the azetidine substrate and/or the applied nitrogen nucleophile. In the case of azetidines **7a-c**, reaction with different alkylamines (benzylamine, allylamine, butylamine, benzyl(methyl)amine and ethanolamine) afforded a broad range of novel enantiopure 3,4-disubstituted 2-(trifluoromethyl)pyrrolidines **10a-g** in good yields (61-89%) and with an excellent diastereoselectivity (*dr* > 99/1, determined by NMR, CDCl$_3$) (Scheme 6).
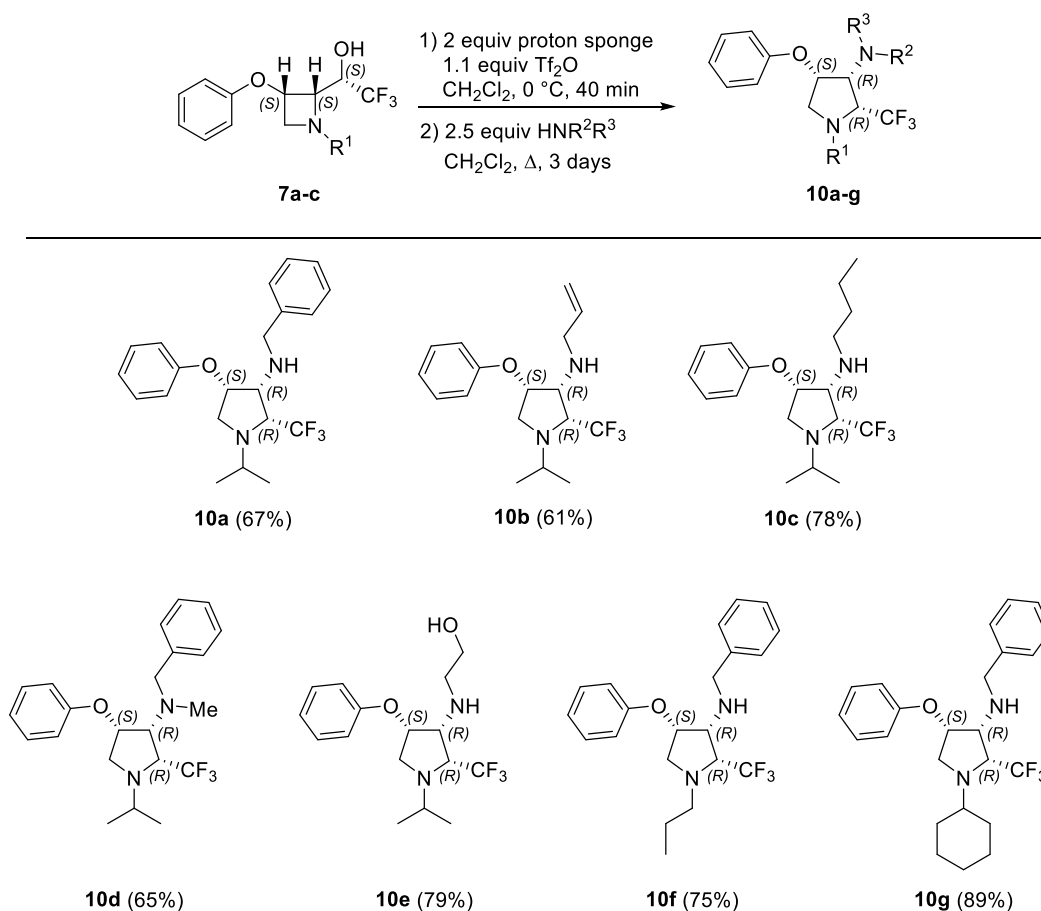
Scheme 6

However, the deployment of 1-benzylazetidine **7d** as a substrate did not yield the anticipated pyrrolidine scaffold upon treatment with benzylamine, even after 7 days at reflux temperature and, instead, the corresponding triflate **9b** was isolated from the reaction mixture in 73% yield (Scheme 7). This discrepancy in reactivity might be attributable to the less electron-donating properties of a benzyl group in contrast to an alkyl group, hampering the generation of the corresponding bicyclic aziridinium intermediate.
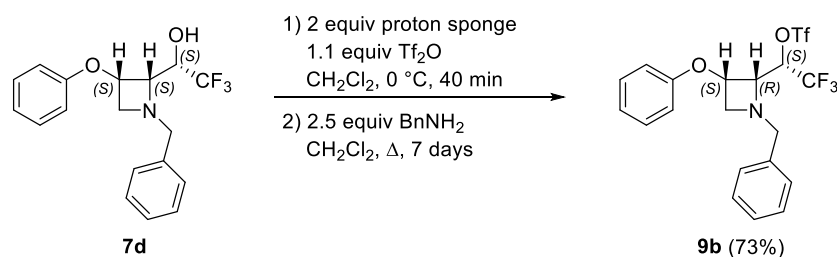
Scheme 7

To overcome this problem, the above-described one-pot reaction was modified to a two-step approach, involving sulfonylation of the hydroxyl moiety in azetidine **7d** followed by ring expansion toward the corresponding 2-(trifluoromethyl)pyrrolidine skeleton in another solvent. To that end, treatment of azetidine **7d** with Tf_2O in the presence of proton sponge afforded azetidine **9b** in an excellent yield of 95% after 40 minutes at 0 °C (Scheme 8). Analogously, the other azetidines **7e-g** and **8b,c** were converted into their triflate-activated derivatives **9c-e** and **11a,b**. Triflate **9c** appeared to be unstable upon silica gel purification and, as a consequence, was used as such in the next step. Remarkably, triflates **9b-e** were obtained in higher yields (90-95%) as compared to their diastereomeric counterparts **11a,b** (71-74%), which could be attributed to the partial degradation of triflates **11a,b** upon column chromatographic purification as complete conversion of alcohols **8b,c** to these compounds was observed.
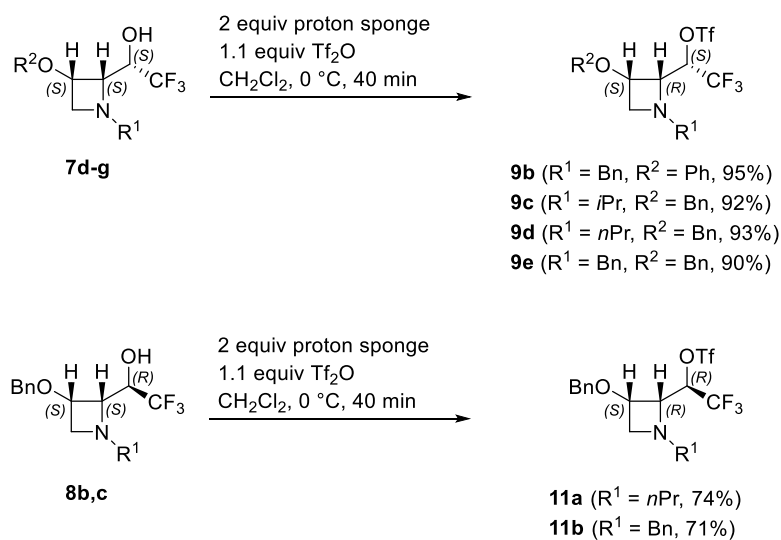
Scheme 8

With the sulfonylated azetidines **9b-e** in hand, the premised azetidine-to-pyrrolidine ring expansion was performed using a higher boiling solvent then CH_2Cl_2. In that respect, azetidines **9b-e** were treated with benzylamine in CH_3CN, affording 3-benzylamino-2-(trifluoromethyl)pyrrolidines **10h-k** in almost quantitative yields (96-99%) and with a high diastereoselectivity (*dr* > 99/1, determined by NMR, $CDCl_3$)

(Scheme 9). Importantly, the obtained yields in this two-step protocol were (in contrast to the one-pot approach, Scheme 6) much higher and the required reaction time for the rearrangement could be reduced significantly (from 3 days to 2-3 hours). The absolute stereochemistry of 3,4-disubstituted 2-(trifluoromethyl)pyrrolidines **10** was unambiguously established by means of a single crystal X-ray analysis of compound **10h** (Figure 4), pointing to the diastereoselective formation of all-*cis*-pyrrolidines **10** in a double S$_N$2-fashion.
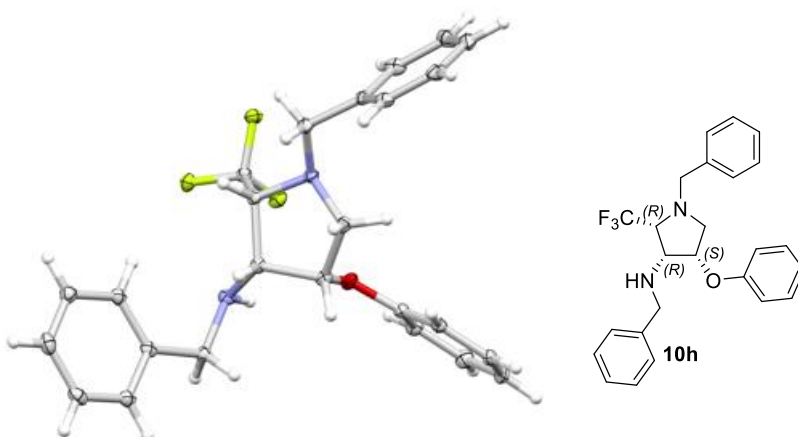
Figure 4

In order to further broaden the scope of this diastereoselective azetidine-to-pyrrolidine rearrangement, other nucleophiles instead of amines were evaluated as well. Reaction of triflate **9c** with 2.5 equiv of benzylalcohol furnished the corresponding 3-benzyloxy-2-(trifluoromethyl)pyrrolidine **10l** in 69% yield after silica gel column chromatography. Attempts to introduce a methoxy substituent at C3 started with treatment of triflate **9b** with 2.5 equiv of sodium methoxide. After 17 hours stirring at reflux conditions in CH$_3$CN, a mixture of 2-(1-hydroxyethyl)azetidine **7d** and the desired 3-methoxy-2-(trifluoromethyl)pyrrolidine **10m** was obtained in a 77/23 ratio. However, by using a 10/1 mixture of CH$_3$CN/MeOH, triflate **9b** was fully converted to pyrrolidine **10m**, which was isolated in an excellent yield (91%). The employment of sulfur nucleophiles was also evaluated upon reaction of **9b** with thiophenol, and the corresponding 3-phenylthio-2-(trifluoromethyl)pyrrolidine **10n** was isolated in a moderate yield (45%) after column chromatography. Efforts were also made concerning the use of carbon nucleophiles to trigger this ring transformation. Unfortunately, reactions with TBACN in CH$_3$CN resulted in complex reaction mixtures, whereas treatment of triflates **9** with KCN in DMSO or CH$_3$CN resulted in full recovery of the initial azetidine substrates **7**.
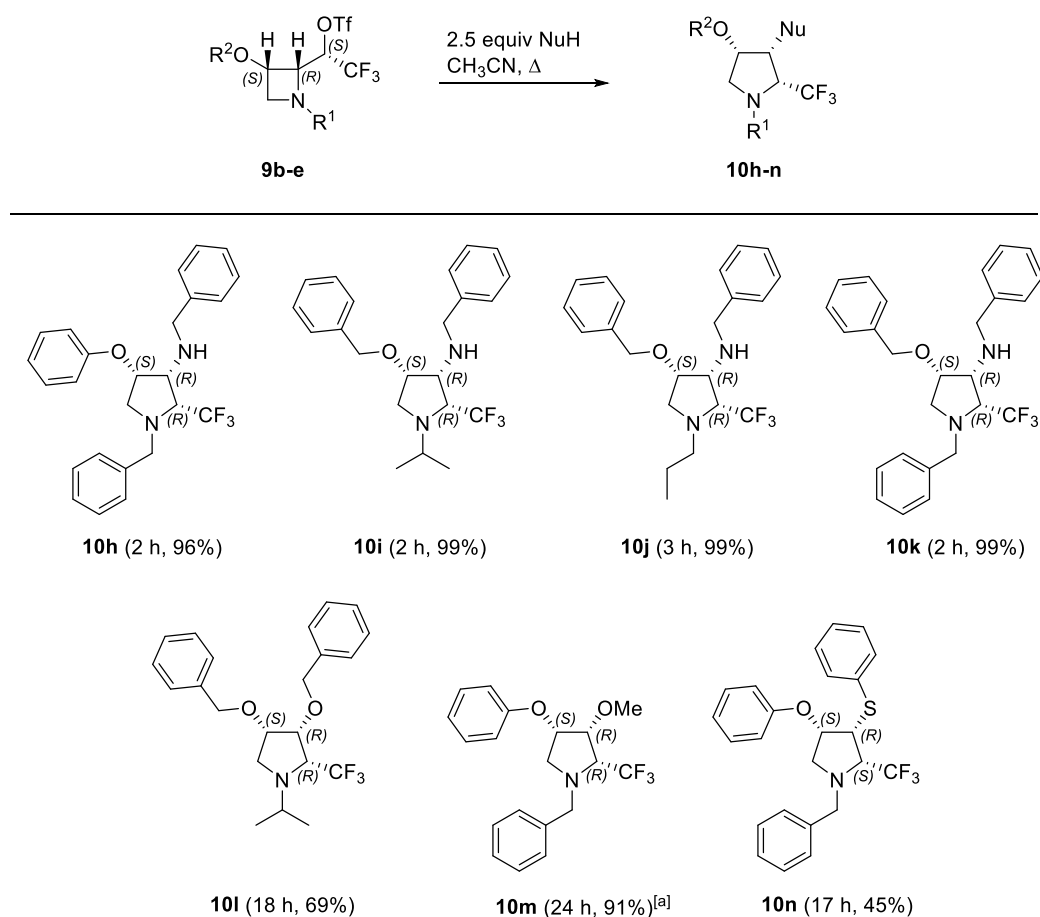
Scheme 9

The introduction of a fluorine substituent was also shown to be possible upon treatment of azetidine **7e** with diethylaminosulfur trifluoride (DAST, 2 equiv) in CH_2Cl_2, and the corresponding 3-fluoro-2-(trifluoromethyl)pyrrolidine **10o** was thus obtained in 88% yield with a high diastereoselectivity ($dr > 99/1$, determined by NMR, $CDCl_3$) (Scheme 10).[56-57,67,89]

Scheme 10

Based on the developed strategy for the synthesis of novel enantiopure 3,4-disubstituted 2-(trifluoromethyl)pyrrolidines **10**, triflates **11** (the diastereomeric counterparts of triflates **9**, epimeric at the

1'-position) were also treated with 2.5 equiv of benzylamine in CH_3CN and stirred during 3 days at reflux conditions. Surprisingly, no ring-expansion products **12** were observed and the starting material was completely recovered (Scheme 11). Apparently, the stereochemistry of the exocyclic CF_3-substituted carbon atom has a profound influence on the ring-rearrangement proclivity of azetidines **9** versus **11**.
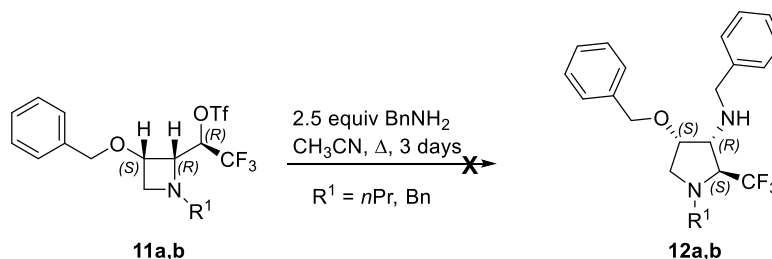
Scheme 11

5. Theoretical rationalization

In order to rationalize this unexpected behavior of (2*R*,3*S*,1'*S*)-azetidines **9** versus (2*R*,3*S*,1'*R*)-azetidines **11** with respect to their ring-transformation ability, a computational analysis was conducted by colleagues at the Center for Molecular Modeling (UGent) to elucidate the underlying factors.

The ring transformation of (2*R*,3*S*,1'*S*)-azetidines **9** to pyrrolidines **10** is proposed to go through a bicyclic intermediate (**9-INT**) as shown in Scheme 12. The initial step, which leads to the bicyclic intermediate, involves a concerted displacement of the triflate leaving group via the nucleophilic attack of the nitrogen lone pair. Pre-reactive conformers (PRC's) and transition states (TS's) leading to the corresponding bicyclic intermediates were analyzed and compared for both azetidines **9** and **11**. It is important to note that only one of the *N*-invertomers for compounds **9** and **11** have the nitrogen lone pair in the right position to lead to an S_N2-type attack. To that end, a thorough conformational search of the reactants was performed to take into account the relative positions of the nitrogen and triflate groups. Calculations have shown in both cases that the most stable invertomers are the ones that could lead to the formation of the bicyclic intermediate.
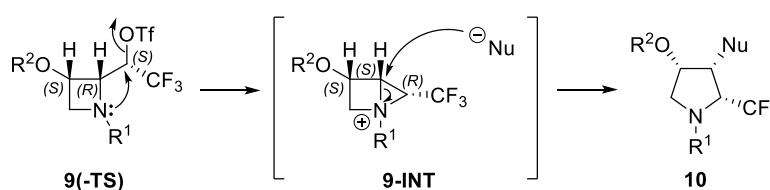
Scheme 12

A free-energy reaction profile has been constructed for both azetidines at the MPW1K/6-311+G(3df,3pd)//M06-2X/6-31+G(d,p) level of theory, where critical distances and angles of PRC's and TS's have also been depicted (Figure 5). When the structures of the pre-reactive conformers are closely

inspected, the close proximity of the CF_3 moiety and the benzyloxy group in **9e-PRC** is shown to lead to a large geometrical distortion, which is reflected in an unusually large bond angle (126° in **9e-PRC** versus 114° in **11b-PRC**). This, in turn, causes a remarkable energy difference of around 35 kJ/mol (MPW1K/6-311+G(3df,3pd)) between the two starting compounds. As a consequence, **11b-PRC** appears to be significantly more stable than **9e-PRC**, making the latter intrinsically more reactive. This result is consistently verified with all four levels of theory employed in this study (Table 3).

Table 3. Relative Gibbs free energies (kJ/mol) of activation (ΔG‡) and reaction (ΔGrxn) with respect to 11b-PRC.

	M06-2X[a]	MPW1K[b]	ωB97X-D[c]	PBE0[d]
11b-PRC	0.0	0.0	0.0	0.0
9e-PRC	30.9	35.1	32.2	34.5
11b-TS	111.9	111.8	106.4	101.7
9e-TS	128.0	127.5	119.2	117.4
11b-INT	9.3	9.9	5.2	10.1
9e-INT	-6.2	-9.2	-18.2	-10.0

[a] Optimizations with C-PCM in acetonitrile (ε = 37.5).
[b,c,d] Energy refinements on M06-2X/6-31+G(d,p) optimized geometries using a 6-311+G(3df,3pd) basis set with C-PCM in acetonitrile (ε = 37.5).

The differences between the activation barriers ($\Delta\Delta G^{\ddagger}$) for the formation of the bicyclic intermediates are around 19 kJ/mol in a consistent manner for all levels of theory (Table 4), clearly indicating the ease of reaction for azetidines **9**. Moreover, **9e-INT** is also thermodynamically more stable than its counterpart **11b-INT**. Finally, the reverse reaction **11b-INT** to **11b-TS** is energetically more favored than the forward reaction of **11b-PRC** to **11b-TS**, and as a consequence, DFT calculations, consistent with experimental work, suggest the formation of a bicyclic intermediate to be unfavorable for azetidines **11**.

Table 4. Relative Gibbs free energies (kJ/mol) of activation (ΔG‡) and reaction (ΔGrxn).

		M06-2X[a]	MPW1K[b]	ωB97X-D[c]	PBE0[d]
9e	$\Delta G^{\ddagger}$	97.1	92.4	86.9	82.9
	ΔG_{rxn}	-37.1	-44.3	-50.4	-44.5
11b	$\Delta G^{\ddagger}$	111.9	111.8	106.4	101.7
	ΔG_{rxn}	9.3	9.9	5.2	10.1

[a] Optimizations with C-PCM in acetonitrile (ε =37.5).
[b,c,d] Energy refinements on M06-2X/6-31+G(d,p) optimized geometries using a 6-311+G(3df,3pd) basis set with C-PCM in acetonitrile (ε =37.5).
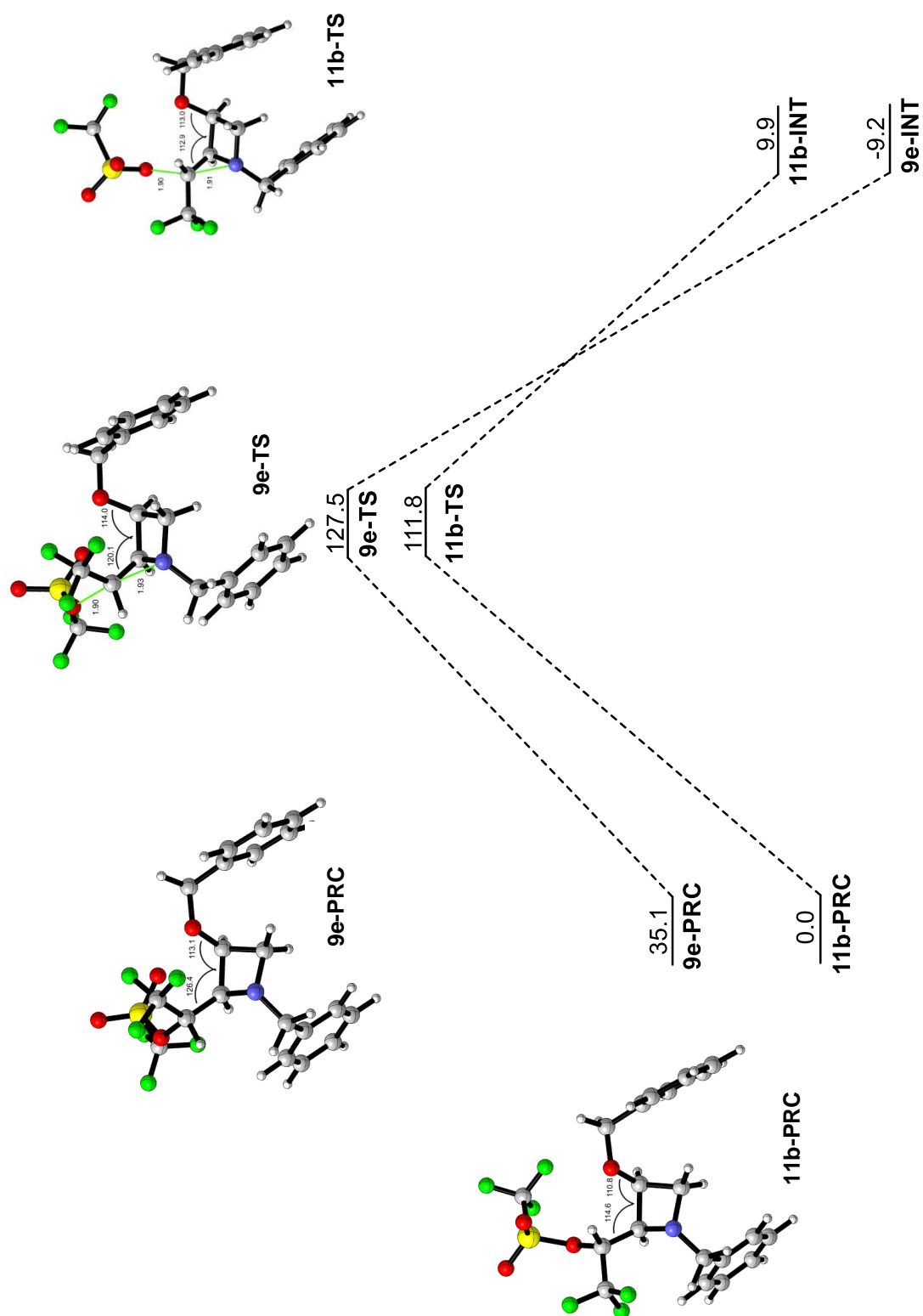
Figure 5.

6. Synthesis of 3-amino-2-(trifluoromethyl)pyrrolidines and subsequent coupling with triphosgene

As the 3-amino-4-hydroxypyrrolidine unit has been reported to be present in compounds associated with diverse biological activities,[90] additional synthetic efforts were performed to evaluate the debenzylation aptitude of 3-benzylamino-substituted azaheterocycles **10**. To that end, a selection of 3-benzylamino-2-(trifluoromethyl)pyrrolidines **10g,i,k** was treated with Pd(OH)$_2$/C (20% w/w) at 4 bar H$_2$ in MeOH, resulting in 3-amino-2-(trifluoromethyl)pyrrolidines **13** and **14** after 4 hours at room temperature in excellent yields (89-91%) (Scheme 13). In the case of pyrrolidine **10k**, a double *N*-debenzylation took place to furnish free diamine **14**.

13a (R^1 = *c*Hex, R^2 = Ph, 89%)
13b (R^1 = *i*Pr, R^2 = Bn, 91%)

14 (89%)
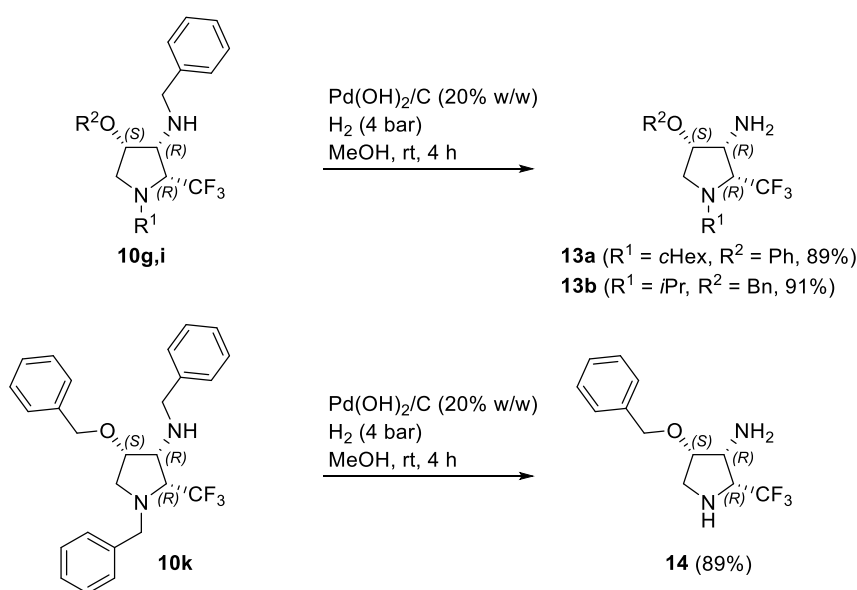
Scheme 13

In order to encourage the *O*-debenzylation of 4-benzyloxy-substituted azaheterocycles **10** as well, in addition to *N*-debenzylation, pyrrolidine **10i** was subjected to more harsh deprotection conditions (Pd(OH)$_2$/C (40% w/w), 5 bar H$_2$) and, eventually, 3-amino-4-hydroxy-2-(trifluoromethyl)pyrrolidine **15** was obtained in 92% yield after 4 days in MeOH at room temperature (Scheme 14). So, depending on the reaction conditions used for the hydrogenolysis of azaheterocycles **10** (containing a benzyl group at either the 1-, 3-amino and/or 4-hydroxy position of the pyrrolidine unit), the deprotection of these molecules can be performed in a selective way through initial *N*- and, if desired, subsequent *O*-debenzylation. Bearing in mind the large number of bioactive compounds accommodating a 3-amino-4-hydroxypyrrolidine entity, this straightforward and high-yielding debenzylation protocol undoubtedly offers perspectives for further elaboration in the framework of bioactive compound development.
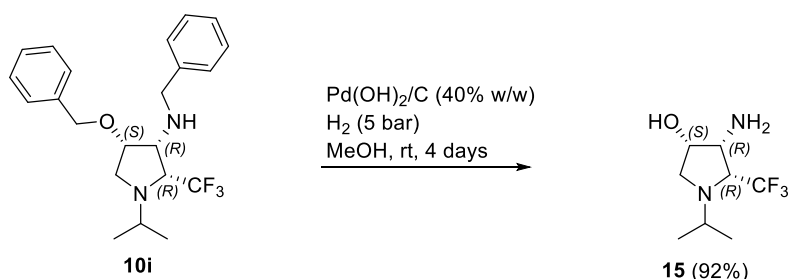
Scheme 14

Furthermore, the free NH_2 and OH moieties in pyrrolidines **13-15** render these scaffolds very promising building blocks for incorporation in larger bioactive structures and for additional synthetic manipulations. In that respect, evaluation of the obtained 3-aminopyrrolidines was performed by treatment of 3-amino-2-(trifluoromethyl)pyrrolidine **13b** with an equimolar amount of triphosgene, affording the corresponding 3-isocyanato-2-(trifluoromethyl)pyrrolidine **16** in 67% yield (Scheme 15). In addition, 3-amino-4-hydroxypyrrolidine **15** was treated with triphosgene as well, applying the same reaction conditions as for the preparation of pyrrolidine **16** (1 equiv triphosgene, CH_2Cl_2, room temperature). After 2 hours, 2-oxa-4,7-diazabicyclo[3.3.0]octan-3-one **17** was obtained in an isolated yield of 81% after silica gel column chromatography (Scheme 15). From these selected examples, it is clear that further synthetic elaboration of the free NH_2 and OH moieties in chiral pyrrolidines **13-15** offers many new opportunities for follow-up studies.
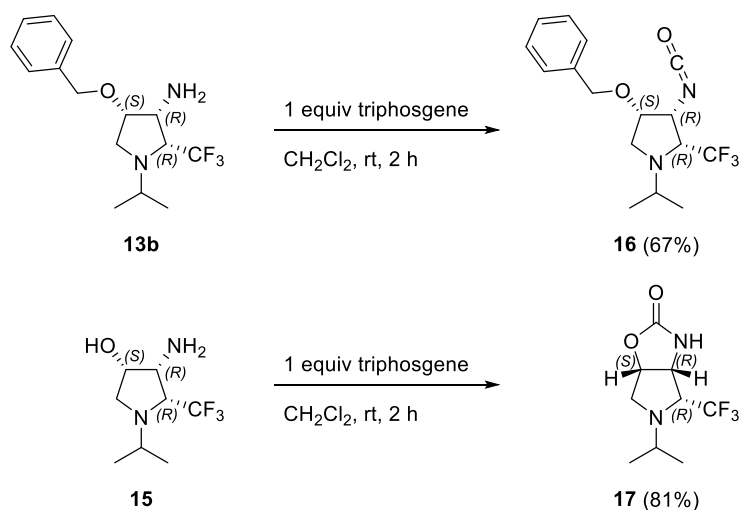
Scheme 15

In a final experiment, evidence for the chiral integrity of the prepared pyrrolidines was provided. In that respect, amidation of 3-amino-2-(trifluoromethyl)pyrrolidine **13b** with an equimolar amount of (1*S*)-(—)-camphanic chloride in CH_2Cl_2 at room temperature for 2 hours on an analytical scale afforded the corresponding 3-(camphanoylamino)pyrrolidine as a single diastereomer (based on ^{1}H NMR and GC

analysis), pointing to the fact that no isomerization took place throughout the complete reaction sequence.

7. Conclusion

In summary, a straightforward and reliable four-step protocol was developed for the synthesis of chiral 3,4-disubstituted 2-(trifluoromethyl)pyrrolidines starting from enantiopure 4-formyl-β-lactams. To that end, trifluoromethylation of these 4-formylazetidin-2-ones resulted in the diastereoselective formation of 4-[(1*S*)-2,2,2-trifluoro-1-hydroxyethyl]-β-lactams as the major isomers. Reduction of the β-lactam carbonyl group and subsequent sulfonylation of the hydroxyl motif afforded the corresponding triflate-activated azetidines without loss of chirality. Owing to the presence of the triflate leaving group, ring expansion of these azetidine scaffolds could be realized through the intermediacy of bicyclic aziridinium ions, although the premised rearrangement appeared to be dependent on the stereochemistry of the exocyclic CF$_3$-substituted carbon atom. Whereas the major (1'*S*)-azetidines were easily converted to 3,4-disubstituted 2-(trifluoromethyl)pyrrolidines with high diastereoselectivity upon reaction with a variety of nitrogen, oxygen, sulfur and fluorine nucleophiles, their diastereomeric counterparts (epimeric at 1' position) were not able to act as substrates for this type of ring rearrangement. Theoretical calculations revealed that the major (1'*S*)-azetidines are less stable than the minor (1'*R*)-azetidines, which in combination with a lower activation barrier of (1'*S*)-azetidines toward the corresponding bicyclic aziridinium ions can explain the remarkable difference in reactivity. Finally, *N*- versus *O*-selective debenzylation of some of the obtained pyrrolidine ring systems was successfully effectuated, enabling the eventual incorporation of these chiral building blocks into larger frameworks and their further synthetic elaboration, as shown by the synthesis of a 2-oxa-4,7-diazabicyclo[3.3.0]octan-3-one scaffold.

8. Experimental details

General methods

^{1}H NMR spectra were recorded at 400 MHz on a Bruker Advance III-400 with solvents as indicated and tetramethylsilane as internal standard. ^{19}F NMR spectra were recorded at 376 MHz on a Bruker Advance III-400 with solvents as indicated. ^{13}C NMR spectra were recorded at 100 MHz on a Bruker Advance III-400 with solvents as indicated. IR spectra were measured with a IRAffinity-1S FT-IR spectrophotometer. Electron spray (ES) mass spectra were obtained with an Agilent 1100 Series MS (ES, 4000V) mass spectrometer. High resolution electron spray (ES-TOF) mass spectra were obtained with an Agilent Technologies 6210 Series time-of-flight mass spectrometer. Melting points were determined on a Kofler bench, type WME Heizbank of Wagner & Munz and were corrected. Optical rotations were taken with a JASCO P-2000 series polarimeter. Tetrahydrofuran and diethyl ether were distilled over sodium benzophenone ketyl, while dichloromethane was distilled from calcium hydride before use. All other solvents and reagents were used as received from the supplier.

Safety

General safety aspects

The practical work in this chapter was performed according to the SynBioC Research Group Internal Guidelines and with the aid of the internal safety document "Safety Instructions: How to work with chemicals". Wherever possible, hazardous or toxic reagents were avoided and/or substituted by safer or greener alternatives.

Specific safety aspects

A list of risks associated with each chemical and recommendations for safe use is available in the corresponding material safety data sheet (MSDS), which can be found on the website of the supplier. A brief overview of the most hazardous chemicals employed in this work will be given below, along with the potential hazards and precautions.

Acetyl chlorides (benzyloxyacetyl chloride, phenoxyacetyl chloride): skin corrosion, specific target organ toxicity following repeated exposure. Avoid contact with water. Avoid inhalation and release in the environment. Wear protective gloves and clothing.

Chloroform: specific target organ toxicity following repeated exposure. Avoid inhalation and wear protective gloves and clothing.

Cyanides (KCN, TBACN): corrosive to metals, acute toxicity after inhalation, skin contact and oral intake, specific target organ toxicity following repeated and acute exposure, acute and chronic aquatic toxicity. Avoid dust formation and inhalation. Wear protective gloves and clothing. Avoid release in the environment.

Diethylaminosulfur trifluoride (DAST): skin corrosion. Avoid inhalation and wear protective gloves and clothing. Keep away from heat, fire, hot surfaces, sparks and ignition sources.

LiAlH$_4$ solutions: flammable liquid, substances and mixtures which in contact with water emit flammable gases, skin corrosion. Avoid contact with air or water and work under an inert atmosphere. Avoid inhalation of vapors. Wear protective gloves and clothing. Keep away from heat, fire, hot surfaces, sparks and ignition sources.

H$_2$-gas: flammable gas, especially when compressed. Keep away from heat, fire, hot surfaces, sparks and ignition sources.

Solvents in general: acute toxicity after inhalation, specific target organ toxicity following single or repeated exposure. Keep away from heat, fire, hot surfaces, sparks and ignition sources. Avoid inhalation and wear protective gloves and clothing.

Triethylamine (Et$_3$N): skin corrosion. Keep away from heat, fire, hot surfaces, sparks and ignition sources. Avoid inhalation and wear protective gloves and clothing.

Triflic anhydride (Tf$_2$O): skin corrosion. Avoid contact with skin and eyes. Avoid inhalation. Wear protective gloves and clothing.

Triphosgene: acute toxicity after inhalation, skin corrosion. Avoid dust formation and inhalation. Wear protective gloves and clothing.

Synthesis of (*R*)-glyceraldehyde acetonide 1

(*R*)-Glyceraldehyde acetonide **1** was synthesized according to literature procedures.[91]

Synthesis of 4-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]azetidin-2-ones 2

As a representative example, the synthesis of (3*R*,4*S*)-1-isopropyl-4-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-3-phenoxyazetidine-2-one **2a** is described. MgSO$_4$ (7.22 g, 60 mmol, 2 equiv) and isopropylamine (1.77 g, 2.58 mL, 30 mmol, 1 equiv) were added to a solution of (*R*)-glyceraldehyde acetonide **1** (3.9 g, 30 mmol, 1 equiv) in anhydrous CH$_2$Cl$_2$ (120 mL). After stirring for 2 hours at room temperature, MgSO$_4$ was removed by filtration. Evaporation of the solvent *in vacuo* afforded the corresponding (*E*)-*N*-[((4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)methylidene]isopropylamine in high purity (> 95% based on ^{1}H NMR spectroscopy), which was used as such in the next reaction step due to its hydrolytic instability. To an ice-cooled solution of (*E*)-*N*-[((4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)methylidene]isopropylamine (5.13 g, 30 mmol, 1 equiv) and triethylamine (9.10 g, 12.53 mL, 90 mmol, 3 equiv) in anhydrous CH$_2$Cl$_2$ (100 mL), a solution of phenoxyacetyl chloride (6.65 g, 5.39 mL, 39 mmol, 1.3 equiv) in CH$_2$Cl$_2$ (10 mL) was added dropwise. After stirring for 15 hours at room temperature, the reaction mixture was poured into water (30 mL) and extracted with EtOAc (3 × 30 mL). Drying (MgSO$_4$), filtration of the drying agent, and removal of the solvent *in vacuo* afforded (3*R*,4*S*)-1-isopropyl-4-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-3-phenoxyazetidin-2-one **2a**, which was isolated by means of recrystallization from EtOH in an overall yield of 73% (6.68 g, 21.9 mmol) as a white powder.

(3*R*,4*S*)-1-Isopropyl-4-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-3-phenoxyazetidin-2-one 2a

White powder. Mp 86 °C. Recrystallization from EtOH. Yield 73%. $[\alpha]_D^{25}$ = +185.3° (*c* = 0.18, CH$_2$Cl$_2$). ^{1}**H NMR** (400 MHz, CDCl$_3$): δ 1.33 and 1.34 (2×3H, 2×d, *J* = 6.6 Hz, (C<u>H</u>$_3$)$_2$CH); 1.39 and 1.47 (2×3H, 2×s, (C<u>H</u>$_3$)$_2$C); 3.67 (1H, d×d, *J* = 8.8, 6.5 Hz, CHO(<u>H</u>CH)O); 3.87 (1H, d×d, *J* = 8.9, 5.2 Hz, C<u>H</u>NCHO); 3.98 (1H, septet, *J* = 6.6 Hz, C<u>H</u>(CH$_3$)$_2$); 4.25 (1H, d×d, *J* = 8.8, 6.6 Hz, CHO(HC<u>H</u>)O); 4.39 (1H, d×d×d, *J* = 8.9, 6.6, 6.5 Hz, C<u>H</u>OCH$_2$O); 5.13 (1H, d, *J* = 5.2 Hz, C<u>H</u>OPh); 7.00-7.04 (1H, m, CH$_{arom}$); 7.07-7.09 (2H, m, 2×CH$_{arom}$); 7.27-7.31 (2H, m, 2×CH$_{arom}$). ^{13}**C NMR** (100 MHz, ref = CDCl$_3$): δ 19.5 and 21.3 ((<u>C</u>H$_3$)$_2$CH); 25.1 and 26.8 ((<u>C</u>H$_3$)$_2$C); 44.9 ((CH$_3$)$_2$<u>C</u>HN); 59.9 (<u>C</u>HNCHO); 67.1 (CHO<u>C</u>H$_2$O); 77.1 (<u>C</u>HOCH$_2$O); 79.3 (CHOPh); 109.6 ((CH$_3$)$_2$<u>C</u>); 115.8 (2×CH$_{arom}$); 122.5 (CH$_{arom}$); 129.6 (2×CH$_{arom}$); 157.5 (C$_{quat,arom}$); 165.3 (C=O). **IR (cm^{-1})**: ν$_{C=O}$ = 1744; ν$_{max}$ = 2976, 1499, 1489, 1458, 1398, 1352, 1259, 1236, 1213, 1155, 1059, 1022, 852, 843, 758, 692, 509. **MS (70 eV)**: *m/z* (%): 306 (M$^+$+1, 100).
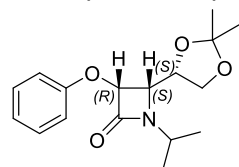
(3*R*,4*S*)-4-[(4*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-3-phenoxy-1-propylazetidin-2-one 2b

White powder. Mp 62 °C. R_f = 0.19 (Petroleumether/EtOAc 6/1). Yield 81%. $[\alpha]_D^{25}$ = +160.9° (*c* = 0.17, CH$_2$Cl$_2$). **^{1}H NMR** (400 MHz, CDCl$_3$): δ 0.95 (3H, t, *J* = 7.4 Hz, C<u>H</u>$_3$CH$_2$); 1.38 and 1.46 (2×3H, 2×s, (C<u>H</u>$_3$)$_2$C); 1.58-1.78 (2H, m, C<u>H</u>$_2$CH$_3$); 3.27 (1H, d×d×d, *J* = 13.7, 7.8, 5.9 Hz, (<u>H</u>CH)N); 3.45 (1H, d×d×d, *J* = 13.7, 7.5, 7.5 Hz, (HC<u>H</u>)N); 3.68 (1H, d×d, *J* = 8.8, 6.2 Hz, CHO(<u>H</u>CH)O); 3.83 (1H, d×d, *J* = 9.0, 5.0 Hz, CHN); 4.18 (1H, d×d, *J* = 8.8, 6.5 Hz, CHO(HC<u>H</u>)O); 4.43 (1H, d×d×d, *J* = 9.0, 6.5, 6.2 Hz, C<u>H</u>OCH$_2$O); 5.20 (1H, d, *J* = 5.0 Hz, CHOPh); 7.00-7.04 (1H, m, CH$_{arom}$); 7.07-7.09 (2H, m, 2×CH$_{arom}$); 7.28-7.32 (2H, m, 2×CH$_{arom}$). **^{13}C NMR** (100 MHz, ref = CDCl$_3$): δ 11.5 (CH$_3$); 20.8 (<u>C</u>H$_2$CH$_3$); 25.1 and 26.8 ((<u>C</u>H$_3$)$_2$C); 43.3 (CH$_2$N); 60.4 (CHN); 66.9 (CHO<u>C</u>H$_2$O); 77.2 (<u>C</u>HOCH$_2$O); 79.8 (CHOPh); 109.7 ((CH$_3$)$_2$<u>C</u>); 115.7 (2×CH$_{arom}$); 122.5 (CH$_{arom}$); 129.6 (2×CH$_{arom}$); 157.4 (C$_{quat,arom}$); 166.0 (C=O). **IR (cm^{-1})**: $v_{C=O}$ = 1748; v_{max} = 2967, 2936, 1599, 1589, 1495, 1371, 1238, 1209, 1155, 1061, 1013, 854, 754, 691, 507. **MS (70 eV)**: *m/z* (%): 306 (M$^+$+1, 100).
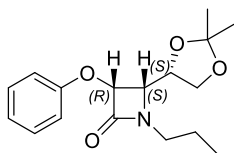
(3*R*,4*S*)-1-Cyclohexyl-4-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-3-phenoxyazetidin-2-one 2c

White powder. Mp 79 °C. R_f = 0.12 (Petroleumether/EtOAc 6/1). Yield 87%. $[\alpha]_D^{25}$ = +166.9° (*c* = 0.17, CH$_2$Cl$_2$). **^{1}H NMR** (400 MHz, CDCl$_3$): δ 1.11-1.34 (3H, m, (C<u>H</u>$_2$)$_5$CHN); 1.39 and 1.47 (2×3H, 2×s, (C<u>H</u>$_3$)$_2$C); 1.59-1.92 (7H, m, (C<u>H</u>$_2$)$_5$CHN); 3.53-3.60 (1H, m, (CH$_2$)$_5$C<u>H</u>N); 3.66 (1H, d×d, *J* = 8.8, 6.5 Hz, CHO(<u>H</u>CH)O); 3.88 (1H, d×d, *J* = 8.9, 5.2 Hz, C<u>H</u>NCHO); 4.23 (1H, d×d, *J* = 8.8, 6.5 Hz, CHO(HC<u>H</u>)O); 4.38 (1H, d×t, *J* = 8.9, 6.5 Hz, C<u>H</u>OCH$_2$O); 5.13 (1H, d, *J* = 5.2 Hz, CHOPh); 7.00-7.03 (1H, m, CH$_{arom}$); 7.07-7.09 (2H, m, 2×CH$_{arom}$); 7.27-7.31 (2H, m, 2×CH$_{arom}$). **^{13}C NMR** (100 MHz, ref = CDCl$_3$): δ 25.1 (<u>C</u>H$_3$CCH$_3$); 25.2, 25.36 and 25.38 (3×(<u>C</u>H$_2$)$_5$CHN); 26.8 (CH$_3$C<u>C</u>H$_3$); 29.8 and 31.1 (2×(<u>C</u>H$_2$)$_5$CHN); 52.9 ((CH$_5$)$_2$<u>C</u>HN); 60.0 (<u>C</u>HNCHO); 67.1 (CHO<u>C</u>H$_2$O); 77.2 (<u>C</u>HOCH$_2$O); 79.2 (<u>C</u>HOCH$_3$); 109.5 ((CH$_3$)$_2$<u>C</u>); 115.8 (2×CH$_{arom}$); 122.4 (CH$_{arom}$); 129.6 (2×CH$_{arom}$); 157.5 (C$_{quat,arom}$); 165.3 (C=O). **IR (cm^{-1})**: $v_{C=O}$ = 1734; v_{max} = 2941, 1599, 1587, 1489, 1283, 1267, 1163, 1121, 1094, 1038, 752, 727, 691. **MS (70 eV)**: *m/z* (%): 346 (M$^+$+1, 100).
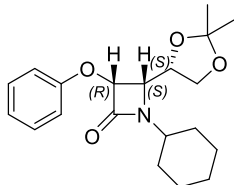
(3*R*,4*S*)-1-Benzyl-4-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-3-phenoxyazetidin-2-one (2d)

White powder. Mp 107 °C. R_f = 0.24 (Petroleumether/EtOAc 6/1). Yield 74%. $[\alpha]_D^{25}$ = +70.1° (*c* = 0.19, CH$_2$Cl$_2$). **^{1}H NMR** (400 MHz, CDCl$_3$): δ 1.36 and 1.38 (2×3H, 2×s, (C<u>H</u>$_3$)$_2$C); 3.61 (1H, d×d, *J* = 8.9, 6.3 Hz, CHO(<u>H</u>CH)O); 3.70 (1H, d×d, *J* = 9.0, 5.1 Hz, CHN); 4.13 (1H, d×d, *J* = 8.9, 6.3 Hz, CHO(HC<u>H</u>)O); 4.29 (1H, d, *J* = 14.6 Hz, (<u>H</u>CH)N); 4.48 (1H, d×t, *J* = 9.0, 6.3 Hz, C<u>H</u>OCH$_2$O); 4.87 (1H, d, *J* = 14.6 Hz, (HC<u>H</u>)N); 5.16 (1H, d, *J* = 5.1 Hz, CHOPh); 7.02-7.08 (3H, m, 3×CH$_{arom}$); 7.26-7.35 (7H, m, 7×CH$_{arom}$). **^{13}C NMR** (100 MHz, ref = CDCl$_3$): δ 25.1 and 26.7 ((C<u>H</u>$_3$)$_2$C); 45.4 (CH$_2$N); 59.4 (CHN); 66.9 (CHO<u>C</u>H$_2$O); 77.1 (<u>C</u>HOCH$_2$O); 80.0 (<u>C</u>HOPh); 109.8 ((CH$_3$)$_2$<u>C</u>); 115.7, 122.5, 127.8, 128.7, 128.9 and 129.7 (10×CH$_{arom}$); 135.6 and 157.3 (2×C$_{quat,arom}$); 165.7 (C=O). **IR (cm^{-1})**: $v_{C=O}$ = 1748; v_{max} = 2988, 1597, 1589, 1497, 1487, 1209, 1061, 1040, 856, 754, 739, 694, 669. **MS (70 eV)**: *m/z* (%): 354 (M$^+$+1, 100).
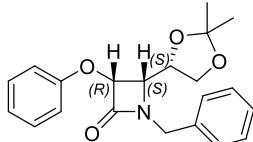
Spectral data of 4-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]azetidin-2-ones **2e-g** correspond with those reported in the literature.[86,92]

Synthesis of 4-[(1*S*)-1,2-dihydroxyethyl]azetidin-2-ones 3

As a representative example, the synthesis of (3*R*,4*S*)-4-[(1*S*)-1,2-dihydroxyethyl]-1-isopropyl-3-phenoxyazetidin-2-one **3a** is described. To a solution of (3*R*,4*S*)-1-isopropyl-4-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-3-phenoxy-azetidin-2-one **2a** (1.83 g, 6 mmol, 1 equiv) in THF/H_2O (1/1, 60 mL) was added *p*TsOH·H_2O (1.14 g, 6 mmol, 1 equiv) in a single portion. After a reflux period of 4 hours, the resulting reaction mixture was allowed to cool to room temperature and was then neutralized to pH 7 with solid $NaHCO_3$. The mixture was extracted with EtOAc (3 × 30 mL), the combined organic layers were dried ($MgSO_4$), and the solvent was removed under reduced pressure to afford (3*R*,4*S*)-4-[(1*S*)-1,2-dihydroxyethyl]-1-isopropyl-3-phenoxyazetidin-2-one **3a** in 99% yield (1.57 g, 5.94 mmol) as a colorless oil.

(3*R*,4*S*)-4-[(1*S*)-1,2-Dihydroxyethyl]-1-isopropyl-3-phenoxyazetidin-2-one 3a

Colorless oil. Yield 99%. $[\alpha]_D^{25}$ = +152.1° (*c* = 0.37, CH_2Cl_2). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.33 and 1.41 (2×3H, 2×d, *J* = 6.7 Hz, (C<u>H</u>$_3$)$_2$CH); 2.17-2.20 (1H, m, CH$_2$O<u>H</u>); 2.76 (1H, d, *J* = 4.2 Hz, CHO<u>H</u>); 3.70-3.75 (1H, m, CHO(<u>H</u>CH)O); 3.79-3.88 (1H, m, CHO(HC<u>H</u>)O); 3.83 (1H, septet, *J* = 6.7 Hz, C<u>H</u>(CH$_3$)$_2$); 3.96 (1H, d×d, *J* = 5.5, 5.3 Hz, C<u>H</u>NCHO); 4.06-4.12 (1H, m, C<u>H</u>OCH$_2$O); 5.15 (1H, d, *J* = 5.3 Hz, CHOPh); 7.01-7.05 (1H, m, CH$_{arom}$); 7.08-7.11 (2H, m, 2×CH$_{arom}$); 7.28-7.32 (2H, m, 2×CH$_{arom}$). **^{13}C NMR** (100 MHz, ref = $CDCl_3$): δ 20.0 and 21.2 ((CH$_3$)$_2$CH); 46.4 ((CH$_3$)$_2$<u>C</u>HN); 58.1 (<u>C</u>HNCHO); 63.8 (CHO<u>C</u>H$_2$O); 71.3 (<u>C</u>HOCH$_2$O); 79.5 (<u>C</u>HOPh); 115.9 (2×CH$_{arom}$); 122.7 (CH$_{arom}$); 129.7 (2×CH$_{arom}$); 157.4 (C$_{quat,arom}$); 165.7 (C=O). **IR (cm^{-1})**: ν$_{OH}$ = 3389; ν$_{C=O}$ = 1740; ν$_{max}$ = 2980, 2951, 1597, 1495, 1339, 1234, 1132, 1092, 1022, 910, 841, 748, 729, 689. **MS (70 eV)**: *m/z* (%): 266 (M$^+$+1, 100).
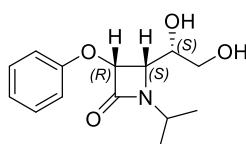
(3*R*,4*S*)-4-[(1*S*)-1,2-Dihydroxyethyl]-3-phenoxy-1-propylazetidin-2-one 3b

Colorless oil. Yield 95%. $[\alpha]_D^{25}$ = +116.5° (*c* = 0.30, CH_2Cl_2). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.93 (3H, t, *J* = 7.4 Hz, C<u>H</u>$_3$CH$_2$); 1.54-1.77 (2H, m, C<u>H</u>$_2$CH$_3$); 2.18 (1H, s (broad), CH$_2$O<u>H</u>); 2.75 (1H, s (broad), CHO<u>H</u>); 3.21 (1H, d×d×d, *J* = 13.8, 8.1, 5.6 Hz, (<u>H</u>CH)N); 3.52 (1H, d×d×d, *J* = 13.8, 7.7, 7.7 Hz, (HC<u>H</u>)N); 3.69-3.73 (1H, m, CHO(<u>H</u>CH)O); 3.79-3.83 (1H, m, CHO(HC<u>H</u>)O); 3.97 (1H, d×d, *J* = 5.1, 5.0 Hz, CHN); 4.11-4.16 (1H, m, C<u>H</u>OCH$_2$O); 5.23 (1H, d, *J* = 5.0 Hz, CHOPh); 7.02-7.04 (1H, m, CH$_{arom}$); 7.09-7.11 (2H, m, 2×CH$_{arom}$); 7.28-7.32 (2H, m, 2×CH$_{arom}$). **^{13}C NMR** (100 MHz, ref = $CDCl_3$): δ 11.5 (CH$_3$); 20.8 (<u>C</u>H$_2$CH$_3$); 43.8 (CH$_2$N); 58.2 (CHN); 64.0 (CHO<u>C</u>H$_2$O); 71.3 (<u>C</u>HOCH$_2$O); 80.1 (CHOPh); 115.9 (2×CH$_{arom}$); 122.7 (CH$_{arom}$); 129.7 (2×CH$_{arom}$); 157.4 (C$_{quat,arom}$); 166.3 (C=O). **IR (cm^{-1})**: ν$_{OH}$ = 3401; ν$_{C=O}$ = 1732; ν$_{max}$ = 1591, 1495, 1416, 1344, 1231, 1090, 1067, 1043, 1028, 908, 891, 752, 729, 691. **MS (70 eV)**: *m/z* (%): 266 (M$^+$+1, 100).
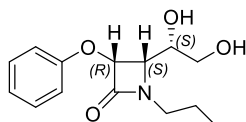
(3*R*,4*S*)-1-Cyclohexyl-4-[(1*S*)-1,2-dihydroxyethyl]-3-phenoxyazetidin-2-one 3c

Colorless oil. Yield 99%. $[\alpha]_D^{25}$ = +102.7° (*c* = 0.20, CH_2Cl_2). **¹H NMR** (400 MHz, CDCl₃): δ 1.17-1.32 (3H, m, (CH_2)₅CHN); 1.61-1.92 (6H, m, (CH_2)₅CHN); 2.01-2.08 (2H, m, CH₂O*H* and (HC*H*)₅CHN); 2.66 (1H, d, *J* = 4.4 Hz, CHO*H*); 3.37-3.44 (1H, m, (CH₂)₅C*H*N); 3.71-3.77 (1H, m, CHO(*H*CH)O); 3.79-3.85 (1H, m, CHO(HC*H*)O); 3.98 (1H, d×d, *J* = 5.2, 5.2 Hz, C*H*NCHO); 4.08-4.13 (1H, m, C*H*OCH₂O); 5.16 (1H, d, *J* = 5.2 Hz, CHOPh); 7.01-7.05 (1H, m, CH$_{arom}$); 7.09-7.10 (2H, m, 2×CH$_{arom}$); 7.27-7.32 (2H, m, 2×CH$_{arom}$). **¹³C NMR** (100 MHz, ref = CDCl₃): δ 25.2, 25.3, 25.4, 30.4 and 31.2 (5×(*C*H₂)₅CHN); 54.4 ((CH₂)₅*C*HN); 58.0 (*C*HNCHO); 63.9 (CHO*C*H₂); 71.4 (*C*HOCH₂); 79.5 (*C*HOPh); 115.9 (2×CH$_{arom}$); 122.7 (CH$_{arom}$); 129.7 (2×CH$_{arom}$); 157.4 (C$_{quat,arom}$); 165.6 (C=O). **IR (cm⁻¹)**: ν$_{OH}$ = 3412; ν$_{C=O}$ = 1728; ν$_{max}$ = 2932, 2855, 1597, 1495, 1364, 1231, 1076, 1043, 907, 893, 752, 729, 689. **MS (70 eV)**: *m/z* (%): 306 (M⁺+1, 100).
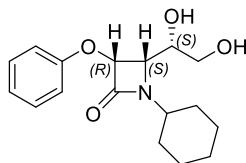
(3*R*,4*S*)-1-Benzyl-4-[(1*S*)-1,2-dihydroxyethyl]-3-phenoxyazetidin-2-one 3d

Colorless oil. Yield 99%. $[\alpha]_D^{25}$ = +71.5° (*c* = 0.46, CH_2Cl_2). **¹H NMR** (400 MHz, CDCl₃): δ 1.91 (1H, t, *J* = 5.8 Hz, CH₂O*H*); 2.46 (1H, d, *J* = 4.3 Hz, CHO*H*); 3.60-3.66 (1H, m, CHO(*H*CH)O); 3.70-3.75 (1H, m, CHO(HC*H*)O); 3.83 (1H, d×d, *J* = 5.2, 5.2 Hz, C*H*NCHO); 4.09-4.14 (1H, m, C*H*OCH₂O); 4.39 and 4.82 (2×1H, 2×d, *J* = 14.9 Hz, N(*H*CH)C$_{quat,arom}$); 5.23 (1H, d, *J* = 5.2 Hz, CHOPh); 7.03-7.06 (1H, m, CH$_{arom}$); 7.10-7.12 (2H, m, 2×CH$_{arom}$); 7.28-7.39 (7H, m, 7×CH$_{arom}$). **¹³C NMR** (100 MHz, ref = CDCl₃): δ 45.8 (N*C*H₂C$_{quat,arom}$); 58.1 (*C*HNCHO); 63.8 (CHO*C*H₂); 71.3 (*C*HOCH₂); 80.4 (*C*HOPh); 115.9 (2×CH$_{arom}$); 122.8 (CH$_{arom}$); 128.0, 128.4, 129.0 and 129.7 (7×CH$_{arom}$); 135.6 and 157.3 (2×C$_{quat,arom}$); 166.4 (C=O). **IR (cm⁻¹)**: ν$_{OH}$ = 3406; ν$_{C=O}$ = 1736; ν$_{max}$ = 1589, 1408, 1350, 1229, 1134, 1076, 1028, 908, 839, 754, 729, 691, 646, 608. **MS (70 eV)**: *m/z* (%): 314 (M⁺+1, 100).
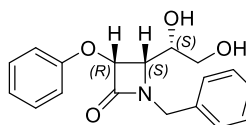
(3*R*,4*S*)-3-Benzyloxy-4-[(1*S*)-1,2-dihydroxyethyl]-1-isopropylazetidin-2-one 3e

Colorless oil. Yield 67%. $[\alpha]_D^{25}$ = +74.1° (*c* = 0.26, CH_2Cl_2). **¹H NMR** (400 MHz, CDCl₃): δ 1.27 (3H, d, *J* = 6.7 Hz, C*H₃*CHCH₃); 1.36 (3H, d, *J* = 6.8 Hz, CH₃CHC*H₃*); 2.41 (1H, t, *J* = 5.6 Hz, CH₂O*H*); 2.93 (1H, d, *J* = 4.1 Hz, CHO*H*); 3.65-3.78 (4H, m, C*H₂*OH, CHNCHO and NC*H*(CH₃)₂); 3.93-3.98 (1H, m, C*H*OH); 4.58 (1H, d, *J* = 5.1 Hz, CHOBn); 4.69 and 4.94 (2×1H, 2×d, *J* = 11.7 Hz, O(*H*CH)C$_{quat,arom}$); 7.31-7.36 (2H, m, 2×CH$_{arom}$). **¹³C NMR** (100 MHz, ref = CDCl₃): δ 20.0 and 21.2 ((*C*H₃)₂CH); 46.0 ((CH₃)₂*C*HN); 58.1 (*C*HNCHO); 63.8 (CH₂OH); 71.3 (CHOH); 73.2 (O*C*H₂C$_{quat,arom}$); 79.8 (CHOBn); 128.1 (2×CH$_{arom}$); 128.2 (CH$_{arom}$); 128.6 (2×CH$_{arom}$); 136.7 (C$_{quat,arom}$); 167.3 (C=O). **IR (cm⁻¹)**: ν$_{OH}$ = 3397; ν$_{C=O}$ = 1717; ν$_{max}$ = 2974, 2936, 2878, 1454, 1404, 1339, 1229, 1215, 1148, 1067, 1022, 910, 779, 733, 696. **MS (70 eV)**: *m/z* (%): 280 (M⁺+1, 100).
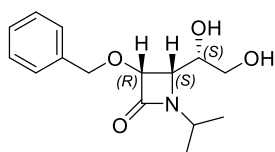
(3*R*,4*S*)-3-Benzyloxy-4-[(1*S*)-1,2-dihydroxyethyl]-1-propylazetidin-2-one 3f

Colorless oil. Yield 76%. $[\alpha]_D^{25}$ = +69.5° (*c* = 0.36, CH_2Cl_2). **¹H NMR** (400 MHz, $CDCl_3$): δ 0.89 (3H, t, *J* = 7.4 Hz, C$\underline{H}_3CH_2$); 1.48-1.70 (2H, m, C$\underline{H}_2CH_3$); 2.50 (1H, s (broad), CH$_2$O$\underline{H}$); 3.01 (1H, s (broad), CHO$\underline{H}$); 3.11 (1H, d×d×d, *J* = 13.8, 8.1, 5.5 Hz, ($\underline{H}$CH)N); 3.46 (1H, d×d×d, *J* = 13.8, 7.8, 7.8 Hz, (HC$\underline{H}$)N); 3.64-3.77 (3H, m, C$\underline{H}_2$OH and CHN); 3.97-4.01 (1H, m, C$\underline{H}$OH); 4.66 (1H, d, *J* = 5.0 Hz, C$\underline{H}$OBn); 4.69 and 4.95 (2×1H, 2×d, *J* = 11.6 Hz, O($\underline{H}$CH)C$_{quat,arom}$); 7.29-7.38 (5H, m, 5×CH$_{arom}$). **¹³C NMR** (100 MHz, ref = $CDCl_3$): δ 11.4 (CH$_3$); 20.7 ($\underline{C}$H$_2$CH$_3$); 43.5 (CH$_2$N); 58.1 (CHN); 64.0 (CH$_2$OH); 71.3 (CHOH); 73.3 (O$\underline{C}$H$_2$C$_{quat,arom}$); 80.5 (CHOBn); 128.1 (2×CH$_{arom}$); 128.3 (CH$_{arom}$); 128.6 (2×CH$_{arom}$); 136.6 (C$_{quat,arom}$); 167.9 (C=O). **IR (cm⁻¹)**: ν_{OH} = 3393; $\nu_{C=O}$ = 1724; ν_{max} = 2965, 2934, 2876, 1454, 1416, 1383, 1342, 1215, 1155, 1070, 1020, 907, 822, 733, 696. **MS (70 eV)**: *m/z* (%): 280 (M⁺+1, 100).
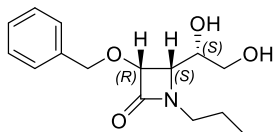
(3*R*,4*S*)-1-Benzyl-3-benzyloxy-4-[(1*S*)-1,2-dihydroxyethyl]azetidin-2-one 3g

Colorless oil. Yield 98%. $[\alpha]_D^{25}$ = +22.2° (*c* = 0.38, $CHCl_3$). **¹H NMR** (400 MHz, $CDCl_3$): δ 2.01 (1H, s (broad), CH$_2$O$\underline{H}$); 2.66 (1H, s (broad), CHO$\underline{H}$); 3.55-3.62 (3H, m, C$\underline{H}_2$OH and C$\underline{H}$NCHO); 3.95-3.96 (1H, m, C$\underline{H}$OH); 4.26 (1H, d, *J* = 15.0 Hz, N($\underline{H}$CH)C$_{quat,arom}$); 4.68 (1H, d, *J* = 5.1 Hz, CHOBn); 4.26 (1H, d, *J* = 11.7 Hz, O($\underline{H}$CH)C$_{quat,arom}$); 4.79 (1H, d, *J* = 15.0 Hz, N(HC$\underline{H}$)C$_{quat,arom}$); 4.97 (1H, d, *J* = 11.7 Hz, O(HC$\underline{H}$)C$_{quat,arom}$); 7.25-7.39 (10H, m, 10×CH$_{arom}$). **¹³C NMR** (100 MHz, ref = $CDCl_3$): δ 45.5 (N$\underline{C}$H$_2$C$_{quat,arom}$); 58.0 ($\underline{C}$HNCHO); 63.9 (CHO$\underline{C}$H$_2$O); 71.0 ($\underline{C}$HOCH$_2$O); 73.4 (O$\underline{C}$H$_2$C$_{quat,arom}$); 80.4 (CHOBn); 127.9 (CH$_{arom}$); 128.1 and 128.30 (4×CH$_{arom}$); 128.35 (CH$_{arom}$); 128.6 and 128.9 (4×CH$_{arom}$); 135.6 and 136.5 (2×C$_{quat,arom}$); 167.7 (C=O). **IR (cm⁻¹)**: ν_{OH} = 3397; $\nu_{C=O}$ = 1728; ν_{max} = 2926, 2876, 1497, 1454, 1406, 1341, 1217, 1155, 1074, 910, 822, 731, 696, 604. **MS (70 eV)**: *m/z* (%): 328 (M⁺+1, 100).
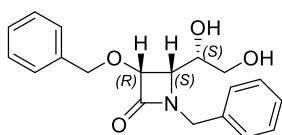
Synthesis of 4-formylazetidin-2-ones 4

As a representative example, the synthesis of (2*R*,3*R*)-1-isopropyl-4-oxo-3-phenoxyazetidine-2-carbaldehyde **4a** is described. To a solution of (3*R*,4*S*)-4-[(1*S*)-1,2-dihydroxyethyl]-1-isopropyl-3-phenoxyazetidin-2-one **3a** (1.59 g, 6 mmol, 1 equiv) in CH_2Cl_2/NaHCO$_3$ (sat. in H_2O) (15/1, 80 mL), NaIO$_4$ (2.96 g, 13.8 mmol, 2.3 equiv) was added portionwise during a period of 10 minutes. The resulting solution was stirred for 2 hours at room temperature. Afterward, the crude mixture was filtered and the resulting filtrate was washed with H_2O (2 × 20 mL). Drying (MgSO$_4$), filtration of the drying agent and evaporation of the solvent *in vacuo* afforded (2*R*,3*R*)-1-isopropyl-4-oxo-3-phenoxyazetidine-2-carbaldehyde **4a** in 94% yield (1.31 g, 5.64 mmol) as a yellow oil, which was purified by means of column chromatography on silica gel (Petroleumether/EtOAc 4/1) to provide an analytically pure sample.

## (2*R*,3*R*)-1-Isopropyl-4-oxo-3-phenoxyazetidine-2-carbaldehyde 4a

Yellow oil. R_f = 0.10 (Petroleumether/EtOAc 4/1). Yield 94%. $[\alpha]_D^{25}$ = +86.3° (*c* = 0.28, CH_2Cl_2). **¹H NMR** (400 MHz, $CDCl_3$): δ 1.27 and 1.28 (2×3H, 2×d, *J* = 6.7 Hz, CH(C*H*₃)₂); 4.06 (1H, septet, *J* = 6.7 Hz, C*H*(CH₃)₂); 4.37 (1H, d×d, *J* = 5.1, 3.8 Hz, CHOC*H*N); 5.37 (1H, d, *J* = 5.1 Hz, C*H*OPh); 7.00-7.06 (3H, m, 3×CH$_{arom}$); 7.26-7.32 (2H, m, 2×CH$_{arom}$); 9.74 (1H, d, *J* = 3.8 Hz, H*C*=O). **¹³C NMR** (100 MHz, ref = $CDCl_3$): δ 20.2 and 21.6 (2×CH₃); 45.0 (*C*H(CH₃)₂); 62.4 (CHO*C*HN); 81.2 (*C*HOPh); 115.6, 122.9 and 129.7 (5×CH$_{arom}$); 156.9 (C$_{quat,arom}$); 164.3 (N*C*=O); 198.4 (H*C*=O). **IR (cm⁻¹)**: ν$_{C=O}$ = 1732; ν$_{max}$ = 2976, 1597, 1589, 1495, 1387, 1344, 1227, 1026, 845, 752, 689. **MS (70 eV)**: *m/z* (%): 234 (M⁺+1, 100). **HRMS (ESI)**: *m/z* calcd for $C_{13}H_{16}NO_3$: 234.1125 [*M*+H]⁺, found: 234.1132.
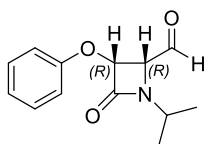
(2*R*,3*R*)-4-Oxo-3-phenoxy-1-propylazetidine-2-carbaldehyde 4b

Yellow oil. R_f = 0.05 (Petroleumether/EtOAc 4/1). Yield 80%. $[\alpha]_D^{25}$ = +72.4° (*c* = 0.36, CH_2Cl_2). **¹H NMR** (400 MHz, $CDCl_3$): δ 0.97 (3H, t, *J* = 7.4 Hz, CH₃); 1.52-1.70 (2H, m, C*H*₂CH₃); 3.29-3.36 (1H, m, (*H*CH)N); 3.39-3.46 (1H, m, (HC*H*)N); 4.38 (1H, d×d, *J* = 5.0, 2.9 Hz, CHN); 5.46 (1H, d, *J* = 5.0 Hz, C*H*OPh); 7.01-7.07 (3H, m, 3×CH$_{arom}$); 7.28-7.32 (2H, m, 2×CH$_{arom}$); 9.74 (1H, d, *J* = 2.9 Hz, H*C*=O). **¹³C NMR** (100 MHz, ref = $CDCl_3$): δ 11.5 (CH₃); 21.2 (*C*H₂CH₃); 43.9 (CH₂N); 63.8 (CHN); 82.2 (CHOPh); 115.5, 123.0 and 129.8 (5×CH$_{arom}$); 156.9 (C$_{quat,arom}$); 165.0 (N*C*=O); 197.7 (H*C*=O). **IR (cm⁻¹)**: ν$_{C=O}$ = 1732; ν$_{max}$ = 2965, 2934, 1597, 1589, 1495, 1412, 1344, 1231, 1130, 1067, 1022, 752, 729, 689. **MS (70 eV)**: *m/z* (%): 234 (M⁺+1, 100). **HRMS (ESI)**: *m/z* calcd for $C_{13}H_{16}NO_3$: 234.1125 [*M*+H]⁺, found: 234.1124.
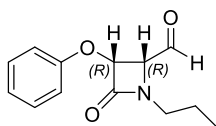
(2*R*,3*R*)-1-Cyclohexyl-4-oxo-3-phenoxyazetidine-2-carbaldehyde 4c

Colorless oil. R_f = 0.29 (Petroleumether/EtOAc 7/3). Yield 78%. $[\alpha]_D^{25}$ = +69.6° (*c* = 0.17, CH_2Cl_2). **¹H NMR** (400 MHz, $CDCl_3$): δ 1.11-2.01 (10H, m, (C*H*₂)₅CHN); 3.66-3.73 (1H, m, (CH₂)₅C*H*N); 4.35 (1H, d×d, *J* = 5.0, 4.1 Hz, CHOC*H*N); 5.36 (1H, d, *J* = 5.0 Hz, C*H*OPh); 6.99-7.06 (3H, m, 3×CH$_{arom}$); 7.26-7.32 (2H, m, 2×CH$_{arom}$); 9.73 (1H, d, *J* = 4.1 Hz, H*C*=O). **¹³C NMR** (100 MHz, ref = $CDCl_3$): δ 24.8, 24.9, 25.1, 30.6 and 31.9 ((*C*H₂)₅CHN); 52.4 ((CH₂)₅*C*HN); 62.6 (CHO*C*HN); 81.3 (*C*HOPh); 115.6, 122.9 and 129.7 (5×CH$_{arom}$); 156.9 (C$_{quat,arom}$); 164.4 (N*C*=O); 198.6 (H*C*=O). **IR (cm⁻¹)**: ν$_{C=O}$ = 1732; ν$_{max}$ = 2932, 2855, 1597, 1589, 1495, 1229, 1076, 1047, 1026, 752, 691. **MS (70 eV)**: *m/z* (%): 274 (M⁺+1, 100). **HRMS (ESI)**: *m/z* calcd for $C_{16}H_{20}NO_3$: 274.1438 [*M*+H]⁺, found: 274.1436.
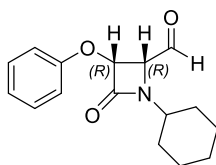
(2*R*,3*R*)-3-Benzyloxy-1-isopropyl-4-oxoazetidine-2-carbaldehyde 4e

Yellow oil. R_f = 0.09 (Petroleumether/EtOAc 7/3). Yield 86%. $[\alpha]_D^{25}$ = +64.7° (*c* = 0.19, $CHCl_3$). **¹H NMR** (400 MHz, $CDCl_3$): δ 1.19 and 1.22 (2×3H, 2×d, *J* = 6.7 Hz, CH(C*H*₃)₂); 4.00 (1H, septet, *J* = 6.7 Hz, C*H*(CH₃)₂); 4.11 (1H, d×d, *J* = 5.1, 4.0 Hz, CHOC*H*N); 4.63 (1H, d, *J* = 11.7 Hz, (*H*CH)O); 4.75 (1H, d, *J* = 11.7 Hz, (HC*H*)O); 4.82 (1H, d, *J* = 5.1 Hz, C*H*OBn); 7.00-7.06 (3H, m, 3×CH$_{arom}$); 7.29-7.37 (2H, m, 2×CH$_{arom}$); 9.65 (1H, d, *J* = 4.0 Hz, H*C*=O). **¹³C NMR** (100 MHz, ref = $CDCl_3$): δ 20.2 and 21.6 (2×CH₃); 44.6 (*C*H(CH₃)₂); 62.5 (CHO*C*HN); 73.3 (CH₂O); 82.4 (CHOBn); 128.2, 128.4 and 128.6 (5×CH$_{arom}$); 136.0 (C$_{quat,arom}$); 165.9 (N*C*=O); 199.9 (H*C*=O). **IR (cm⁻¹)**: ν$_{C=O}$ = 1728; ν$_{max}$ = 2976, 2936,
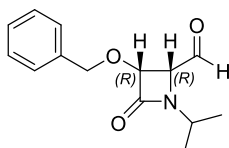
2878, 1454, 1387, 1339, 1210, 1155, 1130, 1009, 912, 733, 698. **MS (70 eV)**: *m/z* (%): 248 (M⁺+1, 100). **HRMS (ESI)**: *m/z* calcd for $C_{14}H_{18}NO_3$: 248.1281 [*M*+H]⁺, found: 248.1281.

(2*R*,3*R*)-3-Benzyloxy-4-oxo-1-propylazetidine-2-carbaldehyde 4f

Colorless oil. Yield 97%. $[\alpha]_D^{25}$ = +71.8° (*c* = 0.20, CH_2Cl_2). **¹H NMR** (400 MHz, CDCl₃): δ 0.92 (3H, t, *J* = 7.4 Hz, CH₃); 1.45-1.64 (2H, m, C<u>H</u>₂CH₃); 3.25 (1H, d×d×d, *J* = 14.1, 8.0, 6.2 Hz, (<u>H</u>CH)N); 3.35 (1H, d×d×d, *J* = 14.1, 8.0, 6.8 Hz, (HC<u>H</u>)N); 4.12 (1H, d×d, *J* = 5.0, 3.2 Hz, CHN); 4.64 (1H, d, *J* = 11.7 Hz, (<u>H</u>CH)O); 4.78 (1H, d, *J* = 11.7 Hz, (HC<u>H</u>)O); 4.92 (1H, d, *J* = 5.0 Hz, CHOPh); 7.31-7.38 (5H, m, 5×CH_arom); 9.62 (1H, d, *J* = 3.2 Hz, HC=O). **¹³C NMR** (100 MHz, ref = CDCl₃): δ 11.4 (CH₃); 21.2 (<u>C</u>H₂CH₃); 43.6 (CH₂N); 64.0 (CHN); 73.4 (CH₂O); 83.4 (CHOBn); 128.3, 128.4 and 128.6 (5×CH_arom); 136.0 (C_quat,arom); 166.5 (NC=O); 199.2 (HC=O). **IR (cm⁻¹)**: ν_{C=O} = 1728; ν_max = 2965, 2934, 2876, 1454, 1408, 1342, 1217, 1155, 1069, 1009, 735, 696. **MS (70 eV)**: *m/z* (%): 248 (M⁺+1, 100). **HRMS (ESI)**: *m/z* calcd for $C_{14}H_{18}NO_3$: 248.1281 [*M*+H]⁺, found: 248.1289.
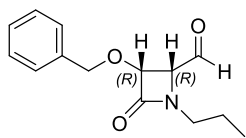
Spectral data of 4-formylazetidin-2-ones **4d,g** correspond with those reported in the literature.[92-93]

Synthesis of 4-(2,2,2-trifluoro-1-hydroxyethyl)azetidin-2-ones 5 and 6

As a representative example, the synthesis of (3*R*,4*S*)-4-[(1*S*)-2,2,2-trifluoro-1-hydroxyethyl]-1-isopropyl-3-phenoxyazetidin-2-one **5a** and (3*R*,4*S*)-4-[(1*R*)-2,2,2-trifluoro-1-hydroxyethyl]-1-isopropyl-3-phenoxyazetidin-2-one **6a** is described. A solution of (2*R*,3*R*)-1-isopropyl-4-oxo-3-phenoxyazetidine-2-carbaldehyde **4a** (2.10 g, 9 mmol, 1 equiv) in dry THF (20 mL) was cooled to -78 °C. Then, CsF (4.10 g, 27 mmol, 3 equiv) and TMSCF₃ (1.41 g, 1.14 mL, 9.9 mmol, 1.1 equiv) were added and the resulting solution was heated up slowly to room temperature during a period of 2 hours. Next, EtOH (10 mL) was added and the solution was stirred for an additional 1 hour at room temperature. Afterward, H₂O was added and the aqueous phases were extracted with EtOAc (3 × 20 mL). Drying (MgSO₄), filtration of the drying agent and evaporation of the solvent *in vacuo* afforded (3*R*,4*S*)-4-[(1*S*)-2,2,2-trifluoro-1-hydroxyethyl]-1-isopropyl-3-phenoxyazetidin-2-one **5a** and (3*R*,4*S*)-4-[(1*R*)-2,2,2-trifluoro-1-hydroxyethyl]-1-isopropyl-3-phenoxyazetidin-2-one **6a** in a diastereomeric ratio of 93/7. Purification of the crude reaction mixture by means of recrystallization from EtOAc/hexane (5/1) afforded (3*R*,4*S*)-4-[(1*S*)-2,2,2-trifluoro-1-hydroxyethyl]-1-isopropyl-3-phenoxyazetidin-2-one **5a** as a white powder in a yield of 74% (2.02 g, 6.66 mmol). This purification method also accounts for the isolation of 4-(2,2,2-trifluoro-1-hydroxyethyl)azetidin-2-ones **5b,c,e**. 4-(2,2,2-Trifluoro-1-hydroxyethyl)azetidin-2-ones **5d,f,g** and **6g** were purified by means of column chromatography on silica gel.
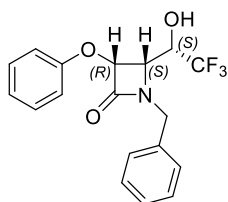
(3*R*,4*S*)-4-[(1*S*)-2,2,2-Trifluoro-1-hydroxyethyl]-1-isopropyl-3-phenoxyazetidin-2-one 5a

White powder. Mp 161 °C. Recrystallization from EtOAc/Hexane (5/1). Yield 74%. $[\alpha]_D^{25}$ = +124.5° (*c* = 0.10, CH_2Cl_2). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.33 and 1.47 (2×3H, 2×d, *J* = 6.8 Hz, 2×CH_3); 2.73 (1H, d, *J* = 5.2 Hz, OH); 3.63 (1H, septet, *J* = 6.8 Hz, C$\underline{H}$(CH_3)$_2$); 4.24 (1H, d×d, *J* = 5.1, 2.2 Hz, CHC$\underline{H}$N); 4.34-4.42 (1H, m, CHCF_3); 5.22 (1H, d, *J* = 5.1 Hz, CHOPh); 7.05-7.12 (3H, m, 3×CH_{arom}); 7.30-7.34 (2H, m, 2×CH_{arom}). **^{19}F NMR** (376 MHz, ref = $CDCl_3$): -76.27 (3F, d, *J* = 8.1 Hz, CF_3). **^{13}C NMR** (100 MHz, ref = $CDCl_3$): δ 20.0 and 20.6 (2×CH_3); 47.5 ($\underline{C}$H(CH_3)$_2$); 55.5 (CH$\underline{C}$HN); 67.9 (q, *J* = 31.3 Hz, $\underline{C}$HCF_3); 79.5 (CHOPh); 116.0 and 123.1 (3×CH_{arom}); 124.3 (q, *J* = 281.3 Hz, CF_3); 129.8 (2×CH_{arom}); 157.1 ($C_{quat,arom}$); 165.3 (C=O). **IR (cm^{-1})**: v_{OH} = 3256; $v_{C=O}$ = 1732; v_{max} = 2984, 1597, 1589, 1413, 1362, 1262, 1229, 1175, 1163, 1130, 1115, 1026, 812, 754, 689, 669. **MS (70 eV)**: *m/z* (%): 304 (M$^+$+1, 100). **HRMS (ESI)**: *m/z* calcd for $C_{14}H_{17}F_3NO_3$: 304.1155 [*M*+H]$^+$, found: 304.1155.
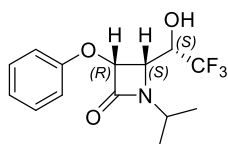
(3*R*,4*S*)-4-[(1*S*)-2,2,2-Trifluoro-1-hydroxyethyl]-3-phenoxy-1-propylazetidin-2-one 5b

White powder. Mp 101 °C. Recrystallization from EtOAc/Hexane (5/1). Yield 29%. $[\alpha]_D^{25}$ = +113.5° (*c* = 0.15, CH_2Cl_2). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.93 (3H, t, *J* = 7.4 Hz, CH_3); 1.52-1.74 (2H, m, C$\underline{H}_2CH_3$); 2.88 (1H, d, *J* = 5.2 Hz, OH); 3.10 (1H, d×d×d, *J* = 13.8, 8.2, 5.5 Hz, ($\underline{H}$CH)N); 3.52-3.59 (1H, m, (HC$\underline{H}$)N); 4.25 (1H, d×d, *J* = 5.0, 1.8 Hz, CHN); 4.35-4.43 (1H, m, CHCF_3); 5.30 (1H, d, *J* = 5.0 Hz, CHOPh); 7.05-7.12 (3H, m, 3×CH_{arom}); 7.30-7.34 (2H, m, 2×CH_{arom}). **^{19}F NMR** (376 MHz, ref = $CDCl_3$): -76.72 (3F, d, *J* = 8.1 Hz, CF_3). **^{13}C NMR** (100 MHz, ref = $CDCl_3$): δ 11.4 (CH_3); 20.5 ($\underline{C}H_2CH_3$); 43.6 (CH_2N); 55.4 (CHN); 67.9 (q, *J* = 31.5 Hz, $\underline{C}$HCF_3); 80.3 (CHOPh); 116.0 and 123.2 (3×CH_{arom}); 124.3 (q, *J* = 276.7 Hz, CF_3); 129.9 (2×CH_{arom}); 157.0 ($C_{quat,arom}$); 165.9 (C=O). **IR (cm^{-1})**: v_{OH} = 3377; $v_{C=O}$ = 1753; v_{max} = 2978, 1495, 1418, 1285, 1236, 1173, 1155, 1150, 1125, 1113, 1028, 750, 689, 665. **MS (70 eV)**: *m/z* (%): 304 (M$^+$+1, 100). **HRMS (ESI)**: *m/z* calcd for $C_{14}H_{17}F_3NO_3$: 304.1155 [*M*+H]$^+$, found: 304.1163.
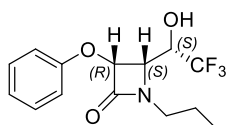
(3*R*,4*S*)-1-Cyclohexyl-4-[(1*S*)-2,2,2-trifluoro-1-hydroxyethyl]-3-phenoxyazetidin-2-one 5c

White powder. Mp 136 °C. Recrystallization from EtOAc/Hexane (15/1). Yield 16%. $[\alpha]_D^{25}$ = +118.0° (*c* = 0.27, CH_2Cl_2). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.17-1.29 (3H, m, NCH(C$\underline{H}_2$)$_5$); 1.61-1.95 (6H, m, NCH(C$\underline{H}_2$)$_5$); 2.11-2.14 (1H, m, NCH(C$\underline{H}_2$)$_5$); 2.86 (1H, d, *J* = 5.4 Hz, OH); 3.18-3.26 (1H, m, NC$\underline{H}$(CH_2)$_5$); 4.25 (1H, d×d, *J* = 5.1, 2.4 Hz, CHC$\underline{H}$N); 4.37 (q×d×d, *J* = 7.9, 5.4, 2.4, CHCF_3); 5.21 (1H, d, *J* = 5.1 Hz, CHOPh); 7.04-7.10 (3H, m, 3×CH_{arom}); 7.28-7.34 (2H, m, 2×CH_{arom}). **^{19}F NMR** (376 MHz, ref = $CDCl_3$): δ -76.29 (3F, d, *J* = 7.9 Hz). **^{13}C NMR** (100 MHz, ref = $CDCl_3$): δ 25.16, 25.19, 25.5, 30.2 and 30.6 (CH(C$\underline{H}_2$)$_5$); 55.3 (CH$\underline{C}$HN); 55.4 (N$\underline{C}$H(CH_2)$_5$); 67.8 (q, *J* = 31.3 Hz, $\underline{C}$HCF_3); 79.4 (CHOPh); 116.0 and 123.1 (3×CH_{arom}); 124.3 (q, *J* = 281.8 Hz, CF_3); 129.8 (2×CH_{arom}); 157.1 ($C_{quat,arom}$); 165.3 (C=O). **IR (cm^{-1})**: v_{OH} = 3252; $v_{C=O}$ = 1724; v_{max} = 2943, 1265, 1229, 1169, 1126, 1098, 808, 746, 689. **MS (70 eV)**: *m/z* (%): 344 (M$^+$+1, 100). **HRMS (ESI)**: *m/z* calcd for $C_{17}H_{21}F_3NO_3$: 344.1468 [*M*+H]$^+$, found: 344.1482.
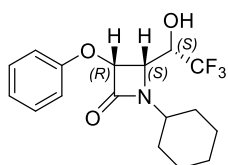
(3*R*,4*S*)-1-Benzyl-4-[(1*S*)-2,2,2-trifluoro-1-hydroxyethyl]-3-phenoxyazetidin-2-one 5d

White powder. Mp 88 °C. R_f = 0.23 (Petroleumether/EtOAc 4/1; 4 CV 0% EtOAc, 24 CV 0-9% EtOAc, 1 CV 9-100% EtOAc, UV = 222 nm). $[\alpha]_D^{25}$ = +11.3° (*c* = 0.16, CH₂Cl₂). **¹H NMR** (400 MHz, CDCl₃): δ 3.06 (1H, d, *J* = 5.5 Hz, OH); 4.08 (1H, d×d, *J* = 5.1, 2.4 Hz, CHC<u>H</u>N); 4.12 (1H, d, *J* = 15.0 Hz, (<u>H</u>CH)N); 4.39 (1H, q×d×d, *J* = 7.7, 5.5, 2.4, CHCF₃); 4.97 (1H, d, *J* = 15.0 Hz, (HC<u>H</u>)N); 5.26 (1H, d, *J* = 5.1 Hz, CHOPh); 7.04-7.10 (3H, m, 3×CH_arom); 7.25-7.39 (7H, m, 7×CH_arom). **¹⁹F NMR** (376 MHz, ref = CDCl₃): δ -76.51 (3F, d, *J* = 7.7 Hz). **¹³C NMR** (100 MHz, ref = CDCl₃): δ 45.7 (CH₂N); 55.0 (CHC<u>H</u>N); 67.9 (q, *J* = 31.5 Hz, <u>C</u>HCF₃); 80.5 (CHOPh); 116.0 and 123.2 (3×CH_arom); 124.2 (q, *J* = 282.4 Hz, CF₃); 128.1, 128.5, 129.0 and 129.8 (7×CH_arom); 135.0 and 157.0 (2×C_quat,arom); 166.1 (C=O). **IR (cm⁻¹)**: ν_OH = 3422; ν_C=O = 1755; ν_max = 1489, 1418, 1229, 1179, 1169, 1125, 1078, 764, 733, 696. **MS (70 eV)**: *m/z* (%): 352 (M⁺+1, 100). **HRMS (ESI)**: *m/z* calcd for C₁₈H₁₇F₃NO₃: 352.1155 [*M*+H]⁺, found: 352.1163.

(3*R*,4*S*)-3-Benzyloxy-4-[(1*S*)-2,2,2-trifluoro-1-hydroxyethyl]-1-isopropylazetidin-2-one 5e

White powder. Mp 101 °C. Recrystallization from EtOAc/Hexane (5/1). Yield 50%. $[\alpha]_D^{25}$ = +79.9° (*c* = 0.35, CHCl₃). **¹H NMR** (400 MHz, CDCl₃): δ 1.27 and 1.42 (2×3H, 2×d, *J* = 6.8 Hz, 2×CH₃); 3.06 (1H, d, *J* = 4.7 Hz, OH); 3.54 (1H, septet, *J* = 6.8 Hz, C<u>H</u>(CH₃)₂); 3.99 (1H, d×d, *J* = 5.1, 2.2 Hz, CHC<u>H</u>N); 4.13-4.20 (1H, m, CHCF₃); 4.65 (1H, d, *J* = 5.1 Hz, CHOPh); 4.70 and 4.94 (2×1H, 2×d, *J* = 11.6 Hz, (HCH)O); 7.31-7.40 (2H, m, 5×CH_arom). **¹⁹F NMR** (376 MHz, ref = CDCl₃): δ -76.10 (3F, d, *J* = 8.1 Hz, CF₃). **¹³C NMR** (100 MHz, ref = CDCl₃): δ 20.1 and 20.6 (2×CH₃); 47.3 (<u>C</u>H(CH₃)₂); 55.4 (CHC<u>H</u>N); 67.9 (q, *J* = 31.3 Hz, <u>C</u>HCF₃); 73.7 (CH₂O); 79.8 (CHOBn); 124.3 (q, *J* = 282.2 Hz, CF₃); 128.3, 128.6 and 128.8 (5×CH_arom); 136.2 (C_quat,arom); 166.9 (C=O). **IR (cm⁻¹)**: ν_OH = 3302; ν_C=O = 1717; ν_max = 2978, 2936, 2886, 1418, 1344, 1263, 1169, 1123, 1024, 986, 818, 702, 756, 685. **MS (70 eV)**: *m/z* (%): 318 (M⁺+1, 100). **HRMS (ESI)**: *m/z* calcd for C₁₅H₁₉F₃NO₃: 318.1312 [*M*+H]⁺, found: 318.1314.
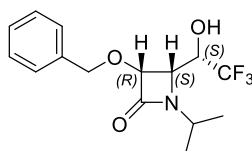
(3*R*,4*S*)-3-Benzyloxy-4-[(1*S*)-2,2,2-trifluoro-1-hydroxyethyl]-1-propylazetidin-2-one 5f

White powder. Mp 101 °C. Reversed phase column chromatography (CH₃CN/H₂O) (40 CV 33% CH₃CN, 5 CV 33-50% CH₃CN, 5 CV 50-100% CH₃CN). $[\alpha]_D^{25}$ = +62.9° (*c* = 0.18, CHCl₃). **¹H NMR** (400 MHz, CDCl₃): δ 0.88 (3H, t, *J* = 7.4 Hz, CH₃); 1.45-1.65 (2H, m, C<u>H</u>₂CH₃); 3.01 (1H, d×d×d, *J* = 14.0, 8.3, 5.4 Hz, (<u>H</u>CH)N); 3.13 (1H, d, *J* = 4.4 Hz, OH); 3.49 (1H, d×d×d, *J* = 14.0, 7.7, 7.7 Hz, (HC<u>H</u>)N); 4.01 (1H, d×d, *J* = 5.0, 1.7 Hz, CHN); 4.13-4.20 (1H, m, CHCF₃); 4.71 (1H, d, *J* = 11.6 Hz, (<u>H</u>CH)O); 4.75 (1H, d, *J* = 5.0 Hz, CHOBn); 4.95 (1H, d, *J* = 11.6 Hz, (HC<u>H</u>)O); 7.32-7.40 (5H, m, 5×CH_arom). **¹⁹F NMR** (376 MHz, ref = CDCl₃): δ -76.55 (3F, d, *J* = 8.2 Hz, CF₃). **¹³C NMR** (100 MHz, ref = CDCl₃): δ 11.3 (CH₃); 20.4 (<u>C</u>H₂CH₃); 43.2 (CH₂N); 55.2 (CHN); 68.1 (q, *J* = 31.4 Hz, <u>C</u>HCF₃); 73.8 (CH₂O); 80.6 (CHOBn); 124.3 (q, *J* = 280.8 Hz, CF₃); 128.3, 128.6 and 128.8 (5×CH_arom); 136.1 (C_quat,arom); 167.4 (C=O). **IR (cm⁻¹)**: ν_OH = 3227; ν_C=O = 1717; ν_max = 2967, 1429, 1344, 1261, 1173, 1011, 691, 687. **MS (70 eV)**: *m/z* (%): 318 (M⁺+1, 100). **HRMS (ESI)**: *m/z* calcd for C₁₅H₁₉F₃NO₃: 318.1312 [*M*+H]⁺, found: 318.1326.
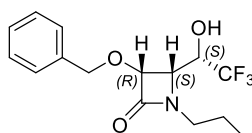
(3*R*,4*S*)-1-Benzyl-3-benzyloxy-4-[(1*S*)-2,2,2-trifluoro-1-hydroxyethyl]azetidin-2-one 5g

White powder. Mp 70 °C. R_f = 0.04 (Petroleumether/EtAc 6/1). Yield 35%. $[\alpha]_D^{25}$ = -9.2° (*c* = 0.19, CHCl₃). **¹H NMR** (400 MHz, CDCl₃): δ 3.02 (1H, d, *J* = 4.7 Hz, OH); 3.85 (1H, d×d, *J* = 5.1, 2.0 Hz, CHC*H*N); 4.02 (1H, d, *J* = 15.0 Hz, (*H*CH)N); 4.12-4.19 (1H, m, CHCF₃); 4.72 (1H, d, *J* = 11.6 Hz, (*H*CH)O); 4.73 (1H, d, *J* = 5.1 Hz, CHOBn); 4.93 (1H, d, *J* = 15.0 Hz, (HC*H*)N); 4.96 (1H, d, *J* = 11.6 Hz, (HC*H*)O); 7.21-7.38 (10H, m, 10×CH_arom). **¹⁹F NMR** (376 MHz, ref = CDCl₃): δ -76.21 (3F, d, *J* = 8.1 Hz, CF₃). **¹³C NMR** (100 MHz, ref = CDCl₃): δ 45.2 (CH₂N); 54.8 (CH*C*HN); 68.1 (q, *J* = 31.5 Hz, *C*HCF₃); 73.8 (CH₂O); 81.0 (CHOBn); 124.1 (q, *J* = 278.9 Hz, CF₃); 127.9, 128.3, 128.4 128.6, 128.8 and 128.9 (10×CH_arom); 135.1 and 136.0 (2×C_quat,arom); 167.3 (C=O). **IR (cm⁻¹)**: ν_OH = 3261; ν_C=O = 1724; ν_max = 3034, 2943, 1420, 1346, 1263, 1163, 1134, 1101, 1026, 825, 669. **MS (70 eV)**: *m/z* (%): 366 (M⁺+1, 100). **HRMS (ESI)**: *m/z* calcd for C₁₉H₁₉F₃NO₃: 366.1312 [*M*+H]⁺, found: 366.1328.
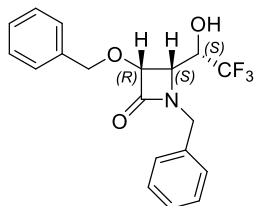
(3*R*,4*S*)-3-Benzyloxy-4-[(1*R*)-2,2,2-trifluoro-1-hydroxyethyl]-1-propylazetidin-2-one 6f

Colorless oil. Reversed phase column chromatography (CH₃CN/H₂O) (40 CV 33% CH₃CN, 5 CV 33-50% CH₃CN, 5 CV 50-100% CH₃CN). $[\alpha]_D^{25}$ = +67.6° (*c* = 0.11, CHCl₃). **¹H NMR** (400 MHz, CDCl₃): δ 0.93 (3H, t, *J* = 7.4 Hz, CH₃); 1.50-1.68 (2H, m, C*H₂*CH₃); 3.03 (1H, d×d×d, *J* = 14.1, 8.1, 5.8 Hz, (*H*CH)N); 3.40 (1H, d×d×d, *J* = 14.1, 7.6, 7.6 Hz, (HC*H*)N); 3.95 (1H, d×d, *J* = 4.7, 4.6 Hz, CHN); 4.09 (1H, d, *J* = 8.8 Hz, OH); 4.23-4.32 (1H, m, CHCF₃); 4.79 (1H, d, *J* = 11.4 Hz, (*H*CH)O); 4.86 (1H, d, *J* = 4.7 Hz, CHOBn); 4.98 (1H, d, *J* = 11.4 Hz, (HC*H*)O); 7.32-7.40 (5H, m, 5×CH_arom). **¹⁹F NMR** (376 MHz, ref = CDCl₃): δ -76.27 (3F, d, *J* = 8.0 Hz, CF₃). **¹³C NMR** (100 MHz, ref = CDCl₃): δ 11.4 (CH₃); 20.8 (*C*H₂CH₃); 42.3 (CH₂N); 55.0 (CHN); 70.0 (q, *J* = 31.3 Hz, *C*HCF₃); 73.8 (CH₂O); 82.2 (CHOBn); 124.3 (q, *J* = 283.1 Hz, CF₃); 128.2, 128.6 and 128.7 (5×CH_arom); 135.7 (C_quat,arom); 166.6 (C=O). **IR (cm⁻¹)**: ν_OH = 3354; ν_C=O = 1740; ν_max = 2967, 2938, 2880, 1342, 1271, 1215, 1173, 1148, 1123, 1090, 1067, 1009, 737, 698. **MS (70 eV)**: *m/z* (%): 318 (M⁺+1, 100). **HRMS (ESI)**: *m/z* calcd for C₁₅H₁₉F₃NO₃: 318.1312 [*M*+H]⁺, found: 318.1325.
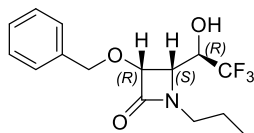
(3*R*,4*S*)-1-Benzyl-3-benzyloxy-4-[(1*R*)-2,2,2-trifluoro-1-hydroxyethyl]azetidin-2-one 6g

Colorless oil. R_f = 0.07 (Petroleumether/EtAc 6/1). Yield 23%. $[\alpha]_D^{25}$ = +33.2° (*c* = 0.16, CHCl₃). **¹H NMR** (400 MHz, CDCl₃): δ 3.78 (1H, d×d, *J* = 4.8, 4.6 Hz, CHC*H*N); 4.04 (1H, d, *J* = 8.9 Hz, OH); 4.08 (1H, d, *J* = 15.2 Hz, (*H*CH)N); 4.12-4.22 (1H, m, CHCF₃); 4.78 (1H, d, *J* = 15.2 Hz, (HC*H*)N); 4.79 (1H, d, *J* = 11.5 Hz, (*H*CH)O); 4.83 (1H, d, *J* = 4.8 Hz, CHOBn); 4.97 (1H, d, *J* = 11.5 Hz, (HC*H*)O); 7.22-7.38 (10H, m, 10×CH_arom). **¹⁹F NMR** (376 MHz, ref = CDCl₃): δ -76.08 (3F, d, *J* = 7.6 Hz, CF₃). **¹³C NMR** (100 MHz, ref = CDCl₃): δ 44.6 (CH₂N); 54.5 (CH*C*HN); 69.7 (q, *J* = 31.4 Hz, *C*HCF₃); 73.9 (CH₂O); 82.5 (CHOBn); 124.2 (q, *J* = 282.9 Hz, CF₃); 128.2, 128.3, 128.6, 128.7 and 129.1 (10×CH_arom); 134.3 and 135.6 (2×C_quat,arom); 166.7 (C=O). **IR (cm⁻¹)**: ν_OH = 3397; ν_C=O = 1744; ν_max = 3032, 2938, 1342, 1271, 1163, 1126, 1094, 1028, 739, 696. **MS (70 eV)**: *m/z* (%): 366 (M⁺+1, 100). **HRMS (ESI)**: *m/z* calcd for C₁₉H₁₉F₃NO₃: 366.1312 [*M*+H]⁺, found: 366.1313.
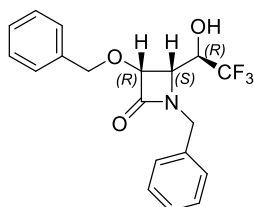
Synthesis of 2-(2,2,2-trifluoro-1-hydroxyethyl)azetidines 7 and 8

As a representative example, the synthesis of (2*S*,3*S*)-2-[(1*S*)-2,2,2-trifluoro-1-hydroxyethyl]-1-isopropyl-3-phenoxyazetidine **7a** is described. To an ice-cooled solution of $AlCl_3$ (0.6 g, 4.5 mmol, 1.5 equiv) in dry Et_2O (20 mL), a solution of $LiAlH_4$ (4.5 mL, 4.5 mmol, 1.5 equiv, 1.0 M in Et_2O) was added via a syringe. Then, the resulting solution was stirred at room temperature for 30 minutes, after which a solution of (3*R*,4*S*)-4-[(1*S*)-2,2,2-trifluoro-1-hydroxyethyl]-1-isopropyl-3-phenoxyazetidin-2-one **5a** (909 mg, 3 mmol, 1 equiv) in dry Et_2O (10 mL) was added at 0 °C, followed by stirring for 2 hours at 0 °C. Afterward, the reaction mixture was quenched with brine (10 mL) to neutralize the excess of $LiAlH_4$. Then, an excess of $MgSO_4$ (5 g) was added and the reaction mixture was filtered. Subsequently, the remaining solids on the filter were washed intensively with EtOAc (5 × 20 mL). Evaporation of the combined organic phases *in vacuo* afforded (2*S*,3*S*)-2-[(1*S*)-2,2,2-trifluoro-1-hydroxyethyl]-1-isopropyl-3-phenoxyazetidine **7a** in a yield of 94% (815 mg, 2.82 mmol) as a white powder, which was purified by means of column chromatography on silica gel (Petroleumether/EtOAc 9/1) to provide an analytically pure sample. Azetidine **7e** appeared to be unstable upon purification on silica gel.

(2*S*,3*S*)-2-[(1*S*)-2,2,2-Trifluoro-1-hydroxyethyl]-1-isopropyl-3-phenoxyazetidine 7a

White powder. Mp 87 °C. R_f = 0.13 (Petroleumether/EtOAc 9/1). Yield 94%. $[\alpha]_D^{25}$ = +39.3° (*c* = 0.15, CH_2Cl_2). **¹H NMR** (400 MHz, $CDCl_3$): δ 1.02 and 1.05 (2×3H, 2×d, *J* = 6.5 Hz, (C<u>H</u>$_3$)$_2$CH); 2.89 (1H, septet, *J* = 6.5 Hz, C<u>H</u>(CH$_3$)$_2$); 3.45-3.49 (1H, m, (<u>H</u>CH)N); 3.68 (1H, d×d, *J* = 9.7, 7.3 Hz, (HC<u>H</u>)N); 4.03-4.06 (1H, m, CHOC<u>H</u>N); 4.22-4.29 (1H, m, CHCF$_3$); 4.93 (1H, d×d×d, *J* = 7.3, 7.3, 3.7 Hz, CHOPh); 5.63 (1H, s (broad), OH); 6.75-6.77 (2H, m, 2×CH$_{arom}$); 6.96-7.00 (1H, m, CH$_{arom}$); 7.25-7.29 (2H, m, 2×CH$_{arom}$). **¹⁹F NMR** (376 MHz, ref = $CDCl_3$): -78.33 (3F, d, *J* = 8.1 Hz, CF$_3$). **¹³C NMR** (100 MHz, ref = $CDCl_3$): δ 16.4 and 20.0 (2×CH$_3$); 51.4 (<u>C</u>H(CH$_3$)$_2$); 53.0 (CH$_2$N); 60.7 (CHO<u>C</u>HN); 64.0 (q, *J* = 30.9 Hz, <u>C</u>HCF$_3$); 66.7 (CHOPh); 114.8 and 121.7 (3×CH$_{arom}$); 125.3 (q, *J* = 281.9 Hz, CF$_3$); 129.7 (2×CH$_{arom}$); 156.8 (C$_{quat,arom}$). **IR (cm⁻¹)**: ν$_{max}$ = 3030, 1599, 1587, 1489, 1227, 1165, 1121, 1094, 908, 752, 727, 692. **MS (70 eV)**: *m/z* (%): 290 (M⁺+1, 100). **HRMS (ESI)**: *m/z* calcd for $C_{14}H_{19}F_3NO_2$: 290.1362 [*M*+H]⁺, found: 290.1364.
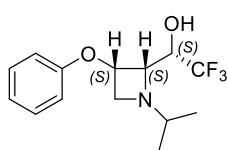
(2*S*,3*S*)-2-[(1*S*)-2,2,2-Trifluoro-1-hydroxyethyl]-3-phenoxy-1-propylazetidine 7b

White powder. Mp 95 °C. R_f = 0.14 (Petroleumether/EtOAc 9/1). Yield 86%. $[\alpha]_D^{25}$ = +96.1° (*c* = 0.25, CH_2Cl_2). **¹H NMR** (400 MHz, $CDCl_3$): δ 0.90 (3H, t, *J* = 7.4 Hz, CH$_3$); 1.36-1.46 (2H, m, C<u>H</u>$_2$CH$_3$); 2.49 (1H, d×d×d, *J* = 11.7, 7.3, 6.2 Hz, CH$_2$(<u>H</u>CH)N); 2.71-2.78 (1H, m, CH$_2$(H<u>C</u>H)N); 3.40 (1H, d×d, *J* = 9.6, 6.5 Hz, CH(<u>H</u>CH)N); 3.63-3.66 (1H, m, CH(HC<u>H</u>)N); 3.82-3.85 (1H, m, CHN); 4.37-4.43 (1H, m, CHCF$_3$); 4.96 (1H, d×d×d, *J* = 6.6, 6.5, 2.5 Hz, CHOPh); 6.05 (1H, s (broad), OH); 6.76-6.78 (2H, m, 2×CH$_{arom}$); 6.96-7.00 (1H, m, CH$_{arom}$); 7.25-7.29 (2H, m, 2×CH$_{arom}$). **¹⁹F NMR** (376 MHz, ref = $CDCl_3$): -78.87 (3F, d, *J* = 8.1 Hz, CF$_3$). **¹³C NMR** (100 MHz, ref = $CDCl_3$): δ 11.5 (CH$_3$); 20.6 (<u>C</u>H$_2$CH$_3$); 58.5 (CH<u>C</u>H$_2$N); 59.2 (CH$_2$<u>C</u>H$_2$N); 64.7 (q, *J* = 30.8 Hz, <u>C</u>HCF$_3$); 65.2 (CHN); 67.8 (CHOPh); 114.8 and 121.6 (3×CH$_{arom}$); 125.2 (q, *J* = 282.0 Hz, CF$_3$); 129.7 (2×CH$_{arom}$); 156.7 (C$_{quat,arom}$). **IR (cm⁻¹)**: ν$_{max}$ = 2963, 1591, 1497, 1489, 1265, 1225, 1165, 1121, 1092, 750, 691. **MS (70 eV)**: *m/z* (%): 290 (M⁺+1, 100). **HRMS (ESI)**: *m/z* calcd for $C_{14}H_{19}F_3NO_2$: 290.1362 [*M*+H]⁺, found: 290.1359.
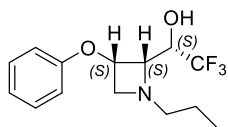
(2*S*,3*S*)-1-Cyclohexyl-2-[(1*S*)-2,2,2-trifluoro-1-hydroxyethyl]-3-phenoxyazetidine 7c

White powder. Mp 99 °C. R_f = 0.11 (Petroleumether/EtOAc 19/1). Yield 71%. $[\alpha]_D^{25}$ = +38.9° (*c* = 0.11, CH$_2$Cl$_2$). **^{1}H NMR** (400 MHz, CDCl$_3$): δ 1.01-1.28 (5H, m, (C$\underline{H}_2$)$_5$CH); 1.63-1.66 (1H, m, (C$\underline{H}_2$)$_5$CH); 1.77-1.84 (4H, m, (C$\underline{H}_2$)$_5$CH); 2.43-2.49 (1H, m, C$\underline{H}$(CH$_2$)$_5$); 3.50 (1H, d×d, *J* = 9.7, 3.9 Hz, ($\underline{H}$CH)N); 3.73 (1H, d×d, *J* = 9.7, 7.4 Hz, (HC$\underline{H}$)N); 4.13-4.15 (1H, m, CHOC$\underline{H}$N); 4.19-4.25 (1H, m, CHCF$_3$); 4.94 (1H, d×d×d, *J* = 7.4, 7.4, 3.9 Hz, CHOPh); 5.59 (1H, s (broad), OH); 6.74-6.76 (2H, m, 2×CH$_{arom}$); 6.96-7.00 (1H, m, CH$_{arom}$); 7.25-7.30 (2H, m, 2×CH$_{arom}$). **^{19}F NMR** (376 MHz, ref = CDCl$_3$): δ -78.17 (3F, d, *J* = 8.1 Hz, CF$_3$). **^{13}C NMR** (100 MHz, ref = CDCl$_3$): δ 24.8, 25.1, 25.7, 27.2 and 30.6 ((C$\underline{H}_2$)$_5$CH); 54.1 (CH$_2$N); 59.9 (C$\underline{H}$(CH$_2$)$_5$); 60.1 (CHOC$\underline{H}$N); 63.9 (q, *J* = 30.8 Hz, C$\underline{H}$CF$_3$); 67.0 (CHOPh); 114.8 and 121.7 (3×CH$_{arom}$); 125.3 (q, *J* = 281.8 Hz, CF$_3$); 129.7 (2×CH$_{arom}$); 156.8 (C$_{quat,arom}$). **IR (cm^{-1})**: v$_{max}$ = 2934, 2857, 1589, 1489, 1234, 1215, 1167, 1123, 1090, 1016, 750, 691, 669. **MS (70 eV)**: *m/z* (%): 330 (M$^+$+1, 100). **HRMS (ESI)**: *m/z* calcd for C$_{17}$H$_{23}$F$_3$NO$_2$: 330.1675 [*M*+H]$^+$, found: 330.1673.
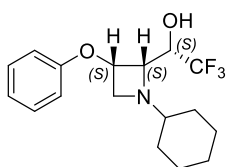
(2*S*,3*S*)-1-Benzyl-2-[(1*S*)-2,2,2-trifluoro-1-hydroxyethyl]-3-phenoxyazetidine 7d

White powder. Mp 110 °C. Reversed phase column chromatography (CH$_3$CN/H$_2$O) (2 CV 40% CH$_3$CN, 20 CV 40-60% CH$_3$CN, 5 CV 60% CH$_3$CN). Yield 43%. $[\alpha]_D^{25}$ = +67.6° (*c* = 0.16, CH$_2$Cl$_2$). **^{1}H NMR** (400 MHz, CDCl$_3$): δ 3.46-3.53 (2H, m, CH$_2$CHO); 3.62 and 4.01 (2×1H, 2×d, *J* = 13.1 Hz, N($\underline{H}$CH)C$_{quat,arom}$); 4.06-4.08 (1H, m, CHOC$\underline{H}$N); 4.26 (1H, ~q, *J* = 8.0 Hz, CHCF$_3$); 4.95 (1H, d×d×d, *J* = 6.5, 6.5, 3.4 Hz, CHOPh); 5.34 (1H, s (broad), OH); 6.71-6.73 (2H, m, 2×CH$_{arom}$); 6.94-6.98 (1H, m, CH$_{arom}$); 7.23-7.7.36 (7H, m, 7×CH$_{arom}$). **^{19}F NMR** (376 MHz, ref = CDCl$_3$): δ -78.68 (3F, d, *J* = 8.0 Hz, CF$_3$). **^{13}C NMR** (100 MHz, ref = CDCl$_3$): δ 57.9 (CH$_2$N); 59.8 (NC$\underline{H}_2$C$_{quat,arom}$); 64.2 (CHOC$\underline{H}$N); 64.9 (q, *J* = 30.9 Hz, C$\underline{H}$CF$_3$); 67.4 (CHOPh); 114.7 and 121.6 (3×CH$_{arom}$); 125.1 (q, *J* = 281.3 Hz, CF$_3$); 127.8, 128.6, 128.7 and 129.7 (7×CH$_{arom}$); 136.3 and 156.7 (2×C$_{quat,arom}$). **IR (cm^{-1})**: v$_{max}$ = 3030, 2698, 1599, 1489, 1362, 1227, 1165, 1121, 1094, 1040, 752, 727, 691. **MS (70 eV)**: *m/z* (%): 338 (M$^+$+1, 100). **HRMS (ESI)**: *m/z* calcd for C$_{18}$H$_{19}$F$_3$NO$_2$: 338.1362 [*M*+H]$^+$, found: 338.1359.
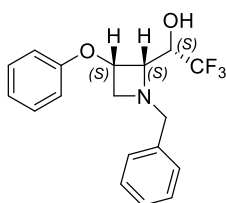
(2*S*,3*S*)-3-Benzyloxy-2-[(1*S*)-2,2,2-trifluoro-1-hydroxyethyl]-1-propylazetidine 7f

Yellow oil. Reversed phase column chromatography (CH$_3$CN/H$_2$O) (3 CV 30-35% CH$_3$CN, 30 CV 35-70% CH$_3$CN, 5 CV 70% CH$_3$CN). Yield 41%. $[\alpha]_D^{25}$ = +50.1° (*c* = 0.24, CHCl$_3$). **^{1}H NMR** (400 MHz, CDCl$_3$): δ 0.87 (3H, t, *J* = 7.4 Hz, CH$_3$); 1.31-1.43 (2H, m, C$\underline{H}_2$CH$_3$); 2.38 (1H, d×d×d, *J* = 11.6, 7.7, 5.9 Hz, CH$_2$($\underline{H}$CH)N); 2.64-2.71 (1H, m, CH$_2$(HC$\underline{H}$)N); 3.11 (1H, d×d, *J* = 9.3, 6.5 Hz, ($\underline{H}$CH)NCHO); 3.52-3.55 (1H, m, (HC$\underline{H}$)NCHO); 3.60-3.63 (1H, m, CHN); 4.26 (1H, d×d×d, *J* = 6.6, 6.5, 2.5 Hz, CHOBn); 4.30 (1H, q×d, J_{HF} = 8.0, *J* = 3.4 Hz, CHCF$_3$); 4.41 and 4.55 (2×1H, 2×d, *J* = 12.2 Hz, ($\underline{H}$C$\underline{H}$)O); 6.05 (1H, s (broad), OH); 7.26-7.35 (5H, m, 5×CH$_{arom}$). **^{19}F NMR** (376 MHz, ref = CDCl$_3$): δ -78.67 (3F, d, *J* = 8.0 Hz, CF$_3$). **^{13}C NMR** (100 MHz, ref = CDCl$_3$): δ 11.5 (CH$_3$); 20.6 (C$\underline{H}_2$CH$_3$); 58.5 (CHOC$\underline{H}_2$N); 59.2 (CH$_2$C$\underline{H}_2$N); 64.7 (q, *J* = 30.7 Hz, C$\underline{H}$CF$_3$); 65.8 (CHN); 69.2 (CHOBn); 71.1 (CH$_2$O); 125.3 (q, *J* = 281.8 Hz, CF$_3$); 127.6 (2×CH$_{arom}$); 127.8 (CH$_{arom}$); 128.5 (2×CH$_{arom}$); 137.4 (C$_{quat,arom}$). **IR (cm^{-1})**: v$_{max}$ = 3076, 2961, 2878, 1456, 1281, 1265, 1165, 1121, 1040, 908, 729, 692. **MS (70 eV)**: *m/z* (%): 304 (M$^+$+1, 100). **HRMS (ESI)**: *m/z* calcd for C$_{15}$H$_{21}$F$_3$NO$_2$: 304.1519 [*M*+H]$^+$, found: 304.1528.
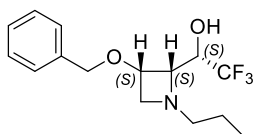
(2*S*,3*S*)-1-Benzyl-3-benzyloxy-2-[(1*S*)-2,2,2-trifluoro-1-hydroxyethyl]azetidine 7g

Colorless oil. R_f = 0.16 (Petroleumether/EtOAc 6/1). Yield 80%. $[\alpha]_D^{25}$ = +48.8° (*c* = 0.2, CHCl₃). **¹H NMR** (400 MHz, CDCl₃): δ 3.22 (1H, d×d, *J* = 9.5, 6.7 Hz, (<u>H</u>CH)NCHO); 3.46-3.53 (1H, m, (HC<u>H</u>)NCHO); 3.52 (1H, d, *J* = 13.1 Hz, N(<u>H</u>CH)C_quat,arom); 3.86-3.88 (1H, m, CHN); 3.94 (1H, d, *J* = 13.1 Hz, N(HC<u>H</u>)C_quat,arom); 4.26 (1H, q×d, *J*_HF = 8.2, *J* = 1.3 Hz, CHCF₃); 4.30 (1H, d×d×d, *J* = 6.9, 6.7, 2.7 Hz, CHOBn); 4.40 and 4.54 (2×1H, 2×d, *J* = 12.1 Hz, (<u>H</u>CH)O); 5.31 (1H, s (broad), OH); 7.20-7.38 (10H, m, 10×CH_arom). **¹⁹F NMR** (376 MHz, ref = CDCl₃): δ -78.58 (3F, d, *J* = 8.2 Hz, CF₃). **¹³C NMR** (100 MHz, ref = CDCl₃): δ 58.1 (CH₂NCHO); 60.0 (NCH₂C_quat,arom); 64.8 (CHN); 65.0 (q, *J* = 30.8 Hz, CHCF₃); 69.0 (CHOBn); 71.2 (CH₂O); 125.4 (q, *J* = 276.7 Hz, CF₃); 127.52 (2×CH_arom); 127.54 and 127.9 (2×CH_arom); 128.51, 128.54 and 128.8 (6×CH_arom); 137.0 and 137.3 (2×C_quat,arom). **IR (cm⁻¹)**: ν_max = 3030, 2930, 2862, 1454, 1265, 1217, 1163, 1115, 1028, 849, 752, 731, 694, 627, 604. **MS (70 eV)**: *m/z* (%): 352 (M⁺+1, 100). **HRMS (ESI)**: *m/z* calcd for C₁₉H₂₁F₃NO₂: 352.1519 [*M*+H]⁺, found: 352.1520.
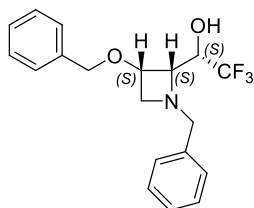
(2*S*,3*S*)-3-Benzyloxy-2-[(1*R*)-2,2,2-trifluoro-1-hydroxyethyl]-1-propylazetidine 8b

Yellow oil. Reversed phase column chromatography (CH₃CN/H₂O) (3 CV 30-35% CH₃CN, 30 CV 35-70% CH₃CN, 5 CV 70% CH₃CN). Yield 15%. Purity = 80%. $[\alpha]_D^{25}$ = +70.0° (*c* = 0.13, CHCl₃). **¹H NMR** (400 MHz, CDCl₃): δ 0.89 (3H, t, *J* = 7.4 Hz, CH₃); 1.36-1.52 (2H, m, C<u>H</u>₂CH₃); 2.29 (1H, d×d×d, *J* = 11.3, 8.4, 6.5 Hz, CH₂(<u>H</u>CH)N); 2.60 (1H, d×d×d, *J* = 11.3, 8.8, 7.0 Hz, CH₂(HC<u>H</u>)N); 2.93 (1H, d×d, *J* = 9.0, 5.6 Hz, (<u>H</u>CH)NCHO); 3.39-3.41 (1H, m, (HC<u>H</u>)NCHO); 3.60-3.62 (1H, m, CHN); 4.15 (1H, q×d, *J*_HF = 8.0, *J* = 4.1 Hz, CHCF₃); 4.40-4.44 (1H, m, CHOBn); 4.41 (1H, d, *J* = 11.6 Hz, (<u>H</u>CH)O); 4.56-4.68 (1H, m, OH); 4.60 (1H, d, *J* = 11.6 Hz, (HC<u>H</u>)O); 7.27-7.39 (5H, m, 5×CH_arom). **¹⁹F NMR** (376 MHz, ref = CDCl₃): δ -76.91 (3F, d, *J* = 8.0 Hz, CF₃). **¹³C NMR** (100 MHz, ref = CDCl₃): δ 11.8 (CH₃); 21.0 (CH₂CH₃); 58.2 (CHOCH₂N); 60.0 (CH₂CH₂N); 65.9 (CHN); 71.4 (q, *J* = 30.1 Hz, CHCF₃); 71.5 (CH₂O); 73.5 (CHOBn); 124.9 (q, *J* = 283.2 Hz, CF₃); 127.9 (2×CH_arom); 128.2 (CH_arom); 128.6 (2×CH_arom); 136.6 (C_quat,arom). **IR (cm⁻¹)**: ν_max = 3435, 2961, 2936, 2876, 1456, 1269, 1153, 1117, 1101, 1045, 1028, 853, 737, 692. **MS (70 eV)**: *m/z* (%): 304 (M⁺+1, 100). **HRMS (ESI)**: *m/z* calcd for C₁₅H₂₁F₃NO₂: 304.1519 [*M*+H]⁺, found: 304.1527.
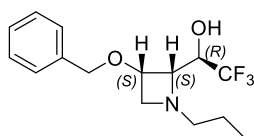
(2*S*,3*S*)-1-Benzyl-3-benzyloxy-2-[(1*R*)-2,2,2-trifluoro-1-hydroxyethyl]azetidine 8c

Colorless oil. R_f = 0.16 (Petroleumether/EtOAc 6/1). Yield 79%. $[\alpha]_D^{25}$ = +78.8° (*c* = 0.21, CHCl₃). **¹H NMR** (400 MHz, CDCl₃): δ 3.05 (1H, d×d, *J* = 9.3320, 5.6164 Hz, (<u>H</u>CH)NCHO); 3.54-3.57 (2H, m, (HC<u>H</u>)NCHO and CHN); 3.63 and 3.74 (2×1H, 2×d, *J* = 12.7 Hz, N(<u>H</u>CH)C_quat,arom); 3.85 (1H, d×q×d, *J* = 8.2, *J*_HF = 8.1, *J* = 3.8 Hz, CHCF₃); 4.40 (1H, d, *J* = 12.1 Hz, (<u>H</u>CH)O); 4.43-4.45 (1H, m, CHOBn); 4.60 (1H, d, *J* = 12.1 Hz, (HC<u>H</u>)O); 4.58 (1H, d, *J* = 8.2 Hz, OH); 7.24-7.36 (10H, m, 10×CH_arom). **¹⁹F NMR** (376 MHz, ref = CDCl₃): δ -76.91 (3F, d, *J* = 8.1 Hz, CF₃). **¹³C NMR** (100 MHz, ref = CDCl₃): δ 57.7 (CH₂NCHO); 61.5 (NCH₂C_quat,arom); 65.2 (CHN); 71.3 (q, *J* = 29.9 Hz, CHCF₃); 71.5 (CH₂O); 73.5 (CHOBn); 124.8 (q, *J* = 283.2 Hz, CF₃); 127.5 (CH_arom); 127.9 (2×CH_arom); 128.2 (CH_arom); 128.5, 128.6 and 128.9 (6×CH_arom); 136.5 and 137.0 (2×C_quat,arom). **IR (cm⁻¹)**: ν_OH = 3447; ν_max = 3030, 2934, 2866, 1454, 1269, 1171, 1117, 1105, 1057, 1028, 854, 713, 692, 604. **MS (70 eV)**: *m/z* (%): 352 (M⁺+1, 100). **HRMS (ESI)**: *m/z* calcd for C₁₉H₂₁F₃NO₂: 352.1519 [*M*+H]⁺, found: 352.1532.
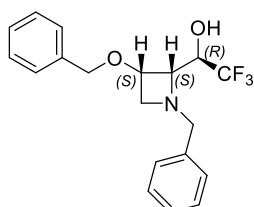
Synthesis of trifluoromethanesulfonates 9 and 11

As a representative example, the synthesis of 1-[(2R,3S)-1-benzyl-3-phenoxyazetidin-2-yl]-(1S)-2,2,2-trifluoroethyl trifluoromethanesulfonate **9b** is described. To an ice-cooled solution of (2S,3S)-1-benzyl-2-[(1S)-2,2,2-trifluoro-1-hydroxyethyl]-3-phenoxyazetidine **7d** (1.01 g, 3 mmol, 1 equiv) in dry CH_2Cl_2 (20 mL), N,N,N',N'-tetramethylnaphthalene-1,8-diamine (1.28 g, 6 mmol, 2 equiv) and triflic anhydride (0.93 g, 0.55 mL, 3.3 mmol, 1.1 equiv) were added via a syringe. Then, the resulting solution was stirred at 0 °C for 40 minutes. Afterward, the solvent was evaporated and the resulting crude solid reaction mixture was washed with Et_2O (3 × 10 mL) and filtered. The filtrate was evaporated and the crude reaction mixture was purified by means of column chromatography on silica gel to afford 1-[(2R,3S)-1-benzyl-3-phenoxyazetidin-2-yl]-(1S)-2,2,2-trifluoroethyl trifluoromethanesulfonate **9b** in 95% yield (1.34 g, 2.85 mmol) as a colorless oil. Triflate **9c** appeared to be unstable upon purification on silica gel.

(1S)-2,2,2-Trifluoro-1-[(2R,3S)-1-isopropyl-3-phenoxyazetidin-2-yl]ethyl trifluoromethanesulfonate 9a

Colorless oil. R_f = 0.29 (Petroleumether/EtOAc 96/4). Yield 61%. $[\alpha]_D^{25}$ = +27.9° (c = 0.54, CH_2Cl_2). **¹H NMR** (400 MHz, $CDCl_3$): δ 0.99 (2×3H, 2×d, J = 6.4 Hz, (C$\underline{H}_3$)$_2$CH); 2.83 (1H, septet, J = 6.4 Hz, C$\underline{H}$(CH$_3$)$_2$); 3.48-3.55 (2H, m, CH$_2$N); 3.96-4.00 (1H, m, CHOC$\underline{H}$N); 4.91 (1H, d×d×d, J = 7.2, 6.4, 3.7 Hz, CHOPh); 5.83 (1H, d×q, J = 8.7 Hz, J_{HF} = 5.9 Hz, CHCF$_3$); 6.76-6.78 (2H, m, 2×CH$_{arom}$); 6.98-7.02 (1H, m, CH$_{arom}$); 7.26-7.30 (2H, m, 2×CH$_{arom}$). **¹⁹F NMR** (376 MHz, ref = $CDCl_3$): δ -78.37 (3F, s, CF$_3$); -63.75 (3F, s (broad), CF$_3$). **¹³C NMR** (100 MHz, ref = $CDCl_3$): δ 16.6 and 20.1 (2×CH$_3$); 53.8 (CH$_2$N); 53.9 ($\underline{C}$H(CH$_3$)$_2$); 59.0 (CHO$\underline{C}$HN); 65.9 (CHOPh); 77.9 (q, J = 32.7 Hz, $\underline{C}$HCF$_3$); 115.1 (2×CH$_{arom}$); 118.5 (q, J = 319.5 Hz, SCF$_3$); 121.9 (CH$_{arom}$); 122.1 (q, J = 281.0 Hz, CH$\underline{C}$F$_3$); 129.7 (2×CH$_{arom}$); 156.2 (C$_{quat,arom}$). **IR (cm⁻¹)**: $v_{S=O}$ = 1223, 1152; v_{max} = 2990, 1591, 1495, 1389, 1028, 756, 691, 637. **MS (70 eV)**: m/z (%): 331 (100), 422 (M⁺+1, 35).
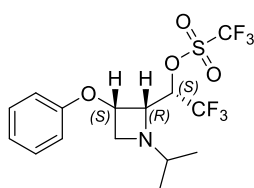
1-[(2R,3S)-1-Benzyl-3-phenoxyazetidin-2-yl]-(1S)-2,2,2-trifluoroethyl trifluoromethanesulfonate 9b

Colorless oil. R_f = 0.25 (Petroleumether/EtOAc 19/1). Yield 95%. $[\alpha]_D^{25}$ = +88.0° (c = 0.17, CH_2Cl_2). **¹H NMR** (400 MHz, $CDCl_3$): δ 2.94 (1H, d×d, J = 9.5, 5.8 Hz, N($\underline{H}$CH)CHO); 3.41-3.43 (1H, m, N(HC$\underline{H}$)CHO); 3.46 (1H, d, J = 12.6 Hz, N($\underline{H}$CH)C$_{quat,arom}$); 3.94 (1H, d×d, J = 9.4, 6.6 Hz, CHN); 4.20 (1H, d, J = 12.6 Hz, N(HC$\underline{H}$)C$_{quat,arom}$); 4.86 (1H, d×d×d, J = 6.6, 5.8, 1.9 Hz, CHOPh); 5.94 (1H, d×q, J = 9.4 Hz, J_{HF} = 5.6 Hz, CHCF$_3$); 6.71-6.74 (2H, m, 2×CH$_{arom}$); 6.95-6.99 (1H, m, CH$_{arom}$); 7.23-7.34 (7H, m, 7×CH$_{arom}$). **¹⁹F NMR** (376 MHz, ref = $CDCl_3$): δ -75.66 till -75.61 (3F, m, CF$_3$); -74.26 till -74.23 (3F, m, CF$_3$). **¹³C NMR** (100 MHz, ref = $CDCl_3$): δ 57.1 (CHOCH$_2$N); 62.0 (N$\underline{C}$H$_2$C$_{quat,arom}$); 62.6 (C$\underline{H}$N); 67.3 (CHOPh); 79.1 (q, J = 33.5 Hz, $\underline{C}$HCF$_3$); 115.0 (2×CH$_{arom}$); 118.4 (q, J = 319.5 Hz, SCF$_3$); 121.7 (q, J = 281.4 Hz, CH$\underline{C}$F$_3$); 121.7 and 127.5 (2×CH$_{arom}$); 128.4, 128.8 and 129.7 (6×CH$_{arom}$); 136.3 and 156.1 (2×C$_{quat,arom}$). **IR (cm⁻¹)**: $v_{S=O}$ = 1213, 1190, 1136; v_{max} = 3032, 1497, 1422, 1366, 1285, 1267, 1101, 991, 858, 752, 725, 691, 611. **MS (70 eV)**: m/z (%): 431 (100), 470 (M⁺+1, 95). **HRMS (ESI)**: m/z calcd for $C_{19}H_{18}F_6NO_4S$: 470.0855 [M+H]⁺, found: 470.0872.
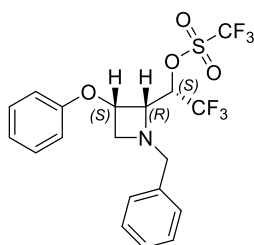
1-[(2*R*,3*S*)-3-Benzyloxy-1-propylazetidin-2-yl]-(1*S*)-2,2,2-trifluoroethyl trifluoromethanesulfonate 9d

Colorless oil. R_f = 0.35 (Petroleumether/EtOAc 5/1). Yield 93%. $[\alpha]_D^{25}$ = +32.6° (*c* = 0.1, CHCl₃). **¹H NMR** (400 MHz, CDCl₃): δ 0.87 (3H, t, *J* = 7.4 Hz, C*H₃*CH₂); 1.27-1.47 (2H, m, CH₃C*H₂*); 2.23 (1H, d×d×d, *J* = 10.9, 9.0, 4.9 Hz, CH₂(*H*CH)N); 2.74 (1H, d×d×d, *J* = 10.9, 9.8, 6.8 Hz, CH₂(HC*H*)N); 2.92 (1H, d×d, *J* = 9.0, 6.0 Hz, N(*H*CH)CHO); 3.54 (1H, d×d, *J* = 9.6, 6.5 Hz, CHN); 3.57-3.59 (1H, m, N(HC*H*)CHO); 4.21 (1H, d×d×d, *J* = 6.5, 6.0, 1.7 Hz, CHOBn); 4.40 and 4.61 (2×1H, 2×d, *J* = 12.1 Hz, (*H*CH)O); 5.69 (1H, d×q, *J* = 9.6 Hz, *J*ₕF = 5.9 Hz, CHCF₃); 7.28-7.37 (5H, m, 5×CHₐᵣₒₘ). **¹⁹F NMR** (376 MHz, ref = CDCl₃): δ -75.69 till -75.64 (3F, m, CF₃); -74.53 till -74.50 (3F, m, CF₃). **¹³C NMR** (100 MHz, ref = CDCl₃): δ 11.5 (CH₃); 20.5 (*C*H₂CH₃); 57.8 (CHO*C*H₂N); 60.9 (CH₂*C*H₂N); 63.7 (*C*HN); 68.4 (CHOBn); 71.0 (CH₂O); 79.2 (q, *J* = 33.1 Hz, *C*HCF₃); 118.4 (q, *J* = 319.5 Hz, S*C*F₃); 121.9 (q, *J* = 276.4 Hz, CH*C*F₃); 127.7 (2×CHₐᵣₒₘ); 127.9 (CHₐᵣₒₘ); 128.5 (2×CHₐᵣₒₘ); 137.1 (Cquat,ₐᵣₒₘ). **IR (cm⁻¹)**: νS=O = 1215, 1134; νmax = 2968, 2878, 1423, 1279, 1028, 988, 934, 860, 752, 696, 638, 611. **MS (70 eV)**: *m/z* (%): 303 (35), 436 (M⁺+1, 55).
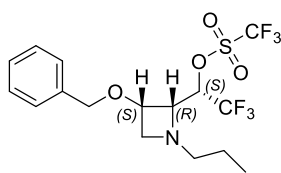
1-[(2*R*,3*S*)-1-Benzyl-3-benzyloxyazetidin-2-yl]-(1*S*)-2,2,2-trifluoroethyl trifluoromethanesulfonate 9e

Colorless oil. R_f = 0.21 (Petroleumether/EtOAc 14/1). Yield 90%. $[\alpha]_D^{25}$ = +72.8° (*c* = 0.17, CHCl₃). **¹H NMR** (400 MHz, CDCl₃): δ 2.94 (1H, d×d, *J* = 9.3, 6.0 Hz, N(*H*CH)CHO); 3.35-3.38 (2H, m, N(*H*CH)Cquat,ₐᵣₒₘ and N(HC*H*)CHO); 3.73 (1H, d×d, *J* = 9.8, 6.5 Hz, CHN); 4.14 (1H, d, *J* = 12.6 Hz, N(HC*H*)Cquat,ₐᵣₒₘ); 4.21 (1H, d×d×d, *J* = 6.5, 6.0, 1.7 Hz, CHOBn); 4.37 and 4.57 (2×1H, 2×d, *J* = 12.1 Hz, (*H*CH)O); 5.81 (1H, d×q, *J* = 9.8 Hz, *J*ₕF = 5.5 Hz, CHCF₃); 7.23-7.35 (5H, m, 5×CHₐᵣₒₘ). **¹⁹F NMR** (376 MHz, ref = CDCl₃): δ -75.63 till -75.58 (3F, m, CF₃); -74.40 till -74.36 (3F, m, CF₃). **¹³C NMR** (100 MHz, ref = CDCl₃): δ 56.8 (CHO*C*H₂N); 62.2 (N*C*H₂Cquat,ₐᵣₒₘ); 63.1 (*C*HN); 68.2 (CHOBn); 70.9 (CH₂O); 79.2 (q, *J* = 33.3 Hz, *C*HCF₃); 118.4 (q, *J* = 319.6 Hz, S*C*F₃); 121.8 (q, *J* = 281.3 Hz, CH*C*F₃); 127.4 (CHₐᵣₒₘ); 127.7 (2×CHₐᵣₒₘ); 128.0 (CHₐᵣₒₘ); 128.3, 128.5 and 128.9 (6×CHₐᵣₒₘ); 136.6 and 137.0 (2×Cquat,ₐᵣₒₘ). **IR (cm⁻¹)**: νS=O = 1211, 1192, 1136; νmax = 3032, 2934, 2868, 1420, 1366, 1267, 1061, 1028, 986, 856, 727, 696, 611. **MS (70 eV)**: *m/z* (%): 484 (M⁺+1, 100). **HRMS (ESI)**: *m/z* calcd for C₂₀H₂₀F₆NO₄S: 484.1012 [*M*+H]⁺, found: 484.1030.
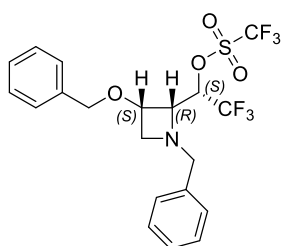
1-[(2*R*,3*S*)-3-Benzyloxy-1-propylazetidin-2-yl]-(1*R*)-2,2,2-trifluoroethyl trifluoromethanesulfonate 11a

Colorless oil. R_f = 0.33 (Petroleumether/EtOAc 9/1). Yield 74%. $[\alpha]_D^{25}$ = -48.6° (*c* = 0.11, CHCl₃). **¹H NMR** (400 MHz, CDCl₃): δ 0.85 (3H, t, *J* = 7.4 Hz, C*H₃*CH₂); 1.57-1.67 (2H, m, CH₃C*H₂*); 3.28-3.42 (~4H, m, CHN and NC*H₂*CHO); 3.45-3.49 (1H, m, CHCF₃); 3.60-3.64 (~1H, m, CH₂C*H₂*N); 3.78-3.82 (1H, m, CHOBn); 4.52 and 4.71 (2×1H, 2×d, *J* = 11.3 Hz, (*H*CH)O); 7.29-7.40 (5H, m, 5×CHₐᵣₒₘ). **¹⁹F NMR** (376 MHz, ref = CDCl₃): δ -75.26 (3F, s, CF₃S); -73.79 (3F, d, *J* = 4.4 Hz, CHCF₃). **¹³C NMR** (100 MHz, ref = CDCl₃): δ 10.7 (CH₃); 21.0 (*C*H₂CH₃); 49.5 (CHO*C*H₂N); 51.3 (q, *J* = 41.3 Hz, *C*HCF₃); 52.0 (CH₂*C*H₂N); 54.4 (*C*HN); 73.8 (CH₂O); 74.4 (CHOBn); 120.0 (q, *J* = 324.7 Hz, S*C*F₃); 122.3 (q, *J* = 276.2 Hz, CH*C*F₃); 128.1 (2×CHₐᵣₒₘ); 128.4 (CHₐᵣₒₘ); 128.7 (2×CHₐᵣₒₘ); 136.7 (Cquat,ₐᵣₒₘ). **IR (cm⁻¹)**: νS=O = 1125, 1161, 1130; νmax = 2972, 2884, 1391, 1288, 1047, 908, 741, 698. **MS (70 eV)**: *m/z* (%): 436 (M⁺+1, 100). **HRMS (ESI)**: *m/z* calcd for C₁₆H₂₃F₆N₂O₄S: 453.1277 [*M*+NH₄]⁺, found: 453.1297.
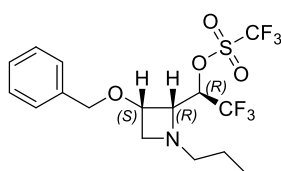
1-[(2*R*,3*S*)-1-Benzyl-3-benzyloxyazetidin-2-yl]-(1*R*)-2,2,2-trifluoroethyl trifluoromethanesulfonate 11b

Colorless oil. R_f = 0.23 (Petroleumether/EtOAc 14/1). Yield 71%. $[\alpha]_D^{25}$ = -35.9° (*c* = 0.16, CHCl₃). **¹H NMR** (400 MHz, CDCl₃): δ 3.14-3.15 (1H, m, CHN); 3.32-3.38 (2H, m, CHCF₃ and N(HCH)CH₂O); 3.49-3.59 (2H, m, N(HCH)CH₂O and CHOBn); 4.38 (1H, d, *J* = 11.3 Hz, (HCH)O); 4.56 (2H, s (broad), NCH₂Cquat,arom); 4.60 (1H, d, *J* = 11.3 Hz, (HCH)O); 7.22-7.41 (10H, m, 10×CHarom). **¹⁹F NMR** (376 MHz, ref = CDCl₃): δ -75.13 (3F, s, CF₃S); -73.82 (3F, d, *J* = 4.4 Hz, CHCF₃). **¹³C NMR** (100 MHz, ref = CDCl₃): δ 48.8 (CHOCH₂N); 51.4 (q, *J* = 41.4 Hz, CHCF₃); 53.7 (NCH₂Cquat,arom); 54.3 (CHN); 73.5 (CH₂O); 73.9 (CHOBn); 120.0 (q, *J* = 322.9 Hz, SCF₃); 122.2 (q, *J* = 275.4 Hz, CHCF₃); 128.2, 128.4, 128.7, 128.8 and 129.1 (10×CHarom); 133.7 and 136.7 (2×Cquat,arom). **IR (cm⁻¹)**: νS=O = 1225, 1148, 1117; νmax = 3034, 2934, 2878, 1387, 1285, 1016, 927, 905, 789, 735, 696, 685, 608. **MS (70 eV)**: *m/z* (%): 442 (100), 484 (M⁺+1, 18). **HRMS (ESI)**: *m/z* calcd for C₂₀H₂₀F₆NO₄S: 484.1012 [*M*+H]⁺, found: 484.1013.
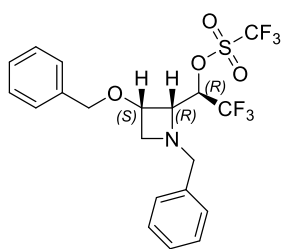
Synthesis of 3,4-disubstituted 2-(trifluoromethyl)pyrrolidines 10a-g

As a representative example, the synthesis of (2*R*,3*R*,4*S*)-3-benzylamino-1-isopropyl-4-phenoxy-2-(trifluoromethyl)pyrrolidine **10a** is described. To an ice-cooled solution of (2*S*,3*S*)-2-[(1*S*)-2,2,2-trifluoro-1-hydroxyethyl]-1-isopropyl-3-phenoxyazetidine **7a** (0.29 g, 1 mmol, 1 equiv) in dry CH₂Cl₂ (20 mL) was added *N,N,N',N'*-tetramethylnaphthalene-1,8-diamine (0.43 g, 2 mmol, 2 equiv) and triflic anhydride (0.31 g, 0.18 mL, 1.1 mmol, 1.1 equiv). Then, the resulting solution was stirred at 0 °C for 40 minutes. Subsequently, benzylamine (0.27 g, 0.27 mL, 2.5 mmol, 2.5 equiv) was added and the reaction mixture was stirred for another 3 days at reflux temperature. Afterward, H₂O was added and the aqueous phases were extracted with CH₂Cl₂ (3 × 20 mL). Drying (MgSO₄), filtration of the drying agent and evaporation of the solvent *in vacuo* afforded a crude reaction mixture, which was purified by means of column chromatography on silica gel to afford (2*R*,3*R*,4*S*)-3-benzylamino-1-isopropyl-4-phenoxy-2-(trifluoromethyl)pyrrolidine **10a** in 67% yield (0.25 g, 0.67 mmol) as a colorless oil.

(2*R*,3*R*,4*S*)-3-Benzylamino-1-isopropyl-4-phenoxy-2-(trifluoromethyl)pyrrolidine 10a

Colorless oil. R_f = 0.15 (Petroleumether/EtOAc 4/1). Yield 67%. $[\alpha]_D^{25}$ = +71.2° (*c* = 0.12, CH₂Cl₂). **¹H NMR** (400 MHz, CDCl₃): δ 0.93 (3H, d, *J* = 6.4 Hz, CH₃CHCH₃); 1.04 (3H, d, *J* = 6.8 Hz, CH₃CHCH₃); 2.20 (1H, s (broad), NH); 2.93 (1H, d×d, *J* = 11.0, 4.6 Hz, N(HCH)CHO); 3.12-3.22 (2H, m, N(HCH)CHO and NCH(CH₃)₂); 3.48-3.60 (2H, m, CHNCHO and CHCF₃); 3.84 (2H, s, NCH₂Cquat,arom); 4.70-4.73 (1H, m, CHO); 6.87-6.90 (2H, m, 2×CHarom); 6.94-6.98 (1H, m, CHarom); 7.22-7.34 (7H, m, 7×CHarom). **¹⁹F NMR** (376 MHz, ref = CDCl₃): -68.66 (3F, d, *J* = 8.5 Hz, CF₃). **¹³C NMR** (100 MHz, ref = CDCl₃): δ 14.9 and 21.1 (2×CH₃); 48.4 (CH₂NCHO); 50.9 (NCH(CH₃)₂); 52.3 (NCH₂Cquat,arom); 61.5 (CHNCHO); 62.1 (q, *J* = 27.9 Hz, CHCF₃); 74.7 (CHO); 115.8 (2×CHarom); 121.1 (CHarom); 126.3 (q, *J* = 283.8 Hz, CF₃); 127.0 (CHarom); 128.0 (2×CHarom); 128.4 (2×CHarom); 129.5 (2×CHarom); 140.1 (Cquat,arom); 157.8 (Cquat,arom). **IR (cm⁻¹)**: νmax = 2968, 1597, 1587, 1495, 1454, 1391, 1366, 1267, 1240, 1179, 1121, 1026, 918, 883, 750, 691, 669, 635, 590, 573, 509. **MS (70 eV)**: *m/z* (%): 379 (M⁺+1, 100). **HRMS (ESI)**: *m/z* calcd for C₂₁H₂₆F₃N₂O: 379.1992 [*M*+H]⁺; found: 379.1985.
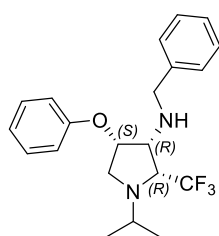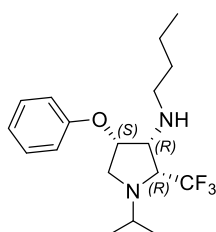
(2*R*,3*R*,4*S*)-3-Allylamino-1-isopropyl-4-phenoxy-2-(trifluoromethyl)pyrrolidine 10b

Yellow oil. R_f = 0.25 (Petroleumether/EtOAc 9/1). Yield 61%. $[\alpha]_D^{25}$ = +67.7° (*c* = 0.11, CH$_2$Cl$_2$). **^{1}H NMR** (400 MHz, CDCl$_3$): δ 0.96 (3H, d, *J* = 6.4 Hz, C**H**$_3$CHCH$_3$); 1.06 (3H, d, *J* = 6.8 Hz, CH$_3$CHC**H**$_3$); 1.93 (1H, s (broad), NH); 2.98 (1H, d×d, *J* = 11.0, 4.6 Hz, N(**H**CH)CHO); 3.12-3.22 (2H, m, N(HC**H**)CHO and NC**H**(CH$_3$)$_2$); 3.28-3.30 (2H, m, NC**H**$_2$CHCH$_2$); 3.49-3.59 (2H, m, C**H**NCHO and C**H**CF$_3$); 4.77-4.79 (1H, m, CHO); 5.06-5.10 (1H, m, (**H**CH)CHCH$_2$); 5.15-5.21 (1H, m, (HC**H**)CHCH$_2$); 5.86 (1H, d×d×d×d, *J* = 17.1, 10.2, 5.9, 5.9 Hz, CH$_2$C**H**CH$_2$N); 6.89-6.91 (2H, m, 2×CH$_{arom}$); 6.94-6.98 (1H, m, CH$_{arom}$); 7.26-7.30 (2H, m, 2×CH$_{arom}$). **^{19}F NMR** (376 MHz, ref = CDCl$_3$): -68.78 (3F, d, *J* = 8.6 Hz, CF$_3$). **^{13}C NMR** (100 MHz, ref = CDCl$_3$): δ 14.9 and 21.0 (2×CH$_3$); 48.5 (**C**H$_2$NCHO); 50.9 (N**C**H(CH$_3$)$_2$); 51.1 (CH$_2$**C**HCH$_2$N); 61.4 (**C**HNCHO); 62.1 (q, *J* = 28.0 Hz, **C**HCF$_3$); 74.7 (CHO); 115.8 (2×CH$_{arom}$); 116.3 (**C**H$_2$CHCH$_2$N); 121.2 (CH$_{arom}$); 126.2 (q, *J* = 283.8 Hz, CF$_3$); 129.5 (2×CH$_{arom}$); 136.7 (CH$_2$**C**HCH$_2$N); 157.7 (C$_{quat,arom}$). **IR (cm^{-1})**: v$_{max}$ = 2970, 1599, 1495, 1366, 1271, 1240, 1179, 1119, 1076, 1028, 995, 918, 883, 872, 752, 691, 629, 509. **MS (70 eV)**: *m/z* (%): 329 (M$^+$+1, 100). **HRMS (ESI)**: *m/z* calcd for C$_{17}$H$_{24}$F$_3$N$_2$O: 329.1835 [*M*+H]$^+$; found: 329.1842.
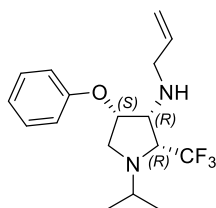
(2*R*,3*R*,4*S*)-3-Butylamino-1-isopropyl-4-phenoxy-2-(trifluoromethyl)pyrrolidine 10c

Colorless oil. R_f = 0.26 (Petroleumether/EtOAc 4/1). Yield 78%. $[\alpha]_D^{25}$ = +62.6° (*c* = 0.18, CH$_2$Cl$_2$). **^{1}H NMR** (400 MHz, CDCl$_3$): δ 0.86 (3H, t, *J* = 7.3 Hz, C**H**$_3$CH$_2$); 0.96 (3H, d, *J* = 6.4 Hz, C**H**$_3$CHCH$_3$); 1.06 (3H, d, *J* = 6.7 Hz, CH$_3$CHC**H**$_3$); 1.25-1.35 (2H, m, CH$_3$C**H**$_2$); 1.40-1.48 (2H, m, CH$_3$CH$_2$C**H**$_2$); 1.71 (1H, s (broad), NH); 2.57-2.66 (2H, m, CH$_2$C**H**$_2$N); 2.98 (1H, d×d, *J* = 11.0, 4.6 Hz, N(**H**CH)CHO); 3.12-3.22 (2H, m, N(HC**H**)CHO and NC**H**(CH$_3$)$_2$); 3.46-3.50 (1H, m, C**H**NCHO); 3.56 (1H, ~p, *J* = 8.7 Hz, C**H**CF$_3$); 4.79-4.82 (1H, m, CHO); 6.89-6.97 (3H, m, 3×CH$_{arom}$); 7.25-7.29 (2H, m, 2×CH$_{arom}$). **^{19}F NMR** (376 MHz, ref = CDCl$_3$): -68.78 (3F, d, *J* = 8.7 Hz, CF$_3$). **^{13}C NMR** (100 MHz, ref = CDCl$_3$): δ 13.9 (**C**H$_3$CH$_2$); 14.9 (**C**H$_3$CHCH$_3$); 20.3 (CH$_3$**C**H$_2$); 21.0 (CH$_3$CH**C**H$_3$); 32.5 (CH$_3$CH$_2$**C**H$_2$); 48.5 (**C**H$_2$NCHO); 48.6 (CH$_2$**C**H$_2$N); 50.9 (N**C**H(CH$_3$)$_2$); 62.1 (q, *J* = 28.0 Hz, **C**HCF$_3$); 62.7 (**C**HNCHO); 74.6 (CHO); 115.8 (2×CH$_{arom}$); 121.1 (CH$_{arom}$); 126.2 (q, *J* = 283.9 Hz, CF$_3$); 129.4 (2×CH$_{arom}$); 157.8 (C$_{quat,arom}$). **IR (cm^{-1})**: v$_{max}$ = 2961, 2930, 1599, 1587, 1494, 1366, 1271, 1240, 1180, 1140, 1115, 1076, 1059, 1028, 881, 750, 691, 631, 507. **MS (70 eV)**: *m/z* (%): 345 (M$^+$+1, 100). **HRMS (ESI)**: *m/z* calcd for C$_{18}$H$_{28}$F$_3$N$_2$O: 345.2148 [*M*+H]$^+$; found: 345.2152.

(2*R*,3*R*,4*S*)-3-(*N*-Benzyl-*N*-methylamino)-1-isopropyl-4-phenoxy-2-(trifluoromethyl)pyrrolidine 10d

Colorless oil. R_f = 0.20 (Petroleumether/EtOAc 9/1). Yield 65%. $[\alpha]_D^{25}$ = +20.3° (*c* = 0.16, CH$_2$Cl$_2$). **^{1}H NMR** (400 MHz, CDCl$_3$): δ 0.97 (3H, d, *J* = 6.4 Hz, C**H**$_3$CHCH$_3$); 1.08 (3H, d, *J* = 6.8 Hz, CH$_3$CHC**H**$_3$); 2.29 (1H, s (broad), NH); 3.07-3.12 (2H, m, N(**H**CH)CHO and C**H**NCHO); 3.19-3.23 (2H, m, N(HC**H**)CHO and NC**H**(CH$_3$)$_2$); 3.61 (1H, d, *J* = 13.0 Hz, N(**H**CH)C$_{quat,arom}$); 3.66 (1H, ~p, *J* = 8.0 Hz, C**H**CF$_3$); 3.79 (1H, d, *J* = 13.0 Hz, N(HC**H**)C$_{quat,arom}$); 4.84-4.86 (1H, m, CHO); 6.89-6.96 (3H, m, 3×CH$_{arom}$); 7.22-7.36 (7H, m, 7×CH$_{arom}$). **^{19}F NMR** (376 MHz, ref = CDCl$_3$): -68.87 (3F, d, *J* = 8.0 Hz, CF$_3$). **^{13}C NMR** (100 MHz, ref = CDCl$_3$): δ 14.4 and 21.2 (2×CH$_3$); 40.6 (CH$_3$N); 48.7 (**C**H$_2$NCHO); 50.9 (N**C**H(CH$_3$)$_2$); 61.3 (N**C**H$_2$C$_{quat,arom}$); 62.7 (q, *J* = 28.3 Hz, **C**HCF$_3$); 68.7 (**C**HNCHO); 75.8 (CHO); 115.7 (2×CH$_{arom}$); 121.0 (CH$_{arom}$); 126.0 (q, *J* = 283.6 Hz, CF$_3$); 126.9 (CH$_{arom}$); 128.1 (2×CH$_{arom}$); 128.9 (2×CH$_{arom}$); 129.5 (2×CH$_{arom}$); 138.9 (C$_{quat,arom}$); 157.5 (C$_{quat,arom}$). **IR (cm^{-1})**: v$_{max}$
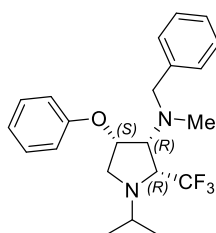
= 2968, 1599, 1587, 1495, 1454, 1391, 1366, 1277, 1240, 1202, 1179, 1119, 1076, 1059, 1028, 934, 908, 885, 908, 750, 733, 691, 669, 642, 507. **MS (70 eV)**: *m/z* (%): 393 (M$^+$+1, 100). **HRMS (ESI)**: *m/z* calcd for $C_{22}H_{28}F_3N_2O$: 393.2148 [*M*+H]$^+$; found: 393.2153.

(2*R*,3*R*,4*S*)-3-[(2-Hydroxyethyl)amino]-1-isopropyl-4-phenoxy-2-(trifluoromethyl)pyrrolidine 10e
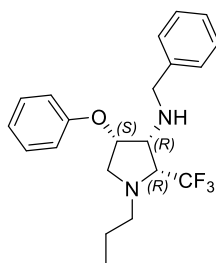
Brown oil. R_f = 0.05 (Petroleumether/EtOAc 19/1). Yield 79%. $[\alpha]_D^{25}$ = +68.2° (*c* = 0.1, CH$_2$Cl$_2$). **^{1}H NMR** (400 MHz, CDCl$_3$): δ 0.97 (3H, d, *J* = 6.4 Hz, C<u>H</u>$_3$CHCH$_3$); 1.07 (3H, d, *J* = 6.8 Hz, CH$_3$CHC<u>H</u>$_3$); 2.24 (2H, s (broad), NH and OH); 2.76 (1H, d×d×d, *J* = 12.3, 6.2, 4.8 Hz, (<u>H</u>CH)NCH$_2$O); 2.88 (1H, d×d×d, *J* = 12.3, 5.5, 4.4 Hz, (HC<u>H</u>)NCH$_2$O); 3.00 (1H, d×d, *J* = 11.0, 4.7 Hz, N(<u>H</u>CH)CHO); 3.13-3.23 (2H, m, N(HC<u>H</u>)CHO and NC<u>H</u>(CH$_3$)$_2$); 3.49-3.61 (4H, m, C<u>H</u>NCHO, CHCF$_3$ and CH$_2$O); 4.77-4.79 (1H, m, CHO); 6.89-6.91 (2H, m, 2×CH$_{arom}$); 6.95-6.99 (1H, m, CH$_{arom}$); 7.26-7.30 (2H, m, 2×CH$_{arom}$). **^{19}F NMR** (376 MHz, ref = CDCl$_3$): -68.62 (3F, d, *J* = 8.5 Hz, CF$_3$). **^{13}C NMR** (100 MHz, ref = CDCl$_3$): δ 14.6 and 21.1 (2×CH$_3$); 48.2 (<u>C</u>H$_2$NCHO); 50.2 (<u>C</u>H$_2$NCH$_2$O); 50.7 (N<u>C</u>H(CH$_3$)$_2$); 60.9 (CH$_2$O); 62.1 (<u>C</u>HNCHO); 62.2 (q, *J* = 27.9 Hz, <u>C</u>HCF$_3$); 74.9 (CHO); 115.7 (2×CH$_{arom}$); 121.3 (CH$_{arom}$); 126.1 (q, *J* = 283.4 Hz, CF$_3$); 129.6 (2×CH$_{arom}$); 157.6 (C$_{quat,arom}$). **IR (cm^{-1})**: ν$_{NH/OH}$ = 3350; ν$_{max}$ = 2968, 2932, 1597, 1587, 1495, 1391, 1366, 1269, 1240, 1179, 1121, 1028, 922, 881, 866, 804, 752, 692, 669, 633, 507. **MS (70 eV)**: *m/z* (%): 215 (M$^+$+1, 100), 333 (M$^+$+1, 65). **HRMS (ESI)**: *m/z* calcd for $C_{16}H_{24}F_3N_2O_2$: 333.1784 [*M*+H]$^+$; found: 333.1776.
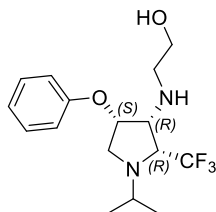
(2*R*,3*R*,4*S*)-3-Benzylamino-4-phenoxy-1-propyl-2-(trifluoromethyl)pyrrolidine 10f

Colorless oil. R_f = 0.32 (Petroleumether/EtOAc 4/1). Yield 75%. $[\alpha]_D^{25}$ = +66.9° (*c* = 0.1, CH$_2$Cl$_2$). **^{1}H NMR** (400 MHz, CDCl$_3$): δ 0.85 (3H, t, *J* = 7.4 Hz, CH$_3$); 1.38-1.49 (2H, m, CH$_3$C<u>H</u>$_2$); 2.32 (1H, s (broad), NH); 2.52 (1H, d×d×d, *J* = 12.1, 7.9, 5.6 Hz, CH$_2$(<u>H</u>CH)N); 2.64 (1H, d×d, *J* = 10.9, 4.1 Hz, N(<u>H</u>CH)CHO); 2.80 (1H, d×d×d, *J* = 12.1, 8.5, 7.9 Hz, CH$_2$(HC<u>H</u>)N); 3.35 (1H, ~d, *J* = 10.9 Hz, N(HC<u>H</u>)CHO); 3.39 (1H, ~p, *J* = 9.1 Hz, CHCF$_3$); 3.64 (1H, d×d, *J* = 9.1, 5.1 Hz, C<u>H</u>NCHO); 3.83 (1H, d, *J* = 13.5 Hz, N(<u>H</u>CH)C$_{quat,arom}$); 3.87 (1H, d, *J* = 13.5 Hz, N(HC<u>H</u>)C$_{quat,arom}$); 4.72-4.74 (1H, m, CHO); 6.89-6.91 (2H, m, 2×CH$_{arom}$); 6.95-6.99 (1H, m, CH$_{arom}$); 7.23-7.34 (7H, m, 7×CH$_{arom}$). **^{19}F NMR** (376 MHz, ref = CDCl$_3$): -68.72 (3F, s (broad), CF$_3$). **^{13}C NMR** (100 MHz, ref = CDCl$_3$): δ 11.4 (CH$_3$); 20.7 (CH$_3$<u>C</u>H$_2$); 52.3 (N<u>C</u>H$_2$C$_{quat,arom}$); 55.4 (<u>C</u>H$_2$NCHO); 57.9 (CH$_2$<u>C</u>H$_2$N); 60.8 (<u>C</u>HNCHO); 65.2 (q, *J* = 27.8 Hz, <u>C</u>HCF$_3$); 74.7 (CHO); 116.0 (2×CH$_{arom}$); 121.3 (CH$_{arom}$); 126.1 (q, *J* = 283.3 Hz, CF$_3$); 127.1 (CH$_{arom}$); 128.0 (2×CH$_{arom}$); 128.4 (2×CH$_{arom}$); 129.5 (2×CH$_{arom}$); 139.9 (C$_{quat,arom}$); 157.7 (C$_{quat,arom}$). **IR (cm^{-1})**: ν$_{max}$ = 2968, 2814, 1597, 1585, 1487, 1452, 1273, 1229, 1175, 1153, 1136, 1115, 1090, 1080, 1061, 1049, 1026, 883, 756, 738, 694, 644. **MS (70 eV)**: *m/z* (%): 379 (M$^+$+1, 100). **HRMS (ESI)**: *m/z* calcd for $C_{21}H_{26}F_3N_2O$: 379.1992 [*M*+H]$^+$; found: 379.1991.

(2*R*,3*R*,4*S*)-3-Benzylamino-1-cyclohexyl-4-phenoxy-2-(trifluoromethyl)pyrrolidine 10g
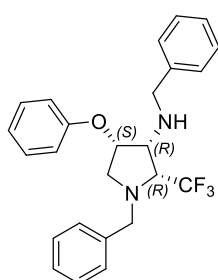
Yellow oil. R_f = 0.27 (Petroleumether/EtOAc 9/1). Yield 89%. $[\alpha]_D^{25}$ = +64.1° (*c* = 0.25, CH$_2$Cl$_2$). **^{1}H NMR** (400 MHz, CDCl$_3$): δ 0.98-1.28 (5H, m, (C$\underline{H}_2$)$_5$CHN); 1.59-1.81 (5H, m, (C$\underline{H}_2$)$_5$CHN); 2.20 (1H, s (broad), NH); 2.64-2.71 (1H, m, (CH$_2$)$_5$C$\underline{H}$N); 3.01 (1H, d×d, *J* = 11.0, 4.7 Hz, N($\underline{H}$CH)CHO); 3.18 (1H, ~d, *J* = 11.0 Hz, N(HC$\underline{H}$)CHO); 3.48-3.51 (1H, m, C$\underline{H}$NCHO); 3.65 (1H, ~p, *J* = 8.8 Hz, C$\underline{H}$CF$_3$); 3.84 (2H, s, NC$\underline{H}_2$C$_{quat,arom}$); 4.69-4.72 (1H, m, CHO); 6.86-6.88 (2H, m, 2×CH$_{arom}$); 6.94-6.97 (1H, m, CH$_{arom}$); 7.21-7.34 (7H, m, 7×CH$_{arom}$). **^{19}F NMR** (376 MHz, ref = CDCl$_3$): -68.52 (3F, d, *J* = 8.8 Hz, CF$_3$). **^{13}C NMR** (100 MHz, ref = CDCl$_3$): δ 25.5, 25.6, 26.08, 26.11 and 31.7 ((CH$_2$)$_5$CHN); 49.8 (CH$_2$NCHO); 52.3 (NCH$_2$C$_{quat,arom}$); 59.8 (CHN(CH$_2$)$_5$); 61.46 (CHNCHO); 61.51 (q, *J* = 27.9 Hz, CHCF$_3$); 74.7 (CHO); 115.8 (2×CH$_{arom}$); 121.1 (CH$_{arom}$); 126.3 (q, *J* = 284.2 Hz, CF$_3$); 127.1 (CH$_{arom}$); 128.0 (2×CH$_{arom}$); 128.4 (2×CH$_{arom}$); 129.5 (2×CH$_{arom}$); 140.1 (C$_{quat,arom}$); 157.8 (C$_{quat,arom}$). **IR (cm^{-1})**: v$_{max}$ = 2928, 2855, 1597, 1587, 1495, 1452, 1238, 1121, 1043, 1026, 995, 910, 891, 750, 733, 691, 648, 627, 507. **MS (70 eV)**: *m/z* (%): 419 (M$^+$+1, 100). **HRMS (ESI)**: *m/z* calcd for C$_{24}$H$_{30}$F$_3$N$_2$O: 419.2305 [*M*+H]$^+$; found: 419.2306.
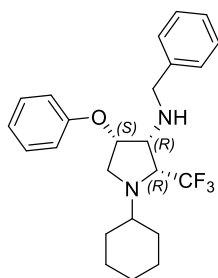
Synthesis of 3,4-disubstituted 2-(trifluoromethyl)pyrrolidines 10h-n

As a representative example, the synthesis of (2*R*,3*R*,4*S*)-1-benzyl-3-benzylamino-4-phenoxy-2-(trifluoromethyl)pyrrolidine **10h** is described. To a solution of 1-[(2*R*,3*S*)-1-benzyl-3-phenoxyazetidin-2-yl]-(1*S*)-2,2,2-trifluoroethyl trifluoromethanesulfonate **9b** (0.47 g, 1 mmol, 1 equiv) in dry CH$_3$CN (20 mL) was added benzylamine (0.27 g, 0.27 mL, 2.5 mmol, 2.5 equiv). Then, the resulting solution was stirred at reflux temperature for 2 hours and, afterward, the reaction mixture was cooled to room temperature. Evaporation of the solvent and the excess of benzylamine *in vacuo* afforded (2*R*,3*R*,4*S*)-1-benzyl-3-benzylamino-4-phenoxy-2-(trifluoromethyl)pyrrolidine **10h** in 96% yield (0.41 g, 0.96 mmol) as a colorless oil, which was purified by means of column chromatography on silica gel to provide an analytically pure sample.

(2*R*,3*R*,4*S*)-1-Benzyl-3-benzylamino-4-phenoxy-2-(trifluoromethyl)pyrrolidine 10h

White crystals. Mp 124 °C. R_f = 0.16 (Petroleumether/EtOAc 9/1). Yield 96%. $[\alpha]_D^{25}$ = +79.4° (*c* = 0.22, CH$_2$Cl$_2$). **^{1}H NMR** (400 MHz, CDCl$_3$): δ 2.29 (1H, s (broad), NH); 2.66 (1H, d×d, *J* = 11.0, 4.1 Hz, N($\underline{H}$CH)CHO); 3.35 (1H, ~d, *J* = 11.0 Hz, N(HC$\underline{H}$)CHO); 3.55-3.64 (2H, m, CHCF$_3$ and C$\underline{H}$NCHO); 3.68 (1H, d, *J* = 13.7 Hz, C$_{quat,arom}$($\underline{H}$CH)NCHCF$_3$); 3.81 (1H, d, *J* = 13.6 Hz, C$_{quat,arom}$($\underline{H}$CH)NCHCHCF$_3$); 3.86 (1H, d, *J* = 13.6 Hz, C$_{quat,arom}$(HC$\underline{H}$)NCHCHCF$_3$); 4.15 (1H, d, *J* = 13.7 Hz, C$_{quat,arom}$(HC$\underline{H}$)NCHCF$_3$); 4.66-4.68 (1H, m, CHO); 6.84-6.86 (2H, m, 2×CH$_{arom}$); 6.94-6.96 (1H, m, CH$_{arom}$); 7.22-7.34 (12H, m, 12×CH$_{arom}$). **^{19}F NMR** (376 MHz, ref = CDCl$_3$): -68.62 (3F, d, *J* = 8.2 Hz, CF$_3$). **^{13}C NMR** (100 MHz, ref = CDCl$_3$): δ 52.3 (C$_{quat,arom}$CH$_2$NCHCHCF$_3$); 55.3 (CH$_2$NCHO); 59.3 (C$_{quat,arom}$CH$_2$NCHCF$_3$); 61.1 (CHNCHO); 64.2 (q, *J* = 27.7 Hz, CHCF$_3$); 74.6 (CHO); 116.0 (2×CH$_{arom}$); 121.3 (CH$_{arom}$); 126.2 (q, *J* = 283.4 Hz, CF$_3$); 127.1 (CH$_{arom}$); 127.2 (CH$_{arom}$); 128.0 (2×CH$_{arom}$); 128.39 (2×CH$_{arom}$); 128.41 (2×CH$_{arom}$); 128.5 (2×CH$_{arom}$); 129.5 (2×CH$_{arom}$); 137.6 (C$_{quat,arom}$); 140.0 (C$_{quat,arom}$); 157.7 (C$_{quat,arom}$). **IR (cm^{-1})**: v$_{max}$ = 1597, 1584, 1485, 1450, 1368, 1294, 1273, 1265, 1248, 1136, 1115, 1061, 1047, 1026, 889, 758, 738, 696, 646, 627, 507. **MS (70 eV)**: *m/z* (%): 427 (M$^+$+1, 100). **HRMS (ESI)**: *m/z* calcd for C$_{25}$H$_{26}$F$_3$N$_2$O: 427.1992 [*M*+H]$^+$; found: 427.1990.
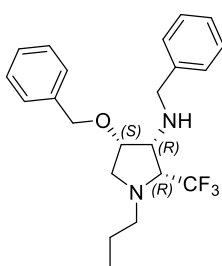
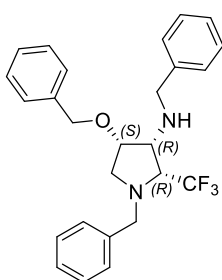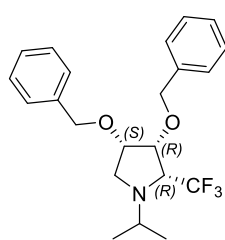## (2*R*,3*R*,4*S*)-3-Benzylamino-4-benzyloxy-1-isopropyl-2-(trifluoromethyl)pyrrolidine 10i

Colorless oil. R_f = 0.28 (Petroleumether/EtOAc 9/1). Yield 99%. $[\alpha]_D^{25}$ = +54.4° (*c* = 0.24, CHCl$_3$). **¹H NMR** (400 MHz, CDCl$_3$): δ 0.90 (3H, d, *J* = 6.4 Hz, C<u>H</u>$_3$CHCH$_3$); 1.09 (3H, d, *J* = 6.7 Hz, CH$_3$CHC<u>H</u>$_3$); 2.13 (1H, s (broad), NH); 2.69 (1H, d×d, *J* = 10.7, 4.5 Hz, N(<u>H</u>CH)CHO); 3.13-3.22 (2H, m, N(<u>H</u>CH)CHO and C<u>H</u>(CH$_3$)$_2$); 3.44 (1H, ~p, *J* = 8.7 Hz, CHCF$_3$); 3.46 (1H, d×d, *J* = 8.7, 5.1 Hz, C<u>H</u>NCHO); 3.73 (1H, d, *J* = 13.8 Hz, C$_{quat,arom}$(<u>H</u>CH)N); 3.77 (1H, d, *J* = 13.8 Hz, C$_{quat,arom}$(HC<u>H</u>)N); 3.92-3.94 (1H, m, CHO); 4.43 (1H, d, *J* = 12.4 Hz, (<u>H</u>CH)O); 4.70 (1H, d, *J* = 12.4 Hz, (HC<u>H</u>)O); 7.23-7.36 (10H, m, 10×CH$_{arom}$). **¹⁹F NMR** (376 MHz, ref = CDCl$_3$): -68.71 (3F, d, *J* = 8.7 Hz, CF$_3$). **¹³C NMR** (100 MHz, ref = CDCl$_3$): δ 14.4 and 21.2 ((<u>C</u>H$_3$)$_2$CH); 47.6 (<u>C</u>H$_2$NCHO); 50.7 ((CH$_3$)$_2$<u>C</u>H); 52.3 (C$_{quat,arom}$<u>C</u>H$_2$N); 61.4 (<u>C</u>HNCHO); 62.1 (q, *J* = 27.7 Hz, <u>C</u>HCF$_3$); 71.5 (CH$_2$O); 75.9 (CHO); 126.3 (q, *J* = 283.4 Hz, CF$_3$); 126.9, 127.5, 127.9, 128.3 (10×CH$_{arom}$); 138.5 (C$_{quat,arom}$); 140.4 (C$_{quat,arom}$). **IR (cm⁻¹)**: ν$_{max}$ = 2968, 2916, 2872, 1454, 1269, 1121, 1069, 1028, 733, 696, 635. **MS (70 eV)**: *m/z* (%): 393 (M⁺+1, 100). **HRMS (ESI)**: *m/z* calcd for C$_{22}$H$_{28}$F$_3$N$_2$O: 393.2148 [*M*+H]⁺; found: 393.2145.
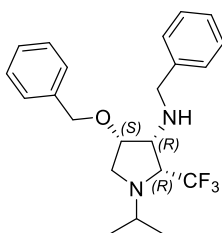
(2*R*,3*R*,4*S*)-3-Benzylamino-4-benzyloxy-1-propyl-2-(trifluoromethyl)pyrrolidine 10j

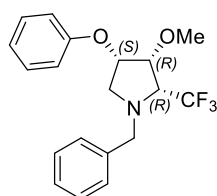Colorless oil. R_f = 0.23 (Petroleumether/EtOAc 9/1). Yield 99%. $[\alpha]_D^{25}$ = +27.2° (*c* = 0.25, CHCl$_3$). **¹H NMR** (400 MHz, CDCl$_3$): δ 0.88 (3H, t, *J* = 7.4 Hz, CH$_3$); 1.40-1.54 (2H, m, C<u>H</u>$_2$CH$_3$); 2.21 (1H, s (broad), NH); 2.41 (1H, d×d, *J* = 10.8, 4.0 Hz, N(<u>H</u>CH)CHO); 2.47 (1H, d×d×d, *J* = 11.9, 8.6, 5.2 Hz, CH$_2$(<u>H</u>CH)N); 2.81 (1H, d×d×d, *J* = 11.9, 9.1, 7.5 Hz, CH$_2$(HC<u>H</u>)N); 3.28 (1H, ~p, *J* = 9.1 Hz, CHCF$_3$); 3.36 (1H, ~d, *J* = 10.8 Hz, N(HC<u>H</u>)CHO); 3.46 (1H, d×d, *J* = 9.1, 5.1 Hz, C<u>H</u>NCHO); 3.74 (1H, d, *J* = 13.6 Hz, C$_{quat,arom}$(<u>H</u>CH)N); 3.79 (1H, d, *J* = 13.6 Hz, C$_{quat,arom}$(HC<u>H</u>)N); 3.95-3.97 (1H, m, CHO); 4.44 (1H, d, *J* = 12.3 Hz, (<u>H</u>CH)O); 4.71 (1H, d, *J* = 12.3 Hz, (HC<u>H</u>)O); 7.23-7.35 (10H, m, 10×CH$_{arom}$). **¹⁹F NMR** (376 MHz, ref = CDCl$_3$): -68.65 (3F, d, *J* = 9.1 Hz, CF$_3$). **¹³C NMR** (100 MHz, ref = CDCl$_3$): δ 11.5 (CH$_3$); 20.7 (<u>C</u>H$_2$CH$_3$); 52.2 (C$_{quat,arom}$<u>C</u>H$_2$NCHCHCF$_3$); 55.0 (<u>C</u>H$_2$NCHO); 58.2 (CH$_2$<u>C</u>H$_2$N); 60.6 (<u>C</u>HNCHO); 65.3 (q, *J* = 27.8 Hz, <u>C</u>HCF$_3$); 71.5 (CH$_2$O); 75.6 (CHO); 126.1 (q, *J* = 283.0 Hz, CF$_3$); 127.1, 127.56, 127.59, 128.0, 128.37, 128.40 (10×CH$_{arom}$); 138.3 (C$_{quat,arom}$); 139.8 (C$_{quat,arom}$). **IR (cm⁻¹)**: ν$_{max}$ = 2963, 2932, 2874, 2810, 1454, 1271, 1139, 1121, 1088, 1065, 1028, 733, 696, 638. **MS (70 eV)**: *m/z* (%): 393 (M⁺+1, 100). **HRMS (ESI)**: *m/z* calcd for C$_{22}$H$_{28}$F$_3$N$_2$O: 393.2148 [*M*+H]⁺; found: 393.2145.

(2*R*,3*R*,4*S*)-1-Benzyl-3-benzylamino-4-benzyloxy-2-(trifluoromethyl)pyrrolidine 10k

Colorless oil. R_f = 0.06 (Petroleumether/EtOAc 9/1). Yield 99%. $[\alpha]_D^{25}$ = +65.6° (*c* = 0.19, CHCl$_3$). **¹H NMR** (400 MHz, CDCl$_3$): δ 2.22 (1H, s (broad), NH); 2.39 (1H, d×d, *J* = 10.9, 3.8 Hz, N(<u>H</u>CH)CHO); 3.15 (1H, ~d, *J* = 10.9 Hz, N(HC<u>H</u>)CHO); 3.40-3.50 (2H, m, CHCF$_3$ and C<u>H</u>NCHO); 3.59 (1H, d, *J* = 13.5 Hz, C$_{quat,arom}$(<u>H</u>CH)NCHCF$_3$); 3.70 (1H, d, *J* = 13.6 Hz, C$_{quat,arom}$(<u>H</u>CH)NCHCHCF$_3$); 3.78 (1H, d, *J* = 13.6 Hz, C$_{quat,arom}$(HC<u>H</u>)NCHCHCF$_3$); 3.88-3.90 (1H, m, CHO); 4.19 (1H, d, *J* = 13.7 Hz, C$_{quat,arom}$(HC<u>H</u>)NCHCF$_3$); 4.35 (1H, d, *J* = 12.3 Hz, (<u>H</u>CH)O); 4.61 (1H, d, *J* = 12.3 Hz, (HC<u>H</u>)O); 7.22-7.34 (15H, m, 15×CH$_{arom}$). **¹⁹F NMR** (376 MHz, ref = CDCl$_3$): -68.63 (3F, d, *J* = 8.7 Hz, CF$_3$). **¹³C NMR** (100 MHz, ref = CDCl$_3$): δ 52.2 (C$_{quat,arom}$<u>C</u>H$_2$NCHCHCF$_3$); 54.8 (<u>C</u>H$_2$NCHO); 59.7 (C$_{quat,arom}$<u>C</u>H$_2$NCHCF$_3$); 61.1 (<u>C</u>HNCHO); 64.4 (q, *J* = 27.5 Hz, <u>C</u>HCF$_3$); 71.3 (CH$_2$O); 75.5 (CHO); 126.2 (q, *J* = 282.8 Hz, CF$_3$);

127.0, 127.2, 127.4, 127.5, 127.9, 128.3, 128.4 and 128.6 (15×CH_{arom}); 138.0 ($C_{quat,arom}$); 138.4 ($C_{quat,arom}$); 140.4 ($C_{quat,arom}$). **IR (cm⁻¹)**: v_{max} = 3028, 2868, 2805, 1495, 1454, 1273, 1140, 1119, 1063, 1028, 735, 696, 629. **MS (70 eV)**: *m/z* (%): 441 (M⁺+1, 100). **HRMS (ESI)**: *m/z* calcd for $C_{26}H_{28}F_3N_2O$: 441.2148 [*M*+H]⁺; found: 441.2152.

(2*R*,3*R*,4*S*)-3,4-Dibenzyloxy-1-isopropyl-2-(trifluoromethyl)pyrrolidine 10l

Colorless oil. R_f = 0.41 (Petroleumether/EtOAc 9/1). Yield 69%. $[\alpha]_D^{25}$ = -8.3° (*c* = 0.16, CHCl₃). **¹H NMR** (400 MHz, CDCl₃): δ 0.87 (3H, d, *J* = 6.4 Hz, C$\underline{H}$₃CHCH₃); 1.09 (3H, d, *J* = 6.8 Hz, CH₃CHC$\underline{H}$₃); 2.83 (1H, d×d, *J* = 10.6, 5.8 Hz, N($\underline{H}$CH)CHO); 3.07-3.17 (2H, m, N(HC$\underline{H}$)CHO and C$\underline{H}$(CH₃)₂); 3.44-3.52 (1H, m, CHCF₃); 3.87-3.91 (1H, m, C$\underline{H}$OCH₂N); 4.09 (1H, d×d, *J* = 7.0, 4.4 Hz, C$\underline{H}$OCHCF₃); 4.63 (1H, d, *J* = 12.4 Hz, $C_{quat,arom}$($\underline{H}$CH)O); 4.674 (1H, d, *J* = 12.0 Hz, $C_{quat,arom}$($\underline{H}$CH)O); 4.675 (1H, d, *J* = 12.4 Hz, $C_{quat,arom}$(HC$\underline{H}$)O); 4.71 (1H, d, *J* = 12.0 Hz, $C_{quat,arom}$(HC$\underline{H}$)O); 7.25-7.37 (10H, m, 10×CH_{arom}). **¹⁹F NMR** (376 MHz, ref = CDCl₃): -68.82 (3F, d, *J* = 7.7 Hz, CF₃). **¹³C NMR** (100 MHz, ref = CDCl₃): δ 13.9 and 21.7 (($\underline{C}$H₃)₂CH); 47.1 ($\underline{C}$H₂NCHO); 50.6 ((CH₃)₂$\underline{C}$H); 62.0 (q, *J* = 28.8 Hz, $\underline{C}$HCF₃); 72.0 and 73.3 (2×$C_{quat,arom}$$\underline{C}$H₂O); 77.0 ($\underline{C}$HOCH₂N); 78.6 ($\underline{C}$HOCHCF₃); 125.7 (q, *J* = 282.2 Hz, CF₃); 127.56, 127.60, 127.63, 128.30 and 128.33 (10×CH_{arom}); 138.0 ($C_{quat,arom}$); 138.4 ($C_{quat,arom}$). **IR (cm⁻¹)**: v_{max} = 2968, 2934, 2876, 1680, 1454, 1364, 1134, 1028, 735, 696. **MS (70 eV)**: *m/z* (%): 393 (M⁺+1, 100). **HRMS (ESI)**: *m/z* calcd for $C_{22}H_{27}F_3NO_2$: 394.1988 [*M*+H]⁺; found: 394.2001.

(2*R*,3*R*,4*S*)-1-Benzyl-3-methoxy-4-phenoxy-2-(trifluoromethyl)pyrrolidine 10m

Colorless oil. R_f = 0.25 (Petroleumether/EtOAc 9/1). Yield 91%. $[\alpha]_D^{25}$ = +32.8° (*c* = 0.12, CH₂Cl₂). **¹H NMR** (400 MHz, CDCl₃): δ 2.84 (1H, d×d, *J* = 11.0, 5.6 Hz, N($\underline{H}$CH)CHO); 3.25 (1H, d×d, *J* = 11.0, 4.3 Hz, N(HC$\underline{H}$)CHO); 3.45 (3H, s, CH₃); 3.63 (1H, q×d, J_{HF} = 7.7, *J* = 7.3 Hz, CHCF₃); 3.70 and 4.14 (2×1H, 2×d, *J* = 13.8 Hz, $C_{quat,arom}$($\underline{H}$CH)N); 4.15 (1H, d×d, *J* = 7.3, 4.6 Hz, CHOMe); 4.70-4.74 (1H, m, CHOPh); 6.89-6.96 (3H, m, 3×CH_{arom}); 7.23-7.32 (7H, m, 7×CH_{arom}). **¹⁹F NMR** (376 MHz, ref = CDCl₃): -68.86 (3F, d, *J* = 7.7 Hz, CF₃). **¹³C NMR** (100 MHz, ref = CDCl₃): δ 54.4 ($\underline{C}$H₂NCHO); 59.3 ($C_{quat,arom}$$\underline{C}$H₂N); 59.9 (CH₃); 64.4 (q, *J* = 29.0 Hz, $\underline{C}$HCF₃); 74.9 (CHOPh); 80.5 (CHOMe); 116.0 (2×CH_{arom}); 121.4 (CH_{arom}); 125.6 (q, *J* = 282.1 Hz, CF₃); 127.3 (CH_{arom}); 128.5, 128.6 and 129.5 (6×CH_{arom}); 137.5 ($C_{quat,arom}$); 157.8 ($C_{quat,arom}$). **IR (cm⁻¹)**: v_{max} = 2936, 1597, 1493, 1373, 1283, 1238, 1134, 1074, 1051, 1016, 752, 737, 691, 662. **MS (70 eV)**: *m/z* (%): 352 (M⁺+1, 100). **HRMS (ESI)**: *m/z* calcd for $C_{19}H_{21}F_3NO_2$: 352.1519 [*M*+H]⁺; found: 352.1536.

(2S,3R,4S)-1-Benzyl-4-phenoxy-3-phenylthio-2-(trifluoromethyl)pyrrolidine 10n

White crystals. Mp 120 °C. R_f = 0.21 (Petroleumether/EtOAc 9/1). Yield 45%. $[\alpha]_D^{25}$ = +132.0° (c = 0.15, CH$_2$Cl$_2$). **^{1}H NMR** (400 MHz, CDCl$_3$): δ 2.79 (1H, d×d, J = 10.8, 4.2 Hz, N(<u>H</u>CH)CHO); 3.26 (1H, ~d, J = 10.8 Hz, N(HC<u>H</u>)CHO); 3.75 (1H, d, J = 13.6 Hz, C$_{quat,arom}$(<u>H</u>CH)N); 3.76-3.84 (1H, m, CHCF$_3$); 3.98 (1H, d×d, J = 9.3, 5.0 Hz, CHS); 4.22 (1H, d, J = 13.6 Hz, C$_{quat,arom}$(HC<u>H</u>)N); 4.84-4.86 (1H, m, CHO); 6.86-6.89 (2H, m, 2×CH$_{arom}$); 6.94-6.96 (1H, m, CH$_{arom}$); 7.22-7.31 (10H, m, 10×CH$_{arom}$); 7.40-7.43 (2H, m, 2×CH$_{arom}$). **^{19}F NMR** (376 MHz, ref = CDCl$_3$): -69.00 (3F, d, J = 8.1 Hz, CF$_3$). **^{13}C NMR** (100 MHz, ref = CDCl$_3$): δ 51.9 (CHS); 56.3 (<u>C</u>H$_2$NCHO); 59.6 (C$_{quat,arom}$<u>C</u>H$_2$N); 64.2 (q, J = 28.6 Hz, <u>C</u>HCF$_3$); 78.4 (CHO); 116.2 (2×CH$_{arom}$); 121.5 (CH$_{arom}$); 125.6 (q, J = 283.6 Hz, CF$_3$); 127.1 (CH$_{arom}$); 127.4 (CH$_{arom}$); 128.5 (4×CH$_{arom}$); 129.1 (2×CH$_{arom}$); 129.5 (2×CH$_{arom}$); 131.1 (2×CH$_{arom}$); 135.8 (C$_{quat,arom}$); 137.5 (C$_{quat,arom}$); 157.7 (C$_{quat,arom}$). **IR (cm^{-1})**: v_{max} = 2941, 1599, 1584, 1489, 1481, 1452, 1439, 1391, 1373, 1306, 1292, 1281, 1229, 1148, 1117, 1074, 1045, 1024, 988, 750, 737, 698, 687. **MS (70 eV)**: m/z (%): 430 (M$^+$+1, 100). **HRMS (ESI)**: m/z calcd for C$_{24}$H$_{23}$F$_3$NOS: 430.1447 [M+H]$^+$; found: 430.1459.
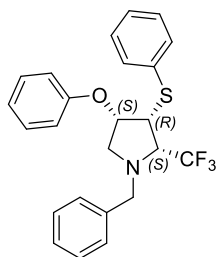
Synthesis of (2R,3R,4S)-4-benzyloxy-3-fluoro-1-isopropyl-2-(trifluoromethyl)pyrrolidine 10o

To an ice-cooled solution of (2S,3S)-3-benzyloxy-2-[(1S)-2,2,2-trifluoro-1-hydroxyethyl]-1-isopropylazetidine **7e** (0.30 g, 1 mmol, 1 equiv) in dry CH$_2$Cl$_2$ (20 mL) was added diethylaminosulfur trifluoride (DAST, 0.32 g, 0.26 mL, 2 mmol, 2 equiv). Then, the resulting solution was heated to reflux and stirred for 2 hours. Afterward, the solution was cooled to room temperature and quenched with sat. NaHCO$_3$ (10 mL). The aqueous layer was extracted with CH$_2$Cl$_2$ (3 × 20 mL), dried with MgSO$_4$, filtrated and evaporated *in vacuo* to afford (2R,3R,4S)-4-benzyloxy-3-fluoro-1-isopropyl-2-(trifluoromethyl)pyrrolidine **10o** in 88% yield (0.27 g, 0.88 mmol). Purification by means of column chromatography on silica gel provided an analytically pure sample.

Colorless oil. R_f = 0.29 (Petroleumether/EtOAc 9/1). Yield 88%. $[\alpha]_D^{25}$ = +9.9° (c = 0.23, CHCl$_3$). **^{1}H NMR** (400 MHz, CDCl$_3$): δ 0.87 (3H, d, J = 6.4 Hz, C<u>H</u>$_3$CHCH$_3$); 1.10 (3H, d, J = 6.8 Hz, CH$_3$CHC<u>H</u>$_3$); 2.99-3.08 (1H, m, C<u>H</u>(CH$_3$)$_2$); 3.07 (2H, d, J = 8.3 Hz, CH$_2$N); 3.51 (1H, q×d×d, J = 11.6, 8.7, 4.4 Hz, CHCF$_3$); 3.80 (1H, d×t×d, J = 21.3, 8.3, 3.9 Hz, CHO); 4.43 (1H, d, J = 12.4 Hz, (<u>H</u>CH)O); 4.70 (1H, d, J = 12.4 Hz, (HC<u>H</u>)O); 5.13 (1H, d×d×d, J = 53.9, 4.4, 3.9 Hz, CHF); 7.29-7.37 (5H, m, 5×CH$_{arom}$). **^{19}F NMR** (376 MHz, ref = CDCl$_3$): -213.57 till -213.42 (1F, m, CHF); -69.26 till -69.20 (3F, m, CF$_3$). **^{13}C NMR** (100 MHz, ref = CDCl$_3$): δ 14.2 and 22.2 ((<u>C</u>H$_3$)$_2$CH); 47.1 (<u>C</u>H$_2$NCHO); 50.8 ((CH$_3$)$_2$<u>C</u>H); 63.5 (q×d, J = 29.6, 16.8 Hz, <u>C</u>HCF$_3$); 72.2 (CH$_2$O); 76.7 (CHO); 89.5 (d, J = 196.1 Hz, CHF); 124.9 (q×d, J = 282.2, 2.9 Hz, CF$_3$); 127.9, 128.1 and 128.5 (5×CH$_{arom}$); 137.4 (C$_{quat,arom}$). **IR (cm^{-1})**: v_{max} = 2970, 2878, 1456, 1366, 1283, 1165, 1138, 1119, 1094, 1030, 833, 737, 698, 658. **MS (70 eV)**: m/z (%): 306 (M$^+$+1, 100). **HRMS (ESI)**: m/z calcd for C$_{15}$H$_{20}$F$_4$NO: 306.1476 [M+H]$^+$; found: 306.1473.
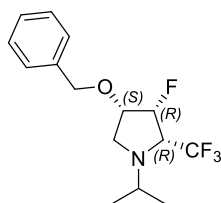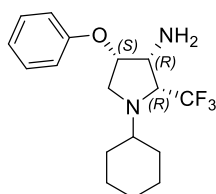
Synthesis of 3-amino-2-(trifluoromethyl)pyrrolidines 13 and 14

As a representative example, the synthesis of (2R,3R,4S)-3-amino-1-cyclohexyl-4-phenoxy-2-(trifluoromethyl)pyrrolidine **13a** is described. To a solution of (2R,3R,4S)-3-benzylamino-1-cyclohexyl-4-phenoxy-2-(trifluoromethyl)pyrrolidine **10g** (84 mg, 0.2 mmol) in methanol (5 mL) was added $Pd(OH)_2$ on activated carbon (20% w/w), and the resulting mixture was placed in a Parr apparatus. The inside of the Parr apparatus was then degassed and filled with hydrogen gas, after which the mixture was stirred for 4 hours at room temperature while applying 4 bar of hydrogen gas. Filtration of the heterogeneous mixture through Celite and evaporation of the solvent *in vacuo* afforded (2R,3R,4S)-3-amino-1-cyclohexyl-4-phenoxy-2-(trifluoromethyl)pyrrolidine **13a** in a yield of 89% (58 mg, 0.178 mmol) as a colorless oil.

(2R,3R,4S)-3-Amino-1-cyclohexyl-4-phenoxy-2-(trifluoromethyl)pyrrolidine 13a

Colorless oil. Yield 89%. $[\alpha]_D^{25}$ = +44.9° (c = 0.77, CHCl$_3$). **¹H NMR** (400 MHz, CDCl$_3$): δ 1.01-1.27 (5H, m, (C$\underline{H}_2$)$_5$CHN); 1.62-1.84 (7H, m, NH$_2$ and (C$\underline{H}_2$)$_5$CHN); 2.65-2.70 (1H, m, (CH$_2$)$_5$C$\underline{H}$N); 3.09 (1H, d×d, J = 10.9, 5.2 Hz, N($\underline{H}$CH)CHO); 3.18 (1H, d×d, J = 10.9, 2.8 Hz, N(HC$\underline{H}$)CHO); 3.50-3.59 (1H, m, CHCF$_3$); 3.78 (1H, d×d, J = 7.8, 5.3 Hz, C$\underline{H}$NCHO); 4.64 (1H, d×d×d, J = 5.3, 5.2, 2.8 Hz, CHO); 6.90-6.98 (3H, m, 3×CH$_{arom}$); 7.25-7.29 (2H, m, 2×CH$_{arom}$). **¹⁹F NMR** (376 MHz, ref = CDCl$_3$): -68.10 (3F, d, J = 8.5 Hz, CF$_3$). **¹³C NMR** (100 MHz, ref = CDCl$_3$): δ 24.8, 25.5, 26.1, 26.2 and 32.1 (($\underline{C}$H$_2$)$_5$CHN); 49.2 (CH$_2$N); 55.4 (CHNH$_2$); 59.4 ($\underline{C}$HN(CH$_2$)$_5$); 62.9 (q, J = 27.0 Hz, $\underline{C}$HCF$_3$); 77.2 (CHO); 115.8 (2×CH$_{arom}$); 121.3 (CH$_{arom}$); 126.1 (q, J = 283.2 Hz, CF$_3$); 129.5 (2×CH$_{arom}$); 157.8 (C$_{quat,arom}$). **IR (cm⁻¹)**: v_{NH2} = 3418; v_{max} = 2930, 2855, 1599, 1587, 1495, 1275, 1240, 1153, 1115, 1043, 754, 692. **MS (70 eV)**: m/z (%): 329 (M⁺+1, 100). **HRMS (ESI)**: m/z calcd for C$_{17}$H$_{24}$F$_3$N$_2$O: 329.1835 [M+H]⁺, found: 329.1843.

(2R,3R,4S)-3-Amino-4-benzyloxy-1-isopropyl-2-(trifluoromethyl)pyrrolidine 13b

Colorless oil. Yield 91%. $[\alpha]_D^{25}$ = +28.3° (c = 0.17, CHCl$_3$). **¹H NMR** (400 MHz, CDCl$_3$): δ 0.91 and 1.10 (2×3H, 2×d, J = 6.6 Hz, (C$\underline{H}_3$)$_2$CH); 1.54 (2H, s (broad), NH$_2$); 2.84 (1H, d×d, J = 10.6, 5.7 Hz, N($\underline{H}$CH)CHO); 3.05 (1H, d×d, J = 10.6, 3.7 Hz, N(HC$\underline{H}$)CHO); 3.15 (1H, septet, J = 6.6 Hz, C$\underline{H}$(CH$_3$)$_2$); 3.31-3.40 (1H, m, CHCF$_3$); 3.46 (1H, d×d, J = 7.4, 5.2 Hz, C$\underline{H}$NCHO); 3.87-3.91 (1H, m, CHO); 4.55 (1H, d, J = 12.2 Hz, ($\underline{H}$CH)O); 4.65 (1H, d, J = 12.2 Hz, (HC$\underline{H}$)O); 7.27-7.37 (5H, m, 5×CH$_{arom}$). **¹⁹F NMR** (376 MHz, ref = CDCl$_3$): -68.84 (3F, d, J = 8.3 Hz, CF$_3$). **¹³C NMR** (100 MHz, ref = CDCl$_3$): δ 13.5 and 21.6 (($\underline{C}$H$_3$)$_2$CH); 47.1 ($\underline{C}$H$_2$NCHO); 50.1 ((CH$_3$)$_2$$\underline{C}$H); 55.0 ($\underline{C}$HNCHO); 63.4 (q, J = 27.7 Hz, $\underline{C}$HCF$_3$); 71.8 (CH$_2$O); 78.4 (CHO); 126.1 (q, J = 282.6 Hz, CF$_3$); 127.4 (2×CH$_{arom}$); 127.6 (CH$_{arom}$); 128.4 (2×CH$_{arom}$); 138.6 (C$_{quat,arom}$). **IR (cm⁻¹)**: v_{max} = 2968, 2916, 2872, 1454, 1269, 1121, 1069, 1028, 733, 696, 635. **MS (70 eV)**: m/z (%): 303 (M⁺+1, 100). **HRMS (ESI)**: m/z calcd for C$_{15}$H$_{22}$F$_3$N$_2$O: 303.1679 [M+H]⁺, found: 303.1688.

(2*R*,3*R*,4*S*)-3-Amino-4-benzyloxy-2-(trifluoromethyl)pyrrolidine 14

Colorless oil. Yield 89%. $[\alpha]_D^{25}$ = +9.5° (*c* = 0.22, CHCl$_3$). **¹H NMR** (400 MHz, CDCl$_3$): δ 1.90 (3H, s (broad), NH$_2$ and NH); 3.11-3.18 (2H, CHOC*H*$_2$N); 3.58-3.66 (1H, m, CHCF$_3$); 3.70 (1H, d×d, *J* = 6.0, 5.4 Hz, C*H*NCHO); 3.88-3.90 (1H, ~d×t, *J* = 6.0, 5.7 Hz, CHO); 4.57 (1H, d, *J* = 12.0 Hz, (*H*CH)O); 4.62 (1H, d, *J* = 12.0 Hz, (HC*H*)O); 7.29-7.38 (5H, m, 5×CH$_{arom}$). **¹⁹F NMR** (376 MHz, ref = CDCl$_3$): -69.88 (3F, d, *J* = 8.3 Hz, CF$_3$). **¹³C NMR** (100 MHz, ref = CDCl$_3$): δ 48.4 (*C*H$_2$NCHO); 53.3 (*C*HNCHO); 61.0 (q, *J* = 27.9 Hz, *C*HCF$_3$); 72.1 (CH$_2$O); 79.0 (CHO); 125.6 (q, *J* = 279.9 Hz, CF$_3$); 127.6, 127.9 and 128.5 (5×CH$_{arom}$); 137.8 (C$_{quat,arom}$). **IR (cm⁻¹)**: ν$_{NH2}$ = 3350; ν$_{max}$ = 2926, 2876, 1454, 1281, 1202, 1113, 1028, 735, 696, 610. **MS (70 eV)**: *m/z* (%): 261 (M⁺+1, 100). **HRMS (ESI)**: *m/z* calcd for C$_{12}$H$_{16}$F$_3$N$_2$O: 261.1209 [*M*+H]⁺; found: 261.1209.

Synthesis of (2*R*,3*R*,4*S*)-3-amino-4-hydroxy-1-isopropyl-2-(trifluoromethyl)pyrrolidine 15

To a solution of (2*R*,3*R*,4*S*)-3-benzylamino-4-benzyloxy-1-isopropyl-2-(trifluoromethyl)pyrrolidine **10i** (78 mg, 0.2 mmol) in methanol (5 mL) was added Pd(OH)$_2$ on activated carbon (40% w/w), and the resulting mixture was placed in a Parr apparatus. The inside of the Parr apparatus was then degassed and filled with hydrogen gas, after which the mixture was stirred for 4 days at room temperature while applying 5 bar of hydrogen gas. Filtration of the heterogeneous mixture through Celite and evaporation of the solvent *in vacuo* afforded (2*R*,3*R*,4*S*)-3-amino-4-hydroxy-1-isopropyl-2-(trifluoromethyl)pyrrolidine **15** in a yield of 92% (39 mg, 0.184 mmol) as a white solid.

White solid. Mp 70°C. Yield 92%. $[\alpha]_D^{25}$ = +40.5° (*c* = 0.40, CHCl$_3$). **¹H NMR** (400 MHz, CDCl$_3$): δ 0.93 (3H, d, *J* = 6.4 Hz, C*H*$_3$CHCH$_3$); 1.10 (3H, d, *J* = 6.8 Hz, CH$_3$CHC*H*$_3$); 2.27 (3H, s (broad), NH$_2$ and OH); 2.81 (1H, d×d, *J* = 10.5, 3.6 Hz, N(*H*CH)CHO); 2.92 (1H, d×d, *J* = 10.5, 5.7 Hz, N(HC*H*)CHO); 3.12-3.22 (1H, m, C*H*(CH$_3$)$_2$); 3.39 (1H, d×q, *J* = 8.0 Hz, *J*$_{HF}$ = 7.9 Hz, CHCF$_3$); 3.53-3.56 (1H, m, C*H*NH$_2$); 4.04-4.07 (1H, m, CHOH). **¹⁹F NMR** (376 MHz, ref = CDCl$_3$): -67.78 (3F, d, *J* = 7.9 Hz, CF$_3$). **¹³C NMR** (100 MHz, ref = CDCl$_3$): δ 13.1 and 21.8 ((*C*H$_3$)$_2$CH); 49.5 ((CH$_3$)$_2$*C*H); 50.0 (CH$_2$N); 55.3 (CHNH$_2$); 62.9 (s (broad), *C*HCF$_3$); 70.5 (CHOH); 126.1 (q, *J* = 281.8 Hz, CF$_3$). **IR (cm⁻¹)**: ν$_{NH2/OH}$ = 3169; ν$_{max}$ = 2970, 2938, 1387, 1271, 1177, 1146, 1101, 1080, 1051, 1020, 945, 908, 889. **MS (70 eV)**: *m/z* (%): 239 (M⁺+1, 100). **HRMS (ESI)**: *m/z* calcd for C$_8$H$_{16}$F$_3$N$_2$O: 213.1209 [*M*+H]⁺, found: 213.1217.

Synthesis of (2*R*,3*R*,4*S*)-4-benzyloxy-3-isocyanato-1-isopropyl-2-(trifluoromethyl)pyrrolidine 16

To a solution of (2*R*,3*R*,4*S*)-3-amino-4-benzyloxy-1-isopropyl-2-(trifluoromethyl)pyrrolidine **13b** (151 mg, 0.5 mmol, 1 equiv) in CH$_2$Cl$_2$ (10 mL) was added triphosgene (149 mg, 0.5 mmol, 1 equiv). The resulting solution was stirred for 2 hours at room temperature. Afterward, the solution was quenched with sat. NaHCO$_3$ (10 mL) and the aqueous phase was extracted with CH$_2$Cl$_2$ (3 × 10 mL). The combined organic phases were dried with MgSO$_4$, filtered and evaporated *in vacuo* to afford a crude reaction mixture, which was purified by means of silica gel column chromatography to afford (2*R*,3*R*,4*S*)-4-

benzyloxy-3-isocyanato-1-isopropyl-2-(trifluoromethyl)pyrrolidine **16** as a colorless oil in a yield of 67% (110 mg, 0.335 mmol).

Colorless oil. R_f = 0.36 (Petroleumether/EtOAc 6/1). Yield 67%. $[\alpha]_D^{25}$ = +5.9° (c = 0.13, CHCl$_3$). **^{1}H NMR** (400 MHz, CDCl$_3$): δ 0.89 (3H, d, J = 6.4 Hz, C$\underline{H}_3$CHCH$_3$); 1.10 (3H, d, J = 6.8 Hz, CH$_3$CHC$\underline{H}_3$); 3.03 (2H, d, J = 7.1 Hz, CH$_2$N); 3.05-3.15 (1H, m, C$\underline{H}$(CH$_3$)$_2$); 3.31-3.40 (1H, q×d, J = 6.7, 6.4 Hz, CHCF$_3$); 3.95 (1H, t×d, J = 7.1, 5.1 Hz, CHO); 4.05-4.07 (1H, m, C$\underline{H}$NCHO); 4.56 (1H, d, J = 11.8 Hz, ($\underline{H}$CH)O); 4.65 (1H, d, J = 11.8 Hz, (HC$\underline{H}$)O); 7.30-7.38 (5H, m, 5×CH$_{arom}$). **^{19}F NMR** (376 MHz, ref = CDCl$_3$): -68.80 (3F, d, J = 6.7 Hz, CF$_3$). **^{13}C NMR** (100 MHz, ref = CDCl$_3$): δ 13.4 and 22.0 (($\underline{C}$H$_3$)$_2$CH); 46.9 ($\underline{C}$H$_2$NCHO); 49.7 ((CH$_3$)$_2$$\underline{C}$H); 55.9 ($\underline{C}$HNCHO); 63.0 (q, J = 29.0 Hz, $\underline{C}$HCF$_3$); 72.1 (CH$_2$O); 77.0 (CHO); 125.0 (q, J = 283.3 Hz, CF$_3$); 126.4 (OCN); 127.8 (2×CH$_{arom}$); 128.1(CH$_{arom}$); 128.6 (2×CH$_{arom}$); 136.9 (C$_{quat,arom}$). **IR (cm^{-1})**: v_{OCN} = 2257; v_{max} = 2974, 1670, 1599, 1566, 1470, 1348, 1277, 1134, 814, 735, 606. **MS (70 eV)**: m/z (%): 329 (M$^+$+1, 100). **HRMS (ESI)**: m/z calcd for C$_{16}$H$_{20}$F$_3$N$_2$O$_2$: 329.1471 [M+H]$^+$, found: 329.1474.
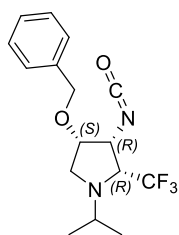
Synthesis of (1*S*,5*R*,6*R*)-7-isopropyl-6-trifluoromethyl-2-oxa-4,7-diazabicyclo[3.3.0]octan-3-one 17

To a solution of (2*R*,3*R*,4*S*)-3-amino-4-hydroxy-1-isopropyl-2-(trifluoromethyl)pyrrolidine **15** (106 mg, 0.5 mmol, 1 equiv) in CH$_2$Cl$_2$ (10 mL) was added triphosgene (149 mg, 0.5 mmol, 1 equiv). The resulting solution was stirred for 2 hours at room temperature. Afterward, the solution was quenched with sat. NaHCO$_3$ (10 mL) and the aqueous phase was extracted with CH$_2$Cl$_2$ (3 × 10 mL). The combined organic phases were dried with MgSO$_4$, filtered and evaporated *in vacuo* to afford a crude reaction mixture, which was purified by means of silica gel column chromatography to afford (1*S*,5*R*,6*R*)-7-isopropyl-6-trifluoromethyl-2-oxa-4,7-diazabicyclo[3.3.0]octan-3-one **17** as a colorless oil in a yield of 81% (96 mg, 0.405 mmol).

Colorless oil. R_f = 0.12 (Petroleumether/EtOAc 1/1). Yield 81%. $[\alpha]_D^{25}$ = +31.5° (c = 0.33, CHCl$_3$). **^{1}H NMR** (400 MHz, CDCl$_3$): δ 0.93 (3H, d, J = 6.4 Hz, C$\underline{H}_3$CHCH$_3$); 1.17 (3H, d, J = 6.8 Hz, CH$_3$CHC$\underline{H}_3$); 2.70 (1H, d×d, J = 11.5, 5.0 Hz, ($\underline{H}$CH)N); 3.16-3.29 (2H, m, CHCF$_3$ and C$\underline{H}$(CH$_3$)$_2$); 3.30 (1H, ~d, J = 11.5 Hz, (HC$\underline{H}$)N); 4.39-4.43 (1H, m, CHNCO); 5.00 (1H, ~d×d, J = 7.8, 5.0 Hz, CHO); 5.50 (1H, s (broad), NH). **^{19}F NMR** (376 MHz, ref = CDCl$_3$): -65.51 (3F, d, J = 6.5 Hz, CF$_3$). **^{13}C NMR** (100 MHz, ref = CDCl$_3$): δ 12.0 and 21.8 (($\underline{C}$H$_3$)$_2$CH); 47.1 ((CH$_3$)$_2$$\underline{C}$H); 50.4 (CH$_2$N); 56.3 ($\underline{C}$HNCO); 64.5 (q, J = 27.8 Hz, $\underline{C}$HCF$_3$); 76.7 (CHO); 124.7 (q, J = 281.1 Hz, CF$_3$); 158.7 (C=O). **IR (cm^{-1})**: v_{NH} = 3269; $v_{C=O}$ = 1751; v_{max} = 2976, 1396, 1277, 1233, 1192, 1161, 1125, 1099, 1055, 1026, 961. **MS (70 eV)**: m/z (%): 239 (M$^+$+1, 100). **HRMS (ESI)**: m/z calcd for C$_9$H$_{14}$F$_3$N$_2$O$_2$: 239.1002 [*M*+H]$^+$, found: 239.1000.
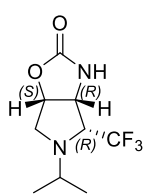
Theoretical calculations

Theoretical calculations were performed in collaboration with Prof. S. Catak and Prof. V. Van Speybroeck (Center for Molecular Modeling, UGent).

Density Functional Theory (DFT) calculations were carried out with the Gaussian 09 software package.[94] The M06-2X[95] functional, well-known for its performance at predicting accurate transition state geometries,[96] was used in conjunction with a 6-31+G(d,p) basis set for conformational analysis on all reactants, transition states and intermediates to identify most plausible conformers. Free energies are reported in kJ/mol at 1 atm and 81 °C. Normal mode analysis has been performed, as well as Intrinsic Reaction Coordinate (IRC)[97] calculations to verify the transition state geometries. The possible pathways under study were modeled using the Conductor-like Polarizable Continuum Model (C-PCM),[98] where the solute is placed in a continuous medium characterized by a dielectric constant, to mimic the solvation effects. Energy refinements at the MPW1K,[99] ωB97X-D,[100] and PBE0[101] levels of theory, combined with a triple-ζ basis set (6-311+G(3df,3pd)), proven to be particularly accurate.[102]

Single crystal X-ray diffraction

X-ray analysis was performed by Prof. Kristof Van Hecke (XStruct, Department of Inorganic and Physical Chemistry, Faculty of Sciences, Ghent University).

For the structures of **5a**, **5e**, **7a**, **7b** and **10h**, X-ray intensity data were collected at 100 K, respectively, on a Rigaku Oxford Diffraction Supernova Dual Source (Cu at zero) diffractometer equipped with an Atlas CCD detector using ω scans and CuKα (λ = 1.54184 Å) radiation. The images were interpreted and integrated with the program CrysAlisPro. Using Olex2, the structures were solved by direct methods using the ShelXS structure solution program and refined by full-matrix least-squares on F^2 using the ShelXL program package. Non-hydrogen atoms were anisotropically refined and the hydrogen atoms in the riding mode and isotropic temperature factors fixed at 1.2 times U(eq) of the parent atoms (1.5 times for methyl and hydroxyl groups).

CCDC 1546934-1546938 contain the supplementary crystallographic data for this paper and can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44-1223-336033; or deposit@ccdc.cam.ac.uk).

Crystal data for compound 5a:

C$_{14}$H$_{16}$F$_3$NO$_3$, M = 303.28, monoclinic, space group $P2_1$ (No. 4), a = 5.9265(3) Å, b = 11.8003(6) Å, c = 10.0928(6) Å, β = 98.240(6)°, V = 698.55(7) Å^3, Z = 2, T = 100 K, ρ_{calc} = 1.442 g cm^{-3}, μ(Cu-Kα) = 1.102 mm^{-1}, F(000) = 316, 6823 reflections measured, 2254 unique (R_{int} = 0.0509) which were used in all calculations. The final R1 was 0.0436 (I >2σ (I)) and wR2 was 0.1192 (all data). The absolute configuration was established with chirality at C1(S), C3(R) and C4(S), with a refined Flack parameter of -0.06(15).

Crystal data for compound 5e:

$C_{15}H_{18}F_3NO_3$, M = 317.30, orthorhombic, space group $P2_12_12_1$ (No. 19), a = 5.73470(7) Å, b = 12.45975(15) Å, c = 20.4676(3) Å, V = 1462.47(3) Å^3, Z = 4, T = 100 K, ρ_{calc} = 1.441 g cm^{-3}, μ(Cu-Kα) = 1.077 mm^{-1}, $F(000)$ = 664, 25106 reflections measured, 3009 unique (R_{int} = 0.0502) which were used in all calculations. The final $R1$ was 0.0369 ($I > 2\sigma\,(I)$) and $wR2$ was 0.0989 (all data). The absolute configuration was established with chirality at C1(S), C3(R) and C4(S), with a refined Flack parameter of -0.03(5).

Crystal data for compound 7a:

$C_{14}H_{18}F_3NO_2$, M = 289.29, trigonal, space group $R3$ (No. 146), a = 27.2782(5) Å, b = 27.2782(5) Å, c = 10.61163(18) Å, V = 6838.2(3) Å^3, Z = 18, T = 100 K, ρ_{calc} = 1.264 g cm^{-3}, μ(Cu-Kα) = 0.933 mm^{-1}, $F(000)$ = 2736, 21663 reflections measured, 5209 unique (R_{int} = 0.0707) which were used in all calculations. The final $R1$ was 0.0826 ($I > 2\sigma\,(I)$) and $wR2$ was 0.2364 (all data). The asymmetric unit contains two molecules, which are almost identical. However, one of the molecules shows positional disorder of the phenyl ring, which could be modeled in two parts, with refined occupancy factors of 0.576(8) and 0.424(8), respectively. The absolute configuration was established with chirality at C1(S), C3(S), C4(S), C15(S), C17(S) and C18(S), with a refined Flack parameter of -0.15(15).

Crystal data for compound 7b:

$C_{14}H_{18}F_3NO_2$, M = 289.29, monoclinic, space group $P2_1$ (No. 4), a = 9.9857(6) Å, b = 14.0575(7) Å, c = 11.0980(6) Å, β = 109.932(7)°, V = 1464.55(15) Å^3, Z = 4, T = 100 K, ρ_{calc} = 1.312 g cm^{-3}, μ(Cu-Kα) = 0.968 mm^{-1}, $F(000)$ = 608, 14048 reflections measured, 4861 unique (R_{int} = 0.0569) which were used in all calculations. The final $R1$ was 0.0524 ($I > 2\sigma\,(I)$) and $wR2$ was 0.1522 (all data). The asymmetric unit contains two molecules, which differ mostly in the orientation of the phenoxy group. The absolute configuration was established with chirality at C1(S), C3(S), C4(S), C15(S), C17(S) and C18(S), with a refined Flack parameter of -0.08(12).

Crystal data for compound 10h:

$C_{25}H_{25}F_3N_2O$, M = 426.47, orthorhombic, space group $P2_12_12_1$ (No. 19), a = 9.58530(14) Å, b = 10.83863(13) Å, c = 20.3107(2) Å, V = 2110.11(4) Å^3, Z = 4, T = 100 K, ρ_{calc} = 1.342 g cm^{-3}, μ(Cu-Kα) = 0.836 mm^{-1}, $F(000)$ = 896, 39897 reflections measured, 4330 unique (R_{int} = 0.0847) which were used in all calculations. The final $R1$ was 0.0449 ($I > 2\sigma\,(I)$) and $wR2$ was 0.1155 (all data). The absolute configuration was established with chirality at C1(R), C3(S) and C4(R), with a refined Flack parameter of 0.14(8).

PART II

LiAlH₄-induced selective ring rearrangement of 2-(2-cyanoethyl)aziridines toward 2-(aminomethyl)pyrrolidines and 3-aminopiperidines as eligible heterocyclic building blocks

Abstract

2-(2-Cyanoethyl)aziridines and 2-aryl-3-(2-cyanoethyl)aziridines were deployed as substrates for an In(OTf)$_3$-mediated regio- and stereoselective ring rearrangement upon treatment with LiAlH$_4$, affording a variety of novel 2-(aminomethyl)pyrrolidines and 3-aminopiperidines, respectively. Further synthetic elaboration of the obtained 3-aminopiperidines resulted in the formation of a peculiar and unexplored conformationally constrained imidazolidinone and diketopiperazine scaffold.

Graphical abstract
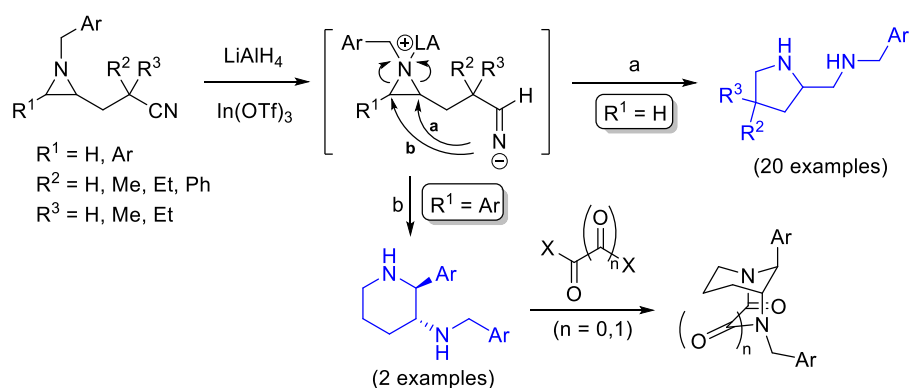
Reference

Dolfen, J.; Vervisch, K.; De Kimpe, N.; D'hooghe, M. "LiAlH$_4$-induced selective ring rearrangement of 2-(2-cyanoethyl)aziridines toward 2-(aminomethyl)pyrrolidines and 3-aminopiperidines as eligible heterocyclic building blocks". *Chem. Eur. J.* **2016**, *22*, 4945-4951 (I.F. 5.77).

1. Introduction

Because of their high ring strain and reactivity, aziridines are generally recognized as valuable substrates for the synthesis of five- and six-membered heterocycles.[11a,14b,103] Contrary to activated aziridines (bearing an electron-withdrawing group at nitrogen), non-activated aziridines (bearing a *N*-electron-donating group) have received considerably less attention in the literature.[11-12,14b,103c,103e,104] Nonetheless, non-activated aziridines often display a different reactivity and applicability as compared to their activated counterparts, providing interesting opportunities for the selective synthesis of a variety of new (heterocyclic) nitrogen compounds.

The main part of known transformations of non-activated aziridines toward important core structures such as pyrrolidines and piperidines involves the incorporation of the aziridine nitrogen atom into the newly formed azaheterocycles.[18,22g,54,105] However, strategies for the selective conversion of non-activated aziridines into pyrrolidines, piperidines and other heterocycles, in which the aziridine unit is deployed as an electrophilic moiety and subjected to ring opening by an (*in situ* created) nucleophilic heteroatom at a remote position, still remain a scarcely investigated research field.[22b-g,24]

In the present chapter, the latter methodology, *i.e.* the deployment of the aziridine unit as an electrophilic moiety in intramolecular reactions, is examined toward the preparation of novel functionalized pyrrolidines and piperidines.

2. Synthesis of 2-(aminomethyl)pyrrolidines through LiAlH₄-induced ring rearrangement of 1-arylmethyl-2-(2-cyanoethyl)aziridines

In previous studies at the Department of Sustainable Organic Chemistry and Technology (UGent), a LiAlH₄-mediated ring rearrangement of 2-(4-chloro-2-cyano-2-phenylbutyl)aziridines **1** and **3** has been developed toward the selective preparation of stereodefined *endo*- and *exo*-1-azabicyclo[2.2.1]heptanes **2** and **4** via a double reductive cyclization protocol (Scheme 1).[24] Application of similar reaction conditions (LiAlH₄, THF, reflux) to 2-(2-cyano-2-phenylbutyl)aziridines **5** afforded 2-aminomethyl-4-ethyl-4-phenylpyrrolidines **6** in high yields via an iminyl anion-interceded regioselective ring opening of the aziridine ring.[25]
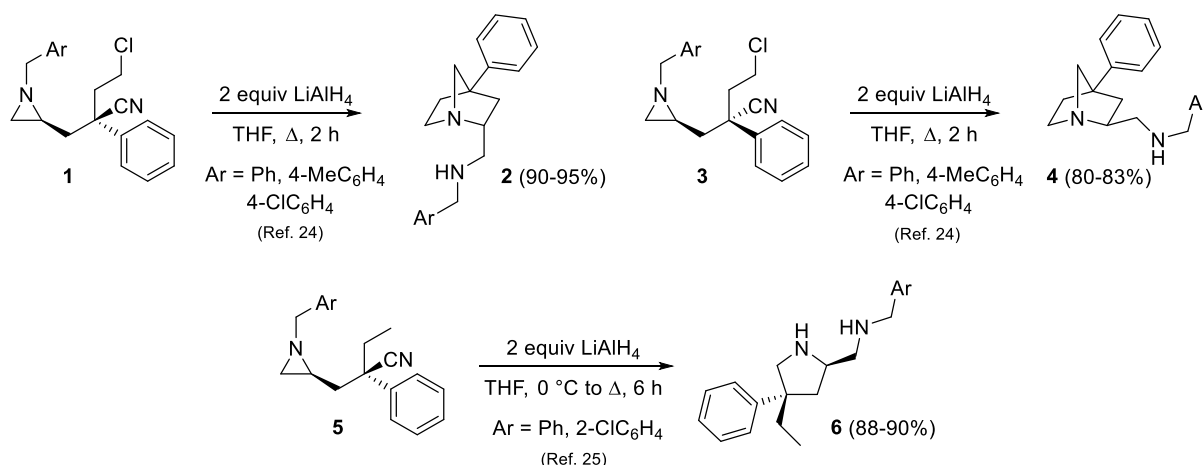
Scheme 1

Bearing in mind the huge number of bioactive compounds accommodating a pyrrolidine or piperidine scaffold and to further broaden the scope of this unprecedented one-step transformation, the feasibility of using other 2-(2-cyanoethyl)aziridine substrates with diverse substitution patterns was evaluated. Thus, 1-arylmethyl-2-(2-cyanoethyl)aziridines **7**, which were prepared from the corresponding 2-(bromomethyl)aziridines by reaction with α-lithiated trimethylsilylacetonitrile, followed by cleavage of the silylated aziridine intermediate upon treatment with aqueous sodium hydroxide,[29] were also treated with 2 equivalents of LiAlH$_4$ in THF at reflux temperature. After 2 hours, no cyclization products were observed and, instead, 2-(3-aminopropyl)aziridines **8** were obtained as the sole reaction products (Scheme 2).

8a (R = H, 75%)
8b (R = Me, 74%)
8c (R = Cl, 71%)
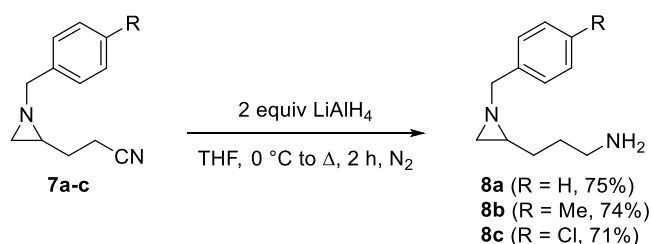
Scheme 2

This discrepancy in reactivity might be attributable to the absence of the *Thorpe-Ingold* effect[106] in 2-(2-cyanoethyl)aziridines **7** (which was not the case for aziridine substrates **1**, **3** and **5**) in combination with the mild Lewis acid activity of LiAlH$_4$ and, as a consequence, activation of the aziridine core seemed to be required to provoke ring opening. To that end, elaborate monitoring of different reaction conditions through variation of Lewis acids, temperature and solvents was performed to effect the LiAlH$_4$-induced ring rearrangement of aziridine **7a** as model substrate toward the preparation of 2-(aminomethyl)pyrrolidine **10a** (Scheme 3, Table 1).

Scheme 3
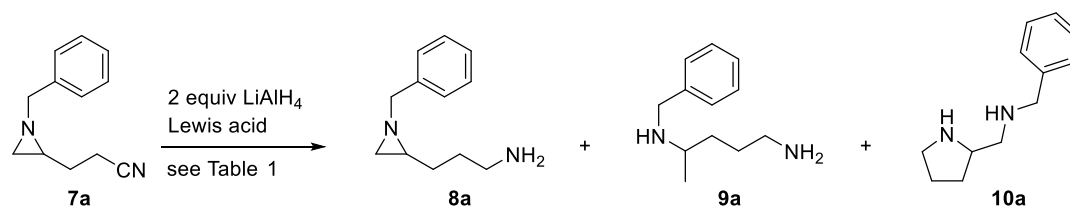
Table 1. Conversion of 1-benzyl-2-(2-cyanoethyl)aziridine 7a upon treatment with diverse Lewis acids.

Entry	Lewis acid	Reaction conditions	Conversion (%)[a]		
			Comp. **8a**	Comp. **9a**	Comp. **10a**
1	0.1 equiv ZnCl$_2$	THF, 0 °C to Δ, 3 h, N$_2$	100	0	0
2	0.1 equiv ZnCl$_2$	Et$_2$O, 0 °C to Δ, 3 h, N$_2$	100	0	0
3	0.25 equiv ZnCl$_2$	THF, 0 °C to Δ, 4 h, N$_2$	100	0	0
4	1 equiv ZnCl$_2$	THF, rt, 19 h, N$_2$	78	22	0
5	1 equiv ZnCl$_2$	THF, 0 °C to Δ, 3 h, N$_2$	66	34	0
6	0.5 equiv FeCl$_3$	THF, 0 °C to Δ, 4 h, N$_2$	79	21	0
7	0.5 equiv AlCl$_3$	THF, 0 °C to Δ, 4 h, N$_2$	77	23	0
8	0.1 equiv Sn(OTf)$_2$	THF, 0 °C to Δ, 3 h, N$_2$	100	0	0
9	0.5 equiv Sn(OTf)$_2$	THF, 0 °C to Δ, 4 h, N$_2$	0	0	100 (90% yield)
10	0.05 equiv Sc(OTf)$_3$	THF, 0 °C to Δ, 4 h, N$_2$	100	0	0
11	0.1 equiv Sc(OTf)$_3$	THF, 0 °C to Δ, 4 h, N$_2$	100	0	0
12	0.2 equiv Sc(OTf)$_3$	THF, 0 °C to Δ, 4 h, N$_2$	19	0	81
13	0.3 equiv Sc(OTf)$_3$	THF, 0 °C to Δ, 4 h, N$_2$	0	0	100 (86% yield)
14	0.5 equiv Sc(OTf)$_3$	THF, 0 °C to Δ, 4 h, N$_2$	0	0	100 (96% yield)
15	0.3 equiv Sc(OTf)$_3$	Et$_2$O, 0 °C to Δ, 4 h, N$_2$	0	0	100 (81% yield)
16	0.2 equiv In(OTf)$_3$	THF, 0 °C to Δ, 4 h, N$_2$	15	0	85
17	0.3 equiv In(OTf)$_3$	THF, 0 °C to Δ, 4 h, N$_2$	0	0	100 (97% yield)
18	0.5 equiv In(OTf)$_3$	THF, 0 °C to Δ, 4 h, N$_2$	0	0	100 (77% yield)
19	0.3 equiv In(OTf)$_3$	Et$_2$O, 0 °C to Δ, 4 h, N$_2$	0	0	100 (59% yield)

[a] Based on ^{1}H NMR analysis (CDCl$_3$) and/or LC-MS analysis of the crude reaction mixture.

In a first approach, the use of 0.1 equivalents of ZnCl$_2$ both in THF and Et$_2$O at reflux temperature afforded 2-(3-aminopropyl)aziridine **8a** (Table 1, Entries 1 and 2). Increasing the number of equivalents of ZnCl$_2$ (from 0.1 to 0.25) was also unsuccessful to trigger the desired ring closure (Table 1, Entry 3). Furthermore, an equimolar amount of ZnCl$_2$ furnished diamine **9a** as a side product (22-34%, Table 1, Entries 4 and 5), which was also the case when the Lewis acid was replaced by FeCl$_3$ or AlCl$_3$ (21-23%, Table 1, Entries 6 and 7). The production of diamine **9a** can be explained by direct hydride-induced aziridine ring opening, instead of the coveted nitrogen anion-interceded intramolecular reaction. The

use of 0.1 equivalents of Sn(OTf)$_2$ in THF again resulted in complete reduction of the cyano moiety without subsequent aziridine ring rearrangement (Table 1, Entry 8). Gratifyingly, when the amount of Sn(OTf)$_2$ was increased to 0.5 equivalents, the desired 2-(aminomethyl)pyrrolidine **10a** was obtained in an excellent yield of 90% (Table 1, Entry 9), and changing Sn(OTf)$_2$ by Sc(OTf)$_3$ or In(OTf)$_3$ as triflate Lewis acids, also resulted in pyrrolidine structure **10a** in moderate to high isolated yields (59-97%, Table 1, Entries 13-15,17-19). Furthermore, the experiments indicated that a minimum amount of 0.3 equivalents of the Lewis acid was required to efficiently effect the ring transformation, as the use of 0.2 equivalents of Sc(OTf)$_3$ or In(OTf)$_3$ also afforded minor 2-(3-aminopropyl)aziridine **8a** (15-19%, Table 1, Entries 12 and 16). As the use of In(OTf)$_3$ produced 2-(aminomethyl)pyrrolidine **10a** in the highest yield, and given the fact that this Lewis acid might be more interesting from an economical point of view as compared to Sn(OTf)$_2$ and Sc(OTf)$_3$, In(OTf)$_3$ was employed as the Lewis acid of choice for further ring-transformation reactions. Thus, 2-(2-cyanoethyl)aziridines **7b-e** were treated with 2 equivalents of LiAlH$_4$ and 0.3 equivalents of In(OTf)$_3$ at reflux temperature, affording the corresponding 2-(aminomethyl)pyrrolidines **10b-e** in good to excellent yields (74-97%) (Scheme 4).

10a (R^1 = H, 97%)
10b (R^1 = 4-Me, 94%)
10c (R^1 = 4-Cl, 83%)
10d (R^1 = 4-OMe, 74%)
10e (R^1 = 2-OMe, 97%)
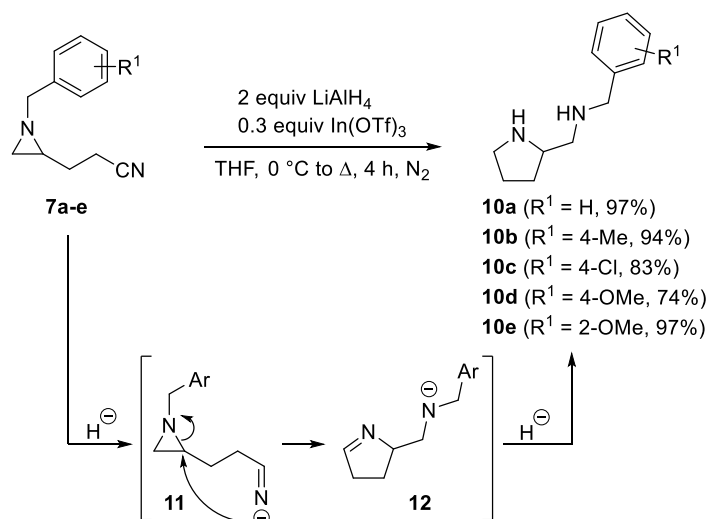
Scheme 4

The proposed reaction mechanism involves initial reduction of the cyano group providing an iminyl anion, followed by regioselective ring opening of the aziridine moiety at the more-hindered carbon atom and hydride reduction of the cyclic imine intermediate (Scheme 4). According to Baldwin's rules, a 5-*exo-tet* ring closure is favored whereas a 6-*endo-tet* is disfavored, which can explain the regioselectivity of this aziridine ring opening.[23] During the cyclization step, In(OTf)$_3$ is believed to activate the aziridine ring causing a higher susceptibility to ring-opening reactions.[107] It should be mentioned that treatment of 2-(3-aminopropyl)aziridine **8a** with 2 molar equiv of LiAlH$_4$ and 0.3 equiv of In(OTf)$_3$ at reflux temperature did not effect pyrrolidine ring formation at all, pointing to the peculiar nature of the above-described iminyl anion-interceded aziridine ring transformation. It should also be noted that the combination In(OTf)$_3$/LiAlH$_4$ is innovative and has not been described before, whereas several other indium-catalyzed reactions in combination with reducing agents have been reported in the literature. For

example, reductive deoxygenation of carbonyl compounds to the corresponding alkanes has successfully been accomplished using $LiAlH_4$ in the presence of $InBr_3$.[108] In another study, reductive coupling of aldehydes has been established using Et_3SiH and $In(OTf)_3$ as a catalyst.[109] The same combination of reducing agent and catalyst has also been employed in a one-pot preparation of azobenzenes from nitrobenzenes.[110]

3. Ring rearrangement of 2-(2-cyanoalkyl)aziridines and 2-(2-cyano-2-phenylethyl)aziridines

In order to examine the effect of a tertiary and quaternary carbon center adjacent to the cyano group on the ring rearrangement aptitude of aziridines **7**, 2-(2-cyanoethyl)aziridines **7** were mono- and dialkylated via deprotonation with LDA followed by quenching with an alkyl iodide, affording aziridines **13** and **14** in moderate to good yields (R^2, R^3 = Me, Et) (38-63%, Scheme 5, Table 2). Many attempts were made toward the separation of the diastereomeric mixtures **13**, **14** and, eventually, only diastereomers **13g** were successfully isolated via preparative HPLC (C18 reversed phase). Consequently, the diastereomeric mixtures were applied for the consecutive ring transformations. To that end, reaction of aziridines **13** and **14** with 2 molar equiv of $LiAlH_4$ and 0.3 equiv of $In(OTf)_3$ afforded pyrrolidines **15** and **16**, respectively, after 2 hours at reflux in excellent yields (78-95%, Table 2). Unfortunately, the obtained diastereomers **15** and **16a** could not be separated via preparative HPLC as well. Nonetheless, all pyrrolidines **15** and **16** were obtained in high yields and high purity, indicating that mono- and dialkylsubstitution in α-position with respect to the cyano moiety does not sterically hinder the ring-closing process. Furthermore, it should be noted that treatment of aziridines **14** with 2 molar equiv of $LiAlH_4$ without the addition of $In(OTf)_3$ resulted in a mixture of 2-(3-aminopropyl)aziridines as major compounds (70-80%) and 2-(aminomethyl)pyrrolidines **16** as minor constituents (20-30%). The partial formation of pyrrolidines **16** in the absence of a Lewis acid in this case could be attributed to the *Thorpe-Ingold* effect,[106] caused by the geminal substitution of the tether in aziridines **14**, and the Lewis acid activity of $LiAlH_4$.
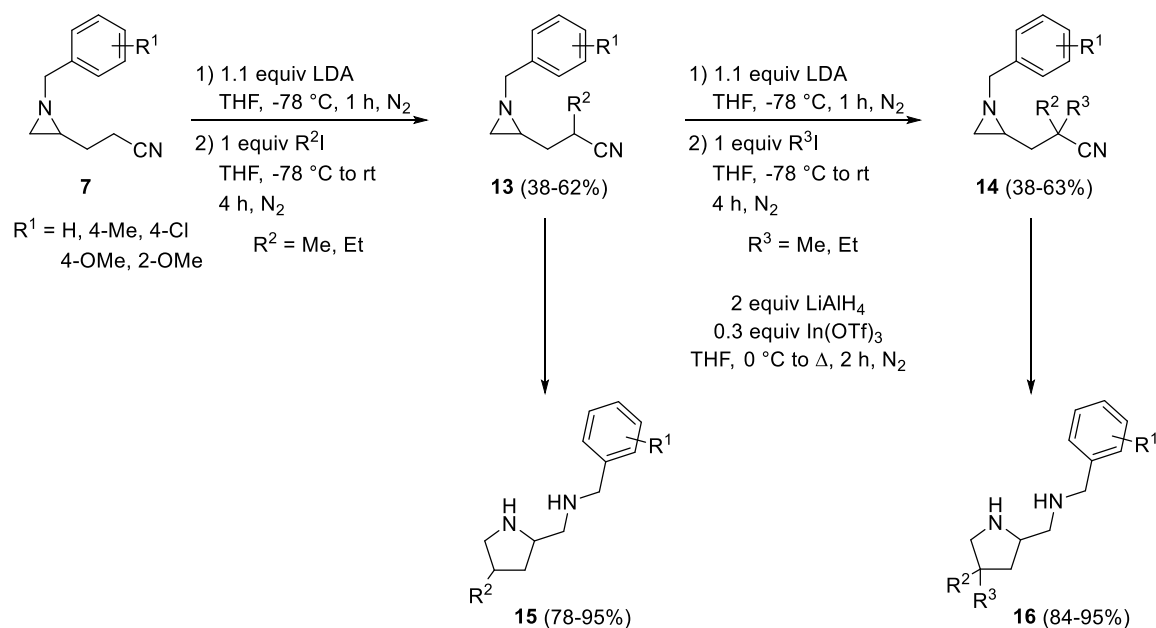
Scheme 5

Table 2. Synthesis of mono- and disubstituted aziridines 13/14 and 2-(aminomethyl)pyrrolidines 15/16.

R^1	R^2	R^3	Aziridines **13/14** (yield [%])[a]	dr[b,c]	Pyrrolidines **15/16** (yield [%])	dr[b,c]
H	Me	H	**13a** (62)	54/46	**15a** (83)	51/49
4-Me	Me	H	**13b** (52)	51/49	**15b** (92)	56/44
4-Cl	Me	H	**13c** (50)	56/44	**15c** (90)	57/43
4-OMe	Me	H	**13d** (38)	59/41	**15d** (95)	56/44
2-OMe	Me	H	**13e** (41)	53/47	**15e** (78)	52/48
H	Et	H	**13f** (52)	53/47	**15f** (81)	52/48
4-Me	Et	H	**13g** (48)	52/48	**15g** (82)	51/49
4-Cl	Et	H	**13h** (62)	51/49	**15h** (90)	51/49
4-OMe	Et	H	**13i** (46)	52/48	**15i** (86)	51/49
4-Me	Et	Me	**14a** (38)	51/49	**16a** (84)	51/49
4-Me	Et	Et	**14b** (63)	-	**16b** (89)	-
4-Cl	Et	Et	**14c** (44)	-	**16c** (95)	-
4-OMe	Et	Et	**14d** (55)	-	**16d** (88)	-

[a] After purification by column chromatography (SiO₂).

[b] Only indicated where appropriate.

[c] Determined by ¹H NMR analysis (CDCl₃) of the crude reaction mixture.

As only three approaches for the synthesis of 2-(aminomethyl)pyrrolidine **10a** (and no other derivatives) have been described[111] and only a few *5-exo-tet* ring-closing reactions onto non-activated aziridines have been reported in the literature,[22a-c,22e,22f] this ring rearrangement provides a useful new synthetic

tool for the preparation of a broad variety of novel heterocycles. In a first approach, single enantiomers were prepared through condensation of commercially available (*R*)- and (*S*)-pyroglutamic acid with benzylamine followed by reduction of the two amide groups by LiAlH$_4$ to afford the (*R*)- and (*S*)-isomer **10a** in an overall yield of 45% and 40%, respectively.[111c] In a second route, DCC-mediated coupling of Boc-protected *L*-proline with benzylamine followed by deprotection in the presence of TFA and immediate reduction of the amide moiety furnished (*S*)-2-(benzylaminomethyl)pyrrolidine in a yield of 63%.[111a] In a final approach, (*S*)-oxo-proline was first treated with chloral and consequently reacted with benzylamine. The corresponding diamide was subsequently reduced with LiAlH$_4$, resulting in the (*S*)-enantiomer **10a** in an overall yield of 70%.[111b]

In the next part of this study, the effect of introducing a phenyl substituent (instead of an alkyl group) in the side chain (R^2 = Ph in compounds **13**) on this type of rearrangement was investigated. In that respect, 2-(2-cyano-2-phenylethyl)aziridines **17** (R^1 = H, 4-Cl, 4-OMe), prepared from the corresponding 2-(bromomethyl)aziridines,[18] were subjected to the above-described hydride-induced ring rearrangement (Scheme 6). The same reaction conditions (2 molar equiv LiAlH$_4$, 0.3 equiv In(OTf)$_3$, 0°C to reflux, 2 hours, N$_2$) were applied as for the regioselective conversion of aziridines **7**, **13** and **14** toward pyrrolidines **10**, **15** and **16**, respectively. However, these conditions did not afford the corresponding 2-aminomethyl-4-phenylpyrrolidines **18**, but resulted in complex mixtures instead.
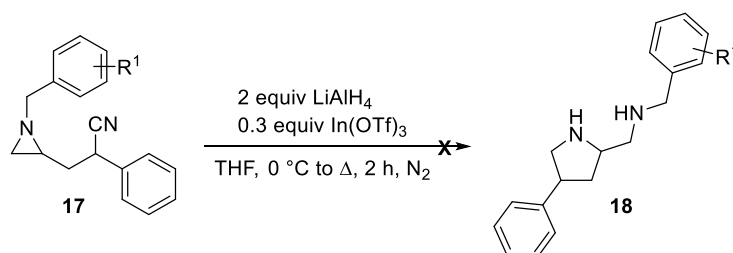
Scheme 6

In order to investigate this unexpected reaction outcome, a subsequent *NH*-derivatization reaction was envisaged next, as free *NH*-moieties could be deduced by means of infrared spectroscopy. To that end, the crude reaction mixture (obtained from the *N*-benzyl-substituted substrate **17a** (R^1 = H)) was treated with 2 equiv of TsCl in pyridine at reflux temperature, and arduous column chromatographic purification resulted in the isolation of *cis*-cyclopropane **19** in a yield of 15% after two steps (Scheme 7).
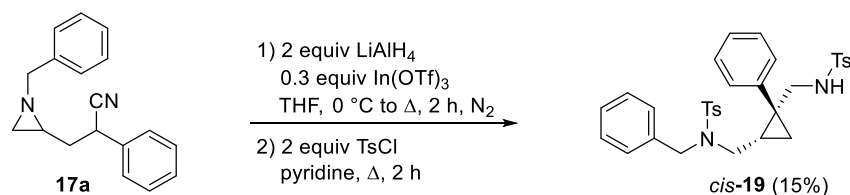
Scheme 7

The molecular identity of *cis*-cyclopropane **19** was unequivocally established by means of a single crystal X-ray analysis (Figure 1), providing clear evidence for the aziridine-to-cyclopropane migration.
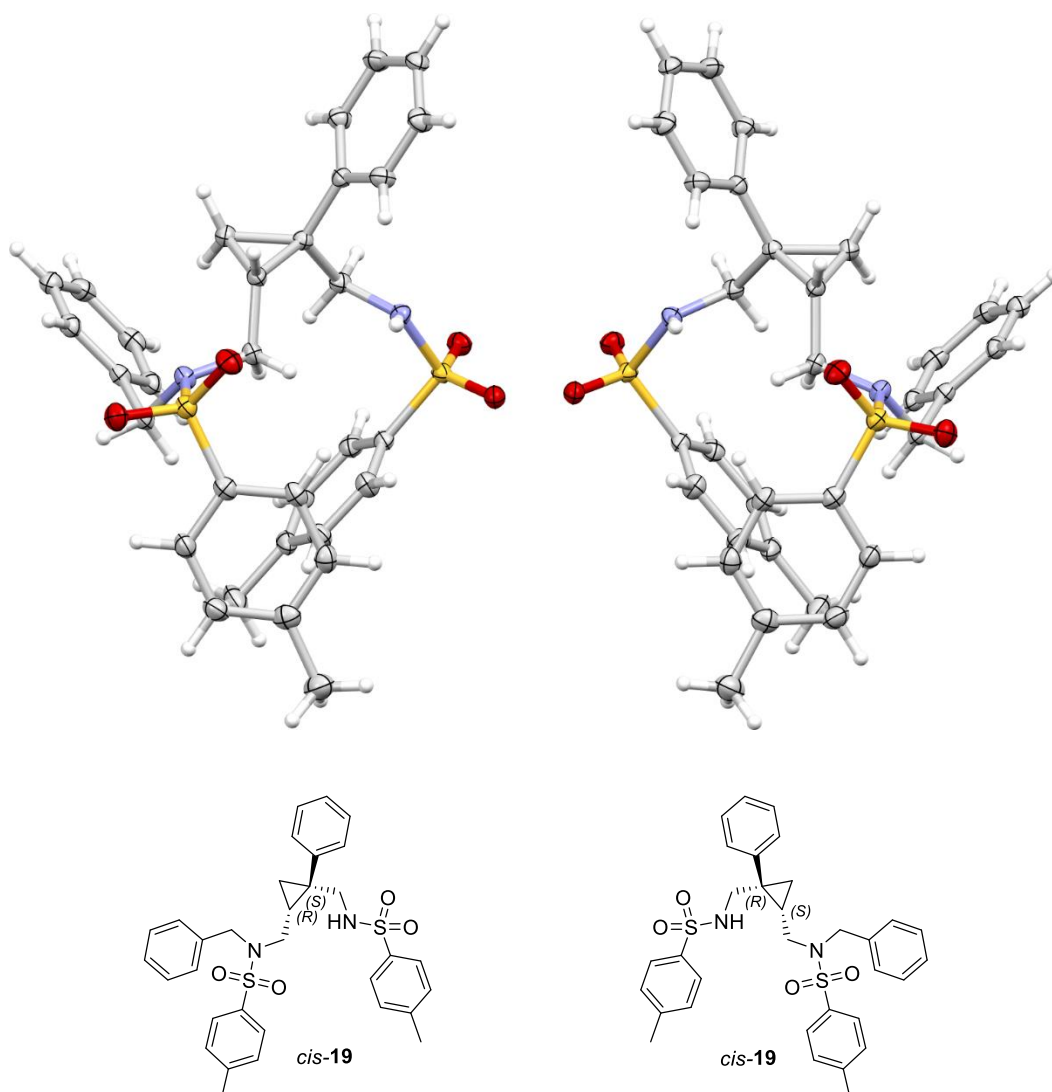
Figure 1

From a mechanistic point of view, the occurrence of this aziridine-to-cyclopropane interconversion can be rationalized by an intramolecular deprotonation in compound **20**, followed by a regioselective ring opening of the aziridine core at the more-hindered carbon atom (Scheme 8). Reduction of the imino group in cyclopropane **21** and subsequent aqueous work-up furnished cyclopropane **23**. Finally, tosylation of the amino moieties afforded cyclopropanes **19**. As a consequence, it appears that the presence of a benzylic proton in substrates **17** adversely affects this ring transformation. Moreover, introduction of an additional alkyl substituent in α-position with regard to the cyano moiety had no restrictions on the desired ring rearrangement as shown by the successful ring transformation of 2-(2-cyano-2-phenylbutyl)aziridines **5** toward the corresponding 2-aminomethyl-4-ethyl-4-phenylpyrrolidines

6 (Scheme 1). In this case, the addition of a Lewis acid did not seem to be necessary, which could be explained by the even stronger *Thorpe-Ingold* effect of the phenyl group compared to an ethyl substituent.
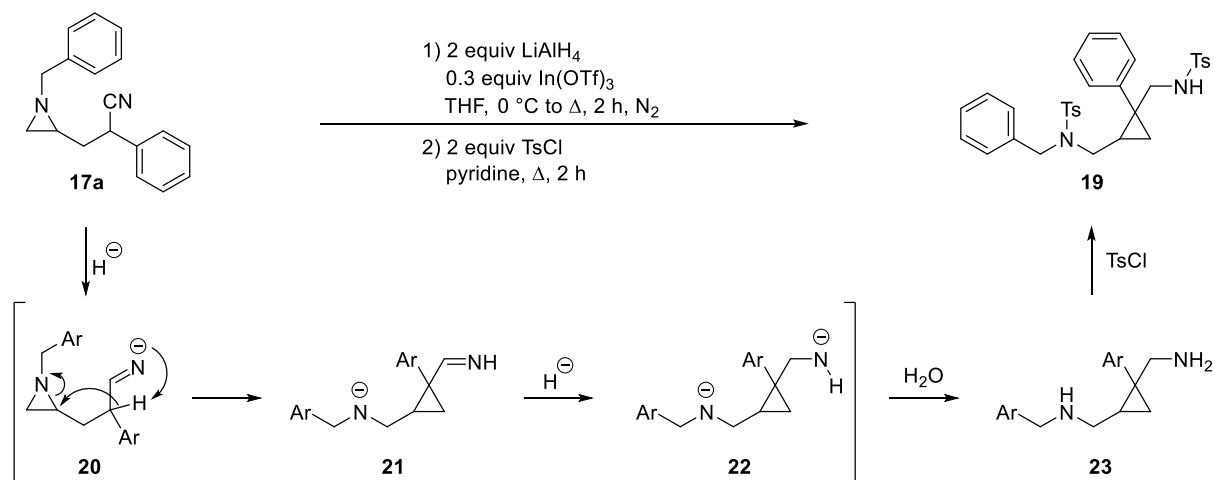
Scheme 8

Taking advantage of the free 1,2-diamino moiety in pyrrolidines **10**, **15** and **16**, a selection of these azaheterocycles was treated with 1 equiv of triphosgene or 1 equiv of carbonyldiimidazole (CDI) in THF at room temperature, affording new 2-oxo-1,3-diazabicyclo[3.3.0]octanes **24** in moderate to good yields after purification (38-57%, Scheme 9, Table 3). Reaction with 1 equiv of oxalylchloride furnished novel 2,3-dioxo-1,4-diazabicyclo[4.3.0]nonanes **25** in 20-27% yield after arduous silica gel purification. Although the separation of diastereomers **24d** could be successfully attained via preparative HPLC, diastereomers **25b** could not be isolated separately.
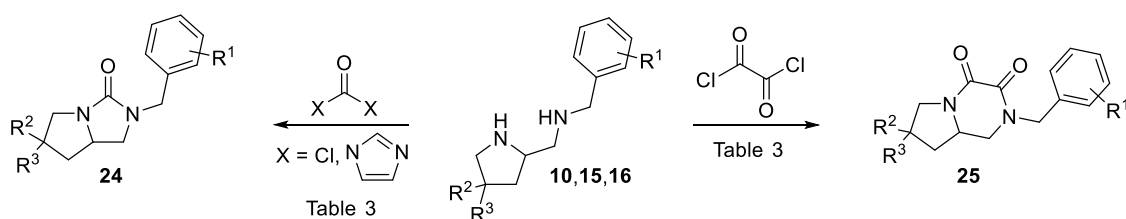
Scheme 9

Table 3. Synthesis of 1,3-diazabicyclo[3.3.0]octan-2-ones 24 and 2,3-dioxo-1,4-diazabicyclo[4.3.0]nonanes 25.

Compound	R^1	R^2	R^3	Reaction conditions	Yield [%][a]	dr[b,c]
24a	H	H	H	1 equiv triphosgene, THF, rt, 3 h	38	-
24b	4-Me	H	H	1 equiv CDI, THF, rt, 17 h	48	-
24c	4-Cl	H	H	1 equiv triphosgene, THF, rt, 4 h	43	-
24d	H	Et	H	1 equiv triphosgene, THF, rt, 4 h	41	60/40
24e	4-Me	Et	Et	1 equiv CDI, THF, rt, 17 h	57	-
25a	4-Cl	H	H	1 equiv oxalylchloride, THF, rt, 2 h	23	-
25b	4-OMe	Et	H	1 equiv oxalylchloride, THF, rt, 2 h	20	53/47
25c	4-Me	Et	Et	1 equiv oxalylchloride, THF, rt, 2 h	27	-

[a] After purification by preparative TLC (SiO_2).

[b] Only indicated where appropriate.

[c] Determined by ^1H NMR analysis ($CDCl_3$) of the crude reaction mixture.

Detailed NMR analysis of the obtained bicyclic compounds **24** and **25** provided additional evidence for the regioselective ring opening of the aziridine unit in 2-(2-cyanoethyl)aziridines **7**, **13** and **14** at the more-substituted carbon atom toward the formation of 2-(aminomethyl)pyrrolidine skeletons. In particular, the appearance of a coupling in the HMBC spectrum of compound **24a** between the benzylic hydrogen atoms and the NCH_2 carbon atom in the imidazolidinone core pointed to the proposed pyrrolidine structure.

Bicyclic imidazolidinones and diketopiperazines can be found as core structures in diverse compounds with pronounced biological properties, rendering azaheterocycles **24** and **25** useful new entities for further studies. For example, imidazolidinones have been incorporated in androgen receptor modulator **26**,[34a,34d] and the indole alkaloid gliocladin C **27** (with cytotoxic activity against lymphocytic leukemia) and dethiosecoemestrin **28** (an antifungal agent) accommodate a bicyclic diketopiperazine structure (Figure 2).[34b,34c]

Androgen receptor modulator **26**   (+)-Gliocladin C **27**   Dethiosecoemestrin **28**
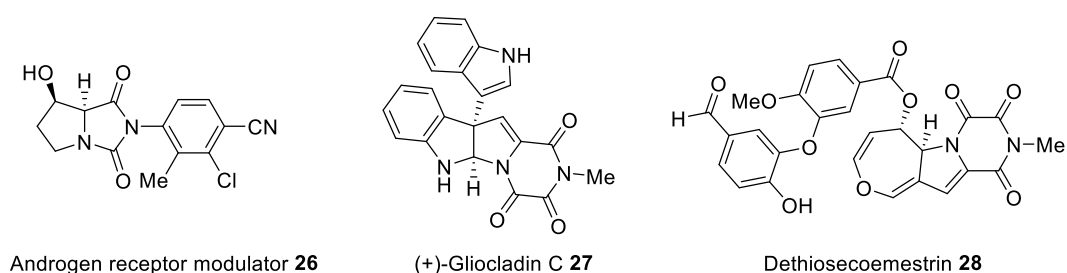
Figure 2

4. Ring rearrangement of 2-aryl-3-(2-cyanoethyl)aziridines

2-Arylaziridines are known to exhibit a different reactivity as compared to their 2-alkyl counterparts. In concreto, the introduction of an aromatic substituent on the aziridine core imposes a strong effect on the regiochemistry of the ring opening of non-activated aziridines. Whereas ring-opening reactions of 2-alkylaziridines usually proceed at the less-hindered carbon atom, nucleophilic attack at 2-arylaziridines is known to preferentially occur at the more-substituted carbon atom of the aziridine moiety.[14b] In order to study the possible effect of introducing an aryl group on the hydride-induced ring transformation of (2-cyanoethyl)aziridines, 3-(2-cyanoethyl)aziridines **29** were prepared from the corresponding 3-chloro-β-lactams[112] in a four-step procedure.[30] Then, the same reaction conditions were applied to 3-(2-cyanoethyl)aziridines **29** (2 molar equiv LiAlH$_4$, 0.3 equiv In(OTf)$_3$, 0°C to reflux, 1 hour, N$_2$), affording 3-aminopiperidines **32** in 56-84% yield through a regioselective ring opening at the benzylic position (Scheme 10). The relative *trans*-stereochemistry of piperidines **32** was confirmed by the vicinal coupling constants between the 2H and 3H protons on the piperidine ring (J_{trans} = 9.2-9.5 Hz), which is in accordance with the literature.[113]
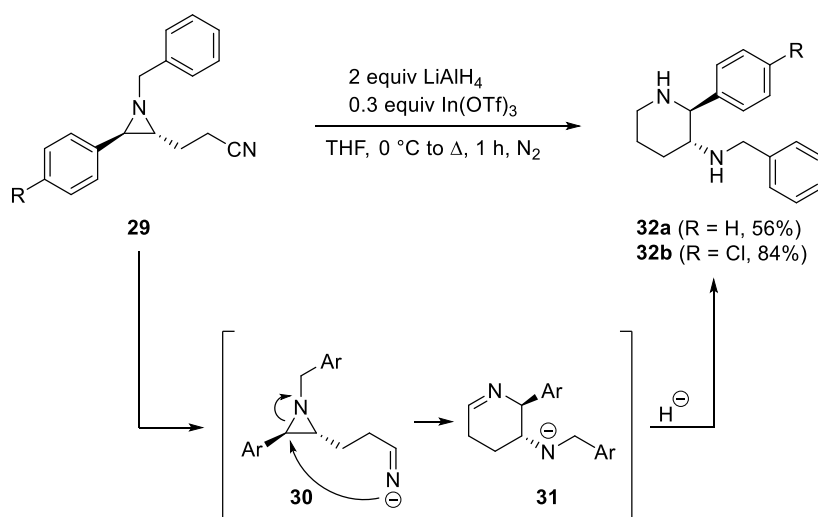
Scheme 10

The selective 3-aminopiperidine formation instead of the synthesis of the isomeric 2-(aminomethyl)pyrrolidine structure was supported by detailed NMR analysis. For example, the appearance of a coupling in the HMBC spectrum of compound **32a** between the benzylic hydrogen atoms and the benzylamino-substituted NHCH carbon atom pointed to the proposed piperidine structure. In contrast to the synthesis of 2-(aminomethyl)pyrrolidines **10**, **15** and **16**, reductive cyclization of 3-(2-cyanoethyl)aziridines **29** thus resulted in selective piperidine formation, indicating that resonance stabilization of the developing benzylic carbenium ion at C2 surpasses the Baldwin's rules. As a result, the ring rearrangement of (2-cyanoethyl)aziridines can be performed in a regiocontrolled manner, depending on the nature of the substituent present on the aziridine core.[114] Whereas 2-(2-cyanoethyl)aziridines were converted into pyrrolidines in a selective way, LiAlH$_4$-promoted ring

rearrangement of 3-(2-cyanoethyl)aziridines afforded piperidine structures as the sole transformation product. It is worth mentioning that treatment of aziridines **29** with 2 molar equiv of LiAlH₄ without the addition of In(OTf)₃ resulted in a complex mixture, proving the necessity of a Lewis acid for this cyclization reaction. In this case, the LiAlH₄-induced ring rearrangement of 3-(2-cyanoethyl)aziridines **29** proceeded with complete retention of configuration, demonstrating a new and convenient way to synthesize *trans*-piperidines **32**.[28,113,115]

Eventually, piperidine **32b** was treated with 1 equiv of CDI, affording constrained imidazolidinone **33** in a yield of 15% after elaborate purification (Scheme 11). Preparation of bicyclic diketopiperazine **34** as a peculiar novel heterocyclic scaffold was realized utilizing 1 equiv of oxalyldiimidazole in THF after 2 days at reflux in 18% yield after purification. In the latter case, oxalyldiimidazole had to be used because oxalylchloride only resulted in dimer formation. The low yields of heterobicycles **33** and **34** can be attributed to a laborious and cumbrous silica gel purification step, as well as to the concurrent formation of dimers.
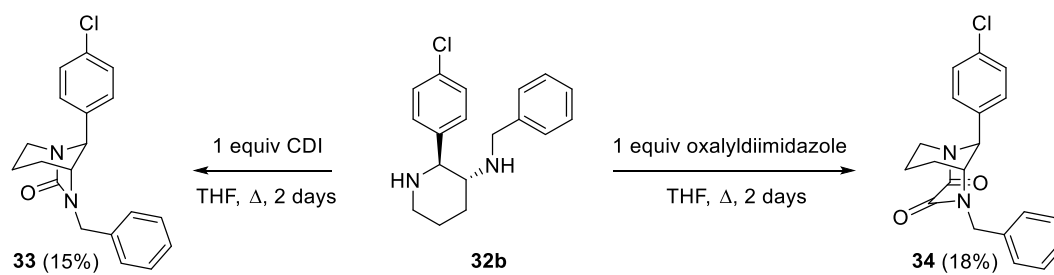
Scheme 11

5. Conclusion

In summary, a general protocol for the regioselective and stereospecific ring transformation of a variety of 2- and 3-(2-cyanoethyl)aziridines was investigated as a new synthetic strategy in the field of heterocyclic synthesis, affording a broad variety of 2-(aminomethyl)pyrrolidines and 3-aminopiperidines. Selection of the substituents on the aziridine core enabled control of the regioselectivity of the ring-opening process. Whereas 2-(2-cyanoethyl)aziridines (bearing no aromatic substituent) were transformed into 2-(aminomethyl)pyrrolidines, 2-aryl-3-(2-cyanoethyl)aziridines were converted into 3-aminopiperidines in a stereospecific way. Owing to the presence of two reactive secondary amino moieties, these versatile heterocyclic scaffolds were treated with different coupling reagents, resulting in novel functionalized imidazolidinone and diketopiperazine scaffolds.

6. Experimental details

General methods

^{1}H NMR spectra were recorded at 300 MHz on a Jeol Eclipse+ 300 or at 400 MHz on a Bruker Advance III-400 with solvents as indicated and tetramethylsilane as internal standard. ^{13}C NMR spectra were recorded at 75 MHz on a Jeol Eclipse+ 300 or at 100 MHz on a Bruker Advance III-400 with solvents as indicated. IR spectra were measured with a Spectrum One FT-IR spectrometer. Electron spray (ES) mass spectra were obtained with an Agilent 1100 Series MS (ES, 4000V) mass spectrometer. High resolution electron spray (ES-TOF) mass spectra were obtained with an Agilent Technologies 6210 Series time-of-flight. Melting points were determined on a Kofler bench, type WME Heizbank of Wagner & Munz and were corrected. Tetrahydrofuran was distilled over sodium benzophenone ketyl before use. All other solvents and reagents were used as received from the supplier.

Preparative HPLC was performed on an Agilent 1100 Series liquid chromatograph using a reversed phase column (Zorbax Eclipse XDB-C18 column, 150 × 21.2 mm, particle size 5 μm) that is thermostatized at 25 °C. The column is connected to a UV-VIS Variable Wavelength Detector (VWD). A mixture of H_2O and CH_3CN is used as eluent, with TFA as additive if needed.

Safety

General safety aspects

The practical work in this chapter was performed according to the SynBioC Research Group Internal Guidelines and with the aid of the internal safety document "Safety Instructions: How to work with chemicals". Wherever possible, hazardous or toxic reagents were avoided and/or substituted by safer or greener alternatives.

Specific safety aspects

A list of risks associated with each chemical and recommendations for safe use is available in the corresponding material safety data sheet (MSDS), which can be found on the website of the supplier. A brief overview of the most hazardous chemicals employed in this work will be given below, along with the potential hazards and precautions.

Bromine (Br$_2$): skin corrosion, acute aquatic toxicity. Avoid inhalation, wear protective gloves and clothing, avoid release in the environment.

Butyllithium solution: flammable and pyrophoric liquid, substances and mixtures which in contact with water emit flammable gases, skin corrosion. Avoid contact with air or water and work under an inert atmosphere. Avoid inhalation of vapors and wear protective gloves and clothing. Keep away from heat, fire, hot surfaces, sparks and ignition sources.

Carbonyldiimidazole (CDI): skin corrosion. Avoid inhalation and wear protective gloves and clothing.

Chloroacetylchloride: skin corrosion, specific target organ toxicity following repeated exposure. Avoid contact with water. Avoid inhalation and release in the environment. Wear protective gloves and clothing.

Chloroform: specific target organ toxicity following repeated exposure. Avoid inhalation and wear protective gloves and clothing.

Iodomethane (MeI): carcinogenic, skin corrosion. Avoid inhalation and wear protective gloves and clothing.

LiAlH₄ solution: flammable liquid, substances and mixtures which in contact with water emit flammable gases, skin corrosion. Avoid contact with air or water and work under an inert atmosphere. Avoid inhalation of vapors. Wear protective gloves and clothing. Keep away from heat, fire, hot surfaces, sparks and ignition sources.

Lithium diisopropylamide solution (LDA): skin corrosion. Keep away from heat, fire, hot surfaces, sparks and ignition sources. Avoid inhalation and wear protective gloves and clothing.

Solvents in general: acute toxicity after inhalation, specific target organ toxicity following single or repeated exposure. Keep away from heat, fire, hot surfaces, sparks and ignition sources. Avoid inhalation and wear protective gloves and clothing.

Triphosgene: acute toxicity after inhalation, skin corrosion. Avoid dust formation and inhalation. Wear protective gloves and clothing.

Synthesis of 1-arylmethyl-2-(2-cyanoethyl)aziridines 7

1-Arylmethyl-2-(2-cyanoethyl)aziridines **7** were prepared according to a literature procedure, and spectral data corresponded with those reported in the literature.[29]

Synthesis of 2-(3-aminopropyl)-1-(arylmethyl)aziridines 8

As a representative example, the synthesis of 2-(3-aminopropyl)-1-benzylaziridine **8a** is described here. To an ice-cooled solution of 1-benzyl-2-(2-cyanoethyl)aziridine **7a** (186 mg, 1 mmol) in dry THF (10 mL), was added a solution of LiAlH₄ (2 mL, 2 mmol, 2 equiv, 1.0 M in THF) via a syringe. Then, the resulting solution was heated under reflux for 2 hours under nitrogen atmosphere. Afterward, the reaction mixture was quenched with brine (10 mL) to neutralize the excess of LiAlH₄. Then, the reaction mixture was filtered through a path of Celite® and extracted with Et₂O (2 × 10 mL). Drying (MgSO₄), filtration of the drying agent and evaporation of the solvent *in vacuo* afforded 2-(3-aminopropyl)-1-benzylaziridine **8a** in a yield of 75% (143 mg, 0.75 mmol).

2-(3-Aminopropyl)-1-benzylaziridine 8a

Yellow oil. R_f = 0.03 (CH$_2$Cl$_2$/MeOH 9/1). Yield 75%. **^{1}H NMR** (400 MHz, CDCl$_3$): δ 1.21-1.50 (7H, m, CHN, (CH$_2$)$_2$CHN and NH$_2$); 1.40 (1H, d, J = 6.0 Hz, CH(HCH)N); 1.62 (1H, d, J = 3.2 Hz, CH(HCH)N); 2.61-2.65 (2H, m, CH$_2$CH$_2$N); 3.32 and 3.50 (2H, 2×d, J = 13.2 Hz, N(HCH)C$_{quat}$); 7.24-7.37 (5H, m, 5×CH$_{arom}$). **^{13}C NMR** (100 MHz, CDCl$_3$): δ 30.3 and 31.6 ((CH$_2$)$_2$CHN); 34.1 (CHCH$_2$N); 39.4 (CHN); 41.8 (CH$_2$CH$_2$N); 65.0 (C$_{quat}$CH$_2$N); 127.0, 128.2 and 128.3 (5×CH$_{arom}$); 139.3 (C$_{quat,arom}$). **IR (cm^{-1})**: ν$_{NH2}$ = 3274; ν$_{max}$ = 3029, 2924, 2856, 1570, 1495, 1452, 1355, 1310, 732, 697. **MS (70 eV)**: m/z (%): 191 (M$^+$+1, 100). **HRMS (ESI)**: m/z calcd for C$_{12}$H$_{19}$N$_2$: 191.1543 [M+H]$^+$; found: 191.1546.
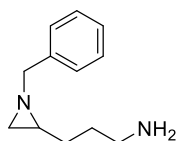
2-(3-Aminopropyl)1-(4-chlorobenzyl)aziridine 8c

Yellow oil. R_f = 0.03 (CH$_2$Cl$_2$/MeOH 9/1). Yield 71%. **^{1}H NMR** (400 MHz, CDCl$_3$): δ 1.39 (1H, d, J = 6.0 Hz, CH(HCH)N); 1.41-1.48 (7H, m, CHN, (CH$_2$)$_2$CHN and NH$_2$); 1.62 (1H, d, J = 3.1 Hz, CH(HCH)N); 2.64-2.67 (2H, m, CH$_2$CH$_2$N); 3.31 and 3.43 (2H, 2×d, J = 13.4 Hz, N(HCH)C$_{quat}$); 7.26-7.32 (4H, m, CH$_{arom}$). **^{13}C NMR** (100 MHz, ref = CDCl$_3$): δ 30.3 and 31.5 ((CH$_2$)$_2$CHN); 34.0 (CHCH$_2$N); 39.6 (CHN); 41.8 (CH$_2$CH$_2$N); 64.2 (C$_{quat}$CH$_2$N); 128.5 and 129.5 (4×CH$_{arom}$); 132.8 and 137.9 (2×C$_{quat,arom}$). **IR (cm^{-1})**: ν$_{NH}$ = 3278; ν$_{max}$ = 2926, 2853, 1490, 1086, 1014, 805. **MS (70 eV)**: m/z (%): 225 (M$^+$+1, 100). **HRMS (ESI)**: m/z calcd for C$_{12}$H$_{18}$ClN$_2$: 225.1153 [M+H]$^+$; found: 225.1153.
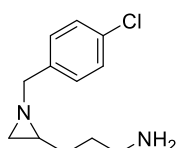
Spectral data of 2-(3-aminopropyl-1-(4-methylbenzyl)aziridine **8b** correspond with those reported in preliminary research at the Department of Sustainable Organic Chemistry and Technology (UGent).[116]

Synthesis of 1-arylmethyl-2-(2-cyanopropyl/butyl)aziridines 13

As a representative example, the synthesis of 1-benzyl-2-(2-cyanopropyl)aziridine **13a** is described. To a solution of diisopropylamine (1.11 g, 1.54 mL, 11 mmol, 1.1 equiv) in dry THF (10 mL), nBuLi (4.4 mL, 11 mmol, 1.1 equiv, 2.5 M in hexanes) was added via a syringe at -78 °C under nitrogen atmosphere, and the resulting solution was stirred for 30 min at -78 °C. Subsequently, a solution of 1-benzyl-2-(2-cyanoethyl)aziridine **7a** (1.86 g, 10 mmol) in THF (10 mL) was added via a syringe at -78 °C, and the resulting solution was stirred for 1 hour at -78 °C. Then, methyl iodide (1.42 g, 0.62 mL, 10 mmol, 1 equiv) was added via a syringe at -78 °C, and the resulting solution was stirred for 4 hours at room temperature. Afterward, the reaction mixture was poured into water (50 mL) and extracted with Et$_2$O (3 × 50 mL). Drying (MgSO$_4$), filtration of the drying agent and evaporation of the solvent *in vacuo* furnished 1-benzyl-2-(2-cyanopropyl)aziridine **13a**, which was purified by means of column chromatography on silica gel (Hexane/EtOAc 5/2) to provide a yellow-orange oil in a yield of 62% (1.24 g, 6.2 mmol).
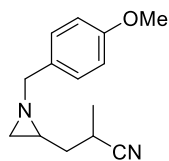
1-Benzyl-2-(2-cyanopropyl)aziridine 13a

Spectral data derived from the mixture of diastereomers

Yellow-orange oil. R_f = 0.08 (Hexane/EtOAc 3/1). Yield 62%. *dr* 54/46. **^{1}H NMR** (400 MHz, CDCl$_3$): δ 1.20 (3H, d, *J* = 7.1 Hz, (CH$_3$)$_{major}$); 1.24 (3H, d, *J* = 7.1 Hz, (CH$_3$)$_{minor}$); 1.30-1.37 (1H, m, CH(HCH)CH$_{minor}$); 1.52 (1H, d, *J* = 5.9 Hz, (HCH)CHN$_{major}$); 1.57 (1H, d, *J* = 6.2 Hz, (HCH)CHN$_{minor}$); 1.60-1.75 (6H, m, CHN$_{major}$, (CHCH$_2$CH)$_{major}$, (HCH)CHN$_{major}$, CHN$_{minor}$, (HCH)CHN$_{minor}$); 1.83 (1H, d×d×d, *J* = 13.9, 10.3, 4.1 Hz, CH(HCH)CH$_{minor}$); 2.52 (1H, d×q×d, *J* = 10.3, 7.1, 4.7 Hz, CHCN$_{minor}$); 2.61 (1H, sextet, *J* = 7.1 Hz, CHCN$_{major}$); 3.32 (1H, d, *J* = 12.8 Hz, (N(HCH)C$_{quat}$)$_{minor}$); 3.37 (2H, d, *J* = 13.1 Hz, (N(HCH)C$_{quat}$)$_{major}$); 3.51 (1H, d, *J* = 13.1 Hz, (N(HCH)C$_{quat}$)$_{major}$); 3.54 (1H, d, *J* = 12.8 Hz, (N(HCH)C$_{quat}$)$_{minor}$); 7.28-7.36 (10H, m, 10×CH$_{arom}$). **^{13}C NMR** (100 MHz, CDCl$_3$): δ 17.2 ((CH$_3$)$_{major}$); 18.2 ((CH$_3$)$_{minor}$); 23.7 (CHCN$_{major}$); 24.4 (CHCN$_{minor}$); 34.0 (CHCH$_2$N)$_{major}$; 34.4 (CHCH$_2$N)$_{minor}$; 36.1 (CHN$_{major}$); 36.8 (CHN$_{minor}$); 37.0 (CH(CH$_2$)CH$_{major}$); 37.8 (CH(CH$_2$)CH$_{minor}$); 64.7 ((NCH$_2$C$_{quat}$)$_{major}$); 64.8 ((NCH$_2$C$_{quat}$)$_{minor}$); 122.7 and 122.8 (2×CN); 127.3, 127.4, 128.3, 128.4, 128.5, 128.6 (10×CH$_{arom}$), 138.77 and 138.85 (2×C$_{quat,arom}$). **IR (cm^{-1})**: v_{CN} = 2238; v_{max} = 2981, 2938, 1454, 1357, 1250, 1160, 1060, 1028, 734, 698. **MS (70 eV)**: *m/z* (%): 201 (M$^+$+1, 100). **HRMS (ESI)**: *m/z* calcd for C$_{13}$H$_{17}$N$_2$: 201.1386 [*M*+H]$^+$; found: 201.1386.
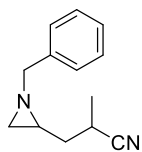
2-(2-Cyanopropyl)-1-(4-methylbenzyl)aziridine 13b

Spectral data derived from the mixture of diastereomers

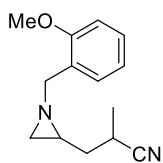Yellow-orange oil. R_f = 0.17 (Hexane/EtOAc 5/2). Yield 52%. *dr* 51/49. **^{1}H NMR** (400 MHz, CDCl$_3$): δ 1.20 (3H, d, *J* = 7.1 Hz, (CH$_3$)$_{major}$); 1.25 (3H, d, *J* = 7.1 Hz, (CH$_3$)$_{minor}$); 1.30-1.37 (1H, m, CH(HCH)CH$_{minor}$); 1.50 (1H, d, *J* = 6.0 Hz, (HCH)CHN$_{major}$); 1.55 (1H, d, *J* = 6.2 Hz, (HCH)CHN$_{minor}$); 1.61-1.73 (6H, m, CHN$_{major}$, (CHCH$_2$CH)$_{major}$, (HCH)CHN$_{major}$, CHN$_{minor}$, (HCH)CHN$_{minor}$); 1.83 (1H, d×d×d, *J* = 14.0, 10.3, 3.8 Hz, CH(HCH)CH$_{minor}$); 2.34 (3H, s, (CH$_{3,tos}$)$_{major}$); 2.35 (3H, s, (CH$_{3,tos}$)$_{minor}$); 2.54 (1H, d×q×d, *J* = 10.3, 7.1, 4.7 Hz, CHCN$_{minor}$); 2.60 (1H, sextet, *J* = 7.1 Hz, CHCN$_{major}$); 3.29 (1H, d, *J* = 13.1 Hz, (N(HCH)C$_{quat}$)$_{minor}$); 3.32 (2H, d, *J* = 13.1 Hz, (N(HCH)C$_{quat}$)$_{major}$); 3.47 (1H, d, *J* = 13.1 Hz, (N(HCH)C$_{quat}$)$_{major}$); 3.49 (1H, d, *J* = 13.1 Hz, (N(HCH)C$_{quat}$)$_{minor}$); 7.14 (2×1H, d, *J* = 7.9 Hz, CH$_{arom,major}$); 7.16 (2×1H, d, *J* = 7.8 Hz, CH$_{arom,minor}$); 7.21 (2×1H, d, *J* = 7.9 Hz, CH$_{arom,major}$); 7.23 (2×1H, d, *J* = 7.8 Hz, CH$_{arom,minor}$). **^{13}C NMR** (100 MHz, ref = CDCl$_3$): δ 17.2 ((CH$_3$)$_{major}$); 18.2 ((CH$_3$)$_{minor}$); 21.12 ((CH$_{3,tos}$)$_{major}$); 21.15 ((CH$_{3,tos}$)$_{minor}$); 23.7 (CHCN$_{major}$); 24.4 (CHCN$_{minor}$); 33.9 (CHCH$_2$N)$_{major}$; 34.3 (CHCH$_2$N)$_{minor}$; 36.1 (CHN$_{major}$); 36.8 (CHN$_{minor}$); 37.0 (CH(CH$_2$)CH$_{major}$); 37.9 (CH(CH$_2$)CH$_{minor}$); 64.4 ((NCH$_2$C$_{quat}$)$_{major}$); 64.6 ((NCH$_2$C$_{quat}$)$_{minor}$); 122.7 and 122.8 (2×CN); 128.3 (2×CH$_{arom,major}$); 128.4 (2×CH$_{arom,minor}$); 129.15 (2×CH$_{arom,major}$); 129.22 (2×CH$_{arom,minor}$); 135.7 ((C$_{quat,arom}$)$_{minor}$); 135.8 and 136.9 (2×(C$_{quat,arom}$)$_{major}$); 137.0 ((C$_{quat,arom}$)$_{minor}$). **IR (cm^{-1})**: v_{CN} = 2238; v_{max} = 2980, 2923, 1738, 1516, 1454, 1410, 1381, 1354, 1246, 1158, 1108, 1059, 1021, 800. **MS (70 eV)**: *m/z* (%): 215 (M$^+$+1, 100). **HRMS (ESI)**: *m/z* calcd for C$_{14}$H$_{19}$N$_2$: 215.1543 [*M*+H]$^+$; found: 215.1547.
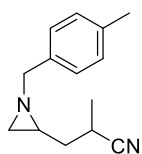
1-(4-Chlorobenzyl)-2-(2-cyanopropyl)aziridine 13c

Spectral data derived from the mixture of diastereomers

Yellow-orange oil. R_f = 0.19 (Hexane/EtOAc 5/2). Yield 50%. *dr* 56/44. **^{1}H NMR** (400 MHz, CDCl$_3$): δ 1.24 (3H, d, *J* = 7.1 Hz, (CH$_3$)$_{major}$); 1.27 (3H, d, *J* = 7.1 Hz, (CH$_3$)$_{minor}$); 1.32-1.39 (1H, m, CH(HCH)CH$_{minor}$); 1.49 (1H, d, *J* = 5.9 Hz, (HCH)CHN$_{major}$); 1.55 (1H, d, *J* = 6.2 Hz, (HCH)CHN$_{minor}$); 1.61-1.77 (6H, m, CHN$_{major}$, (CHCH$_2$CH)$_{major}$, (HCH)CHN$_{major}$, CHN$_{minor}$, (HCH)CHN$_{minor}$); 1.83 (1H, d×d×d, *J* = 13.8, 10.3, 4.2 Hz, CH(HCH)CH$_{minor}$); 2.55 (1H, d×q×d, *J* = 10.3, 7.1, 4.7 Hz, CHCN$_{minor}$); 2.64 (1H, sextet, *J* = 7.1 Hz, CHCN$_{major}$); 3.33 (1H, d, *J* = 13.1 Hz, (N(HCH)C$_{quat}$)$_{minor}$); 3.38 (2H, d, *J* = 13.2 Hz, (N(HCH)C$_{quat}$)$_{major}$); 3.44 (1H, d, *J* = 13.2 Hz, (N(HCH)C$_{quat}$)$_{major}$); 3.47 (1H, d, *J* = 13.1 Hz, (N(HCH)C$_{quat}$)$_{minor}$); 7.26-7.34 (8H, m, 8×CH$_{arom}$). **^{13}C NMR** (100 MHz, CDCl$_3$): δ 17.4 ((CH$_3$)$_{major}$); 18.2 ((CH$_3$)$_{minor}$); 23.8 (CHCN$_{major}$); 24.4 (CHCN$_{minor}$); 33.8 (CHCH$_2$N)$_{major}$; 34.4 (CHCH$_2$N)$_{minor}$; 36.4 (CHN$_{major}$); 36.9 (CHN$_{minor}$); 37.0 (CH(CH$_2$)CH$_{major}$); 37.7 (CH(CH$_2$)CH$_{minor}$); 63.9 ((NCH$_2$C$_{quat}$)$_{major}$); 64.0 ((NCH$_2$C$_{quat}$)$_{minor}$); 122.6 and 122.7 (2×CN); 128.6, 128.7, 129.5, 129.7 (8×CH$_{arom}$); 133.1, 133.2, 137.3 and 137.4 (4×C$_{quat,arom}$). **IR (cm^{-1})**: v_{CN} = 2239; v_{max} = 2982, 2926, 1737, 1491, 1455, 1407, 1352, 1245, 1160, 1087, 1062, 1014, 806. **MS (70 eV)**: *m/z* (%): 235 (M$^+$+1, 100). **HRMS (ESI)**: *m/z* calcd for C$_{13}$H$_{16}$ClN$_2$: 235.0997 [*M*+H]$^+$; found: 235.0993.
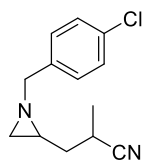
### 2-(2-Cyanopropyl)- 1-(4-methoxybenzyl)aziridine 13d

Spectral data derived from the mixture of diastereomers.

Yellow-orange oil. R_f = 0.06 (Hexane/EtOAc 5/2). Yield 38%. *dr* 59/41. **^{1}H NMR** (400 MHz, CDCl$_3$): δ 1.20 (3H, d, *J* = 7.0 Hz, (CH$_3$)$_{major}$); 1.24 (3H, d, *J* = 7.1 Hz, (CH$_3$)$_{minor}$); 1.28-1.34 (1H, m, CH(HCH)CH$_{minor}$); 1.50 (1H, d, *J* = 6.0 Hz, (HCH)CHN$_{major}$); 1.55 (1H, d, *J* = 6.2 Hz, (HCH)CHN$_{minor}$); 1.59-1.74 (6H, m, CHN$_{major}$, (CHCH$_2$CH)$_{major}$, (HCH)CHN$_{major}$, CHN$_{minor}$, (HCH)CHN$_{minor}$); 1.84 (1H, d×d×d, *J* = 14.0, 10.4, 3.8 Hz, CH(HCH)CH$_{minor}$); 2.51 (1H, d×q×d, *J* = 10.4, 7.1, 4.7 Hz, CHCN$_{minor}$); 2.60 (1H, sextet, *J* = 7.0 Hz, CHCN$_{major}$); 3.22 (1H, d, *J* = 12.7 Hz, (N(HCH)C$_{quat}$)$_{minor}$); 3.29 (2H, d, *J* = 12.8 Hz, (N(HCH)C$_{quat}$)$_{major}$); 3.45 (1H, d, *J* = 12.8 Hz, (N(HCH)C$_{quat}$)$_{major}$); 3.51 (1H, d, *J* = 12.7 Hz, (N(HCH)C$_{quat}$)$_{minor}$); 3.80 (3H, s, CH$_3$O$_{major}$); 3.81 (3H, s, CH$_3$O$_{minor}$); 6.87 (2×1H, d, *J* = 8.7 Hz, CH$_{arom,major}$); 6.89 (2×1H, d, *J* = 8.6 Hz, CH$_{arom,minor}$); 7.24 (2×1H, d, *J* = 8.7 Hz, CH$_{arom,major}$); 7.26 (2×1H, d, *J* = 8.6 Hz, CH$_{arom,minor}$). **^{13}C NMR** (100 MHz, ref = CDCl$_3$): δ 17.2 ((CH$_3$)$_{major}$); 18.2 ((CH$_3$)$_{minor}$); 23.8 (CHCN$_{major}$); 24.4 (CHCN$_{minor}$); 33.8 (CHCH$_2$N)$_{major}$; 34.2 (CHCH$_2$N)$_{minor}$; 36.0 (CHN$_{major}$); 36.8 (CHN$_{minor}$); 37.0 (CH(CH$_2$)CH$_{major}$); 37.9 (CH(CH$_2$)CH$_{minor}$); 55.3 (2×CH$_3$O); 64.1 ((NCH$_2$C$_{quat}$)$_{major}$); 64.2 ((NCH$_2$C$_{quat}$)$_{minor}$); 113.88 (2×CH$_{arom,major}$); 113.94 (2×CH$_{arom,minor}$); 122.7 and 122.8 (2×CN); 129.5 (2×CH$_{arom,major}$); 129.7 (2×CH$_{arom,minor}$); 130.96 ((C$_{quat,arom}$)$_{minor}$); 131.00 and 158.92 (2×(C$_{quat,arom}$)$_{major}$); 158.95 ((C$_{quat,arom}$)$_{minor}$). **IR (cm^{-1})**: v_{CN} = 2239; v_{max} = 2937, 2836, 1737, 1612, 1512, 1456, 1355, 1301, 1243, 1175, 1108, 1032, 818, 752. **MS (70 eV)**: *m/z* (%): 231 (M$^+$+1, 100). **HRMS (ESI)**: *m/z* calcd for C$_{14}$H$_{19}$N$_2$O: 231.1492 [*M*+H]$^+$; found: 231.1487.

2-(2-Cyanopropyl)- 1-(2-methoxybenzyl)aziridine 13e

Spectral data derived from the mixture of diastereomers.

Yellow-orange oil. R_f = 0.09 (Hexane/EtOAc 5/2). Yield 41%. *dr* 53/47. **^{1}H NMR** (400 MHz, CDCl$_3$): δ 1.24 (3H, d, *J* = 7.0 Hz, (CH$_3$)$_{major}$); 1.24 (3H, d, *J* = 7.1 Hz, (CH$_3$)$_{minor}$); 1.32-1.36 (1H, m, CH(<u>H</u>CH)CH$_{minor}$); 1.50 (1H, d, *J* = 5.8 Hz, (<u>H</u>CH)CHN$_{major}$); 1.55 (1H, d, *J* = 6.2 Hz, (<u>H</u>CH)CHN$_{minor}$); 1.62-1.80 (6H, m, CHN$_{major}$, (CHC<u>H$_2$</u>CH)$_{major}$, (HC<u>H</u>)CHN$_{major}$, CHN$_{minor}$, (HC<u>H</u>)CHN$_{minor}$); 1.84 (1H, d×d×d, *J* = 13.6, 10.0, 4.1 Hz, CH(HC<u>H</u>)CH$_{minor}$); 2.53 (1H, d×q×d, *J* = 10.0, 7.1, 4.7 Hz, CHCN$_{minor}$); 2.63 (1H, sextet, *J* = 7.0 Hz, CHCN$_{major}$); 3.39 (1H, d, *J* = 13.3 Hz, (N(<u>H</u>CH)C$_{quat}$)$_{minor}$); 3.44 (2H, d, *J* = 13.6 Hz, (N(<u>H</u>CH)C$_{quat}$)$_{major}$); 3.53 (1H, d, *J* = 13.6 Hz, (N(HC<u>H</u>)C$_{quat}$)$_{major}$); 3.57 (1H, d, *J* = 13.3 Hz, (N(HC<u>H</u>)C$_{quat}$)$_{minor}$); 3.83 (3H, s, CH$_3$O$_{major}$); 3.84 (3H, s, CH$_3$O$_{minor}$); 6.86-6.89 (2H, m, CH$_{arom}$); 6.94-6.98 (2H, m, CH$_{arom}$); 7.24-7.29 (2H, m, CH$_{arom}$); 7.38-7.40 (2H, m, CH$_{arom}$). **^{13}C NMR** (100 MHz, ref = CDCl$_3$): δ 17.3 ((CH$_3$)$_{major}$); 18.3 ((CH$_3$)$_{minor}$); 23.8 (<u>C</u>HCN$_{major}$); 24.4 (<u>C</u>HCN$_{minor}$); 34.0 (CH<u>C</u>H$_2$N)$_{major}$; 34.4 (CH<u>C</u>H$_2$N)$_{minor}$; 36.1 (CHN$_{major}$); 36.8 (CHN$_{minor}$); 37.1 (CH(<u>C</u>H$_2$)CH$_{major}$); 38.0 (CH(<u>C</u>H$_2$)CH$_{minor}$); 55.3 (CH$_3$O$_{major}$); 55.4 (CH$_3$O$_{minor}$); 58.6 (2×N<u>C</u>H$_2$C$_{quat}$); 110.2 and 110.3 (2×CH$_{arom}$); 120.5 (2×CH$_{arom}$); 122.85 and 122.87 (2×CN); 127.17 and 127.23 (2×C$_{quat,arom}$); 128.4, 128.5, 129.7 and 130.0 (4×CH$_{arom}$); 157.11 and 157,14 (2×C$_{quat,arom}$). **IR (cm^{-1})**: ν$_{CN}$ = 2239; ν$_{max}$ = 2939, 1737, 1602, 1588, 1492, 1462, 1439, 1357, 1287, 1241, 1159, 1110, 1050, 1027, 754. **MS (70 eV)**: *m/z* (%): 231 (M$^+$+1, 100). **HRMS (ESI)**: *m/z* calcd for C$_{14}$H$_{19}$N$_2$O: 231.1492 [*M*+H]$^+$; found: 231.1489.
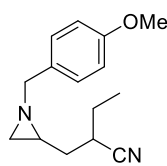
1-Benzyl-2-(2-cyanobutyl)aziridine 13f

Spectral data derived from the mixture of diastereomers

Yellow oil. R_f = 0.20 (Hexane/EtOAc 5/2). Yield 52%. *dr* 53/47. **^{1}H NMR** (400 MHz, CDCl$_3$): δ 0.96 (3H, t, *J* = 7.4 Hz, (C<u>H$_3$</u>CH$_2$)$_{major}$); 1.00 (3H, t, *J* = 7.4 Hz, (C<u>H$_3$</u>CH$_2$)$_{minor}$); 1.33 (1H, d×d×d, *J* = 13.8, 8.0, 4.6 Hz, CH(<u>H</u>CH)CH$_{minor}$); 1.47-1.58 (6H, m, (CH$_3$C<u>H$_2$</u>)$_{major}$, (<u>H</u>CH)CHN$_{major}$, (CH$_3$C<u>H$_2$</u>)$_{minor}$, (<u>H</u>CH)CHN$_{minor}$,); 1.61-1.68 (2H, m, CH(<u>H</u>CH)CH$_{major}$, CHN$_{major}$); 1.70 (1H, d, *J* = 5.9 Hz, (HC<u>H</u>)CHN$_{major}$); 1.71-1.76 (3H, m, CHN$_{minor}$, CH(HC<u>H</u>)CH$_{major}$, (HC<u>H</u>)CHN$_{minor}$,); 1.84 (1H, d×d×d, *J* = 13.8, 10.5, 4.1 Hz, CH(HC<u>H</u>)CH$_{minor}$); 2.35-2.48 (2H, m, CHCN); 3.33 (2H, 2×d, *J* = 13.0 Hz, (N(<u>H</u>CH)C$_{quat}$)$_{major}$ and (N(<u>H</u>CH)C$_{quat}$)$_{minor}$); 3.53 (2H, 2×d, *J* = 13.0 Hz, (N(HC<u>H</u>)C$_{quat}$)$_{major}$ and (N(HC<u>H</u>)C$_{quat}$)$_{minor}$); 7.27-7.36 (10H, m, 10×CH$_{arom}$). **^{13}C NMR** (100 MHz, CDCl$_3$): δ 11.4 ((<u>C</u>H$_3$CH$_2$)$_{minor}$); 11.5 ((<u>C</u>H$_3$CH$_2$)$_{major}$); 24.7 ((CH$_3$<u>C</u>H$_2$)$_{major}$); 25.7 ((CH$_3$<u>C</u>H$_2$)$_{minor}$); 31.4 (<u>C</u>HCN$_{major}$); 32.0 (<u>C</u>HCN$_{minor}$); 33.9 (CH<u>C</u>H$_2$N)$_{major}$; 34.5 (CH<u>C</u>H$_2$N)$_{minor}$; 35.1 (CH(<u>C</u>H$_2$)CH$_{major}$); 35.6 (CH(<u>C</u>H$_2$)CH$_{minor}$); 36.3 (CHN$_{major}$); 36.9 (CHN$_{minor}$); 64.7 and 64.8 (2×N<u>C</u>H$_2$C$_{quat}$); 121.89 and 121.92 (2×CN); 127.3, 127.4, 128.3, 128.46, 128.50 and 128.6 (10×CH$_{arom}$); 138.8 and 138.9 (2×C$_{quat,arom}$). **IR (cm^{-1})**: ν$_{CN}$ = 2237; ν$_{max}$ = 2969, 2934, 1454, 1357, 1249, 1160, 1065, 1028, 734, 698. **MS (70 eV)**: *m/z* (%): 215 (M$^+$+1, 100). **HRMS (ESI)**: *m/z* calcd for C$_{14}$H$_{19}$N$_2$: 215.1543 [*M*+H]$^+$; found: 215.1548.
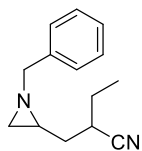
2-(2-Cyanobutyl)-1-(4-methylbenzyl)aziridine 13g

Yield 48%. *dr* 52/48.

Major isomer
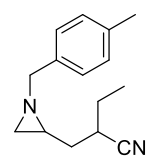
Colorless oil. R_f = 0.17 (Hexane/EtOAc 5/2). **¹H NMR** (400 MHz, CDCl₃): δ 0.96 (3H, t, *J* = 7.4 Hz, C<u>H</u>₃CH₂); 1.45-1.53 (3H, m, CH₃C<u>H</u>₂, (<u>H</u>CH)CHN); 1.59-1.76 (4H, m, CHN, CH(C<u>H</u>₂)CH, (HC<u>H</u>)CHN); 2.34 (3H, s, C<u>H</u>₃C_{quat}); 2.40-2.47 (1H, m, C<u>H</u>CN); 3.26 (1H, d, *J* = 12.9 Hz, N(<u>H</u>CH)C_{quat}); 3.51 (1H, d, *J* = 12.9 Hz, N(HC<u>H</u>)C_{quat}); 7.15 (2H, 2×d, *J* = 7.9 Hz, 2×CH_{arom}); 7.21 (2H, 2×d, *J* = 7.9 Hz, 2×CH_{arom}). **¹³C NMR** (100 MHz, CDCl₃): δ 11.5 (<u>C</u>H₃CH₂); 21.1 (<u>C</u>H₃C_{quat}); 24.7 (CH₃<u>C</u>H₂); 31.4 (<u>C</u>HCN); 33.9 (CH<u>C</u>H₂N); 35.1 (CH(<u>C</u>H₂)CH); 36.2 (CHN); 64.5 (N<u>C</u>H₂C_{quat}); 122.0 (CN); 128.3 and 129.2 (4×CH_{arom}); 135.8 and 136.9 (2×C_{quat,arom}). **IR (cm⁻¹)**: ν_{CN} = 2235; ν_{max} = 2968, 2930, 2877, 2235, 1515, 1459, 1409, 1383, 1354, 1252, 1159, 1066, 1021, 858, 800. **MS (70 eV)**: *m/z* (%): 229 (M⁺+1, 100). **HRMS (ESI)**: *m/z* calcd for C₁₅H₂₁N₂: 229.1699 [*M*+H]⁺; found: 229.1699.

Minor isomer
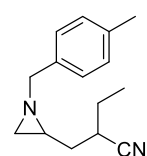
Colorless oil. R_f = 0.17 (Hexane/EtOAc 5/2). **¹H NMR** (400 MHz, CDCl₃): δ 1.00 (3H, t, *J* = 7.4 Hz, C<u>H</u>₃CH₂); 1.34 (1H, d×d×d, *J* = 13.8, 7.9, 4.5 Hz, CH(<u>H</u>CH)CH); 1.51-1.59 (3H, m, (CH₃C<u>H</u>₂), (<u>H</u>CH)CHN); 1.68-1.74 (2H, m, CHN, (HC<u>H</u>)CHN); 1.84 (1H, d×d×d, *J* = 13.8, 10.5, 4.0 Hz, CH(HC<u>H</u>)CH); 2.35 (3H, s, C<u>H</u>₃C_{quat}); 2.41 (1H, d×d×d×d, *J* = 10.5, 7.0, 7.0, 4.5 Hz, C<u>H</u>CN); 3.31 (1H, d, *J* = 12.8 Hz, N(<u>H</u>CH)C_{quat}); 3.48 (1H, d, *J* = 12.8 Hz, N(HC<u>H</u>)C_{quat}); 7.16 (2H, 2×d, *J* = 7.9 Hz, 2×CH_{arom}); 7.23 (2H, 2×d, *J* = 7.9 Hz, 2×CH_{arom}). **¹³C NMR** (100 MHz, ref = CDCl₃): δ 11.4 (<u>C</u>H₃CH₂); 21.1 (<u>C</u>H₃C_{quat}); 25.7 (CH₃<u>C</u>H₂); 32.0 (<u>C</u>HCN); 34.4 (CH<u>C</u>H₂N); 35.8 (CH(<u>C</u>H₂)CH); 36.9 (CHN); 64.6 (N<u>C</u>H₂C_{quat}); 121.9 (CN); 128.4 and 129.2 (4×CH_{arom}); 135.8, and 137.0 (2×C_{quat,arom}). **IR (cm⁻¹)**: ν_{CN} = 2237; ν_{max} = 2969, 2932, 1734, 1516, 1460, 1354, 1247, 1160, 1065, 800. **MS (70 eV)**: *m/z* (%): 229 (M⁺+1, 100). **HRMS (ESI)**: *m/z* calcd for C₁₅H₂₁N₂: 229.1699 [*M*+H]⁺; found: 229.1697.

1-(4-Chlorobenzyl)-2-(2-cyanobutyl)aziridine 13h

Spectral data derived from the mixture of diastereomers

Yellow oil. R_f = 0.13 (Hexane/EtOAc 5/2). Yield 62%. *dr* 51/49. **¹H NMR** (400 MHz, CDCl₃): δ 1.00 (3H, t, *J* = 7.7 Hz, (C<u>H</u>₃CH₂)_{major}); 1.02 (3H, t, *J* = 7.7 Hz, (C<u>H</u>₃CH₂)_{minor}); 1.36 (1H, d×d×d, *J* = 13.8, 7.9, 4.7 Hz, CH(<u>H</u>CH)CH_{minor}); 1.48 (1H, d, *J* = 5.9 Hz, (<u>H</u>CH)CHN_{major}); 1.50-1.59 (5H, m, (CH₃C<u>H</u>₂)_{major}, (<u>H</u>CH)CHN_{minor}, (CH₃C<u>H</u>₂)_{minor}); 1.61-1.66 (2H, m, CH(<u>H</u>CH)CH_{major}, CHN_{major}); 1.69 (1H, d, *J* = 5.9 Hz, (HC<u>H</u>)CHN_{major}); 1.70-1.78 (3H, m, CHN_{minor}, (HC<u>H</u>)CHN_{minor}, CH(HC<u>H</u>)CH_{major}); 1.84 (1H, d×d×d, *J* = 13.8, 10.5, 4.3 Hz, CH(HC<u>H</u>)CH_{minor}); 2.40-2.51 (2H, m, CHCN); 3.36 (1H, d, *J* = 13.1 Hz, N(<u>H</u>CH)C_{quat}); 3.401-3.403 (2H, m, NCH₂C_{quat}); 3.44 (1H, d, *J* = 13.1 Hz,(N(<u>H</u>CH)C_{quat}); 7.26-7.34 (8H, m, 8×CH_{arom}). **¹³C NMR** (100 MHz, CDCl₃): δ 11.4 ((<u>C</u>H₃CH₂)_{minor}); 11.5 ((<u>C</u>H₃CH₂)_{major}); 24.9 ((CH₃<u>C</u>H₂)_{major}); 25.7 ((CH₃<u>C</u>H₂)_{minor}); 31.5 (<u>C</u>HCN_{major}); 32.0 (<u>C</u>HCN_{minor}); 33.8 (CH<u>C</u>H₂N)_{major}; 34.5 (CH<u>C</u>H₂N)_{minor}; 35.0 (CH(<u>C</u>H₂)CH_{major}); 35.6 (CH(<u>C</u>H₂)CH_{minor}); 36.5 (CHN_{major}); 37.0 (CHN_{minor}); 63.92 and 64.03 (2×N<u>C</u>H₂C_{quat}); 121.78 and 121.82 (2×CN); 128.6, 128.7, 129.6 and 129.7 (8×CH_{arom}); 133.07, 133.13, 137.3 and 137.4 (4×C_{quat,arom}). **IR (cm⁻¹)**: ν_{CN} = 2237; ν_{max} = 2969, 2933, 1490, 1461, 1407, 1350, 1248, 1161, 1086, 1015, 857, 804, 666. **MS (70 eV)**: *m/z* (%): 249 (M⁺+1, 100). **HRMS (ESI)**: *m/z* calcd for C₁₄H₁₈ClN₂: 249.1153 [*M*+H]⁺; found: 249.1160.
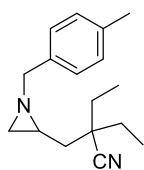
1-(4-Methoxybenzyl)-2-(2-cyanobutyl)aziridine 13i

Spectral data derived from the mixture of diastereomers

Yellow orange oil. R_f = 0.09 (Hexane/EtOAc 5/2). Yield 46%. *dr* 52/48. **^{1}H NMR** (400 MHz, CDCl$_3$): δ 0.97 (3H, t, *J* = 7.4 Hz, (C<u>H</u>$_3$CH$_2$)$_{major}$); 1.00 (3H, t, *J* = 7.4 Hz, (C<u>H</u>$_3$CH$_2$)$_{minor}$); 1.31 (1H, d×d×d, *J* = 13.8, 8.0, 4.5 Hz, CH(<u>H</u>CH)CH$_{minor}$); 1.46-1.59 (6H, m, (CH$_3$C<u>H</u>$_2$)$_{major}$, (<u>H</u>CH)CHN$_{major}$, (CH$_3$C<u>H</u>$_2$)$_{minor}$, (<u>H</u>CH)CHN$_{minor}$,); 1.60-1.75 (6H, m, CHN$_{major}$, CHC<u>H</u>$_2$CH$_{major}$, (HC<u>H</u>)CHN$_{major}$, CHN$_{minor}$, (HC<u>H</u>)CHN$_{minor}$); 1.84 (1H, d×d×d, *J* = 13.9, 10.6, 3.9 Hz, CH(HC<u>H</u>)CH$_{minor}$); 2.35-2.47 (2H, m, CHCN); 3.245 (1H, d, *J* = 12.8 Hz, N(<u>H</u>CH)C$_{quat}$); 3.248 (1H, d, *J* = 12.6 Hz, N(<u>H</u>CH)C$_{quat}$); 3.486 (1H, d, *J* = 12.8 Hz, N(HC<u>H</u>)C$_{quat}$); 3.490 (1H, d, *J* = 12.6 Hz, N(HC<u>H</u>)C$_{quat}$); 3.80 (3H, s, CH$_3$O$_{major}$); 3.81 (3H, s, CH$_3$O$_{minor}$); 6.86-6.90 (4H, m, 4×CH$_{arom}$); 7.23-7.27 (4H, m, 4×CH$_{arom}$). **^{13}C NMR** (100 MHz, CDCl$_3$, ref = CDCl$_3$): δ 11.4 ((<u>C</u>H$_3$CH$_2$)$_{minor}$); 11.6 ((<u>C</u>H$_3$CH$_2$)$_{major}$); 24.7 ((CH$_3$<u>C</u>H$_2$)$_{major}$); 25.7 ((CH$_3$<u>C</u>H$_2$)$_{minor}$); 31.4 (<u>C</u>HCN$_{major}$); 32.0 (<u>C</u>HCN$_{minor}$); 33.8 (CH<u>C</u>H$_2$N)$_{major}$; 34.3 (CH<u>C</u>H$_2$N)$_{minor}$; 35.1 (CH(<u>C</u>H$_2$)CH$_{major}$); 35.7 (CH(<u>C</u>H$_2$)CH$_{minor}$); 36.2 (CHN$_{major}$); 36.8 (CHN$_{minor}$); 55.29 and 55.30 (2×CH$_3$O); 64.1 and 64.2 (2×N<u>C</u>H$_2$C$_{quat}$); 113.88 and 113.94 (4×CH$_{arom}$); 121.9 (2×CN); 129.6 and 129.7 (4×CH$_{arom}$); 130.98, 131.02, 158.9 and 159.0 (4×C$_{quat,arom}$). **IR (cm^{-1})**: ν$_{CN}$ = 2236; ν$_{max}$ = 2967, 2934, 1612, 1512, 1462, 1301, 1243, 1175, 1033, 808. **MS (70 eV)**: *m/z* (%): 245 (M$^+$+1, 43). **HRMS (ESI)**: *m/z* calcd for C$_{15}$H$_{21}$N$_2$O: 245.1648 [*M*+H]$^+$; found: 245.1653.

Synthesis of 1-arylmethyl-2-(2-alkyl-2-cyanobutyl)aziridines 14

The synthesis of 1-arylmethyl-2-(2-alkyl-2-cyanobutyl)aziridines **14** was analogous to the synthesis of 1-arylmethyl-2-(2-cyanopropyl/butyl)aziridines **13**, using 1-arylmethyl-2-(2-cyanopropyl/butyl)aziridines **13** as starting material.

2-(2-Cyano-2-methylbutyl)-1-(4-methylbenzyl)aziridine 14a

Spectral data derived from the mixture of diastereomers

Colorless oil. R_f = 0.11 (Hexane/EtOAc 5/2). Yield 38%. *dr* 51/49. **^{1}H NMR** (400 MHz, CDCl$_3$): δ 0.99 (3H, t, *J* = 7.6 Hz, C<u>H</u>$_3$CH$_2$); 1.03 (3H, t, *J* = 7.7 Hz, C<u>H</u>$_3$CH$_2$); 1.27 and 1.29 (2×3H, 2×s, 2×CH$_3$C$_{quat}$); 1.39-1.57 (6H, m, 2×(<u>H</u>CH)CH$_3$, 2×(<u>H</u>CH)CHN and 2×CH(<u>H</u>CH)C$_{quat}$); 1.60-1.80 (8H, m, 2×(HC<u>H</u>)CH$_3$, 2×(HC<u>H</u>)CHN, 2×CH and 2×CH(HC<u>H</u>)C$_{quat}$); 2.34 (2×3H, 2×s, 2×CH$_{3,tos}$); 3.30 and 3.31 (2×1H, 2×d, *J* = 12.9 Hz, N(<u>H</u>CH)C$_{quat}$); 3.53 and 3.54 (2×1H, 2×d, *J* = 12.9 Hz, N(HC<u>H</u>)C$_{quat}$); 7.14 (4×1H, 4×d, *J* = 7.9 Hz, 4×CH$_{arom}$); 7.22 (4×1H, 4×d, *J* = 7.9 Hz, 4×CH$_{arom}$). **^{13}C NMR** (100 MHz, ref = CDCl$_3$): δ 9.10 and 9.14 (2×<u>C</u>H$_3$CH$_2$); 21.1 (2×CH$_{3,tos}$); 23.3 and 23.8 (2×<u>C</u>H$_3$C$_{quat}$); 31.9 and 32.9 (2×CH$_3$<u>C</u>H$_2$); 33.3 and 33.4 (2×CH<u>C</u>H$_2$N); 35.5 and 35.6 (2×CHN); 36.8 and 36.9 (2×C$_{quat}$); 42.1 and 42.3 (2×CH<u>C</u>H$_2$C$_{quat}$); 64.39 and 64.40 (2×N<u>C</u>H$_2$C$_{quat}$); 124.1 (2×CN); 128.4 and 129.1 (8×CH$_{arom}$); 135.6 and 136.9 (4×C$_{quat,arom}$). **IR (cm^{-1})**: ν$_{CN}$ = 2232; ν$_{max}$ = 2974, 2925, 1515, 1459, 1381, 1355, 1250, 1157, 1066, 802. **MS (70 eV)**: *m/z* (%): 243 (M$^+$+1, 100). **HRMS (ESI)**: *m/z* calcd for C$_{16}$H$_{23}$N$_2$: 243.1856 [*M*+H]$^+$; found: 243.1852.
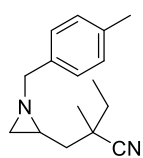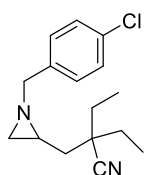
2-(2-Cyano-2-ethylbutyl)-1-(4-methylbenzyl)aziridine 14b

Yellow oil. R_f = 0.18 (Hexane/EtOAc 5/2). Yield 63%. **^{1}H NMR** (400 MHz, CDCl$_3$): δ 0.94 and 0.98 (2×3H, t, J = 7.4 Hz, 2×CH$_3$); 1.47-1.65 (9H, m, CH(HCH)N, 2×CH$_2$CH$_3$, CHN, CHCH$_2$C$_{quat}$, CH(HCH)N); 3.33 (1H, d, J = 12.9 Hz, N(HCH)C$_{quat}$); 2.34 (3H, s, CH$_{3,tos}$); 3.48 (1H, d, J = 12.9 Hz, N(HCH)C$_{quat}$); 7.14 (2×1H, d, J = 8.0 Hz, 2×CH$_{arom}$); 7.22 (2×1H, d, J = 8.0 Hz, 2×CH$_{arom}$). **^{13}C NMR** (100 MHz, CDCl$_3$): δ 8.6 and 8.7 (2×CH$_3$); 21.1 (CH$_{3,tos}$); 28.4 and 28.9 (2×CH$_2$CH$_3$); 33.5 (CHCH$_2$N); 35.3 (CHCH$_2$C$_{quat}$); 38.7 (CHN); 41.3 (C$_{quat}$CN); 64.5 (NCH$_2$C$_{quat}$); 123.6 (CN); 128.4 and 129.1 (4×CH$_{arom}$); 135.7 and 136.9 (2×C$_{quat,arom}$). **IR (cm^{-1})**: ν$_{CN}$ = 2230; ν$_{max}$ = 2972, 1515, 1458, 1383, 1354, 1248, 1156, 1062, 1020, 969. **MS (70 eV)**: m/z (%): 257 (M$^+$+1, 100). **HRMS (ESI)**: m/z calcd for C$_{17}$H$_{25}$N$_2$: 257.2012 [M+H]$^+$; found: 257.2011.

1-(4-Chlorobenzyl)-2-(2-cyano-2-ethylbutyl)aziridine 14c

Yellow oil. R_f = 0.27 (Hexane/EtOAc 5/2). Yield 44%. **^{1}H NMR** (400 MHz, CDCl$_3$): δ 0.96 and 0.99 (2×3H, t, J = 7.4 Hz, 2×CH$_3$); 1.48 (1H, d, J = 5.8 Hz, CH(HCH)N); 1.50-1.68 (8H, m, 2×CH$_2$CH$_3$, CHN, CHCH$_2$C$_{quat}$, CH(HCH)N); 3.29 (1H, d, J = 13.2 Hz, N(HCH)C$_{quat}$); 3.53 (1H, d, J = 13.2 Hz, N(HCH)C$_{quat}$); 7.26-7.32 (4H, m, 4×CH$_{arom}$). **^{13}C NMR** (100 MHz, CDCl$_3$): δ 8.6 and 8.7 (2×CH$_3$); 28.5 and 28.9 (2×CH$_2$CH$_3$); 33.6 (CHCH$_2$N); 35.6 (CHCH$_2$C$_{quat}$); 38.7 (CHN), 41.3 (C$_{quat}$CN); 63.9 (NCH$_2$C$_{quat}$); 123.5 (CN); 128.6 and 129.7 (4×CH$_{arom}$); 133.0 and 137.3 (2×C$_{quat,arom}$). **IR (cm^{-1})**: ν$_{CN}$ = 2230; ν$_{max}$ = 2972, 1491, 1458, 1407, 1384, 1352, 1247, 1157, 1087, 1015, 806, 666. **MS (70 eV)**: m/z (%): 277/279 (M$^+$+1, 100). **HRMS (ESI)**: m/z calcd for C$_{16}$H$_{22}$ClN$_2$: 277.1466 [M+H]$^+$; found: 277.1462.

2-(2-Cyano-2-ethylbutyl)-1-(4-methoxybenzyl)aziridine 14d

Yellow oil. R_f = 0.09 (Hexane/EtOAc 5/2). Yield 55%. **^{1}H NMR** (400 MHz, CDCl$_3$): δ 0.94 and 0.98 (2×3H, t, J = 7.5 Hz, 2×CH$_3$); 1.48 (1H, d, J = 4.3 Hz, CH(HCH)N); 1.50-1.67 (8H, m, 2×CH$_2$CH$_3$, CHN, CHCH$_2$C$_{quat}$, CH(HCH)N); 3.32 (1H, d, J = 12.8 Hz, N(HCH)C$_{quat}$); 3.43 (1H, d, J = 12.8 Hz, N(HCH)C$_{quat}$); 3.80 (3H, s, CH$_3$O); 6.87 (2×1H, d, J = 8.5 Hz, 2×CH$_{arom}$); 7.25 (2×1H, d, J = 8.5 Hz, 2×CH$_{arom}$). **^{13}C NMR** (100 MHz, ref = CDCl$_3$): δ 8.6 and 8.7 (2×CH$_3$); 28.3 and 28.8 (2×CH$_2$CH$_3$); 33.4 (CHCH$_2$N); 35.2 (CHCH$_2$C$_{quat}$); 38.7 (CHN), 41.4 (C$_{quat}$CN); 55.3 (CH$_3$O); 64.2 (NCH$_2$C$_{quat}$); 113.8 (C$_{quat,arom}$); 123.6 (CN); 129.7 and 130.9 (4×CH$_{arom}$); 158.9 (C$_{quat,arom}$). **IR (cm^{-1})**: ν$_{CN}$ = 2232; ν$_{max}$ = 2968, 2935, 2836, 1612, 1512, 1460, 1356, 1301, 1244, 1175, 1108, 1063, 1033, 819, 767, 704. **MS (70 eV)**: m/z (%): 273 (M$^+$+1, 100). **HRMS (ESI)**: m/z calcd for C$_{17}$H$_{25}$N$_2$O: 273.1961 [M+H]$^+$; found: 273.1956.
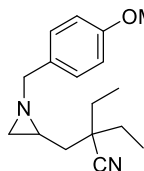
Synthesis of 2-(arylmethylaminomethyl)pyrrolidines 10, 15 and 16

As a representative example, the synthesis of 2-(benzylaminomethyl)pyrrolidine **10a** is described. To an ice-cooled solution of 1-benzyl-2-(2-cyanoethyl)aziridine **7a** (186 mg, 1 mmol) and In(OTf)$_3$ (169 mg, 0.3 mmol, 0.3 equiv) in dry THF (10 mL), was added a solution of LiAlH$_4$ (2 mL, 2 mmol, 2 equiv, 1.0 M in THF) via a syringe. Then, the resulting solution was heated under reflux for 4 hours under nitrogen atmosphere. Afterward, the reaction mixture was quenched with brine (10 mL) to neutralize the excess of LiAlH$_4$. Then, the reaction mixture was filtered through a path of Celite® and extracted with Et$_2$O (2 × 10 mL). Drying (MgSO$_4$), filtration of the drying agent and evaporation of the solvent *in vacuo* afforded 2-(benzylaminomethyl)pyrrolidine **10a** in a yield of 97% (184 mg, 0.97 mmol), which was purified by

means of preparative TLC on silica gel (CH₂Cl₂/MeOH/triethylamine 9/1/0.1) to provide an analytically pure sample.

2-(Benzylaminomethyl)pyrrolidine 10a

Yellow oil. R_f = 0.13 (CH₂Cl₂/MeOH/triethylamine 9/1/0.1). Yield 97%. **¹H NMR** (400 MHz, CDCl₃): δ 1.34 (1H, d×d×d×d, J = 12.4, 8.8, 7.2, 7.0 Hz, CH(HCH)CH₂); 1.64-1.81 (2H, m, CH₂CH₂N); 1.87 (1H, d×d×d×d, J = 12.4, 8.6, 7.2, 5.1 Hz, CH(HCH)CH₂); 1.96 (2H, s (broad), 2×NH); 2.54 (1H, d×d, J = 11.6, 4.7 Hz, CH(HCH)N); 2.65 (1H, d×d, J = 11.6, 8.1 Hz, CH(HCH)N); 2.89-2.93 (2H, m, CH₂CH₂N); 3.26 (1H, d×t×d, J = 8.1, 7.2, 4.7 Hz, CHN); 3.81 (2H, m, NCH₂C_quat); 7.22-7.32 (5H, m, CH_arom). **¹³C NMR** (100 MHz, ref = CDCl₃): δ 25.7 (CH₂CH₂N); 29.6 (CHCH₂CH₂); 46.4 (CH₂CH₂N); 54.2 (NCH₂C_quat); 54.4 (CHCH₂N); 58.4 (CHN); 126.9, 128.1 and 128.4 (5×CH_arom); 140.5 (C_quat, arom). **IR (cm⁻¹)**: ν_NH = 3292; ν_max = 2929, 2361, 1542, 1494, 1451, 1401, 1269, 810, 734, 698. **MS (70 eV)**: m/z (%): 191 (M⁺+1, 100). **HRMS (ESI)**: m/z calcd for C₁₂H₁₉N₂: 191.1543 [M+H]⁺; found: 191.1546.
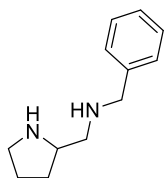
2-(4-Methylbenzylaminomethyl)pyrrolidine 10b

Yellow oil. R_f = 0.11 (CH₂Cl₂/MeOH/triethylamine 9/1/0.1). Yield 94%. **¹H NMR** (400 MHz, CDCl₃): δ 1.37 (1H, d×d×d×d, J = 12.5, 8.6, 7.2, 7.0 Hz, CH(HCH)CH₂); 1.66-1.82 (2H, m, CH₂CH₂N); 1.89 (1H, d×d×d×d, J = 12.5, 8.5, 7.2, 5.2 Hz, CH(HCH)CH₂); 2.33 (3H, s, CH₃); 2.53 (1H, d×d, J = 11.8, 8.4 Hz, CH(HCH)N); 2.65 (1H, d×d, J = 11.8, 4.6 Hz, CH(HCH)N); 2.74 (2H, s (broad), 2×NH); 2.94 (2H, t, J = 6.9 Hz, CH₂CH₂N); 3.31 (1H, d×t×d, J = 8.4, 7.2, 4.6 Hz, CHN); 3.76 (2H, s, NCH₂C_quat); 7.12 (2H, d, J = 7.9 Hz, 2×CH_arom); 7.20 (2H, d, J = 7.9 Hz, 2×CH_arom). **¹³C NMR** (100 MHz, CDCl₃): δ 21.1 (CH₃); 25.3 (CH₂CH₂N); 29.3 (CHCH₂CH₂); 46.2 (CH₂CH₂N); 53.3 (CHCH₂N); 53.7 (NCH₂C_quat); 58.5 (CHN); 128.1 and 129.1 (4×CH_arom); 136.6 and 137.1 (2×C_quat, arom). **IR (cm⁻¹)**: ν_max = 2925, 2361, 1456, 1255, 1159, 1030, 909, 804 754, 729, 637. **MS (70 eV)**: m/z (%): 205 (M⁺+1, 100). **HRMS (ESI)**: m/z calcd for C₁₃H₂₁N₂: 205.1699 [M+H]⁺; found: 205.1697.
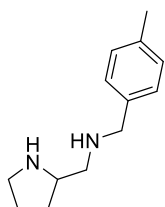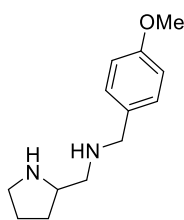
2-(4-Chlorobenzylaminomethyl)pyrrolidine 10c

Yellow oil. R_f = 0.14 (CH₂Cl₂/MeOH/triethylamine 9/1/0.1). Yield 83%. **¹H NMR** (400 MHz, CDCl₃): δ 1.37 (1H, d×d×d×d, J = 12.4, 8.7, 7.2, 7.0 Hz, CH(HCH)CH₂); 1.67-1.82 (2H, m, CH₂CH₂N); 1.89 (1H, d×d×d×d, J = 12.4, 8.5, 7.2, 5.1 Hz, CH(HCH)CH₂); 2.42 (2H, s (broad), 2×NH); 2.51 (1H, d×d, J = 11.7, 8.4 Hz, CH(HCH)N); 2.65 (1H, d×d, J = 11.7, 4.6 Hz, CH(HCH)N); 2.94 (2H, t, J = 6.8 Hz, CH₂CH₂N); 3.29 (1H, d×t×d, J = 8.4, 7.2, 4.6 Hz, CHN); 3.76 (2H, s, NCH₂C_quat); 7.23-7.34 (4H, m, 4×CH_arom). **¹³C NMR** (100 MHz, ref = CDCl₃): δ 25.4 (CH₂CH₂N); 29.4 (CHCH₂CH₂); 46.3 (CH₂CH₂N); 53.3 (NCH₂C_quat); 53.5 (CHCH₂N); 58.5 (CHN); 128.5 and 129.5 (4×CH_arom); 132.6 and 138.8 (2×C_quat, arom). **IR (cm⁻¹)**: ν_NH = 3289; ν_max = 2930, 2360, 1490, 1457, 1407, 1276, 1256, 1158, 1089, 1030, 1014, 802, 638. **MS (70 eV)**: m/z (%): 225 (M⁺+1, 100). **HRMS (ESI)**: m/z calcd for C₁₂H₁₈ClN₂: 225.1153 [M+H]⁺; found: 225.1145.
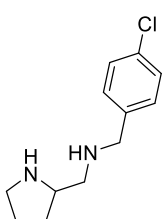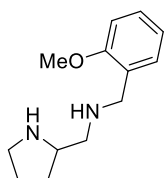
2-(4-Methoxybenzylaminomethyl)pyrrolidine 10d

Yellow oil. R_f = 0.03 (CH$_2$Cl$_2$/MeOH 9/1). Yield 74%. **^{1}H NMR** (400 MHz, CDCl$_3$): δ 1.37 (1H, d×d×d×d, J = 12.5, 8.6, 7.0, 7.0 Hz, CH(<u>H</u>CH)CH$_2$); 1.68-1.84 (2H, m, C<u>H</u>$_2$CH$_2$N); 1.90 (1H, d×d×d×d, J = 12.5, 8.5, 7.4, 5.2 Hz, CH(HC<u>H</u>)CH$_2$); 2.53 (1H, d×d, J = 11.8, 8.6 Hz, CH(<u>H</u>CH)N); 2.67 (1H, d×d, J = 11.8, 4.6 Hz, CH(HC<u>H</u>)N); 2.73 (2H, s (broad), 2×NH); 2.95 (2H, t, J = 6.9 Hz, CH$_2$CH$_2$N); 3.28-3.35 (1H, m, CHN); 3.74 (2H, s, NCH$_2$C$_{quat}$); 3.80 (3H, s, CH$_3$); 6.86 (2H, d, J = 8.7 Hz, 2×CH$_{arom}$); 7.23 (2H, d, J = 8.7 Hz, 2×CH$_{arom}$). **^{13}C NMR** (100 MHz, CDCl$_3$): δ 25.4 (<u>C</u>H$_2$CH$_2$N); 29.4 (CH<u>C</u>H$_2$CH$_2$); 46.2 (CH$_2$<u>C</u>H$_2$N); 53.3 (CH<u>C</u>H$_2$N); 53.4 (N<u>C</u>H$_2$C$_{quat}$); 55.3 (CH$_3$); 58.5 (CHN); 113.8 and 129.3 (4×CH$_{arom}$); 132.3 and 158.7 (2×C$_{quat, arom}$). **IR (cm^{-1})**: v_{NH} = 3300; v_{max} = 2933, 2835, 1511, 1244, 1175, 1030, 814, 638. **MS (70 eV)**: m/z (%): 221 (M$^+$+1, 100). **HRMS (ESI)**: m/z calcd for C$_{13}$H$_{21}$N$_2$O: 221.1648 [M+H]$^+$; found: 221.1647.

2-(2-Methoxybenzylaminomethyl)pyrrolidine 10e

Yellow oil. R_f = 0.12 (CH$_2$Cl$_2$/MeOH 9/1). Yield 97%. **^{1}H NMR** (400 MHz, CDCl$_3$): δ 1.43-1.56 (1H, m, CH(<u>H</u>CH)CH$_2$); 1.82-1.92 (2H, m, C<u>H</u>$_2$CH$_2$N); 1.95-2.03 (1H, m, CH(HC<u>H</u>)CH$_2$); 2.61 (1H, d×d, J = 12.7, 9.2 Hz, CH(<u>H</u>CH)N); 2.79 (1H, d×d, J = 12.7, 4.6 Hz, CH(HC<u>H</u>)N); 3.08 (1H, d×t, J = 11.3, 7.0 Hz, CH$_2$(<u>H</u>CH)N); 3.14 (1H, d×t, J = 11.3, 7.0 Hz, CH$_2$(HC<u>H</u>)N); 3.57 (1H, d×t×d, J = 9.2, 7.2, 4.6 Hz, CHN); 3.837 (2H, s, NCH$_2$C$_{quat}$); 3.841 (3H, s, CH$_3$); 4.77 (2H, s (broad), 2×NH); 6.85-6.93 (2H, m, 2×CH$_{arom}$); 7.22-7.28 (2H, m, 2×CH$_{arom}$). **^{13}C NMR** (100 MHz, CDCl$_3$): δ 24.4 (<u>C</u>H$_2$CH$_2$N); 28.6 (CH<u>C</u>H$_2$CH$_2$); 45.5 (CH$_2$<u>C</u>H$_2$N); 49.0 (N<u>C</u>H$_2$C$_{quat}$); 50.3 (CH<u>C</u>H$_2$N); 55.3 (CH$_3$); 58.5 (CHN); 110.4, 120.6 and 126.7 (3×CH$_{arom}$); 128.9 (C$_{quat,arom}$); 130.2 (CH$_{arom}$); 157.7 (C$_{quat,arom}$). **IR (cm^{-1})**: v_{NH} = 3297; v_{max} = 2938, 2838, 1492, 1463, 1276, 1240, 1224, 1155, 1028, 753, 637. **MS (70 eV)**: m/z (%): 221 (M$^+$+1, 100). **HRMS (ESI)**: m/z calcd for C$_{13}$H$_{21}$N$_2$O: 221.1648 [M+H]$^+$; found: 221.1646.

2-Benzylaminomethyl-4-methylpyrrolidine 15a

Spectral data derived from the mixture of diastereomers

Yellow oil. R_f = 0.17 (CH$_2$Cl$_2$/MeOH/triethylamine 95/5/1). Yield 83%. dr 51/49. **^{1}H NMR** (400 MHz, CDCl$_3$): δ 0.93-0.98 (1H, m, CH(<u>H</u>CH)CH$_{minor}$); 1.00 (3H, d, J = 6.8 Hz, (CH$_3$)$_{major}$); 1.02 (3H, d, J = 6.4 Hz, (CH$_3$)$_{minor}$); 1.49 (1H, d×d×d, J = 12.7, 8.0, 7.2 Hz, CH(<u>H</u>CH)CH$_{major}$); 1.61 (1H, d×d×d, J = 12.7, 7.9, 5.8 Hz, CH(HC<u>H</u>)CH$_{major}$); 2.05-2.25 (3H, m, CH(HC<u>H</u>)CH$_{minor}$, (C<u>H</u>CH$_3$)$_{minor}$ and (C<u>H</u>CH$_3$)$_{major}$); 2.45 (1H, d×d, J = 10.8, 8.8 Hz, (<u>H</u>CH)NCHN$_{minor}$); 2.49 (1H, d×d, J = 10.5, 7.6 Hz, (<u>H</u>CH)NCHN$_{major}$); 2.52-2.71 (4H, m, CH$_3$CHC<u>H</u>$_2$N$_{major}$ and CH$_3$CHC<u>H</u>$_2$N$_{minor}$); 2.84-2.86 (4H, 4×s, 4×NH); 3.10 (1H, d×d, J = 10.8, 7.1 Hz, (HC<u>H</u>)NCHN$_{minor}$); 3.12 (1H, d×d, J = 10.5, 6.9 Hz, (HC<u>H</u>)NCHN$_{major}$); 3.35-3.46 (2H, m, CHN$_{minor}$ and CHN$_{major}$); 3.79 (2H, s, (NCH$_2$C$_{quat}$)$_{major}$); 3.80 (2H, s, (NCH$_2$C$_{quat}$)$_{minor}$); 7.22-7.34 (10H, m, 10×CH$_{arom}$). **^{13}C NMR** (100 MHz, ref = CDCl$_3$): δ 18.1 ((CH$_3$)$_{minor}$); 18.7 ((CH$_3$)$_{major}$); 33.0 ((<u>C</u>HCH$_3$)$_{major}$); 34.6 ((<u>C</u>HCH$_3$)$_{minor}$); 37.6 (CH(<u>C</u>H$_2$)CH$_{major}$); 38.6 (CH(<u>C</u>H$_2$)CH$_{minor}$); 23.7 (<u>C</u>HCN$_{major}$); 24.4 (<u>C</u>HCN$_{minor}$); 34.0 (CH<u>C</u>H$_2$N)$_{major}$); 53.3 (<u>C</u>H$_2$NCHN$_{minor}$); 53.7 and 53.9 (2×CH$_2$N); 53.97 (2×CH$_2$N); 54.00 (CH$_2$N); 57.9 (CHN$_{major}$); 59.2 (CHN$_{minor}$); 127.0 (2×CH$_{arom}$); 128.2 (4×CH$_{arom}$); 128.4 (4×CH$_{arom}$); 140.1 and 140.2 (2×C$_{quat,arom}$). **IR (cm^{-1})**: v_{NH} = 3302; v_{max} = 2956, 1547, 1494, 1453, 1407, 1360, 1255, 1224, 1157, 1030, 811, 739, 698, 638. **MS (70 eV)**: m/z (%): 205 (M$^+$+1, 100). **HRMS (ESI)**: m/z calcd for C$_{13}$H$_{21}$N$_2$: 205.1699 [M+H]$^+$; found: 205.1694.
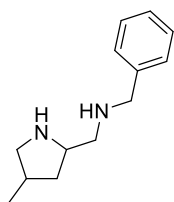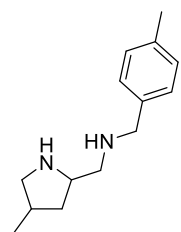
4-Methyl-2-(4-methylbenzylaminomethyl)pyrrolidine 15b
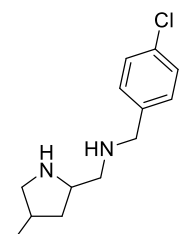
Spectral data derived from the mixture of diastereomers

Yellow oil. R_f = 0.08 (CH$_2$Cl$_2$/MeOH/triethylamine 95/5/0.5). Yield 92%. *dr* 56/44. **^{1}H NMR** (400 MHz, CDCl$_3$): δ 0.93-0.96 (1H, m, CH(HCH)CH$_{minor}$); 0.99 (3H, d, *J* = 6.8 Hz, (CH$_3$)$_{major}$); 1.01 (3H, d, *J* = 6.5 Hz, (CH$_3$)$_{minor}$); 1.46 (1H, d×d×d, *J* = 12.7, 7.9, 7.0 Hz, CH(HCH)CH$_{major}$); 1.59 (1H, d×d×d, *J* = 12.7, 7.9, 5.9 Hz, CH(HCH)CH$_{major}$); 1.99-2.24 (3H, m, CH(HCH)CH$_{minor}$, (CHCH$_3$)$_{minor}$ and (CHCH$_3$)$_{major}$); 2.32 (6H, 2×3H, 2×CH$_{3,tos}$); 2.43 (1H, d×d, *J* = 10.8, 8.7 Hz, (HCH)NCHN$_{minor}$); 2.46 (1H, d×d, *J* = 10.4, 7.7 Hz, (HCH)NCHN$_{major}$); 2.51-2.67 (4H, m, CH$_3$CHCH$_2$N$_{major}$ and CH$_3$CHCH$_2$N$_{minor}$); 2.84 (4H, 4×s, 4×NH); 3.07 (1H, d×d, *J* = 10.8, 7.3 Hz, (HCH)NCHN$_{minor}$); 3.10 (1H, d×d, *J* = 10.4, 6.7 Hz, (HCH)NCHN$_{major}$); 3.31-3.41 (2H, m, CHN$_{minor}$ and CHN$_{major}$); 3.75 (2×2H, 2×s, (NCH$_2$C$_{quat}$)$_{major}$ and (NCH$_2$C$_{quat}$)$_{minor}$); 7.12 (4×1H, 4×d, *J* = 7.8 Hz, 4×CH$_{arom}$); 7.19 (4×1H, 4×d, *J* = 7.8 Hz, 4×CH$_{arom}$). **^{13}C NMR** (100 MHz, ref = CDCl$_3$): δ 18.3 ((CH$_3$)$_{minor}$); 18.8 ((CH$_3$)$_{major}$); 21.1 (2×CH$_{3,tos}$); 33.1 ((CHCH$_3$)$_{major}$); 34.7 ((CHCH$_3$)$_{minor}$); 37.8 (CH(CH$_2$)CH$_{major}$); 38.7 (CH(CH$_2$)CH$_{minor}$); 53.4 (CH$_2$NCHN$_{minor}$); 53.73, 53.74, 54.07, 54.13 and 54.2 (5×CH$_2$N); 57.8 (CHN$_{major}$); 59.1 (CHN$_{minor}$); 128.1 (4×CH$_{arom}$); 129.1 (4×CH$_{arom}$); 136.5 (2×C$_{quat,arom}$); 137.2 (2×C$_{quat,arom}$). **IR (cm^{-1})**: v_{NH} = 3292; v_{max} = 2952, 2924, 2869, 1514, 1455, 1406, 1258, 1158, 1116, 1031, 909, 844, 803, 729, 638. **MS (70 eV)**: *m/z* (%): 219 (M$^+$+1, 100). **HRMS (ESI)**: *m/z* calcd for C$_{14}$H$_{23}$N$_2$: 219.1856 [*M*+H]$^+$; found: 219.1849.

2-(4-Chlorobenzylaminomethyl)-4-methylpyrrolidine 15c

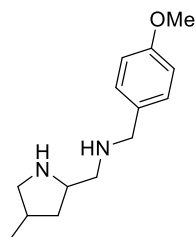Spectral data derived from the mixture of diastereomers

Yellow oil. R_f = 0.11 (CH$_2$Cl$_2$/MeOH/triethylamine 95/5/0.5). Yield 90%. *dr* 57/43. **^{1}H NMR** (400 MHz, CDCl$_3$): δ 0.94-0.98 (1H, m, CH(HCH)CH$_{minor}$); 1.00 (3H, d, *J* = 6.8 Hz, (CH$_3$)$_{major}$); 1.02 (3H, d, *J* = 6.4 Hz, (CH$_3$)$_{minor}$); 1.49 (1H, d×d×d, *J* = 12.8, 8.1, 7.0 Hz, CH(HCH)CH$_{major}$); 1.61 (1H, d×d×d, *J* = 12.8, 7.9, 5.7 Hz, CH(HCH)CH$_{major}$); 2.05-2.25 (3H, m, CH(HCH)CH$_{minor}$, (CHCH$_3$)$_{minor}$ and (CHCH$_3$)$_{major}$); 2.45 (1H, d×d, *J* = 11.1, 8.8 Hz, (HCH)NCHN$_{minor}$); 2.50 (1H, d×d, *J* = 10.5, 7.4 Hz, (HCH)NCHN$_{major}$); 2.50-2.68 (4H, m, CH$_3$CHCH$_2$N$_{major}$ and CH$_3$CHCH$_2$N$_{minor}$); 2.81 (4H, 4×s, 4×NH); 3.10 (1H, d×d, *J* = 11.1, 7.3 Hz, (HCH)NCHN$_{minor}$); 3.12 (1H, d×d, *J* = 10.5, 6.7 Hz, (HCH)NCHN$_{major}$); 3.34-3.44 (2H, m, CHN$_{minor}$ and CHN$_{major}$); 3.757 (2H, s, (NCH$_2$C$_{quat}$)$_{major}$); 3.761 (2H, s, (NCH$_2$C$_{quat}$)$_{minor}$); 7.24-7.32 (8H, m, 8×CH$_{arom}$). **^{13}C NMR** (100 MHz, ref = CDCl$_3$): δ 18.1 ((CH$_3$)$_{minor}$); 18.7 ((CH$_3$)$_{major}$); 33.1 ((CHCH$_3$)$_{major}$); 34.7 ((CHCH$_3$)$_{minor}$); 37.7 (CH(CH$_2$)CH$_{major}$); 38.6 (CH(CH$_2$)CH$_{minor}$); 53.25 and 53.28 (2×NCH$_2$C$_{quat}$); 53.4 (CH$_2$NCHN$_{minor}$); 53.9 (CH$_3$CHCH$_2$N$_{major}$); 54.0 (CH$_3$CHCH$_2$N$_{minor}$); 54.1 (CH$_2$NCHN$_{major}$); 57.8 (CHN$_{major}$); 59.2 (CHN$_{minor}$); 128.5 (4×CH$_{arom}$); 129.5 (4×CH$_{arom}$); 132.6 (2×C$_{quat,arom}$); 138.79 and 138.82 (2×C$_{quat,arom}$). **IR (cm^{-1})**: v_{NH} = 3292; v_{max} = 2954, 2870, 1490, 1455, 1407, 1256, 1224, 1158, 1089, 1030, 1014, 802, 733, 638. **MS (70 eV)**: *m/z* (%): 239 (M$^+$+1, 100). **HRMS (ESI)**: *m/z* calcd for C$_{13}$H$_{20}$ClN$_2$: 239.1310 [*M*+H]$^+$; found: 239.1306.

2-(4-Methoxybenzylaminomethyl)-4-methylpyrrolidine 15d
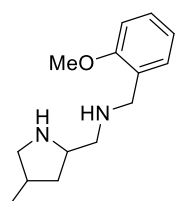
Spectral data derived from the mixture of diastereomers

Yellow oil. R_f = 0.09 (CH$_2$Cl$_2$/MeOH/triethylamine 95/5/0.5). Yield 95%. *dr* 56/44. **¹H NMR** (400 MHz, CDCl$_3$): δ 0.93-0.96 (1H, m, CH(H̲CH)CH$_{minor}$); 0.99 (3H, d, *J* = 6.7 Hz, (CH$_3$)$_{major}$); 1.01 (3H, d, *J* = 6.4 Hz, (CH$_3$)$_{minor}$); 1.47 (1H, d×d×d, *J* = 12.7, 8.0, 7.1 Hz, CH(H̲CH)CH$_{major}$); 1.59 (1H, d×d×d, *J* = 12.7, 8.0, 5.8 Hz, CH(HC̲H)CH$_{major}$); 2.04-2.27 (3H, m, CH(HC̲H)CH$_{minor}$, (C̲HCH$_3$)$_{minor}$ and (C̲HCH$_3$)$_{major}$); 2.43 (1H, d×d, *J* = 11.1, 8.6 Hz, (H̲CH)NCHN$_{minor}$); 2.44-2.67 (8H, m, CH$_3$CHCH̲$_2$N$_{major}$, CH$_3$CHCH̲$_2$N$_{minor}$ and 4×NH); 2.47 (1H, d×d, *J* = 10.4, 7.4 Hz, (H̲CH)NCHN$_{major}$); 3.07 (1H, d×d, *J* = 11.1, 7.0 Hz, (HC̲H)NCHN$_{minor}$); 3.10 (1H, d×d, *J* = 10.4, 6.7 Hz, (HC̲H)NCHN$_{major}$); 3.31-3.41 (2H, m, CHN$_{minor}$ and CHN$_{major}$); 3.73 (2×2H, 2×s, 2×NCH$_2$C$_{quat}$); 3.79 (2×3H, 2×s, 2×CH$_3$O); 6.85 (4×1H, 4×d, *J* = 8.5 Hz, 4×CH$_{arom}$); 7.23 (4×1H, 4×d, *J* = 8.5 Hz, 4×CH$_{arom}$). **¹³C NMR** (100 MHz, ref = CDCl$_3$): δ 18.3 ((CH$_3$)$_{minor}$); 18.8 ((CH$_3$)$_{major}$); 33.1 ((C̲HCH$_3$)$_{major}$); 34.8 ((C̲HCH$_3$)$_{minor}$); 37.8 (CH(C̲H$_2$)CH$_{major}$); 38.7 (CH(C̲H$_2$)CH$_{minor}$); 53.41 and 53.44 (2×NC̲H$_2$C$_{quat}$); 53.5 (C̲H$_2$NCHN$_{minor}$); 54.07 and 54.14 (2×CH$_3$CHC̲H$_2$N); 54.2 (C̲H$_2$NCHN$_{major}$); 55.3 (2×CH$_3$O); 57.8 (CHN$_{major}$); 59.1 (CHN$_{minor}$); 113.8 (4×CH$_{arom}$); 129.3 (4×CH$_{arom}$); 132.37 and 132.39 (2×C$_{quat,arom}$); 158.6 (2×C$_{quat,arom}$). **IR (cm⁻¹)**: ν_{NH} = 3308; ν_{max} = 2957, 2837, 1611, 1585, 1511, 1360, 1244, 1177, 1109, 1029, 813, 756, 638. **MS (70 eV)**: *m/z* (%): 235 (M⁺+1, 100). **HRMS (ESI)**: *m/z* calcd for C$_{14}$H$_{23}$N$_2$O: 235.1805 [*M*+H]⁺; found: 235.1807.

2-(2-Methoxybenzylaminomethyl)-4-methylpyrrolidine 15e

Spectral data derived from the mixture of diastereomers

Yellow oil. R_f = 0.14 (CH$_2$Cl$_2$/MeOH/triethylamine 95/5/0.5). Yield 78%. *dr* 52/48. **¹H NMR** (400 MHz, CDCl$_3$): δ 0.93-0.96 (1H, m, CH(H̲CH)CH$_{minor}$); 1.00 (3H, d, *J* = 6.7 Hz, (CH$_3$)$_{major}$); 1.01 (3H, d, *J* = 6.4 Hz, (CH$_3$)$_{minor}$); 1.48 (1H, d×d×d, *J* = 12.7, 7.5, 7.5 Hz, CH(H̲CH)CH$_{major}$); 1.59 (1H, d×d×d, *J* = 12.7, 7.9, 5.9 Hz, CH(HC̲H)CH$_{major}$); 2.04-2.26 (3H, m, CH(HC̲H)CH$_{minor}$, (C̲HCH$_3$)$_{minor}$ and (C̲HCH$_3$)$_{major}$); 2.45 (1H, d×d, *J* = 10.4, 8.8 Hz, (H̲CH)NCHN$_{minor}$); 2.51-2.68 (4H, m, CH$_3$CHCH̲$_2$N$_{major}$, CH$_3$CHCH̲$_2$N$_{minor}$); 2.48 (1H, d×d, *J* = 10.4, 7.6 Hz, (H̲CH)NCHN$_{major}$); 3.05 (4×1H, 4×s, 4×NH); 3.10 (1H, d×d, *J* = 10.4, 7.8 Hz, (HC̲H)NCHN$_{minor}$); 3.12 (1H, d×d, *J* = 10.4, 6.9 Hz, (HC̲H)NCHN$_{major}$); 3.35-3.45 (2H, m, CHN$_{minor}$ and CHN$_{major}$); 3.80 (2×2H, 2×s, 2×NCH$_2$C$_{quat}$); 3.83 (2×3H, 2×s, 2×CH$_3$O); 6.85-6.93 (4H, m, 4×CH$_{arom}$); 7.22-7.27 (4H, m, 4×CH$_{arom}$). **¹³C NMR** (100 MHz, ref = CDCl$_3$): δ 18.3 ((CH$_3$)$_{minor}$); 18.8 ((CH$_3$)$_{major}$); 33.0 ((C̲HCH$_3$)$_{major}$); 34.6 ((C̲HCH$_3$)$_{minor}$); 37.7 (CH(C̲H$_2$)CH$_{major}$); 38.7 (CH(C̲H$_2$)CH$_{minor}$); 49.25 and 49.28 (2×NC̲H$_2$C$_{quat}$); 53.3 (C̲H$_2$NCHN$_{minor}$); 53.7 and 53.8 (2×CH$_3$CHC̲H$_2$N); 54.0 (C̲H$_2$NCHN$_{major}$); 55.3 (2×CH$_3$O); 57.7 (CHN$_{major}$); 59.1 (CHN$_{minor}$); 110.3 (2×CH$_{arom}$); 120.4 (2×CH$_{arom}$); 128.0 (2×C$_{quat,arom}$); 128.3 (2×CH$_{arom}$); 129.9 (2×CH$_{arom}$); 157.6 (2×C$_{quat,arom}$). **IR (cm⁻¹)**: ν_{NH} = 3308; ν_{max} = 2955, 2838, 1601, 1588, 1541, 1492, 1438, 1458, 1438, 1404, 1360, 1286, 1239, 1158, 1104, 1049, 1029, 811, 753, 638. **MS (70 eV)**: *m/z* (%): 235 (M⁺+1, 100). **HRMS (ESI)**: *m/z* calcd for C$_{14}$H$_{23}$N$_2$O: 235.1805 [*M*+H]⁺; found: 235.1808.

2-Benzylaminomethyl-4-ethylpyrrolidine 15f
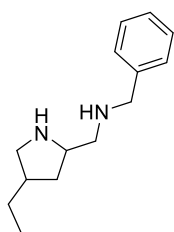
Spectral data derived from the mixture of diastereomers

Yellow oil. R_f = 0.09 (CH_2Cl_2/MeOH/triethylamine 95/5/0.5). Yield 81%. *dr* 52/48. **^{1}H NMR** (400 MHz, CDCl$_3$): δ 0.89 (3H, t, *J* = 7.3 Hz, (CH$_3$)$_{major}$); 0.89 (3H, t, *J* = 7.4 Hz, (CH$_3$)$_{minor}$); 0.94 (1H, d×d×d, *J* = 12.1, 9.1, 9.1 Hz, CH(H̲CH)CH$_{minor}$); 1.34 (1H, p, *J* = 7.3 Hz, (CH̲$_2$CH$_3$)$_{major}$); 1.37 (1H, p, *J* = 7.4 Hz, (CH̲$_2$CH$_3$)$_{minor}$); 1.50 (1H, d×d×d, *J* = 12.7, 7.6, 7.6 Hz, CH(H̲CH)CH$_{major}$); 1.58 (1H, d×d×d, *J* = 12.7, 8.3, 5.9 Hz, CH(HCH̲)CH$_{major}$); 1.90-2.14 (3H, m, CH(HCH̲)CH$_{minor}$, (CH̲CH$_2$CH$_3$)$_{minor}$ and (CH̲CH$_2$CH$_3$)$_{major}$); 2.31 (4×1H, 4×s, 4×NH); 2.48 (1H, d×d, *J* = 10.9, 8.2 Hz, (H̲CH)NCHN$_{minor}$); 2.51 (1H, d×d, *J* = 10.5, 7.9 Hz, (H̲CH)NCHN$_{major}$); 2.55 (1H, d×d, *J* = 11.7, 9.4 Hz, CH$_3$CH$_2$CH(H̲CH)N$_{minor}$); 2.57 (1H, d×d, *J* = 11.5, 9.4 Hz, CH$_3$CH$_2$CH(H̲CH)N$_{major}$); 2.63 (1H, d×d, *J* = 11.5, 4.8 Hz, CH$_3$CH$_2$CH(HCH̲)N$_{major}$); 2.65 (1H, d×d, *J* = 11.7, 4.5 Hz, CH$_3$CH$_2$CH(HCH̲)N$_{minor}$); 3.08 (1H, d×d, *J* = 10.9, 7.4 Hz, (HCH̲)NCHN$_{minor}$); 3.12 (1H, d×d, *J* = 10.5, 6.9 Hz, (HCH̲)NCHN$_{major}$); 3.29-3.36 (2H, m, CHN$_{minor}$ and CHN$_{major}$); 3.80 (2×2H, 2×s, 2×NCH$_2$C$_{quat}$); 7.21-7.32 (10H, m, 10×CH$_{arom}$). **^{13}C NMR** (100 MHz, ref = CDCl$_3$): δ 12.9 ((CH$_3$)$_{major}$); 13.0 ((CH$_3$)$_{minor}$); 27.2 (2×CH$_3$CH̲$_2$); 35.9 (CH(CH̲$_2$)CH$_{major}$); 36.9 (CH(CH̲$_2$)CH$_{minor}$); 40.7 ((CH̲CH$_2$CH$_3$)$_{major}$); 42.3 ((CH̲CH$_2$CH$_3$)$_{minor}$); 51.8 (CH̲$_2$NCHN$_{minor}$); 52.5 (CH̲$_2$NCHN$_{major}$); 54.1 and 54.2 (2×NCH$_2$C$_{quat}$); 54.6 and 54.7 (2×CH$_3$CH$_2$CHCH̲$_2$N); 57.7 (CHN$_{major}$); 58.9 (CHN$_{minor}$); 126.9 (2×CH$_{arom}$); 128.1 (4×CH$_{arom}$); 128.4 (4×CH$_{arom}$); 140.5 (2×C$_{quat,arom}$). **IR (cm^{-1})**: ν$_{NH}$ = 3299; ν$_{max}$ = 2957, 2922, 2873, 1494, 1453, 1378, 1358, 1256, 1224, 1119, 1074, 1030, 807, 732, 697, 638. **MS (70 eV)**: *m/z* (%): 219 (M$^+$+1, 100). **HRMS (ESI)**: *m/z* calcd for C$_{14}$H$_{23}$N$_2$: 219.1856 [*M*+H]$^+$; found: 219.1857.

4-Ethyl-2-(4-methylbenzylaminomethyl)pyrrolidine 15g
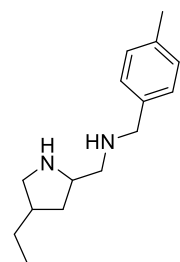
Spectral data derived from the mixture of diastereomers

Yellow oil. R_f = 0.08 (CH_2Cl_2/MeOH/triethylamine 95/5/0.5). Yield 82%. *dr* 51/49. **^{1}H NMR** (400 MHz, CDCl$_3$): δ 0.88 (3H, t, *J* = 7.3 Hz, (CH$_3$)$_{major}$); 0.89 (3H, t, *J* = 7.4 Hz, (CH$_3$)$_{minor}$); 0.93 (1H, d×d×d, *J* = 12.2, 9.5, 9.5 Hz, CH(H̲CH)CH$_{minor}$); 1.34 (1H, p, *J* = 7.3 Hz, (CH̲$_2$CH$_3$)$_{major}$); 1.36 (1H, p, *J* = 7.4 Hz, (CH̲$_2$CH$_3$)$_{minor}$); 1.49 (1H, d×d×d, *J* = 12.7, 7.6, 7.6 Hz, CH(H̲CH)CH$_{major}$); 1.57 (1H, d×d×d, *J* = 12.7, 8.2, 5.8 Hz, CH(HCH̲)CH$_{major}$); 1.90-2.13 (3H, m, CH(HCH̲)CH$_{minor}$, (CH̲CH$_2$CH$_3$)$_{minor}$ and (CH̲CH$_2$CH$_3$)$_{major}$); 2.33 (2×3H, 2×s, 2×CH$_{3,tos}$); 2.37 (4×1H, 4×s, 4×NH); 2.466 (1H, d×d, *J* = 10.2, 8.2 Hz, (H̲CH)NCHN$_{minor}$); 2.470 (1H, d×d, *J* = 10.4, 8.6 Hz, (H̲CH)NCHN$_{major}$); 2.52 (1H, d×d, *J* = 11.6, 8.5 Hz, CH$_3$CH$_2$CH(H̲CH)N$_{minor}$); 2.54 (1H, d×d, *J* = 11.7, 8.7 Hz, CH$_3$CH$_2$CH(H̲CH)N$_{major}$); 2.62 (1H, d×d, *J* = 11.7, 4.6 Hz, CH$_3$CH$_2$CH(HCH̲)N$_{major}$); 2.64 (1H, d×d, *J* = 11.6, 4.6 Hz, CH$_3$CH$_2$CH(HCH̲)N$_{minor}$); 3.07 (1H, d×d, *J* = 10.2, 7.4 Hz, (HCH̲)NCHN$_{minor}$); 3.12 (1H, d×d, *J* = 10.4, 6.9 Hz, (HCH̲)NCHN$_{major}$); 3.26-3.34 (2H, m, CHN$_{minor}$ and CHN$_{major}$); 3.75 (2×2H, 2×s, 2×NCH$_2$C$_{quat}$); 7.12 (4×1H, 4×d, *J* = 7.9 Hz, 4×CH$_{arom}$); 7.20 (4×1H, 4×d, *J* = 7.9 Hz, 4×CH$_{arom}$). **^{13}C NMR** (100 MHz, ref = CDCl$_3$): δ 12.9 ((CH$_3$)$_{major}$); 13.0 ((CH$_3$)$_{minor}$); 21.1 (2×CH$_{3,tos}$); 27.2 (2×CH$_3$CH̲$_2$); 35.8 (CH(CH̲$_2$)CH$_{major}$); 36.8 (CH(CH̲$_2$)CH$_{minor}$); 40.7 ((CH̲CH$_2$CH$_3$)$_{major}$); 42.3 ((CH̲CH$_2$CH$_3$)$_{minor}$); 51.8 (CH̲$_2$NCHN$_{minor}$); 52.5 (CH̲$_2$NCHN$_{major}$); 53.82 and 53.85 (2×NCH̲$_2$C$_{quat}$); 54.46 and 54.51 (2×CH$_3$CH$_2$CHCH̲$_2$N); 57.8 (CHN$_{major}$); 58.9 (CHN$_{minor}$); 128.1 (4×CH$_{arom}$); 129.1 (4×CH$_{arom}$); 136.4 (2×C$_{quat,arom}$); 137.3 and 137.4 (2×C$_{quat,arom}$). **IR (cm^{-1})**: ν$_{NH}$ = 3290; ν$_{max}$ = 2957, 2922, 2873, 1514, 1457, 1408, 1256, 1224, 1158, 1114, 1030, 844, 803, 755, 637. **MS (70 eV)**: *m/z* (%): 233 (M$^+$+1, 100). **HRMS (ESI)**: *m/z* calcd for C$_{15}$H$_{25}$N$_2$: 233.2012 [*M*+H]$^+$; found: 233.2015.

2-(4-Chlorobenzylaminomethyl)-4-ethylpyrrolidine 15h

Spectral data derived from the mixture of diastereomers

Yellow oil. R_f = 0.08 (CH$_2$Cl$_2$/MeOH/triethylamine 95/5/0.5). Yield 90%. *dr* 51/49. **^{1}H NMR** (400 MHz, CDCl$_3$): δ 0.89 (3H, t, *J* = 7.3 Hz, (CH$_3$)$_{major}$); 0.89 (3H, t, *J* = 7.4 Hz, (CH$_3$)$_{minor}$); 0.96 (1H, d×d×d, *J* = 12.3, 9.3, 9.3 Hz, CH(HC<u>H</u>)CH$_{minor}$); 1.35 (1H, p, *J* = 7.3 Hz, (C<u>H</u>$_2$CH$_3$)$_{major}$); 1.37 (1H, p, *J* = 7.4 Hz, (C<u>H</u>$_2$CH$_3$)$_{minor}$); 1.51 (1H, d×d×d, *J* = 12.7, 7.6, 7.6 Hz, CH(<u>H</u>CH)CH$_{major}$); 1.59 (1H, d×d×d, *J* = 12.7, 8.2, 5.8 Hz, CH(HC<u>H</u>)CH$_{major}$); 1.91-2.14 (3H, m, CH(HC<u>H</u>)CH$_{minor}$, (C<u>H</u>CH$_2$CH$_3$)$_{minor}$ and (C<u>H</u>CH$_2$CH$_3$)$_{major}$); 2.44 (4×1H, 4×s, 4×NH); 2.49 (1H, d×d, *J* = 10.9, 8.7 Hz, (<u>H</u>CH)NCHN$_{minor}$); 2.50-2.57 (2H, m, CH$_3$CH$_2$CH(<u>H</u>CH)N$_{minor}$ and CH$_3$CH$_2$CH(<u>H</u>CH)N$_{major}$); 2.52 (1H, d×d, *J* = 10.4, 7.9 Hz, (<u>H</u>CH)NCHN$_{major}$); 2.62 (1H, d×d, *J* = 9.6, 4.5 Hz, CH$_3$CH$_2$CH(HC<u>H</u>)N$_{major}$); 2.64 (1H, d×d, *J* = 9.7, 4.5 Hz, CH$_3$CH$_2$CH(HC<u>H</u>)N$_{minor}$); 3.10 (1H, d×d, *J* = 10.9, 7.3 Hz, (HC<u>H</u>)NCHN$_{minor}$); 3.12 (1H, d×d, *J* = 10.5, 7.0 Hz, (HC<u>H</u>)NCHN$_{major}$); 3.29-3.37 (2H, m, CHN$_{minor}$ and CHN$_{major}$); 3.76 (2×2H, 2×s, 2×NCH$_2$C$_{quat}$); 7.24-7.29 (8H, m, 8×CH$_{arom}$). **^{13}C NMR** (100 MHz, ref = CDCl$_3$): δ 12.8 ((CH$_3$)$_{major}$); 12.9 ((CH$_3$)$_{minor}$); 27.0 and 27.1 (2×CH$_3$<u>C</u>H$_2$); 35.7 (CH(<u>C</u>H$_2$)CH$_{major}$); 36.6 (CH(<u>C</u>H$_2$)CH$_{minor}$); 40.6 ((<u>C</u>HCH$_2$CH$_3$)$_{major}$); 42.2 ((<u>C</u>HCH$_2$CH$_3$)$_{minor}$); 51.7 (<u>C</u>H$_2$NCHN$_{minor}$); 52.4 (<u>C</u>H$_2$NCHN$_{major}$); 53.31 and 53.34 (2×N<u>C</u>H$_2$C$_{quat}$); 54.1 and 54.2 (2×CH$_3$CH$_2$CH<u>C</u>H$_2$N); 57.7 (CHN$_{major}$); 58.9 (CHN$_{minor}$); 128.5 (4×CH$_{arom}$); 129.5 (4×CH$_{arom}$); 132.6 (2×C$_{quat,arom}$); 138.8 and 138.9 (2×C$_{quat,arom}$). **IR (cm^{-1})**: v_{NH} = 3293; v_{max} = 2958, 2925, 2874, 1542, 1490, 1459, 1406, 1278, 1257, 1224, 1159, 1089, 1030, 1014, 802, 638. **MS (70 eV)**: *m/z* (%): 253 (M$^+$+1, 100). **HRMS (ESI)**: *m/z* calcd for C$_{14}$H$_{22}$ClN$_2$: 253.1466 [*M*+H]$^+$; found: 253.1467.

4-Ethyl-2-(4-methoxybenzylaminomethyl)pyrrolidine 15i

Spectral data derived from the mixture of diastereomers
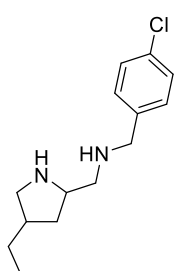
Yellow oil. R_f = 0.07 (CH$_2$Cl$_2$/MeOH/triethylamine 95/5/0.5). Yield 86%. *dr* 51/49. **^{1}H NMR** (400 MHz, CDCl$_3$): δ 0.89 (3H, t, *J* = 7.4 Hz, (CH$_3$)$_{major}$); 0.89 (3H, t, *J* = 7.3 Hz, (CH$_3$)$_{minor}$); 0.91-0.96 (1H, m, CH(HC<u>H</u>)CH$_{minor}$); 1.34 (1H, p, *J* = 7.4 Hz, (C<u>H</u>$_2$CH$_3$)$_{major}$); 1.36 (1H, p, *J* = 7.3 Hz, (C<u>H</u>$_2$CH$_3$)$_{minor}$); 1.49 (1H, d×d×d, *J* = 12.8, 7.6, 7.6 Hz, CH(<u>H</u>CH)CH$_{major}$); 1.57 (1H, d×d×d, *J* = 12.8, 7.9, 5.9 Hz, CH(HC<u>H</u>)CH$_{major}$); 1.90-2.10 (7H, m, CH(HC<u>H</u>)CH$_{minor}$, (C<u>H</u>CH$_2$CH$_3$)$_{minor}$, (C<u>H</u>CH$_2$CH$_3$)$_{major}$ and 4×NH); 2.47 (1H, d×d, *J* = 10.9, 8.5 Hz, (<u>H</u>CH)NCHN$_{minor}$); 2.52 (1H, d×d, *J* = 10.0, 8.0 Hz, (<u>H</u>CH)NCHN$_{major}$); 2.54 (1H, d×d, *J* = 11.5, 8.0 Hz, CH$_3$CH$_2$CH(<u>H</u>CH)N$_{minor}$); 2.55-2.66 (3H, m, CH$_3$CH$_2$CH(<u>H</u>CH)N$_{major}$, CH$_3$CH$_2$CH(HC<u>H</u>)N$_{major}$ and CH$_3$CH$_2$CH(HC<u>H</u>)N$_{minor}$); 3.07 (1H, d×d, *J* = 10.9, 7.5 Hz, (HC<u>H</u>)NCHN$_{minor}$); 3.10 (1H, d×d, *J* = 10.0, 6.9 Hz, (HC<u>H</u>)NCHN$_{major}$); 3.26-3.32 (2H, m, CHN$_{minor}$ and CHN$_{major}$); 3.73 (2×2H, 2×s, 2×NCH$_2$C$_{quat}$); 3.79 (2×3H, 2×s, 2×CH$_3$O); 6.85 (4×1H, 4×d, *J* = 8.5 Hz, 4×CH$_{arom}$); 7.23 (4×1H, 4×d, *J* = 8.5 Hz, 4×CH$_{arom}$). **^{13}C NMR** (100 MHz, ref = CDCl$_3$): δ 12.9 ((CH$_3$)$_{major}$); 13.0 ((CH$_3$)$_{minor}$); 27.2 (2×CH$_3$<u>C</u>H$_2$); 35.9 (CH(<u>C</u>H$_2$)CH$_{major}$); 37.0 (CH(<u>C</u>H$_2$)CH$_{minor}$); 40.7 ((<u>C</u>HCH$_2$CH$_3$)$_{major}$); 42.4 ((<u>C</u>HCH$_2$CH$_3$)$_{minor}$); 51.9 (<u>C</u>H$_2$NCHN$_{minor}$); 52.6 (<u>C</u>H$_2$NCHN$_{major}$); 53.55 and 53.57 (2×N<u>C</u>H$_2$C$_{quat}$); 54.7 (2×CH$_3$CH$_2$CH<u>C</u>H$_2$N); 55.3 (2×CH$_3$O); 57.7 (CHN$_{major}$); 58.9 (CHN$_{minor}$); 113.8 (4×CH$_{arom}$); 129.3 (4×CH$_{arom}$); 132.6 (2×C$_{quat,arom}$); 158.6 (2×C$_{quat,arom}$). **IR (cm^{-1})**: v_{NH} = 3303; v_{max} = 2957, 2928, 2874, 1611, 1585, 1511, 1461, 1403, 1360, 1300, 1244, 1176, 1107, 1032, 812, 731, 638. **MS (70 eV)**: *m/z* (%): 249 (M$^+$+1, 100). **HRMS (ESI)**: *m/z* calcd for C$_{15}$H$_{25}$N$_2$O: 249.1961 [*M*+H]$^+$; found: 249.1965.
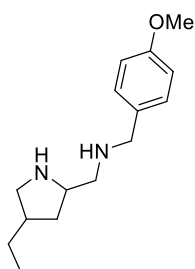
4-Ethyl-4-methyl-2-(4-methylbenzylaminomethyl)pyrrolidine 16a

Spectral data derived from the mixture of diastereomers

Yellow oil. R_f = 0.02 (CH$_2$Cl$_2$/MeOH 95/5). Yield 84%. *dr* 51/49. **^{1}H NMR** (400 MHz, CDCl$_3$): δ 0.85 and 0.86 (2×3H, 2×t, *J* = 7.5 Hz, 2×C<u>H</u>$_3$CH$_2$); 0.97 and 1.00 (2×3H, 2×s, 2×CH$_3$C$_{quat}$); 1.10 (1H, d×d, *J* = 12.7, 8.2 Hz, CH(<u>H</u>CH)CH); 1.16 (1H, d×d, *J* = 12.4, 8.7 Hz, CH(<u>H</u>CH)CH); 1.36 and 1.38 (2×2H, 2×q, *J* = 7.5 Hz, 2×C<u>H</u>$_2$CH$_3$); 1.62 (1H, d×d, *J* = 12.4, 7.2 Hz, CH(HC<u>H</u>)CH); 1.75 (1H, d×d, *J* = 12.7, 7.8 Hz, CH(HC<u>H</u>)CH); 2.08 (4×1H, 4×s, 4×NH); 2.33 (2×3H, 2×s, 2×CH$_{3,tos}$); 2.52-2.71 (8H, m, 2×C<u>H</u>$_2$NCHN and 2×C<u>H</u>$_2$NC$_{quat}$CH$_3$); 3.33 (1H, d×d×d×d, *J* = 8.2, 7.9, 7.8, 4.9 Hz, CH); 3.33 (1H, d×d×d×d, *J* = 8.7, 8.4, 7.2, 4.8 Hz, CH); 3.74 and 3.78 (2×2H, 2×d, *J* = 13.7 Hz, 2×NCH$_2$C$_{quat}$); 7.12 (4×1H, 4×d, *J* = 7.9 Hz, 4×CH$_{arom}$); 7.20 (4×1H, 4×d, *J* = 7.9 Hz, 4×CH$_{arom}$). **^{13}C NMR** (100 MHz, ref = CDCl$_3$): δ 9.3 and 9.7 (2×<u>C</u>H$_3$CH$_2$); 21.1 (2×CH$_{3,tos}$); 24.0 and 24.8 (2×<u>C</u>H$_3$C$_{quat}$); 32.5 and 33.7 (2×CH$_3$<u>C</u>H$_2$); 42.9 (<u>C</u>$_{quat}$CH$_3$); 43.0 (CH<u>C</u>H$_2$C$_{quat}$); 43.3 (<u>C</u>$_{quat}$CH$_3$); 43.4 (CH<u>C</u>H$_2$C$_{quat}$); 53.9 (2×N<u>C</u>H$_2$C$_{quat}$); 54.86 and 54.92 (2×<u>C</u>H$_2$NCHN); 58.1 and 58.5 (2×CHN); 58.6 (2×CH$_3$C$_{quat}$<u>C</u>H$_2$N); 128.1 (4×CH$_{arom}$); 129.0 (4×CH$_{arom}$); 136.4 (2×C$_{quat,arom}$); 137.4 (2×C$_{quat,arom}$). **IR (cm^{-1})**: ν$_{NH}$ = 3284; ν$_{max}$ = 2959, 2921, 2858, 1547, 1514, 1456, 1401, 1379, 1281, 1257, 1223, 1156, 1108, 1030, 804, 755, 637. **MS (70 eV)**: *m/z* (%): 247 (M$^+$+1, 100). **HRMS (ESI)**: *m/z* calcd for C$_{16}$H$_{27}$N$_2$: 247.2169 [*M*+H]$^+$; found: 247.2167.
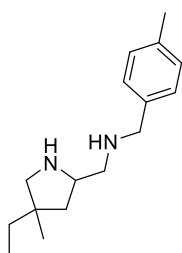
4,4-Diethyl-2-(4-methylbenzylaminomethyl)pyrrolidine 16b

Yellow oil. R_f = 0.06 (CH$_2$Cl$_2$/MeOH 95/5). Yield 89%. **^{1}H NMR** (400 MHz, CDCl$_3$): δ 0.81 (2×3H, 2×t, *J* = 7.5 Hz, 2×CH$_3$); 1.08 (1H, d×d, *J* = 12.6, 8.3 Hz, CH(<u>H</u>CH)C$_{quat}$); 1.30-1.45 (2×2H, m, 2×C<u>H</u>$_2$CH$_3$); 1.69 (1H, d×d, *J* = 12.6, 7.5 Hz, CH(HC<u>H</u>)C$_{quat}$); 1.96 (2H, s (broad), 2×NH); 2.33 (3H, s, CH$_{3,tos}$); 2.56 (1H, d×d, *J* = 11.6, 7.9 Hz, CH(<u>H</u>CH)N); 2.62 (1H, d×d, *J* = 11.6, 4.9 Hz, CH(HC<u>H</u>)N); 2.63 (1H, d, *J* = 11.0 Hz, CH$_2$C$_{quat}$(<u>H</u>CH)N); 2.67 (1H, d, *J* = 11.0 Hz, CH$_2$C$_{quat}$(HC<u>H</u>)N); 3.30 (1H, d×d×d×d, *J* = 8.3, 7.9, 7.5, 4.9 Hz, CHN); 3.76 (2H, s, NCH$_2$C$_{quat,arom}$); 7.12 (2×1H, 2×d, *J* = 7.8 Hz, 2×CH$_{arom}$); 7.20 (2×1H, 2×d, *J* = 7.8 Hz, 2×CH$_{arom}$);. **^{13}C NMR** (100 MHz, ref = CDCl$_3$): δ 8.8 and 9.2 (2×CH$_3$); 21.1 (CH$_{3,tos}$); 28.4 and 29.8 (2×<u>C</u>H$_2$CH$_3$); 41.7 (CH<u>C</u>H$_2$C$_{quat}$); 46.4 (C$_{quat}$); 54.0 (N<u>C</u>H$_2$C$_{quat,arom}$); 53.5 (CH<u>C</u>H$_2$N); 54.9 (<u>C</u>H$_2$NCHN); 56.8 (N<u>C</u>H$_2$C$_{quat}$); 58.3 (CHN); 128.1 and 129.0 (4×CH$_{arom}$); 136.4 and 137.4 (2×C$_{quat, arom}$). **IR (cm^{-1})**: ν$_{NH}$ = 3286; ν$_{max}$ = 2961, 2920, 2861, 1514, 1456, 1402, 1378, 1281, 1255, 1223, 1158, 1030, 803, 755, 637. **MS (70 eV)**: *m/z* (%): 261 (M$^+$+1, 100). **HRMS (ESI)**: *m/z* calcd for C$_{17}$H$_{29}$N$_2$: 261.2325 [*M*+H]$^+$; found: 261.2327.
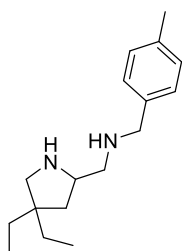
2-(4-Chlorobenzylaminomethyl)-4,4-diethylpyrrolidine 16c

Yellow oil. R_f = 0.06 (CH$_2$Cl$_2$/MeOH 95/5). Yield 95%. **^{1}H NMR** (400 MHz, CDCl$_3$): δ 0.81 (2×3H, 2×t, *J* = 7.4 Hz, 2×CH$_3$); 1.13 (1H, d×d, *J* = 12.8, 8.4 Hz, CH(<u>H</u>CH)C$_{quat}$); 1.31-1.46 (2×2H, m, 2×C<u>H</u>$_2$CH$_3$); 1.71 (1H, d×d, *J* = 12.8, 7.7 Hz, CH(HC<u>H</u>)C$_{quat}$); 2.34 (2H, s (broad), 2×NH); 2.55 (1H, d×d, *J* = 12.2, 4.4 Hz, CH(<u>H</u>CH)N); 2.62 (1H, d×d, *J* = 12.2, 7.8 Hz, CH(HC<u>H</u>)N); 2.66 (1H, d, *J* = 11.1 Hz, CH$_2$C$_{quat}$(<u>H</u>CH)N); 2.71 (1H, d, *J* = 11.1 Hz, CH$_2$C$_{quat}$(HC<u>H</u>)N); 3.35 (1H, d×d×d×d, *J* = 8.4, 7.8, 7.7, 4.4 Hz, CHN); 3.77 (2H, s, NCH$_2$C$_{quat,arom}$); 7.24-7.32 (4H, m, 4×CH$_{arom}$). **^{13}C NMR** (100 MHz, ref = CDCl$_3$): δ 8.8 and 9.2 (2×CH$_3$); 28.2 and 29.6 (2×<u>C</u>H$_2$CH$_3$); 41.3 (CH<u>C</u>H$_2$C$_{quat}$); 46.4 (C$_{quat}$); 53.4 (N<u>C</u>H$_2$C$_{quat,arom}$); 53.5 (CH<u>C</u>H$_2$N); 54.3 (<u>C</u>H$_2$NCHN); 56.5 (N<u>C</u>H$_2$C$_{quat}$); 58.2 (CHN); 128.5 and 129.5 (4×CH$_{arom}$); 132.6 and 138.8 (2×C$_{quat, arom}$). **IR (cm^{-1})**: ν$_{NH}$ = 3288; ν$_{max}$ = 2962, 2922,
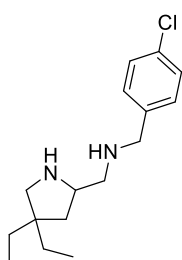
2859, 1547, 1490, 1456, 1406, 1283, 1089, 1014, 801, 700, 638. **MS (70 eV)**: m/z (%): 281/283 (M$^+$+1, 100). **HRMS (ESI)**: m/z calcd for $C_{16}H_{26}ClN_2$: 281.1779 [M+H]$^+$; found: 281.1774.

4,4-Diethyl-2-(4-methoxybenzylaminomethyl)pyrrolidine 16d

Yellow oil. R_f = 0.05 (CH_2Cl_2/MeOH 95/5). Yield 88%. **^{1}H NMR** (400 MHz, CDCl$_3$): δ 0.81 (2×3H, 2×t, J = 7.4 Hz, 2×CH$_3$); 1.09 (1H, d×d, J = 12.7, 8.4 Hz, CH(HCH)C$_{quat}$); 1.30-1.43 (2×2H, m, 2×CH$_2$CH$_3$); 1.70 (1H, d×d, J = 12.7, 7.6 Hz, CH(HCH)C$_{quat}$); 1.97 (2H, s (broad), 2×NH); 2.56 (1H, d×d, J = 11.6, 8.0 Hz, CH(HCH)N); 2.62 (1H, d×d, J = 11.6, 4.8 Hz, CH(HCH)N); 2.64 (1H, d, J = 11.0 Hz, CH$_2$C$_{quat}$(HCH)N); 2.68 (1H, d, J = 11.0 Hz, CH$_2$C$_{quat}$(HCH)N); 3.31 (1H, d×d×d×d, J = 8.4, 8.0, 7.6, 4.4 Hz, CHN); 3.73 (2H, s, NCH$_2$C$_{quat,arom}$); 3.79 (3H, s, CH$_3$O); 6.85 (2×1H, 2×d, J = 8.6 Hz, 2×CH$_{arom}$); 7.23 (2×1H, 2×d, J = 8.6 Hz, 2×CH$_{arom}$). **^{13}C NMR** (100 MHz, ref = CDCl$_3$): δ 8.8 and 9.2 (2×CH$_3$); 28.4 and 29.8 (2×CH$_2$CH$_3$); 41.6 (CHCH$_2$C$_{quat}$); 46.4 (C$_{quat}$); 53.6 (NCH$_2$C$_{quat,arom}$); 54.8 (CH$_2$NCHN); 55.3 (CH$_3$O); 56.8 (NCH$_2$C$_{quat}$); 58.3 (CHN); 113.7 and 129.3 (4×CH$_{arom}$); 132.6 and 158.6 (2×C$_{quat, arom}$). **IR (cm^{-1})**: v_{NH} = 3293; v_{max} = 2960, 2933, 2858, 1611, 1585, 1511, 1457, 1403, 1378, 1300, 1244, 1175, 1102, 1035, 807. **MS (70 eV)**: m/z (%): 277 (M$^+$+1, 100). **HRMS (ESI)**: m/z calcd for $C_{17}H_{29}N_2O$: 277.2274 [M+H]$^+$; found: 277.2270.
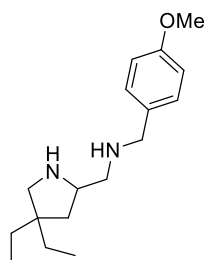
Synthesis of 1-arylmethyl-2-(2-cyano-2-phenylethyl)aziridines 17

1-Arylmethyl-2-(2-cyano-2-phenylethyl)aziridines **17** were prepared according to a literature procedure, and spectral data corresponded with those reported in the literature.[18]

Synthesis of *cis*-2-[(*N*-benzyl-*N*-tosyl)aminomethyl]-1-phenyl-1-(tosylaminomethyl)-cyclopropane 19

To an ice-cooled solution of 1-benzyl-2-(2-cyano-2-phenylethyl)aziridine **17a** (131 mg, 0.5 mmol) and In(OTf)$_3$ (85 mg, 0.15 mmol, 0.3 equiv) in dry THF (10 mL), was added a solution of LiAlH$_4$ (1 mL, 1 mmol, 2 equiv, 1.0 M in THF) via a syringe. Then, the resulting solution was heated under reflux for 2 hours under nitrogen atmosphere. Afterward, the reaction mixture was quenched with brine (10 mL) to neutralize the excess of LiAlH$_4$. Then, the reaction mixture was filtered through a path of Celite® and extracted with Et$_2$O (2 × 10 mL). Drying (MgSO$_4$), filtration of the drying agent and evaporation of the solvent *in vacuo* afforded a crude reaction mixture. In the next step, the obtained mixture was dissolved in pyridine (10 mL), and *para*-toluenesulfonylchloride (TsCl, 191 mg, 1 mmol, 2 equiv) was added at room temperature, after which the resulting solution was stirred for 2 hours at reflux temperature. Afterward, the reaction mixture was quenched with saturated NaHCO$_3$ (10 mL), poured into water (20 mL) and extracted with EtOAc (3 × 20 mL). Then, the organic phases were washed with a 10% CuSO$_4$-solution (5 × 10 mL) and brine (3 × 10 mL). Drying (MgSO$_4$), filtration of the drying agent and evaporation of the solvent *in vacuo* afforded *cis*-2-[(*N*-benzyl-*N*-tosyl)aminomethyl]-1-phenyl-1-(tosylaminomethyl)cyclopropane **19**, which was purified by means of preparative TLC on silica gel (Hexane/EtOAc 2/1) to provide a white powder in a yield of 15% (43 mg, 0.075 mmol).

White powder. Mp 210 °C. R_f = 0.24 (Hexane/EtOAc 2/1). Yield 15%. **¹H NMR** (400 MHz, CDCl₃): δ 0.49 (1H, d×d, J = 6.2, 5.3 Hz, CH(HCH)C_quat); 0.85 (1H, d×d, J = 8.8, 5.3 Hz, CH(HCH)C_quat); 1.18 (1H, d×d×d×d, J = 8.8, 7.5, 6.3, 6.2 Hz, CH(HCH)C_quat); 2.40 and 2.45 (2×3H, 2×s, 2×CH₃); 2.98 (1H, d×d, J = 13.1, 6.2 Hz, NH(HCH)); 3.07 (1H, d×d, J = 15.0, 7.5 Hz, CH(HCH)N); 3.15 (1H, d×d, J = 13.1, 6.1 Hz, NH(HCH)); 3.56 (1H, d×d, J = 15.0, 6.3 Hz, CH(HCH)N); 4.25 (1H, d, J = 14.9 Hz, C_quat,arom(HCH)N); 4.44 (1H, m, NH); 4.46 (1H, d, J = 14.9 Hz, C_quat,arom(HCH)N); 6.92-6.94 (2H, m, 2×CH_arom); 7.15-7.16 (2H, m, 2×CH_arom); 7.19 (2×1H, 2×d, J = 8.0 Hz, 2×CH_arom); 7.26-7.29 (6H, m, 6×CH_arom); 7.33 (2×1H, 2×d, J = 8.0 Hz, 2×CH_arom,tos); 7.53 (2×1H, 2×d, J = 8.3 Hz, 2×CH_arom); 7.76 (2×1H, 2×d, J = 8.3 Hz, 2×CH_arom). **¹³C NMR** (100 MHz, CDCl₃): δ 17.9 (CHCH₂C_quat); 21.5 and 21.6 (2×CH₃); 23.4 (CHCH₂C_quat); 30.4 (C_quat); 47.8 (NHCH₂); 48.1 (CHCH₂N); 52.7 (C_quat,aromCH₂N); 126.98 (2×CH_arom); 127.02 (2×CH_arom); 127.3 (2×CH_arom); 127.9, 128.4, 128.6, 128.68 and 128.74 (8×CH_arom); 129.6 (2×CH_arom); 129.9 (2×CH_arom); 136.38, 136.44, 136.5, 142.0, 143.2 and 143.5 (6×C_quat,arom). **IR (cm⁻¹)**: ν_max = 3279, 1447, 1407, 1342, 1161, 1094, 1062, 915, 818, 769, 746, 720, 703, 665. **MS (70 eV)**: m/z (%): 575 (M⁺+1, 100). **HRMS (ESI)**: m/z calcd for C₃₂H₃₅N₂O₄S₂: 575.2033 [M+H]⁺; found: 575.2034.
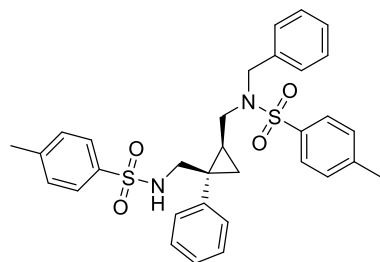
Synthesis of 3-arylmethyl-1,3-diazabicyclo[3.3.0]octan-2-ones 24 and 4-arylmethyl-1,4-diazabicyclo[4.3.0]nonan-2,3-diones 25

As a representative example, the synthesis of 3-benzyl-1,3-diazabicyclo[3.3.0]octan-2-one **19a** is described. To a solution of 2-(benzylaminomethyl)pyrrolidine **10a** (380 mg, 2 mmol) in dry THF (20 mL) was added triphosgene (593 mg, 2 mmol, 1 equiv). Then, the resulting solution was stirred for 3 hours at room temperature. Afterward, the reaction mixture was poured into water (20 mL) and extracted with EtOAc (3 × 20 mL). Drying (MgSO₄), filtration of the drying agent and evaporation of the solvent *in vacuo* afforded 3-benzyl-1,3-diazabicyclo[3.3.0]octan-2-one **24a**, which was purified by means of preparative TLC on silica gel (Hexane/EtOAc 1/1) to provide a colorless oil in a yield of 38% (164 mg, 0.76 mmol).

3-Benzyl-1,3-diazabicyclo[3.3.0]octan-2-one 24a

Colorless oil. R_f = 0.15 (Hexane/EtOAc 1/1). Yield 38%. **¹H NMR** (400 MHz, CDCl₃): δ 1.31 (1H, d×d×d×d, J = 12.2, 9.7, 9.7, 9.7 Hz, (HCH)CHN); 1.74-1.85 (1H, m, (HCH)CH₂N); 1.88-1.99 (2H, m, (HCH)CHN and (HCH)CH₂N); 3.06-3.12 (2H, m, (HCH)NCHN and (HCH)N(CH₂)₂); 3.39 (1H, d×d, J = 8.7, 8.3 Hz, (HCH)NCHN); 3.61 (1H, d×d×d×d, J = 9.7, 8.3, 6.0, 1.9 Hz, CHN); 3.71 (1H, d×d×d, J = 11.5, 7.9, 7.3 Hz, (HCH)N(CH₂)₂); 4.40 (2H, s, C_quatCH₂N); 7.23-7.34 (5H, m, 5×CH_arom). **¹³C NMR** (100 MHz, ref = CDCl₃): δ 25.1 (CH₂CH₂N); 30.8 (CH₂CHN); 45.8 (CH₂N(CH₂)₂); 46.8 (CH₂NCHN); 47.8 (C_quatCH₂N); 56.5 (CHN); 127.4 (CH_arom); 128.0 (2×CH_arom); 128.6 (2×CH_arom); 137.1 (C_quat,arom); 163.7 (C_quatO). **IR (cm⁻¹)**: ν_C=O = 1686; ν_max 2929, 1490, 1423, 1356, 1318, 1267, 1214, 1140, 1076, 766, 701, 636. **MS (70 eV)**: m/z (%): 217 (M⁺+1, 100). **HRMS (ESI)**: m/z calcd for C₁₃H₁₇N₂O: 217.1335 [M+H]⁺; found: 217.1331.
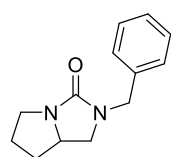
3-(4-Methylbenzyl)-1,3-diazabicyclo[3.3.0]octan-2-one 24b

Colorless oil. R_f = 0.16 (Hex/EA 1/1). Yield 48%. **¹H NMR** (400 MHz, CDCl₃): δ 1.29 (1H, d×d×d×d, J = 12.2, 9.7, 9.7, 9.7 Hz, (H̱CH)CHN); 1.73-1.84 (1H, m, (H̱CH)CH₂N); 1.87-1.98 (2H, m, (HC̱H)CHN and (HC̱H)CH₂N); 2.33 (3H, s, CH₃); 3.04-3.11 (2H, m, (H̱CH)NCHN and (H̱CH)N(CH₂)₂); 3.37 (1H, d×d, J = 8.9, 8.2 Hz, (HC̱H)NCHN); 3.59 (1H, d×d×d×d, J = 9.7, 8.2, 6.0, 1.9 Hz, CHN); 3.70 (1H, d×d×d, J = 11.4, 7.9, 7.4 Hz, (HC̱H)N(CH₂)₂); 4.35 (2H, s, C_{quat}CH₂N); 7.13 (4H, s, 4×CH_{arom}). **¹³C NMR** (100 MHz, ref = CDCl₃): δ 21.1 (CH₃); 25.1 (C̱H₂CH₂N); 30.8 (C̱H₂CHN); 45.8 (C̱H₂N(CH₂)₂); 46.7 (C̱H₂NCHN); 47.5 (C_{quat}C̱H₂N); 56.5 (CHN); 128.0 (2×CH_{arom}); 129.3 (2×CH_{arom}); 134.0 and 137.1 (2×C_{quat,arom}); 163.7 (C_{quat}O). **IR (cm⁻¹)**: ν_{C=O} = 1686; ν_{max} = 2924, 1514, 1488, 1426, 1352, 1318, 1266, 1214, 923, 803, 767, 727, 644, 625. **MS (70 eV)**: m/z (%): 231 (M⁺+1, 100). **HRMS (ESI)**: m/z calcd for C₁₄H₁₉N₂O: 231.1492 [M+H]⁺; found: 231.1492.

3-(4-Chlorobenzyl)-1,3-diazabicyclo[3.3.0]octan-2-one 24c

Colorless oil. R_f = 0.18 (Hexane/EtOAc 1/1). Yield 43%. **¹H NMR** (400 MHz, CDCl₃): δ 1.29 (1H, d×d×d×d, J = 12.4, 9.7, 9.7, 9.7 Hz, (H̱CH)CHN); 1.74-1.86 (1H, m, (H̱CH)CH₂N); 1.89-1.99 (2H, m, (HC̱H)CHN and (HC̱H)CH₂N); 3.05-3.12 (2H, m, (H̱CH)NCHN and (H̱CH)N(CH₂)₂); 3.39 (1H, d×d, J = 8.8, 8.3 Hz, (HC̱H)NCHN); 3.61 (1H, d×d×d×d, J = 9.7, 8.3, 6.0, 2.0 Hz, CHN); 3.69 (1H, d×d×d, J = 11.5, 7.7, 7.7 Hz, (HC̱H)N(CH₂)₂); 4.35 (2H, s, C_{quat}CH₂N); 7.18 (2H, d, J = 8.4 Hz, 2×CH_{arom}); 7.29 (2H, d, J = 8.4 Hz, 2×CH_{arom}). **¹³C NMR** (100 MHz, ref = CDCl₃): δ 25.1 (C̱H₂CH₂N); 30.8 (C̱H₂CHN); 45.7 (C̱H₂N(CH₂)₂); 46.8 (C̱H₂NCHN); 47.1 (C_{quat}C̱H₂N); 56.5 (CHN); 128.8 (2×CH_{arom}); 129.3 (2×CH_{arom}); 133.3 and 135.6 (2×C_{quat,arom}); 163.6 (C_{quat}O). **IR (cm⁻¹)**: ν_{C=O} = 1687; ν_{max} = 2931, 1489, 1434, 1407, 1352, 1319, 1274, 1215, 1141, 1091, 1014, 800, 766, 728, 656, 617. **MS (70 eV)**: m/z (%): 251/253 (M⁺+1, 100). **HRMS (ESI)**: m/z calcd for C₁₃H₁₆ClN₂O: 251.0946 [M+H]⁺; found: 251.0954.
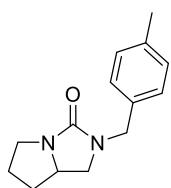
3-Benzyl-7-ethyl-1,3-diazabicyclo[3.3.0]octan-2-one 24d

Yield 41%. *dr* 60/40.

Major isomer

Colorless oil. R_f = 0.35 (Hexane/EtOAc 1/1). **¹H NMR** (400 MHz, CDCl₃): δ 0.91 (3H, t, J = 7.4 Hz, CH₃); 1.38 (2H, p, CH̱₂CH₃); 1.57 (1H, d×d×d, J = 12.7, 8.5, 8.2 Hz, CH(H̱CH)CHN); 1.67 (1H, d×d×d, J = 12.7, 7.6, 5.2 Hz, CH(HC̱H)CHN); 2.01-2.11 (1H, m, CH̱CH₂CH₃); 2.62 (1H, d×d, J = 11.9, 6.7 Hz, CH₃CH₂CH(H̱CH)N); 3.01 (1H, d×d, J = 8.9, 2.5 Hz, (H̱CH)NCHN); 3.40 (1H, d×d, J = 8.9, 8.3 Hz, (HC̱H)NCHN); 3.74 (1H, d×d×d×d, J = 8.3, 8.2, 7.6, 2.5 Hz, CHN); 3.95 (1H, d×d, J = 11.9, 7.7 Hz, CH₃CH₂CH(HC̱H)N); 4.37 (1H, d, J = 15.0 Hz, C_{quat}(H̱CH)N); 4.41 (1H, d, J = 15.0 Hz, C_{quat}(HC̱H)N); 7.22-7.34 (5H, m, 5×CH_{arom}). **¹³C NMR** (100 MHz, ref = CDCl₃): δ 12.6 (CH₃); 27.2 (C̱H₂CH₃); 37.3 (CHC̱H₂CH); 40.2 (CH₃CH₂C̱H); 47.7 (C_{quat}C̱H₂N); 47.9 (C̱H₂NCHN); 52.3 (CH₃CH₂CHC̱H₂N); 54.9 (CHN); 127.4, 128.0 and 128.6 (5×CH_{arom}); 137.1 (C_{quat,arom}); 163.8 (C_{quat}O). **IR (cm⁻¹)**: ν_{C=O} = 1690; ν_{max} = 2930, 2874, 1489, 1422, 1355, 1271, 1216, 1145, 1077, 1029, 991, 943, 767, 700. **MS (70 eV)**: m/z (%): 245 (M⁺+1, 100). **HRMS (ESI)**: m/z calcd for C₁₅H₂₁N₂O: 245.1648 [M+H]⁺; found: 245.1658.
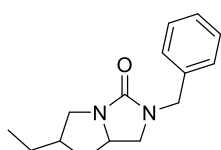
Minor isomer

White crystals. Mp 84°C. R_f = 0.35 (Hexane/EtOAc 1/1). **^{1}H NMR** (400 MHz, CDCl$_3$): δ 0.92 (3H, t, J = 7.4 Hz, CH$_3$); 1.00 (1H, d×d×d, J = 11.5, 11.2, 10.9 Hz, CH(H̲CH)CHN); 1.42 (1H, d×d×q, J = 14.0, 14.0, 7.4 Hz, (H̲CH)CH$_3$); 1.48 (1H, d×d×q, J = 14.0, 14.0, 7.4 Hz, (HCH̲)CH$_3$); 2.00 (1H, d×d×d, J = 11.5, 5.9, 5.7 Hz, CH(HCH̲)CHN); 2.11-2.23 (1H, m, CH̲CH$_2$CH$_3$); 3.08 (1H, d×d, J = 9.0, 2.4 Hz, (H̲CH)NCHN); 3.24 (1H, d×d, J = 11.5, 8.5 Hz, CH$_3$CH$_2$CH(H̲CH)N); 3.29 (1H, d×d, J = 11.5, 8.8 Hz, CH$_3$CH$_2$CH(HCH̲)N); 3.35 (1H, d×d, J = 9.0, 8.4 Hz, (HCH̲)NCHN); 3.67 (1H, d×d×d×d, J = 10.9, 8.4, 5.7, 2.4 Hz, CHN); 4.36 (1H, d, J = 15.0 Hz, C$_{quat}$(H̲CH)N); 4.41 (1H, d, J = 15.0 Hz, C$_{quat}$(HCH̲)N); 7.23-7.35 (5H, m, 5×CH$_{arom}$). **^{13}C NMR** (100 MHz, ref = CDCl$_3$): δ 12.9 (CH$_3$); 27.5 (C̲H$_2$CH$_3$); 37.7 (CHC̲H$_2$CH); 42.2 (CH$_3$C̲H$_2$CH); 46.6 (C̲H$_2$NCHN); 47.7 (C$_{quat}$C̲H$_2$N); 51.6 (CH$_3$CH$_2$CHC̲H$_2$N); 56.8 (CHN); 127.4, 128.0 and 128.6 (5×CH$_{arom}$); 137.1 (C$_{quat,arom}$); 163.8 (C$_{quat}$O). **IR (cm^{-1})**: $v_{C=O}$ = 1681; v_{max} = 2962, 2243, 1490, 1438, 1356, 1266, 906, 768, 725, 701. **MS (70 eV)**: m/z (%): 245 (M$^+$+1, 100). **HRMS (ESI)**: m/z calcd for C$_{15}$H$_{21}$N$_2$O: 245.1648 [M+H]$^+$; found: 245.1655.
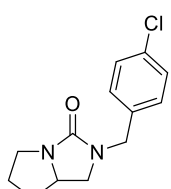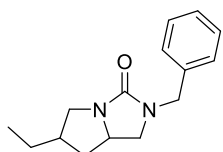
7,7-Diethyl-3-(4-methylbenzyl)-1,3-diazabicyclo[3.3.0]octan-2-one 24e

Colorless oil. R_f = 0.25 (Hexane/EtOAc 3/1). Yield 57%. **^{1}H NMR** (400 MHz, CDCl$_3$): δ 0.83 and 0.85 (2×3H, 2×t, J = 7.4 Hz, 2×CH̲$_3$CH$_2$); 1.19 (1H, d×d, J = 12.5, 9.8 Hz, (H̲CH)CHN); 1.35-1.47 (4H, m, 2×CH̲$_2$CH$_3$); 1.75 (1H, d×d, J = 12.5, 6.5 Hz, (HCH̲)CHN); 2.33 (3H, s, CH$_{3,tos}$); 2.82 (1H, d, J = 11.8 Hz, C$_{quat}$(H̲CH)N); 3.00 (1H, d×d, J = 8.9, 2.2 Hz, (H̲CH)NCHN); 3.35 (1H, d×d, J = 8.9, 8.7 Hz, (HCH̲)NCHN); 3.53 (1H, d, J = 11.8 Hz, C$_{quat}$(HCH̲)N); 3.73-3.80 (1H, m, CHN); 4.32 (1H, d, J = 14.9 Hz, C$_{quat,arom}$(H̲CH)N); 4.37 (1H, d, J = 14.9 Hz, C$_{quat,arom}$(HCH̲)N); 7.13 (4H, s, 4×CH$_{arom}$). **^{13}C NMR** (100 MHz, ref = CDCl$_3$): δ 8.4 and 9.0 (2×CH$_3$); 21.1 (CH$_{3,tos}$); 27.7 and 29.3 (2×C̲H$_2$CH$_3$); 42.4 (C̲H$_2$CHN); 47.2 (C̲H$_2$NCHN); 47.4 (C$_{quat}$); 47.5 (C$_{quat,arom}$C̲H$_2$N); 55.5 (CHN); 56.4 (C$_{quat}$C̲H$_2$N); 128.0 (2×CH$_{arom}$); 129.3 (2×CH$_{arom}$); 134.1 and 137.1 (2×C$_{quat,arom}$); 163.5 (C$_{quat}$O). **IR (cm^{-1})**: $v_{C=O}$ = 1686; v_{max} = 2963, 1488, 1427, 1352, 1279, 1214, 908, 766, 727, 645. **MS (70 eV)**: m/z (%): 287 (M$^+$+1, 100). **HRMS (ESI)**: m/z calcd for C$_{18}$H$_{27}$N$_2$O: 287.2118 [M+H]$^+$; found: 287.2121.
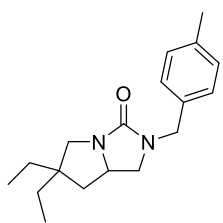
4-(4-Chlorobenzyl)-1,3-diazabicyclo[4.3.0]nonan-2,3-dione 25a

Colorless oil. R_f = 0.03 (Hexane/EtOAc 1/1). Yield 23%. **^{1}H NMR** (400 MHz, CDCl$_3$): δ 1.29 (1H, d×d×d×d, J = 12.1, 11.9, 10.4, 7.3 Hz, (H̲CH)CHN); 1.89 (1H, d×d×d×d, J = 12.4, 12.1, 9.5, 9.5, 6.7 Hz, (H̲CH)CH$_2$N); 2.05-2.16 (2H, m, (HCH̲)CHN and (HCH̲)CH$_2$N); 3.30-3.39 (2H, m, CH̲$_2$NCHN); 3.59-3.70 (CH̲$_2$N(CH$_2$)$_2$); 3.85-3.93 (1H, m, CHN); 4.56 (1H, d, J = 14.7 Hz, C$_{quat}$(H̲CH)N); 4.73 (1H, d, J = 14.7 Hz, C$_{quat}$(HCH̲)N); 7.23 (2H, d, J = 8.4 Hz, 2×CH$_{arom}$); 7.32 (2H, d, J = 8.4 Hz, 2×CH$_{arom}$). **^{13}C NMR** (100 MHz, ref = CDCl$_3$): δ 23.3 (C̲H$_2$CH$_2$N); 30.4 (C̲H$_2$CHN); 45.4 (C̲H$_2$N(CH$_2$)$_2$); 49.7 (C̲H$_2$NCHN); 50.1 (C$_{quat}$C̲H$_2$N); 55.2 (CHN); 129.1 (2×CH$_{arom}$); 129.7 (2×CH$_{arom}$); 134.1 and 134.3 (2×C$_{quat,arom}$); 155.5 and 158.4 (2×C$_{quat}$O). **IR (cm^{-1})**: $v_{C=O}$ = 1665; v_{max} = 2958, 2881, 1489, 1452, 1408, 1376, 1264, 1224, 1204, 1165, 1089, 1031, 1014, 840, 799, 730, 638. **MS (70 eV)**: m/z (%): 279/281 (M$^+$+1, 100). **HRMS (ESI)**: m/z calcd for C$_{14}$H$_{16}$ClN$_2$O$_2$: 279.0895 [M+H]$^+$; found: 279.0901.
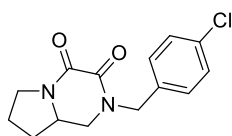
8-Ethyl-4-(4-methoxybenzyl)-1,4-diazabicyclo[4.3.0]nonan-2,3-dione 25b

Spectral data derived from the mixture of diastereomers

Yellow oil. R_f = 0.27 (CH$_2$Cl$_2$/MeOH 95/5). Yield 20%. *dr* 53/47. **^{1}H NMR** (400 MHz, CDCl$_3$): δ 0.92 and 0.93 (2×3H, 2×t, *J* = 7.4 Hz, 2×CH$_3$CH$_2$); 1.21-1.27 (1H, m, (HCH)CHN); 1.35-1.50 (2H, m, 2×CH$_2$CH$_3$); 1.71 (1H, d×d×d, *J* = 12.8, 8.1, 8.1 Hz, (HCH)CHN); 1.85 (1H, d×d×d, *J* = 12.8, 6.9, 4.1 Hz, (HCH)CHN); 2.11-2.23 (3H, m, (HCH)CHN and 2×CHCH$_2$CH$_3$); 3.16-3.42 (6H, m, 2×CH(HCH)N, 2×CH$_2$NCHN); 3.77-3.80 (1H, m, CH(HCH)N); 3.80 (2×3H, 2×s, 2×CH$_3$O); 3.87-4.00 (3H, m, CH(HCH)N and 2×CHN); 4.53 (1H, d, *J* = 14.4 Hz, C$_{quat,arom}$(HCH)N); 4.55 (1H, d, *J* = 14.4 Hz, C$_{quat,arom}$(HCH)N); 4.67 (1H, d, *J* = 14.4 Hz, C$_{quat,arom}$(HCH)N); 4.68 (1H, d, *J* = 14.4 Hz, C$_{quat,arom}$(HCH)N); 6.86 (2×1H, 2×d, *J* = 8.6 Hz, 2×CH$_{arom}$); 6.87 (2×1H, 2×d, *J* = 8.6 Hz, 2×CH$_{arom}$); 7.20-7.22 (4H, m, 4×CH$_{arom}$). **^{13}C NMR** (100 MHz, CDCl$_3$): δ 12.3 and 12.5 (2×CH$_3$CH$_2$); 26.3 and 26.8 (2×CH$_2$CH$_3$); 34.9 and 36.6 (2×CH$_2$CHN); 38.4 and 39.1 (2×CHCH$_2$CH$_3$); 49.5 and 49.6 (2×CH$_2$NCHN); 49.97 and 50.00 (2×C$_{quat,arom}$CH$_2$N); 50.6 (2×CHCH$_2$N); 53.6 (CHN); 55.3 (2×CH$_3$O); 55.5 (CHN); 114.2 (4×CH$_{arom}$); 127.8 (2×C$_{quat,arom}$); 129.79 and 129.82 (4×CH$_{arom}$); 155.6, 155.7, 158.1, 158.3 and 159.5 (2×C$_{quat,arom}$ and 4×C$_{quat}$O). **IR (cm^{-1})**: $v_{C=O}$ = 1675; v_{max} = 2960, 1611, 1513, 1453, 1375, 1247, 1176, 1032, 818. **MS (70 eV)**: *m/z* (%): 303 (M$^+$+1, 100). **HRMS (ESI)**: *m/z* calcd for C$_{17}$H$_{23}$N$_2$O$_3$: 303.1703 [*M*+H]$^+$; found: 303.1706.
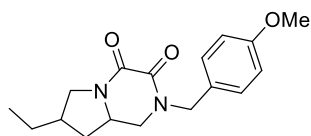
8,8-Diethyl-4-(4-methylbenzyl)-1,4-diazabicyclo[4.3.0]nonan-2,3-dione 25c

Colorless oil. R_f = 0.16 (EtOAc). Yield 27%. **^{1}H NMR** (400 MHz, CDCl$_3$): δ 0.84 (2×3H, 2×t, *J* = 7.4 Hz, 2×CH$_3$CH$_2$); 1.32-1.51 (5H, m, (HCH)CHN and 2×CH$_2$CH$_3$); 1.90 (1H, d×d, *J* = 12.5, 6.0 Hz, (HCH)CHN); 2.34 (3H, s, CH$_{3,tos}$); 3.23-3.33 (2H, m, CH$_2$NCHN); 3.38 (1H, d, *J* = 11.8 Hz, C$_{quat}$(HCH)N); 3.43 (1H, d, *J* = 11.8 Hz, C$_{quat}$(HCH)N); 3.96-4.04 (1H, m, CHN); 4.55 (1H, d, *J* = 14.9 Hz, C$_{quat,arom}$(HCH)N); 4.71 (1H, d, *J* = 14.9 Hz, C$_{quat,arom}$(HCH)N); 7.14-7.19 (4H, m, 4×CH$_{arom}$). **^{13}C NMR** (100 MHz, ref = CDCl$_3$): δ 8.8 and 9.2 (2×CH$_3$); 21.1 (CH$_{3,tos}$); 29.2 and 30.5 (2×CH$_2$CH$_3$); 40.0 (CH$_2$CHN); 44.3 (C$_{quat}$); 49.8 (CH$_2$NCHN); 50.3 (C$_{quat,arom}$CH$_2$N); 54.1 (CHN); 55.3 (C$_{quat}$CH$_2$N); 128.4 (2×CH$_{arom}$); 129.6 (2×CH$_{arom}$); 134.7 and 137.9 (2×C$_{quat,arom}$); 155.9 and 158.3 (2×C$_{quat}$O). **IR (cm^{-1})**: $v_{C=O}$ = 1667; v_{max} = 2963, 1448, 1411, 1375, 1261, 1211, 805, 731. **MS (70 eV)**: *m/z* (%): 315 (M$^+$+1, 100). **HRMS (ESI)**: *m/z* calcd for C$_{19}$H$_{27}$N$_2$O$_2$: 315.2067 [*M*+H]$^+$; found: 315.2073.
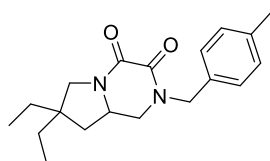
Synthesis of *trans*-2-aryl-1-benzyl-3-(2-cyanoethyl)aziridines 29

trans-2-Aryl-1-benzyl-3-(2-cyanoethyl)aziridines **29** were prepared according to a literature procedure, and spectral data corresponded with those reported in the literature.[30]

Synthesis of *trans*-2-aryl-3-benzylaminopiperidines 32

As a representative example, the synthesis of *trans*-3-benzylamino-2-phenylpiperidine **32a** is described. To an ice-cooled solution of *trans*-1-benzyl-3-(2-cyanoethyl)-2-phenylaziridine **29a** (524 mg, 2 mmol) and In(OTf)$_3$ (337 mg, 0.6 mmol, 0.3 equiv) in dry THF (20 mL), was added a solution of LiAlH$_4$ (4 mL, 4 mmol, 2 equiv, 1.0 M in THF) via a syringe. Then, the resulting solution was heated under reflux for 1 hour under nitrogen atmosphere. Afterward, the reaction mixture was quenched with brine (20 mL) to

neutralize the excess of LiAlH$_4$. Then, the reaction mixture was filtered through a path of Celite® and extracted with Et$_2$O (2 × 20 mL). Drying (MgSO$_4$), filtration of the drying agent and evaporation of the solvent *in vacuo* afforded *trans*-3-benzylamino-2-phenylpiperidine **32a**, which was purified by means of column chromatography on silica gel (CH$_2$Cl$_2$/MeOH 95/5) to provide an orange oil in a yield of 56% (298 mg, 1.12 mmol).

trans-3-Benzylamino-2-phenylpiperidine 32a

Orange oil. R_f = 0.19 (CH$_2$Cl$_2$/MeOH 95/5). Yield 56%. **^{1}H NMR** (400 MHz, CDCl$_3$): δ 1.32 (1H, d×d×d×d, J = 12.8, 12.8, 11.1, 4.2 Hz, CH(H<u>C</u>H)CH$_2$); 1.62-1.80 (2H, m, C<u>H</u>$_2$CH$_2$N); 2.20-2.26 (1H, m, CH(HC<u>H</u>)CH$_2$); 2.66 (1H, d×d×d, J = 11.9, 11.9, 3.4 Hz, CH$_2$(<u>H</u>CH)N); 2.73 (1H, d×d×d, J = 10.8, 9.5, 4.2 Hz, C<u>H</u>CH$_2$); 2.85 (2H, s (broad), 2×NH); 3.04-3.09 (1H, m, CH$_2$(HC<u>H</u>)N); 3.43 (1H, d, J = 13.4 Hz, N(<u>H</u>CH)C$_{quat}$); 3.44 (1H, d, J = 9.5 Hz, C$_{quat}$CHN); 3.64 (1H, d, J = 13.4 Hz, N(HC<u>H</u>)C$_{quat}$); 6.98-7.00 (2H, m, 2×CH$_{arom}$); 7.16-7.37 (8H, m, 8×CH$_{arom}$). **^{13}C NMR** (100 MHz, ref = CDCl$_3$): δ 24.5 (<u>C</u>H$_2$CH$_2$N); 30.8 (<u>C</u>H$_2$CH); 46.7 (CH$_2$<u>C</u>H$_2$N); 50.6 (N<u>C</u>H$_2$C$_{quat}$); 58.5 (<u>C</u>HCH$_2$); 67.6 (C$_{quat}$<u>C</u>HN); 126.9 (CH$_{arom}$); 127.8, 128.2 and 128.3 (6×CH$_{arom}$); 128.5 (CH$_{arom}$); 128.9 (2×CH$_{arom}$); 139.9 and 140.0 (2×C$_{quat,arom}$). **IR (cm^{-1})**: ν$_{max}$ = 2934, 2854, 1494, 1454, 1350, 1277, 1243, 1224, 1162, 1076, 1029, 907, 754, 697, 637. **MS (70 eV)**: *m/z* (%): 267 (M$^+$+1, 100). **HRMS (ESI)**: *m/z* calcd for C$_{18}$H$_{23}$N$_2$: 267.1856 [*M*+H]$^+$; found: 267.1851.
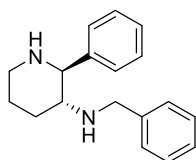
trans-3-Benzylamino-2-(4-chlorophenyl)piperidine 32b

Yellow oil. R_f = 0.16 (CH$_2$Cl$_2$/MeOH 95/5). Yield 84%. **^{1}H NMR** (400 MHz, CDCl$_3$): δ 1.29 (1H, d×d×d×d, J = 12.9, 12.9, 10.9, 4.1 Hz, CH(H<u>C</u>H)CH$_2$); 1.64 (1H, d×d×d×d×d, J = 12.8, 12.8, 12.8, 4.1, 3.4 Hz, (<u>H</u>CH)CH$_2$N); 1.73-1.79 (1H, m, (HC<u>H</u>)CH$_2$N); 2.10 (2H, s (broad), 2×NH); 2.17-2.27 (1H, m, CH(HC<u>H</u>)CH$_2$); 2.61 (1H, d×d×d, J = 10.9, 9.2, 3.9 Hz, C<u>H</u>CH$_2$); 2.71 (1H, d×d×d, J = 11.9, 11.9, 3.4 Hz, CH$_2$(<u>H</u>CH)N); 3.05-3.10 (1H, m, CH$_2$(HC<u>H</u>)N); 3.38 (1H, d, J = 9.2 Hz, C$_{quat}$CHN); 3.43 (1H, d, J = 13.4 Hz, N(<u>H</u>CH)C$_{quat}$); 3.65 (1H, d, J = 13.4 Hz, N(HC<u>H</u>)C$_{quat}$); 6.99-7.01 (2H, m, 2×CH$_{arom}$); 7.18-7.29 (7H, m, 7×CH$_{arom}$). **^{13}C NMR** (100 MHz, ref = CDCl$_3$): δ 25.1 (<u>C</u>H$_2$CH$_2$N); 31.2 (<u>C</u>H$_2$CH); 47.0 (CH$_2$<u>C</u>H$_2$N); 50.8 (N<u>C</u>H$_2$C$_{quat}$); 59.0 (<u>C</u>HCH$_2$); 67.5 (C$_{quat}$<u>C</u>HN); 126.9 (CH$_{arom}$); 127.9, 128.3, 128.8 and 129.5 (8×CH$_{arom}$); 133.7, 140.0 and 140.1 (3×C$_{quat,arom}$). **IR (cm^{-1})**: ν$_{NH}$ = 3304; ν$_{max}$ = 2932, 2852, 1602, 1491, 1453, 1248, 1224, 1159, 1089, 1029, 1014, 820, 734, 697, 638. **MS (70 eV)**: *m/z* (%): 301/303 (M$^+$+1, 100). **HRMS (ESI)**: *m/z* calcd for C$_{18}$H$_{22}$ClN$_2$: 301.1466 [*M*+H]$^+$; found: 301.1456.
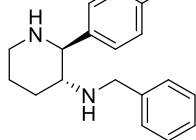
Synthesis of *trans*-6-benzyl-8-(4-chlorophenyl)-1,6-diazabicyclo[3.2.1]octan-7-one 33

To a solution of *trans*-3-benzylamino-2-(4-chlorophenyl)piperidine **32b** (600 mg, 2 mmol) in dry THF (20 mL) was added carbonyldiimidazole (CDI, 324 mg, 2 mmol, 1 equiv). Then, the resulting solution was stirred for 2 days at reflux conditions. Afterward, the reaction mixture was poured into water (20 mL) and extracted with EtOAc (3 × 20 mL). Drying (MgSO$_4$), filtration of the drying agent and evaporation of the solvent *in vacuo* afforded *trans*-6-benzyl-8-(4-chlorophenyl)-1,6-diazabicyclo[3.2.1]octan-7-one **33**, which was purified by means of preparative TLC on silica gel (EtOAc) to provide colorless oil in a yield of 15% (98 mg, 0.3 mmol).

Colorless oil. R_f = 0.19 (EtOAc). Yield 15%. **¹H NMR** (400 MHz, CDCl₃): δ 1.43-1.48 (1H, m, (HCH)CH₂N); 1.64-1.77 (2H, m, CH₂CHN); 2.05-2.17 (1H, m, (HCH)CH₂N); 3.10 (1H, d×d×d, J = 13.3, 13.3, 3.2 Hz, CH₂(HCH)N); 3.44-3.45 (1H, m, CHNCO); 3.68 (1H, d, J = 13.2 Hz, C_quat(HCH)N); 3.77 (1H, d, J = 13.2 Hz, C_quat(HCH)N); 4.07-4.11 (1H, m, CH₂(HCH)N); 5.26 (1H, s (broad), C_quatCHN); 7.07 (1H, s, CH_arom); 7.20-7.40 (7H, m, 7×CH_arom); 7.95 (1H, s, CH_arom). **¹³C NMR** (100 MHz, ref = CDCl₃): δ 19.2 (CH₂CH₂N); 24.6 (CH₂CHN); 42.4 (CH₂CH₂N); 51.3 (C_quatCH₂N); 53.9 (CHNCO); 60.2 (C_quatCHN); 117.7, 127.4, 127.7, 128.0, 128.7, 129.4 and 129.9 (8×CH_arom); 133.6 (2×C_quat,arom); 135.2 (C_quat,arom); 137.0 (CH_arom); 153.2 (C_quatO). **IR (cm⁻¹)**: ν_C=O = 1691; ν_max = 2934, 1492, 1420, 1279, 1249, 1094, 1030, 749, 703. **MS (70 eV)**: m/z (%): 327/329 (M⁺+1, 100). **HRMS (ESI)**: m/z calcd for C₁₉H₂₀ClN₂O: 327.1259 [M+H]⁺; found: 327.1261.
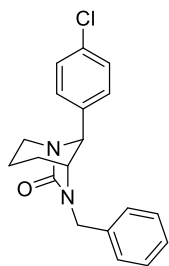
Synthesis of *trans*-4-benzyl-9-(4-chlorophenyl)-1,4-diazabicyclo[3.3.1]nonane-2,3-dione 34

To a solution of *trans*-3-benzylamino-2-(4-chlorophenyl)piperidine **32b** (600 mg, 2 mmol) in dry THF (20 mL) was added 1,1'-oxalyldiimidazole (380 mg, 2 mmol, 1 equiv). Then, the resulting solution was stirred for 2 days at reflux conditions. Afterward, the reaction mixture was poured into water (20 mL) and extracted with EtOAc (3 × 20 mL). Drying (MgSO₄), filtration of the drying agent and evaporation of the solvent *in vacuo* afforded *trans*-4-benzyl-9-(4-chlorophenyl)-1,4-diazabicyclo[3.3.1]nonane-2,3-dione **34**, which was purified by means of preparative TLC on silica gel (EtOAc) to provide a colorless oil in a yield of 18% (127 mg, 0.36 mmol).

Colorless oil. R_f = 0.16 (EtOAc). Yield 18%. **¹H NMR** (400 MHz, CDCl₃): δ 1.20 (1H, d×d×d×d, J = 12.4, 10.4, 10.4, 7.5 Hz, (HCH)CHN); 1.65-1.79 (2H, m, CH₂CH₂N); 1.93 (1H, d×d×d×d, J = 12.4, 6.1, 5.9, 3.1 Hz, (HCH)CHN); 3.31 (1H, d×d×d, J = 12.4, 9.2, 7.8 Hz, CH₂(HCH)N); 3.60 (1H, d, J = 14.8 Hz, C_quat(HCH)N); 3.31 (1H, d×d×d, J = 12.4, 7.8, 3.5 Hz, CH₂(HCH)N); 4.17 (1H, d×d×d, J = 10.4, 5.9, 4.7 Hz, CHNCO); 4.39 (1H, d, J = 4.7 Hz, C_quatCHN); 5.48 (1H, d, J = 13.2 Hz, C_quat(HCH)N); 7.00-7.02 (2H, m, 2×CH_arom); 7.23-7.26 (2H, m, 2×CH_arom); 7.33-7.37 (5H, m, 5×CH_arom). **¹³C NMR** (100 MHz, ref = CDCl₃): δ 22.9 (CH₂CH₂N); 28.7 (CH₂CHN); 45.6 (CH₂CH₂N); 48.9 (C_quatCH₂N); 58.2 (CHNCO); 60.2 (C_quatCHN); 128.2, 128.5, 129.0 and 129.4 (9×CH_arom); 132.4, 135.3 and 135.9 (3×C_quat,arom); 155.6 and 158.3 (2×C_quatO). **IR (cm⁻¹)**: ν_C=O = 1691; ν_max = 2954, 1492, 1452, 1365, 1233, 1156, 1093, 1013, 910, 845, 731, 700. **MS (70 eV)**: m/z (%): 355/357 (M⁺+1, 100). **HRMS (ESI)**: m/z calcd for C₂₀H₂₀ClN₂O₂: 355.1208 [M+H]⁺; found: 355.1213.
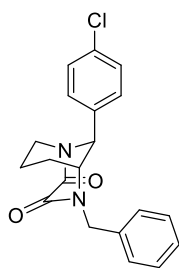
Single crystal X-ray diffraction

X-ray analysis was performed by Prof. Kristof Van Hecke (XStruct, Department of Inorganic and Physical Chemistry, Faculty of Sciences, Ghent University).

For the structure of *cis*-2-[(*N*-benzyl-*N*-tosyl)aminomethyl]-1-phenyl-1-(tosylaminomethyl)cyclopropane *cis*-**19**, X-ray intensity data was collected at 100 K, on a Rigaku Oxford Diffraction Supernova Dual Source (Cu at zero) diffractometer equipped with an Atlas CCD detector using ω scans and CuKα (λ = 1.54184 Å) radiation. The images were interpreted and integrated with the program CrysAlisPro. Using

Olex2, the structure was solved by direct methods using the ShelXS structure solution program and refined by full-matrix least-squares on F^2 using the ShelXL program package. Non-hydrogen atoms were anisotropically refined and the hydrogen atoms in the riding mode and isotropic temperature factors fixed at 1.2 times U(eq) of the parent atoms (1.5 times for methyl groups). The hydrogen atom H2 was located from a difference Fourier electron density map and unrestrained refined (with an isotropic temperature factor of 1.2 times U(eq) of the parent atom N2). The asymmetric unit has chirality at C16 (*S*) and C17 (*R*). But obviously, because of the centro-symmetric space group, also the inverse configuration is present in the crystal structure.

Crystal data for compound *cis*-19:

$C_{32}H_{34}N_2O_4S_2$, $M = 574.73$, triclinic, space group *P*-1 (No. 2), $a = 9.6491(3)$ Å, $b = 10.9398(3)$ Å, $c = 14.8427(4)$ Å, $\alpha = 109.020(2)°$, $\beta = 97.224(3)°$, $\gamma = 92.175(3)°$, $V = 1464.28(8)$ Å^3, $Z = 2$, $T = 100$ K, $\rho_{calc} = 1.304$ g cm^{-3}, μ(Cu-Kα) $= 1.967$ mm^{-1}, $F(000) = 608$, 27903 reflections measured, 5958 unique ($R_{int} = 0.0324$) which were used in all calculations. The final $R1$ was 0.0342 ($I > 2\sigma (I)$) and $wR2$ was 0.0893 (all data).

PART III

Concise synthesis of 3-(aminomethyl)pyrrolizidines via an In(OTf)$_3$-mediated ring rearrangement of 2-[2-(1-pyrrolin-2-yl)alkyl]aziridines

Abstract

In this study, an efficient ring rearrangement of 2-[2-(1-pyrrolin-2-yl)alkyl]aziridines, prepared from 2-(bromomethyl)aziridines, toward novel *trans*- and *cis*-3-aminomethyl-substituted pyrrolizidines was developed. To that end, addition of In(OTf)$_3$ as an appropriate Lewis acid catalyst resulted in the formation of intermediate pyrrolizidinium salts via regioselective aziridine ring opening, which were then trapped by a hydride or cyanide nucleophile. Column chromatographic purification allowed the isolation of the major *trans*-isomers, exclusively.

Graphical abstract
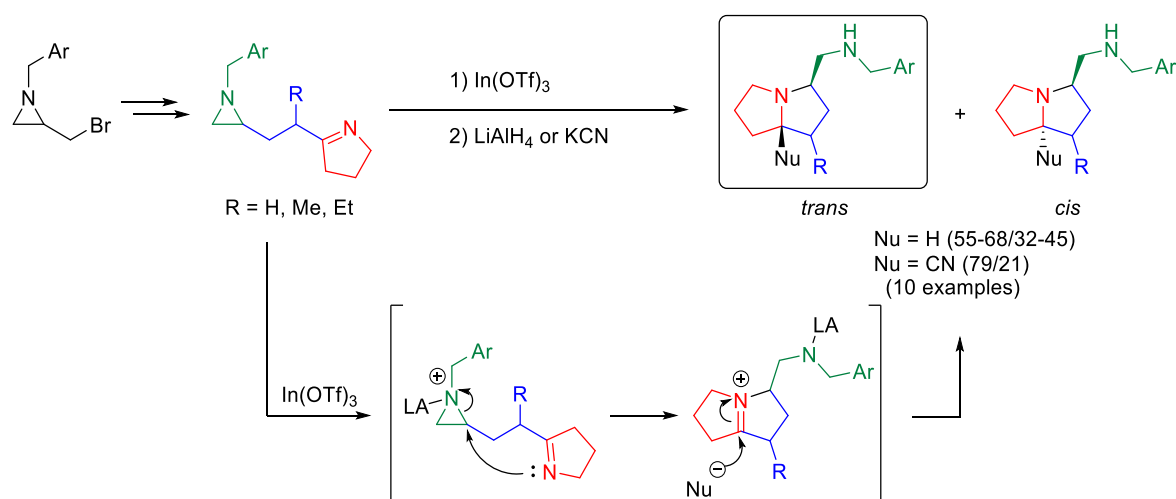
Reference

Dolfen, J.; D'hooghe, M. "Concise synthesis of 3-(aminomethyl)pyrrolizidines via an In(OTf)$_3$-mediated ring rearrangement of 2-[2-(1-pyrrolin-2-yl)alkyl]aziridines". *Synthesis* **2017**, *49*, 2215-2222 (I.F. 2.65).

1. Introduction

Biologically active alkaloids, isolated from a variety of natural sources, have inspired many chemists in the pursuit of novel types of drugs and pharmaceuticals.[35] These compounds often accommodate a 1-azabicyclic framework, with pyrrolizidines, indolizidines and quinolizidines as important representative structures (e.g. australine **1**,[117] swainsonine **2**[118] and sparteine **3**[119] (Figure 1)). Although several strategies toward 1-azabicyclo[m.n.0]alkanes are available, novel routes to access these scaffolds are still desirable. Also, many of these bicyclic alkaloids are polyhydroxylated, whereas amino(alkyl)-substituted representatives are more scarce and received considerably less attention in the literature.

(+)-Australine **1**
(*antiviral*)

(-)-Swainsonine **2**
(*anticancer*)

Sparteine **3**
(*antiarrhythmic*)
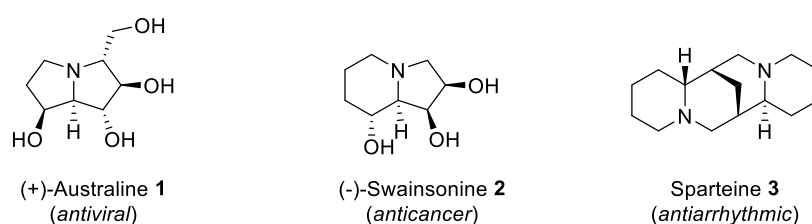
Figure 1

In this chapter, the developed intramolecular LiAlH$_4$-induced ring expansion of non-activated 2-(cyanoethyl)aziridines will be applied on more complex aziridine substrates (aziridinyl pyrrolines and aziridinyl piperideines) to enable the construction of amino(methyl)-substituted 1-azabicyclic skeletons.

2. Synthesis of 3-(aminomethyl)pyrrolizidines through ring rearrangement of 2-[2-(1-pyrrolin-2-yl)ethyl]aziridines

Plants are known to produce secondary metabolites as a defense mechanism against invading organisms and environmental stress.[120] Among these non-essential metabolites, pyrrolizidine alkaloids (accommodating a 1-azabicyclo[3.3.0]octane scaffold) are the most common compounds to target herbivores.[121] Furthermore, many of these bicyclic azaheterocycles have attracted considerable attention from medicinal chemists due to their pronounced biological activities[122] and, as a consequence, numerous methods have been developed over the years for their synthesis.[35a,123]

In this part, the synthesis of 3-aminomethyl-substituted pyrrolizidines is discussed starting from 2-methyl-1-pyrroline in a two-step procedure, involving exocyclic alkylation with 2-(bromomethyl)aziridines, followed by a regioselective ring transformation upon reaction with an appropriate Lewis acid and a nucleophile. The 3-(aminomethyl)pyrrolizidine skeleton is of biological importance and appears for example in the pyrrolizidine alkaloids (+)- and (-)-pochonine, which are known to show glycosidase inhibition activity (Figure 2).[124] The convenient synthesis of the basic 3-(aminomethyl)pyrrolizidine scaffold might thus also be of relevance within the framework of more elaborate bioactive compound development.

(+)-pochonine **4**   (-)-pochonine **5**
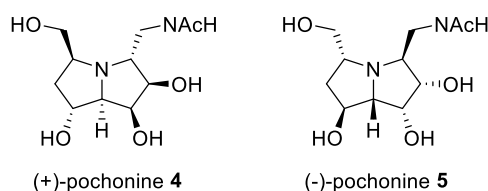
Figure 2

The numbering and nomenclature of pyrrolizidines was performed according to the literature (Figure 3).[125] In substituted pyrrolizidines, the descriptors *cis* and *trans* are related to the relative position of the hydrogen atom on carbon atom 7a with respect to the hydrogen atom on the substituted carbon atom.
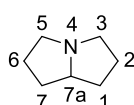
Figure 3

The preparation of the starting material to produce aminomethyl-substituted pyrrolizidines was inspired by a previous route developed at the Department of Sustainable Organic Chemistry and Technology (UGent).[126] Herein, alkylation of cyclic imines (including 2-methyl-1-pyrroline) with a variety of ω,ω'-dihaloalkanes has been employed as an initial step in the synthesis of a broad range of indolizidines and quinolizidines (Scheme 1).
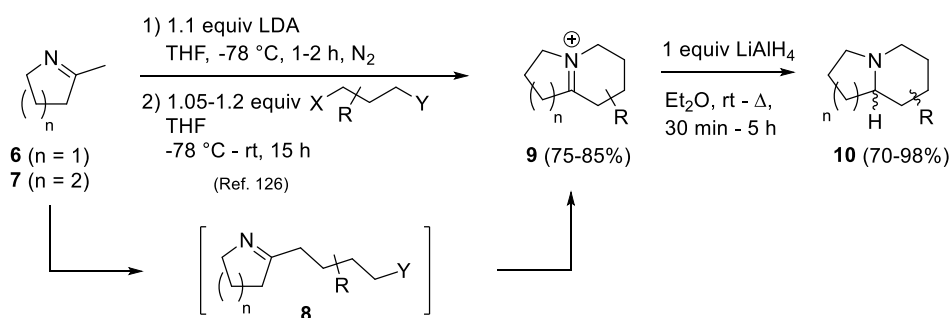
Scheme 1

In accordance, freshly distilled 2-methyl-1-pyrroline (**6**) (104 °C, 1 atm) was deprotonated to furnish the corresponding aza-allylic anion at 0 °C using LDA, and subsequent addition of 2-(bromomethyl)aziridines **11**[43] resulted in the desired new 2-[2-(1-pyrrolin-2-yl)ethyl]aziridines **12** in excellent yields (87-93%, Scheme 2, Table 1). Then, the obtained aziridines **12** were confronted with 1 equiv of LiAlH$_4$ and 0.3 equiv of In(OTf)$_3$ in THF at reflux temperature but these reaction conditions unfortunately resulted in complex reaction mixtures which stands in sharp contrast to the use of (2-

cyanoethyl)aziridines as substrates. To overcome this problem, the reagents (LiAlH$_4$, In(OTf)$_3$) were added in a different order, i.e. initial addition of In(OTf)$_3$ followed by addition of LiAlH$_4$. This method was relied on preliminary research at the Department of Sustainable Organic Chemistry and Technology (UGent) which showed that *in situ* formed 2-(ω-haloalkyl)-1-pyrrolines **8** (obtained from the reaction of deprotonated 2-methyl-1-pyrroline (**6**) with ω,ω'-dihaloalkanes) were quickly transformed into the corresponding bicyclic salts **9** (Scheme 1). To that end, aziridines **12** were stirred in THF in the presence of 0.3 equiv of In(OTf)$_3$ during one hour at room temperature, leading to the *in situ* formation of an intermediate bicyclic salt. Consecutive reduction with LiAlH$_4$ resulted in *trans-* and *cis-*3-(arylmethylaminomethyl)pyrrolizidines **13** in a 56-58/42-44 ratio. After silica gel column chromatography, the major *trans*-isomers **13** were isolated in pure form, and the *trans*-configuration was supported by NOE experiments, as no NOE effect was observed between the hydrogen atoms at C3 and C7a (only the *cis*-isomers are expected to provoke a NOE effect between these protons). Unfortunately, the *cis*-isomers could not be isolated from the reaction mixtures. This In(OTf)$_3$-mediated ring expansion of non-activated aziridines **12** mirrors the selective preparation of a library of 2-(aminomethyl)pyrrolidines and 3-aminopiperidines starting from polysubstituted 2-(cyanoethyl)aziridines.[25] Analogous to the ring rearrangement of 2-(cyanoethyl)aziridines, the addition of a sub-equimolar amount (0.3 equiv) of In(OTf)$_3$ appeared to be appropriate to effect the desired ring transformation of aziridine substrates **12** toward pyrrolizidines **13**.
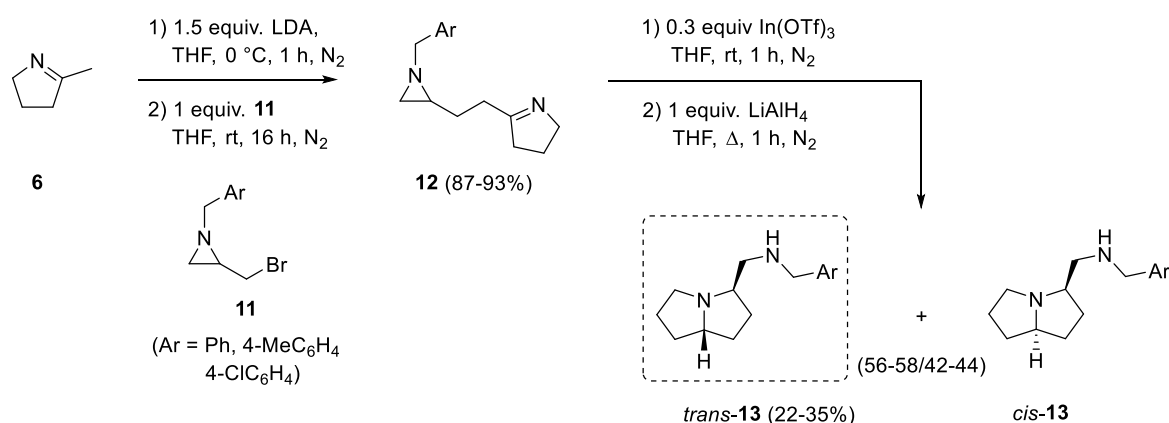
Scheme 2

Table 1. Synthesis of 1-arylmethyl-2-[2-(1-pyrrolin-2-yl)ethyl]aziridines 12 and 3-(aminomethyl)pyrrolizidines 13.

Entry	Ar	Compound **12** (yield [%])	Compound *trans*-**13** (yield [%])[a]	*trans/cis* (**13**)[b]
1	Ph	**12a** (93)	*trans*-**13a** (22)	58/42
2	4-MeC$_6$H$_4$	**12b** (87)	*trans*-**13b** (35)	56/44
3	4-ClC$_6$H$_4$	**12c** (90)	*trans*-**13c** (22)	56/44

[a] After purification by column chromatography (SiO$_2$).

[b] Determined by ^{1}H NMR spectroscopy (CDCl$_3$).

2-Methyl-1-pyrroline (**6**) has been equally deployed in only one case for the synthesis of pyrrolizidines, although the protocol produced 7a-substituted representatives. Reaction with LDA and ethylene oxide afforded the corresponding 2-(3-hydroxypropyl)-1-pyrroline, which was then treated with a variety of isonitriles.[127] In literature, only two procedures concerning a one-step aziridine-to-pyrrolizidine ring transformation (without the presence of any additional ring on the pyrrolizidine scaffold) are available. In a first literature route, a set of 2,6-disubstituted pyrrolizidines has been obtained via a Pd- and Lewis acid-cocatalyzed rearrangement of vinyl aziridines in good yields (51-86%),[128] whereas in a second literature approach, reaction of 2-bromomethyl-1-(pent-4-enyl)aziridines with tributyltin hydride and AIBN in benzene has afforded 2,6-disubstituted pyrrolizidines in moderate yields (49-63%) via a cascade of radical reactions.[129] Other (recent) contributions to the preparation of substituted pyrrolizidines involve for example the 1,3-dipolar cycloaddition of azomethine ylides **17/18** (*in situ* generated from *L*-proline (ester) **14** and aldehydes **15**) with β-trifluoromethyl acrylamides,[130] 1,3-diketones[131] and dipolarophiles **16**,[132] resulting in a library of polyfunctionalized (trifluoromethylated) pyrrolizidines **19** and **20** (Scheme 3).
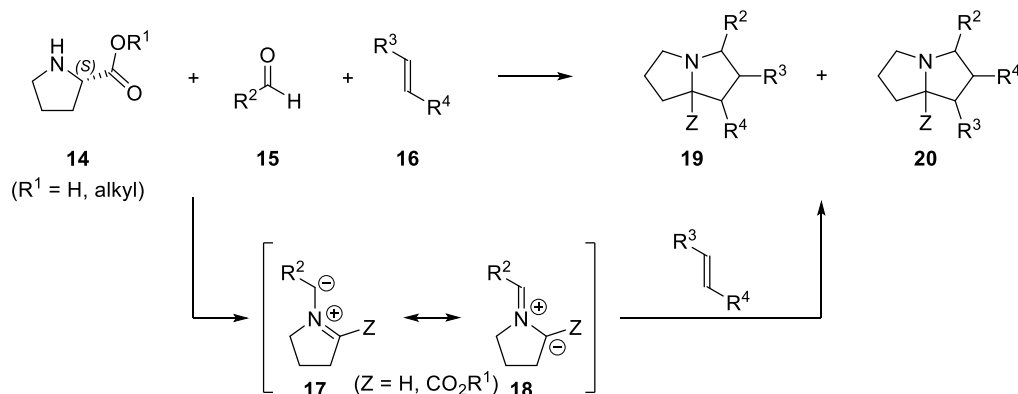
Scheme 3

3. Synthesis of 1-substituted 3-(aminomethyl)pyrrolizidines through ring rearrangement of 2-[2-(1-pyrrolin-2-yl)alkyl]aziridines

In order to introduce more complexity and to study the effect of an exocyclic tertiary carbon center adjacent to the imino moiety on the ring-rearrangement aptitude of 2-[2-(1-pyrrolin-2-yl)alkyl]aziridines, aziridines **12** were treated with LDA followed by addition of an alkyl iodide, affording monoalkylated aziridines **21** (R = Me, Et) in good yields after column chromatography (49-67%, Scheme 4, Table 2). Several attempts were performed toward the separation of the diastereomeric mixtures **21**, but all of them failed and these mixtures were used as such in the next step. Furthermore, separation of these diastereomers **21** might be useless due to the risk of epimerization of the newly introduced stereocenter through the enamine stage. Analogous to the ring transformation of aziridines **12**, substrates **21** were treated with 0.3 equiv of In(OTf)₃ in THF during one hour at room temperature. Consecutive LiAlH₄-induced reduction of the *in situ* formed bicyclic intermediates afforded *trans*- and *cis*-1-alkyl-3-

(arylmethylaminomethyl)pyrrolizidines **22** in a 55-68/32-45 ratio. Labor-intensive chromatographic purification of these mixtures resulted in the isolation of the major *trans*-isomers **22** in moderate yields (25-31%), and an analytically pure sample of one diastereomer resulting from the mixture of *trans*-**22c** could be obtained as well. The stereochemistry of this pyrrolizidine *trans*-**22c** isomer was assigned via 2D-NOESY experiments. Unfortunately, the *cis*-isomers could not be isolated from the reaction mixtures.

Scheme 4
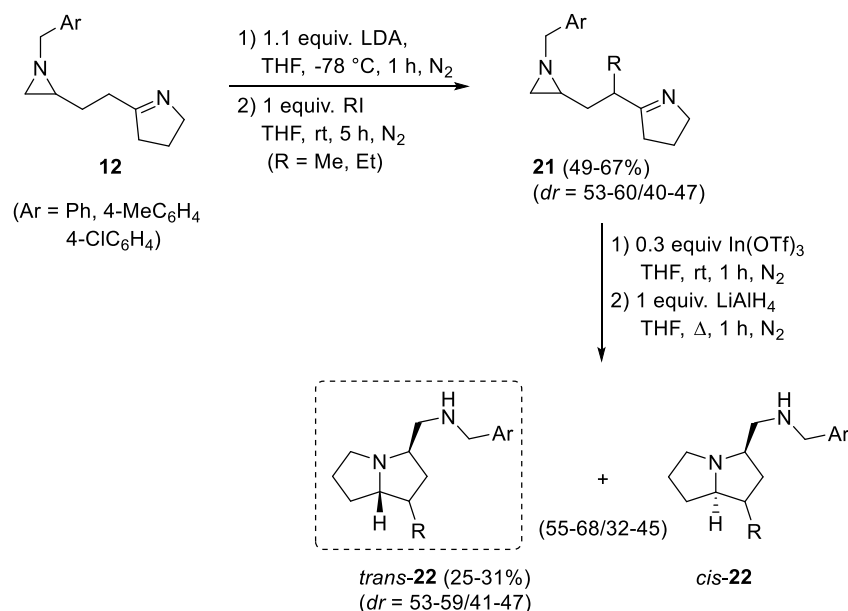
Table 2. Synthesis of 1-arylmethyl-2-[2-(1-pyrrolin-2-yl)alkyl]aziridines 21 and 1-alkyl-3-(aminomethyl)pyrrolizidines 22.

Entry	Ar	R	Compound **21** (yield [%])[a]	dr (**21**)[b]	Compound *trans*-**22** (yield [%])[a]	dr (*trans*-**22**)[b,c]	*trans/cis* (**22**)[b]
1	Ph	Me	**21a** (64)	53/47	*trans*-**22a** (26)	54/46	55/45
2	Ph	Et	**21b** (67)	53/47	*trans*-**22b** (28)	53/47	58/42
3	4-MeC$_6$H$_4$	Me	**21c** (60)	59/41	*trans*-**22c** (29)	58/42	57/43
4	4-MeC$_6$H$_4$	Et	**21d** (55)	60/40	*trans*-**22d** (25)	59/41	68/32
5	4-ClC$_6$H$_4$	Me	**21e** (49)	54/46	*trans*-**22e** (25)	54/46	59/41
6	4-ClC$_6$H$_4$	Et	**21f** (66)	58/42	*trans*-**22f** (31)	56/44	59/41

[a] After purification by column chromatography (SiO$_2$).
[b] Determined by ^{1}H NMR spectroscopy (CDCl$_3$).
[c] Before purification.

Subsequently, efforts were made to introduce an exocyclic quaternary center in α-position with respect to the imino moiety in aziridines **21**. In a first experiment, aziridine **21b** (R^1 = Et) was subjected to the same reaction conditions as for the synthesis of aziridines **21** ((i) 1.1 equiv LDA, THF, -78 °C, 1 h, N$_2$;

(ii) 1 equiv EtI, THF, -78 °C to rt, 5 h, N$_2$) (Scheme 5, Table 3, Entry 1). Unfortunately, the starting material was completely recovered and several other attempts to force the exocyclic α-alkylation of aziridines **21a,b** using different bases and reaction conditions appeared to be unsuccessful as well (Table 3). It is worth mentioning that a color change of the reaction mixture from yellow to orange was observed when the base was added at -78 °C, indicating that the deprotonation of aziridines **21a,b** probably succeeded and subsequent alkylation did not.
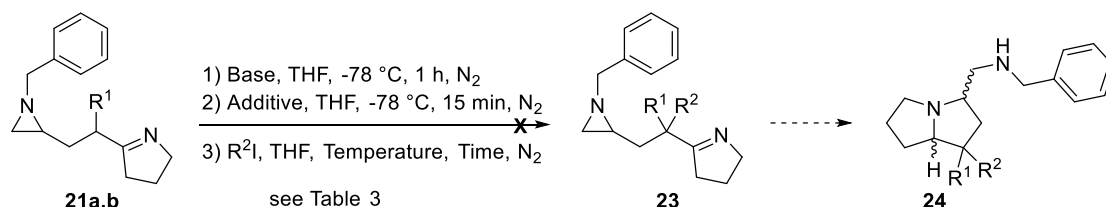
Scheme 5

Table 3. Attempts toward the α-alkylation of aziridines 21a,b.

R^1	Base	Additive	Alkylating agents	Temperature, Time	Conversion
Et	1.1 equiv LDA	-	1 equiv EtI	-78 °C to rt, 5 h	No reaction
Me	1.1 equiv LDA	-	1 equiv MeI	-78 °C to rt, 20 h	No reaction
Me	1.3 equiv LDA	-	1.3 equiv MeI	-78 °C to rt, 5 h	No reaction
Me	1.1 equiv LDA	-	5 equiv MeI	-78 °C to rt, 5 h	No reaction
Me	2 equiv LDA	-	5 equiv MeI	-78 °C to rt, 5 h	No reaction
Me	1.5 equiv LDA	1.5 equiv HMPA	5 equiv MeI	-78 °C to rt, 4 h	No reaction
Me	1.5 equiv LiHMDS	1.5 equiv HMPA	5 equiv MeI	-78 °C to rt, 4 h	No reaction
Me	2 equiv LDA	-	5 equiv EtI	-78 °C to Δ, 4 h	No reaction

4. Attempts toward the synthesis of amino(methyl)-substituted indolizidines

Next, endeavors were done to examine the effect of an aziridine aromatic substituent on the premised ring rearrangement, as the introduction of an aromatic group might impose a strong effect on the regiochemistry of the ring transformation (*vide supra*).[14b] However, attempts to obtain the desired aziridine substrate **26** via substitution of 3-(tosyloxymethyl)aziridine **25** (X = OTs) with the aza-allylic anion of 2-methyl-1-pyrroline (**6**) did not succeed. Similarly, the reaction of *in situ* deprotonated 2-methyl-1-pyrroline (**6**) with 3-(iodomethyl)aziridine **25** (X = I) gave no satisfying results (Scheme 6, Table 4).
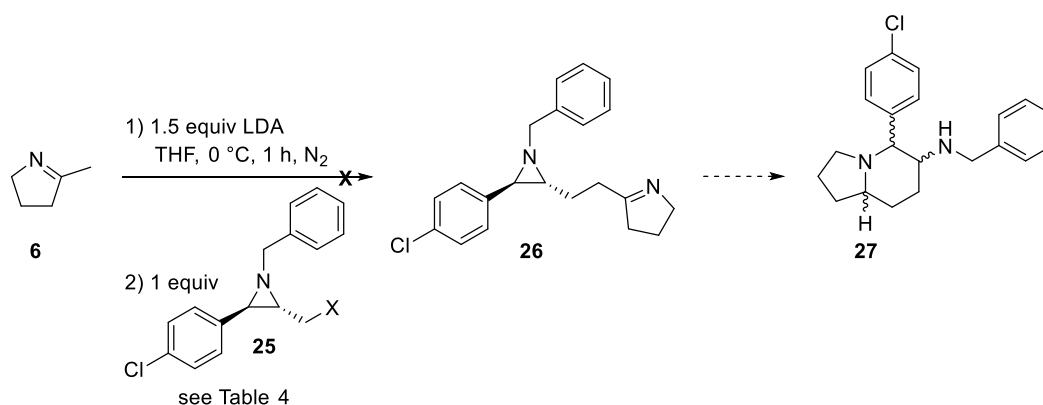
Scheme 6

Table 4. Treatment of the aza-allylic anion of 2-methyl-1-pyrroline (6) with 2-arylaziridines 25.

X	Reaction conditions	Conversion
OTs	THF, rt, 24 h, N_2	No reaction
OTs	THF, Δ, 24 h, N_2	No reaction
I	THF, rt, 22 h, N_2	Complex reaction mixture
I	THF, Δ, 4 h, N_2	Complex reaction mixture

In accordance to the synthesis of substituted pyrrolizidines through ring rearrangement of 2-[2-(1-pyrrolin-2-yl)alkyl]aziridines, the preparation of larger ring systems (referring to indolizidines) was investigated by variation of the starting cyclic imine. In particular, 6-methyl-2,3,4,5-tetrahydropyridine (**7**) was selected as the higher homologue of 2-methyl-1-pyrroline (**6**) and was obtained from 2-methylpiperidine following a literature procedure.[133] The deprotonation aptitude of 2-methyl-1-piperideine (**7**) was corroborated by quenching the corresponding *in situ* formed aza-allylic anion (after treatment with LDA either at 0 °C or -78 °C) with methyl iodide on an analytical scale, affording the corresponding 2-ethyl-1-piperideine in quantitative yield. Next, piperideine **7** was deprotonated with 1.5 equiv of LDA in THF at -78 °C followed by reaction with 2-(bromomethyl)aziridine **28** (X = Br) under the same reaction conditions as described above, but no conversion was observed. Also, variation of reaction temperature and the addition of HMPA or Ag-salts did not afford any trace of the desired aziridinyl piperideine **29** (Scheme 7, Table 5).
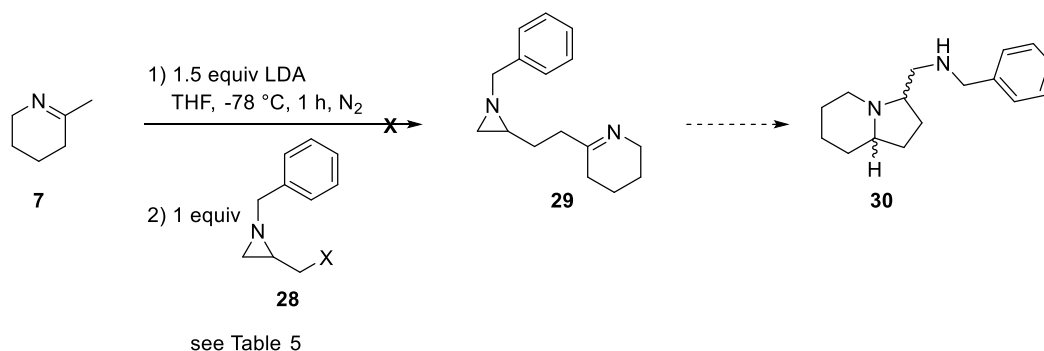
Scheme 7

Table 5. Attempts toward the synthesis of aziridinyl piperideine 29.

X	Additive	Reaction conditions	Conversion
Br	-	THF, rt, 17 h, N_2	No reaction
Br	-	THF, Δ, 20 h, N_2	No reaction
I	-	THF, rt, 17 h, N_2	No reaction
I	-	THF, Δ, 18 h, N_2	No reaction
Br	0.1 equiv HMPA	THF, rt, 24 h, N_2	No reaction
Br	0.5 equiv HMPA	THF, rt, 24 h, N_2	No reaction
Br	1 equiv HMPA	THF, rt, 24 h, N_2	No reaction
Br	1 equiv $AgBF_4$	THF, rt, 24 h, N_2	No reaction
Br	1 equiv $AgNO_3$	THF, rt, 24 h, N_2	No reaction
Br	-	MW, THF, 110 °C, 12 h	No reaction

5. Evaluation of the synthesis of 7a-substituted pyrrolizidines

Next to the deployment of hydride to neutralize the ring-rearrangement product of 2-[2-(1-pyrrolin-2-yl)ethyl]aziridine **12a**, other nucleophiles were used as well. To that end, reaction of aziridine **12a** with 0.3 equiv of In(OTf)$_3$ in THF and subsequent addition of 1 equiv of KCN furnished *trans*- and *cis*-α-aminonitriles **33** in a 79/21 ratio (Scheme 8). Again, column chromatographic purification (SiO$_2$) resulted in the isolation of the major *trans*-isomer **33** in 34% yield. The relative configuration of the isolated nitrile **33** was assumed to be *trans* based on the results obtained after hydride addition, as depicted in Scheme 2. Further derivatization of the isolated nitrile **33** could provide additional evidence for the relative *trans*-stereochemistry. In accordance with the nomenclature of *trans/cis*-pyrrolizidines **13** and **22**, the use of descriptors *cis* and *trans* for 7a-cyanopyrrolizidines **33** refers to the relative position of the cyano group on carbon atom 7a with respect to the hydrogen atom on the substituted carbon atom 3. Bearing in mind the importance of α-aminonitriles as precursors for the synthesis of α-amino acids and other valuable nitrogen compounds,[134] the obtained bicyclic α-aminonitrile *trans*-**33** is of interest as only a limited number of similar azabicycles are known in the literature.[135] Besides the use of hydride and cyanide

nucleophiles, also the deployment of thiocyanate to neutralize the *in situ* formed bicyclic salt **32** was evaluated, but unfortunately, the corresponding 7a-substituted pyrrolizidine could not be produced.

From a mechanistic point of view, addition of In(OTf)$_3$ leads to the activation of aziridine **12a**, which becomes prone to intramolecular attack by the nucleophilic nitrogen of the cyclic imino moiety, affording bicyclic salt **32**. Attempts to isolate this salt failed but, nevertheless, the occurrence of this intermediate was corroborated by means of NMR analysis (^{13}C NMR, δ 190.0 (C=N$^+$), CDCl$_3$). Importantly, the aziridine ring opening occurs in a regioselective way as expected, since a 5-*exo-tet* ring closure is favored and a 6-*endo-tet* is disfavored according to Baldwin's rules.[23] Consecutive nucleophilic addition of cyanide across iminium ion **32** produces *trans*- and *cis*-α-aminonitriles **33**. The same mechanism also applies for the synthesis of pyrrolizidines **13** and **22**, in which the pyrrolizidinium salt is neutralized by hydride addition across the iminium bond. The regioselective formation of a pyrrolizidine structure instead of the isomeric indolizidine scaffold was corroborated by means of detailed NMR analysis of compound **13c**. The appearance of a coupling in the HMBC spectrum of compound **13c** between the benzylic hydrogen atoms and the exocyclic NHCH$_2$ carbon atom pointed to the proposed pyrrolizidine structure. It is worth mentioning that, instead of In(OTf)$_3$, other Lewis acids were employed as well to induce the premised ring transformation of aziridine **12a**. To that end, reaction with 0.3 or 1 equiv of AlCl$_3$ both resulted in pyrrolizidine salt formation, whereas deployment of LiClO$_4$ required the addition of minimum 1 equiv to promote the ring rearrangement at room temperature.
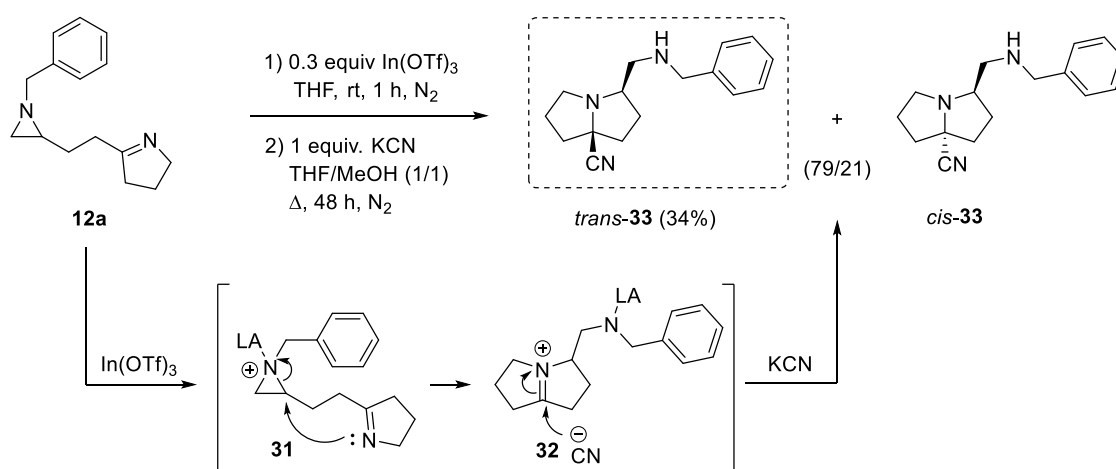
Scheme 8

6. Conclusion

In conclusion, 1-arylmethyl-2-[2-(1-pyrrolin-2-yl)alkyl]aziridines were prepared and deployed as eligible substrates for a regioselective In(OTf)$_3$-induced ring rearrangement. The *in situ* formed pyrrolizidinium intermediates were successfully trapped with hydride and cyanide nucleophiles, leading to a variety of novel *trans*- and *cis*-3-aminomethyl-substituted pyrrolizidines. Column chromatographic purification

eventually afforded the major *trans*-isomers. Besides 2-(cyanoethyl)aziridines, also aziridinyl pyrrolines appeared thus to be excellent precursors to illustrate the deployment of aziridines as electrophilic moieties toward the construction of medium-sized azaheterocycles. Subsequently, in order to further broaden the scope of this novel aziridine-to-pyrrolizidine ring rearrangement, many efforts were devoted to vary the substitution pattern of the aziridine starting material. Unfortunately, efforts to introduce an exocyclic quaternary center in α-position with respect to the imino moiety, an aziridine aromatic ring substituent or a piperideine ring system (instead of 1-pyrroline) did not afford the corresponding aziridine substrates.

7. Experimental details

General methods

^{1}H NMR spectra were recorded at 400 MHz on a Bruker Advance III-400 with solvents as indicated and tetramethylsilane as internal standard. ^{13}C NMR spectra were recorded at 100 MHz on a Bruker Advance III-400 with solvents as indicated. IR spectra were measured with a Spectrum One FT-IR spectrometer or a IRAffinity-1S FT-IR spectrophotometer. Electron spray (ES) mass spectra were obtained with an Agilent 1100 Series MS (ES, 4000V) mass spectrometer. High resolution electron spray (ES-TOF) mass spectra were obtained with an Agilent Technologies 6210 Series time-of-flight mass spectrometer. Tetrahydrofuran was distilled over sodium benzophenone ketyl before use. 2-Methyl-1-pyrroline was distilled before use (104 °C, 1 atm). All other solvents and reagents were used as received from the supplier.

Safety

General safety aspects

The practical work in this chapter was performed according to the SynBioC Research Group Internal Guidelines and with the aid of the internal safety document "Safety Instructions: How to work with chemicals". Wherever possible, hazardous or toxic reagents were avoided and/or substituted by safer or greener alternatives.

Specific safety aspects

A list of risks associated with each chemical and recommendations for safe use is available in the corresponding material safety data sheet (MSDS), which can be found on the website of the supplier. A brief overview of the most hazardous chemicals employed in this work will be given below, along with the potential hazards and precautions.

Bromine (Br$_2$): skin corrosion, acute aquatic toxicity. Avoid inhalation, wear protective gloves and clothing, avoid release in the environment.

Butyllithium solution: flammable and pyrophoric liquid, substances and mixtures which in contact with water emit flammable gases, skin corrosion. Avoid contact with air or water and work under an inert atmosphere. Avoid inhalation of vapors and wear protective gloves and clothing. Keep away from heat, fire, hot surfaces, sparks and ignition sources.

Chloroform: specific target organ toxicity following repeated exposure. Avoid inhalation and wear protective gloves and clothing.

Chloroacetylchloride: skin corrosion, specific target organ toxicity following repeated exposure. Avoid contact with water. Avoid inhalation and release in the environment. Wear protective gloves and clothing.

Cyanides (KCN): corrosive to metals, acute toxicity after inhalation, skin contact and oral intake, specific target organ toxicity following repeated and acute exposure, acute and chronic aquatic toxicity. Avoid dust formation and inhalation. Wear protective gloves and clothing. Avoid release in the environment.

Iodomethane (MeI): carcinogenic, skin corrosion. Avoid inhalation and wear protective gloves and clothing.

LiAlH₄ solution: flammable liquid, substances and mixtures which in contact with water emit flammable gases, skin corrosion. Avoid contact with air or water and work under an inert atmosphere. Avoid inhalation of vapors. Wear protective gloves and clothing. Keep away from heat, fire, hot surfaces, sparks and ignition sources.

Lithium diisopropylamide solution (LDA): skin corrosion. Keep away from heat, fire, hot surfaces, sparks and ignition sources. Avoid inhalation and wear protective gloves and clothing.

Solvents in general: acute toxicity after inhalation, specific target organ toxicity following single or repeated exposure. Keep away from heat, fire, hot surfaces, sparks and ignition sources. Avoid inhalation and wear protective gloves and clothing.

Synthesis of 2-(bromomethyl)aziridines 11

2-(Bromomethyl)aziridines **11** were prepared according to literature procedures, and spectral data corresponded with those reported in the literature.[43]

Synthesis of 1-arylmethyl-2-[2-(1-pyrrolin-2-yl)ethyl]aziridines 12

As a representative example, the synthesis of 1-benzyl-2-[2-(1-pyrrolin-2-yl)ethyl]aziridine **12a** is described. To a solution of diisopropylamine (1.52 g, 2.1 mL, 15 mmol, 1.5 equiv) in dry THF (20 mL), *n*BuLi (6 mL, 15 mmol, 1.5 equiv, 2.5 M in hexane) was added through a syringe at 0 °C under a nitrogen atmosphere, and the resulting solution was stirred for 30 min at 0 °C. Subsequently, 2-methyl-1-pyrroline (**6**) (0.83 g, 0.95 mL, 10 mmol, 1 equiv) was added through a syringe at 0 °C and the resulting solution was stirred for one hour at 0 °C. Then, a solution of 1-benzyl-2-(bromomethyl)aziridine **11** (2.25 g, 10

mmol, 1 equiv) in THF (10 mL) was added through a syringe at 0 °C and the resulting solution was stirred for 16 h at room temperature. Afterward, the reaction mixture was poured into water (50 mL) and extracted with Et₂O (3 × 50 mL). Drying (MgSO₄), filtration of the drying agent, and evaporation of the solvent *in vacuo* furnished 1-benzyl-2-[2-(1-pyrrolin-2-yl)ethyl]aziridine **12a** in a 93% yield (2.12 g, 9.3 mmol) as an orange oil. Because of the high purity of the obtained aziridines **12** (purity > 95%, ¹H NMR), these compounds were used as such in the next step.

1-Benzyl-2-[2-(1-pyrrolin-2-yl)ethyl]aziridine 12a

Orange oil. Yield 93%. **¹H NMR** (400 MHz, CDCl₃): δ 1.43 (1H, d, *J* = 6.2 Hz, CH(H̲CH)N); 1.52-1.61 (2H, m, CHN en CH₂(H̲CH)CHN); 1.65 (1H, d, *J* = 3.2 Hz, CH(HCH̲)N); 1.78-1.87 (3H, m, NCH₂CH̲₂ en CH₂(HCH̲)CHN); 2.26-2.37 (4H, m, 2×CH₂C=N); 3.25 (1H, d, *J* = 13.1 Hz, N(H̲CH)Cquat); 3.52 (1H, d, *J* = 13.1 Hz, N(HCH̲)Cquat); 3.75-3.80 (2H, m, CH₂CH̲₂N); 7.24-7.33 (5H, m, CHarom). **¹³C NMR** (100 MHz, CDCl₃): δ 22.5 (C̲H₂CH₂N); 29.6 (CH₂C̲H₂CHN); 31.4 (C̲H₂CH₂CHN); 34.2 (CHC̲H₂N); 37.3 ((CH₂)₂C̲H₂CN); 39.1 (CHN); 60.8 (CH₂C̲H₂N); 65.0 (CquatC̲H₂N); 127.0 (CHarom); 128.28 (2×CHarom); 128.31 (2×CHarom); 139.4 (Cquat,arom); 177.7 (C=N). **IR (cm⁻¹)**: νC=N = 1643; νmax = 2922, 1452, 732, 698. **MS (70 eV):** *m/z* (%): 229 (M⁺+1, 100). **HRMS (ESI)**: *m/z* calcd for C₁₅H₂₁N₂: 229.1699 [*M*+H]⁺; found: 229.1703.
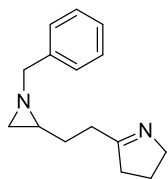
1-(4-Methylbenzyl)-2-[2-(1-pyrrolin-2-yl)ethyl]aziridine 12b

Orange oil. Yield 88%. **¹H NMR** (400 MHz, CDCl₃): δ 1.40 (1H, d, *J* = 6.2 Hz, CH(H̲CH)N); 1.52-1.59 (2H, m, CHN en CH₂(H̲CH)CHN); 1.62 (1H, d, *J* = 3.2 Hz, CH(HCH̲)N); 1.77-1.87 (3H, m, NCH₂CH̲₂ en CH₂(HCH̲)CHN); 2.28-2.37 (7H, m, 2×CH₂C=N and CH₃); 3.20 (1H, d, *J* = 13.0 Hz, N(H̲CH)Cquat); 3.48 (1H, d, *J* = 13.0 Hz, N(HCH̲)Cquat); 3.75-3.80 (2H, m, CH₂CH̲₂N); 7.12 (2H, d, *J* = 7.9 Hz, 2×CHarom); 7.20 (2H, d, *J* = 7.9 Hz, 2×CHarom). **¹³C NMR** (100 MHz, CDCl₃): δ 21.1 (CH₃); 22.5 (C̲H₂CH₂N); 29.6 (CH₂C̲H₂CHN); 31.4 (C̲H₂CH₂CHN); 34.1 (CHC̲H₂N); 37.3 ((CH₂)₂C̲H₂CN); 39.0 (CHN); 60.8 (CH₂C̲H₂N); 64.7 (CquatC̲H₂N); 128.3 (2×CHarom); 129.0 (2×CHarom); 136.3 and 136.6 (2×Cquat,arom); 177.7 (C=N). **IR (cm⁻¹)**: νC=N = 1643; νmax = 2920, 2864, 2831, 1515, 1448, 1430, 1352, 1066, 1020, 796. MS (70 eV): *m/z* (%): 243 (M⁺+1, 100). **HRMS (ESI)**: *m/z* calcd for C₁₆H₂₃N₂: 243.1856 [*M*+H]⁺; found: 243.1854.
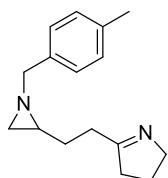
1-(4-Chlorobenzyl)-2-[2-(1-pyrrolin-2-yl)ethyl]aziridine 12c

Orange oil. Yield 90%. **¹H NMR** (400 MHz, CDCl₃): δ 1.40 (1H, d, *J* = 5.9 Hz, CH(H̲CH)N); 1.52-1.61 (2H, m, CHN en CH₂(H̲CH)CHN); 1.64 (1H, d, *J* = 2.8 Hz, CH(HCH̲)N); 1.78-1.86 (3H, m, NCH₂CH̲₂ en CH₂(HCH̲)CHN); 2.22-2.43 (4H, m, 2×CH₂C=N); 3.22 (1H, d, *J* = 13.3 Hz, N(H̲CH)Cquat); 3.46 (1H, d, *J* = 13.3 Hz, N(HCH̲)Cquat); 3.75-3.79 (2H, m, CH₂CH̲₂N); 7.24-7.30 (4H, m, CHarom). **¹³C NMR** (100 MHz, CDCl₃): δ 22.5 (C̲H₂CH₂N); 29.5 (CH₂C̲H₂CHN); 31.4 (C̲H₂CH₂CHN); 34.2 (CHC̲H₂N); 37.3 ((CH₂)₂C̲H₂CN); 39.2 (CHN); 60.9 (CH₂C̲H₂N); 64.2 (CquatC̲H₂N); 128.4 (2×CHarom); 129.6 (2×CHarom); 132.8 and 138.0 (2×Cquat,arom); 177.6 (C=N). **IR (cm⁻¹)**: νC=N = 1642; νmax = 2920, 2865, 2831, 1490, 1086, 1014, 805. MS (70 eV): *m/z* (%): 263/265 (M⁺+1, 100). **HRMS (ESI)**: *m/z* calcd for C₁₅H₂₀ClN₂: 263.1310 [*M*+H]⁺; found: 263.1302.
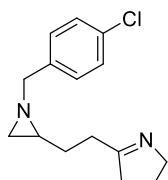
Synthesis of 1-arylmethyl-2-[2-(1-pyrrolin-2-yl)alkyl]aziridines 21

As a representative example, the synthesis of 1-benzyl-2-[2-(1-pyrrolin-2-yl)propyl]aziridine **21a** is described. To a solution of diisopropylamine (1.11 g, 1.54 mL, 11 mmol, 1.1 equiv) in dry THF (10 mL), nBuLi (4.4 mL, 11 mmol, 1.1 equiv, 2.5 M in hexane) was added via a syringe at -78 °C under nitrogen atmosphere, and the resulting solution was stirred for 30 min at -78 °C. Subsequently, a solution of 1-benzyl-2-[2-(1-pyrrolin-2-yl)ethyl]aziridine **12a** (2.28 g, 10 mmol) in THF (10 mL) was added via a syringe at -78 °C, and the resulting solution was stirred for 1 hour at -78 °C. Then, methyl iodide (1.42 g, 0.62 mL, 10 mmol, 1 equiv) was added via a syringe at -78 °C, and the resulting solution was stirred for 5 hours at room temperature. Afterward, the reaction mixture was poured into water (50 mL) and extracted with Et$_2$O (3 × 50 mL). Drying (MgSO$_4$), filtration of the drying agent and evaporation of the solvent *in vacuo* furnished 1-benzyl-2-[2-(1-pyrrolin-2-yl)propyl]aziridine **21a**, which was purified by means of column chromatography on silica gel (EtOAc/triethylamine 100/5) to provide an orange oil in 64% yield (1.55 g, 6.4 mmol).

1-Benzyl-2-[2-(1-pyrrolin-2-yl)propyl]aziridine 21a

Spectral data derived from the mixture of diastereomers

Orange oil. R_f = 0,22 (EtOAc/triethylamine 100/5). Yield 64%. *dr* 53/47. **¹H NMR** (400 MHz, CDCl$_3$): δ 1.091 (3H, d, J = 6.8 Hz, (CH$_3$)$_{minor}$); 1.093 (3H, d, J = 6.9 Hz, (CH$_3$)$_{major}$); 1.39-1.45 (3H, m, 2×CH(HCH)N and CH(HCH)CH); 1.48-1.55 (1H, m, CH(HCH)CH); 1.56-1.61 (4H, m, 2×CHN and 2×CH(HCH)N); 1.65-1.73 (1H, m, CH(HCH)CH); 1.76-1.88 (5H, m, CH(HCH)CH and 2×CH$_2$CH$_2$N); 2.17-2.26 (1H, m, (HCH)C=N); 2.34-2.48 (3H, m, (HCH)C=N and CH$_2$C=N); 2.55 (1H, sextet, J = 6.9 Hz, (CHCH$_3$)$_{major}$); 2.63 (1H, sextet, J = 6.8 Hz, (CHCH$_3$)$_{minor}$); 3.28 (1H, d, J = 13.1 Hz, N(HCH)C$_{quat}$); 3.30 (1H, d, J = 13.1 Hz, N(HCH)C$_{quat}$); 3.44 (1H, d, J = 13.1 Hz, N(HCH)C$_{quat}$); 3.46 (1H, d, J = 13.1 Hz, N(HCH)C$_{quat}$); 3.77-3.80 (4H, m, 2×CH$_2$CH$_2$N); 7.24-7.34 (10H, m, 10×CH$_{arom}$). **¹³C NMR** (100 MHz, CDCl$_3$): δ 17.8 ((CH$_3$)$_{minor}$); 18.5 ((CH$_3$)$_{major}$); 22.45 and 22.49 (2×CH$_2$CH$_2$N); 34.2, 34.3 and 34.4 (CH$_2$CN and 2×CHCH$_2$N); 35.0 (CH$_2$CN); 36.6 ((CHCH$_3$)$_{major}$); 37.0 ((CHCH$_3$)$_{minor}$); 37.7 (CHCH$_2$CH); 37.76 (CHN); 37.81 (CHCH$_2$CH); 37.84 (CHN); 60.5 ((CH$_2$CH$_2$N)$_{minor}$); 60.6 ((CH$_2$CH$_2$N)$_{major}$); 64.8 and 64.9 (2×C$_{quat}$CH$_2$N); 127.0, 128.1, 128.30 and 128.34 (10×CH$_{arom}$); 139.4 (2×C$_{quat,arom}$); 181.5 and 181.9 (2×C=N). **IR (cm⁻¹)**: ν$_{C=N}$ = 1638; ν$_{max}$ = 2963, 2928, 2866, 1495, 1452, 1356, 1161, 1063, 1028, 964, 914. **MS (70 eV):** m/z (%): 243 (M⁺+1, 100). **HRMS (ESI)**: m/z calcd for C$_{16}$H$_{23}$N$_2$: 243.1856 [M+H]⁺; found: 243.1852.
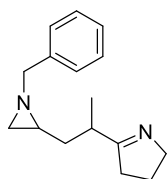
1-Benzyl-2-[2-(1-pyrrolin-2-yl)butyl]aziridine 21b

Spectral data derived from the mixture of diastereomers

Orange oil. R_f = 0,22 (EtOAc/triethylamine 100/5). Yield 67%. *dr* 53/47. **¹H NMR** (400 MHz, CDCl₃): δ 0.80 (3H, t, *J* = 7.4 Hz, (C$\underline{H}$₃CH₂)minor); 0.82 (3H, t, *J* = 7.4 Hz, (C$\underline{H}$₃CH₂)major); 1.36-1.39 (2H, m, 2×CH($\underline{H}$CH)N); 1.44-1.54 (7H, m, (CH($\underline{H}$CH)CH)minor, 2×CHN and 2×C$\underline{H}$₂CH₃); 1.56-1.67 (4H, m, 2×CH(HC$\underline{H}$)N and (CHC$\underline{H}$₂CH)major); 1.71-1.87 (5H, m, (CH(HC$\underline{H}$)CH)minor and 2×C$\underline{H}$₂CH₂N); 2.14-2.23 (1H, m, ($\underline{H}$CH)C=N); 2.30-2.40 (2H, m, (HC$\underline{H}$)C=N and ($\underline{H}$CH)C=N); 2.42-2.55 (3H, m, (CHC=N)minor, (HC$\underline{H}$)C=N and (CHC=N)major); 3.16 (1H, d, *J* = 13.3 Hz, (N($\underline{H}$CH)Cquat)major); 3.33 (1H, d, *J* = 13.1 Hz, (N($\underline{H}$CH)Cquat)minor); 3.40 (1H, d, *J* = 13.1 Hz, (N(HC$\underline{H}$)Cquat)minor); 3.52 (1H, d, *J* = 13.3 Hz, (N(HC$\underline{H}$)Cquat)major); 3.78-3.81 (4H, m, 2×CH₂C$\underline{H}$₂N); 7.25-7.34 (10H, m, 10×CHarom). **¹³C NMR** (100 MHz, CDCl₃): δ 11.6 (($\underline{C}$H₃CH₂)minor); 11.7 (($\underline{C}$H₃CH₂)major); 22.4 (2×$\underline{C}$H₂CH₂N); 25.6 (($\underline{C}$H₂CH₃)major); 25.9 (($\underline{C}$H₂CH₃)minor); 34.1 ($\underline{C}$H₂CN); 34.3 (2×CH$\underline{C}$H₂N); 35.0 ($\underline{C}$H₂CN); 35.8 ((CH$\underline{C}$H₂CH)minor); 36.1 ((CH$\underline{C}$H₂CH)major); 37.9 and 38.0 (2×CHN); 43.8 (($\underline{C}$HCN)minor); 44.6 (($\underline{C}$HCN)major); 60.4 ((CH₂$\underline{C}$H₂N)major); 60.5 ((CH₂$\underline{C}$H₂N)minor); 64.7 ((Cquat$\underline{C}$H₂N)major); 64.9 ((Cquat$\underline{C}$H₂N)minor); 126.97, 127.02, 128.1, 128.31 and 128.33 (10×CHarom); 139.37 ((Cquat,arom)minor); 139.41 (Cquat,arom)major); 180.6 ((C=N)minor); 181.0 ((C=N)major). **IR (cm⁻¹)**: ν$_{C=N}$ = 1672; ν$_{max}$ = 2930, 1494, 1453, 1357, 1266, 1073, 1028, 731, 698. **MS (70 eV):** *m/z* (%): 257 (M⁺+1, 100). **HRMS (ESI)**: *m/z* calcd for C₁₇H₂₅N₂: 257.2012 [*M*+H]⁺; found: 257.2015.

1-(4-Methylbenzyl)-2-[2-(1-pyrrolin-2-yl)propyl]aziridine 21c

Spectral data derived from the mixture of diastereomers

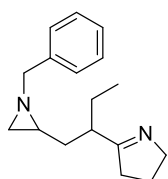Orange oil. R_f = 0,24 (EtOAc/triethylamine 100/5). Yield 60%. *dr* 59/41. **¹H NMR** (400 MHz, CDCl₃): δ 1.09 (2×3H, 2×d, *J* = 7.0 Hz, 2×C$\underline{H}$₃CH); 1.37 (1H, m, 2×CH($\underline{H}$CH)N and CH($\underline{H}$CH)CH); 1.47-1.58 (5H, m, CH(HC$\underline{H}$)CH, 2×CHN and 2×CH(HC$\underline{H}$)N); 1.65-1.72 (1H, m, CH(HC$\underline{H}$)CH); 1.76-1.87 (5H, m, CH(HC$\underline{H}$)CH and 2×C$\underline{H}$₂CH₂N); 2.17-2.26 (1H, m, ($\underline{H}$CH)C=N); 2.33 (2×3H, 2×s, 2×CH₃,tos); 2.33-2.59 (4H, m, (HC$\underline{H}$)C=N, CH₂C=N and (C$\underline{H}$CH₃)major); 2.63 (1H, sextet, *J* = 7.0 Hz, (C$\underline{H}$CH₃)minor); 3.23 (1H, d, *J* = 13.1 Hz, (N($\underline{H}$CH)Cquat)minor); 3.25 (1H, d, *J* = 12.9 Hz, (N($\underline{H}$CH)Cquat)major); 3.40 (1H, d, *J* = 12.9 Hz, (N(HC$\underline{H}$)Cquat)major); 3.45 (1H, d, *J* = 13.1 Hz, (N(HC$\underline{H}$)Cquat)minor); 3.76-3.80 (4H, m, 2×CH₂C$\underline{H}$₂N); 7.119 (2×1H, 2×d, *J* = 8.0 Hz, 2×CHarom); 7.122 (2×1H, 2×d, *J* = 7.7 Hz, 2×CHarom); 7.19 (2×1H, 2×d, *J* = 7.7 Hz, 2×CHarom); 7.20 (2×1H, 2×d, *J* = 8.0 Hz, 2×CHarom). **¹³C NMR** (100 MHz, CDCl₃): δ 17.8 ((CH₃)minor); 18.5 ((CH₃)major); 21.1 (2×CH₃,tos); 22.4 and 22.5 (2×$\underline{C}$H₂CH₂N); 34.1, 34.2 and 34.4 ($\underline{C}$H₂CN and 2×CH$\underline{C}$H₂N); 35.0 ($\underline{C}$H₂CN); 36.6 (($\underline{C}$HCH₃)major); 37.0 (($\underline{C}$HCH₃)minor); 37.72 and 37.74 (2×CHN); 37.8 (2×CH$\underline{C}$H₂CH); 60.5 ((CH₂$\underline{C}$H₂N)minor); 60.6 ((CH₂$\underline{C}$H₂N)major); 64.5 ((Cquat$\underline{C}$H₂N)minor); 64.6 ((Cquat$\underline{C}$H₂N)major); 128.1, 128.3, 128.96 and 129.00 (8×CHarom); 136.30 and 136.31 (2×Cquat,arom); 136.6 (2×Cquat,arom); 181.5 and 181.9 (2×C=N). **IR (cm⁻¹)**: ν$_{C=N}$ = 1638; ν$_{max}$ = 2924, 1515, 1456, 1354, 1302, 1160, 1063, 1021, 965, 801. **MS (70 eV):** *m/z* (%): 257 (M⁺+1, 100). **HRMS (ESI)**: *m/z* calcd for C₁₇H₂₅N₂: 257.2012 [*M*+H]⁺; found: 257.2002.

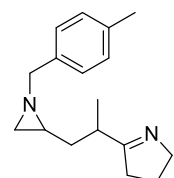### 1-(4-Methylbenzyl)-2-[2-(1-pyrrolin-2-yl)butyl]aziridine 21d

Spectral data derived from the mixture of diastereomers

Orange oil. R_f = 0,23 (EtOAc/triethylamine 100/5). Yield 55%. *dr* 60/40. **^{1}H NMR** (400 MHz, CDCl$_3$): δ 0.80 (3H, t, *J* = 7.4 Hz, (C$\underline{H}_3$CH$_2$)$_{minor}$); 0.81 (3H, t, *J* = 7.4 Hz, (C$\underline{H}_3$CH$_2$)$_{major}$); 1.35 (1H, d, *J* = 6.2 Hz, (CH($\underline{H}$CH)N)$_{minor}$); 1.36 (1H, d, *J* = 5.8 Hz, (CH($\underline{H}$CH)N)$_{major}$); 1.42-1.66 (11H, m, (CH($\underline{H}$CH)CH)$_{minor}$, 2×CHN, 2×C$\underline{H}_2$CH$_3$, 2×CH(HC$\underline{H}$)N and (CHC$\underline{H}_2$CH)$_{major}$); 1.73 (1H, d×d×d, *J* = 12.8, 9.2, 4.1 Hz, (CH(HC$\underline{H}$)CH)$_{minor}$); 1.76-1.87 (4H, m, 2×C$\underline{H}_2$CH$_2$N); 2.14-2.23 (1H, m, ($\underline{H}$CH)C=N); 2.30-2.40 (2H, m, (HC$\underline{H}$)C=N and ($\underline{H}$CH)C=N); 2.33 (2×3H, 2×s, 2×CH$_{3,tos}$); 2.42-2.55 (3H, m, (CHC=N)$_{minor}$, (HC$\underline{H}$)C=N and (CHC=N)$_{major}$); 3.12 (1H, d, *J* = 13.2 Hz, (N($\underline{H}$CH)C$_{quat}$)$_{major}$); 3.29 (1H, d, *J* = 13.0 Hz, (N($\underline{H}$CH)C$_{quat}$)$_{minor}$); 3.37 (1H, d, *J* = 13.0 Hz, (N(HC$\underline{H}$)C$_{quat}$)$_{minor}$); 3.47 (1H, d, *J* = 13.2 Hz, (N(HC$\underline{H}$)C$_{quat}$)$_{major}$); 3.77-3.81 (4H, m, 2×CH$_2$C$\underline{H}_2$N); 7.12 (4×1H, 4×d, *J* = 7.9 Hz, 4×CH$_{arom}$); 7.19 (4×1H, 4×d, *J* = 7.9 Hz, 4×CH$_{arom}$). **^{13}C NMR** (100 MHz, CDCl$_3$): δ 11.6 (($\underline{C}$H$_3$CH$_2$)$_{minor}$); 11.7 (($\underline{C}$H$_3$CH$_2$)$_{major}$); 21.1 (2×CH$_{3,tos}$); 22.4 (2×$\underline{C}$H$_2$CH$_2$N); 25.6 (($\underline{C}$H$_2$CH$_3$)$_{major}$); 25.9 (($\underline{C}$H$_2$CH$_3$)$_{minor}$); 34.0, 34.1 and 34.2 (($\underline{C}$H$_2$CN) and 2×CH$\underline{C}$H$_2$); 34.9 ($\underline{C}$H$_2$CN); 35.8 ((CH$\underline{C}$H$_2$CH)$_{minor}$); 36.2 ((CH$\underline{C}$H$_2$CH)$_{major}$); 37.8 (2×CHN); 43.8 (($\underline{C}$HCN)$_{minor}$); 44.6 (($\underline{C}$HCN)$_{major}$); 60.4 ((CH$_2\underline{C}$H$_2$N)$_{major}$); 60.5 ((CH$_2\underline{C}$H$_2$N)$_{minor}$); 64.4 ((C$_{quat}\underline{C}$H$_2$N)$_{major}$); 64.6 ((C$_{quat}\underline{C}$H$_2$N)$_{minor}$); 128.1, 128.3, 128.96 and 129.00 (8×CH$_{arom}$); 136.29 ((C$_{quat,arom}$)$_{minor}$); 136.33 and 136.5 ((2×C$_{quat,arom}$)$_{major}$); 136.6 ((C$_{quat,arom}$)$_{minor}$); 180.6 ((C=N)$_{minor}$); 181.0 ((C=N)$_{major}$). **IR (cm^{-1})**: $v_{C=N}$ = 1637; v_{max} = 2961, 2925, 2866, 1515, 1450, 1354, 1306, 1249, 1160, 1065, 1021, 966, 799. **MS (70 eV):** *m/z* (%): 271 (M$^+$+1, 100). **HRMS (ESI):** *m/z* calcd for C$_{18}$H$_{27}$N$_2$: 271.2169 [*M*+H]$^+$; found: 271.2161.

1-(4-Chlorobenzyl)-2-[(1-pyrrolin-2-yl)propyl]aziridine 21e
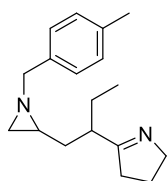
Spectral data derived from the mixture of diastereomers

Orange oil. R_f = 0,20 (EtOAc/triethylamine 100/5). Yield 49%. *dr* 54/46. **^{1}H NMR** (400 MHz, CDCl$_3$): δ 1.100 (3H, d, *J* = 6.9 Hz, (CH$_3$)$_{minor}$); 1.104 (3H, d, *J* = 7.0 Hz, (CH$_3$)$_{major}$); 1.37 (1H, d, *J* = 6.2 Hz, CH($\underline{H}$CH)N); 1.38 (1H, d, *J* = 5.8 Hz, CH($\underline{H}$CH)N); 1.39-1.45 (1H, m, (CH($\underline{H}$CH)CH)$_{minor}$); 1.48-1.60 (5H, m, (CH($\underline{H}$CH)CH)$_{major}$, 2×CHN and 2×CH(HC$\underline{H}$)N); 1.65-1.73 (1H, m, (CH(HC$\underline{H}$)CH)$_{major}$); 1.77-1.87 (5H, m, (CH(HC$\underline{H}$)CH)$_{minor}$ and 2×C$\underline{H}_2$CH$_2$N); 2.20-2.29 (1H, m, ($\underline{H}$CH)C=N); 2.36-2.59 (4H, m, (HC$\underline{H}$)C=N, CH$_2$C=N and (C$\underline{H}$CH$_3$)$_{major}$); 2.64 (1H, sextet, *J* = 6.9 Hz, (C$\underline{H}$CH$_3$)$_{minor}$); 3.22 (1H, d, *J* = 13.5 Hz, (N($\underline{H}$CH)C$_{quat}$)$_{minor}$); 3.28 (1H, d, *J* = 13.3 Hz, (N($\underline{H}$CH)C$_{quat}$)$_{major}$); 3.37 (1H, d, *J* = 13.3 Hz, (N(HC$\underline{H}$)C$_{quat}$)$_{major}$); 3.44 (1H, d, *J* = 13.5 Hz, (N(HC$\underline{H}$)C$_{quat}$)$_{minor}$); 3.76-3.80 (4H, m, 2×CH$_2$C$\underline{H}_2$N); 7.23-7.30 (8H, m, 8×CH$_{arom}$). **^{13}C NMR** (100 MHz, CDCl$_3$): δ 17.8 ((CH$_3$)$_{minor}$); 18.5 ((CH$_3$)$_{major}$); 22.4 (($\underline{C}$H$_2$CH$_2$N)$_{major}$); 22.5 (($\underline{C}$H$_2$CH$_2$N)$_{minor}$); 34.2, 34.3 and 34.4 ($\underline{C}$H$_2$CN and 2×CH$\underline{C}$H$_2$); 35.0 ($\underline{C}$H$_2$CN); 36.6 (($\underline{C}$HCH$_3$)$_{major}$); 37.0 (($\underline{C}$HCH$_3$)$_{minor}$); 37.6 ((CH$\underline{C}$H$_2$CH)$_{minor}$); 37.7 ((CH$\underline{C}$H$_2$CH)$_{major}$); 37.9 (2×CHN); 60.5 ((CH$_2\underline{C}$H$_2$N)$_{minor}$); 60.6 ((CH$_2\underline{C}$H$_2$N)$_{major}$); 64.0 ((C$_{quat}\underline{C}$H$_2$N)$_{minor}$); 64.1 ((C$_{quat}\underline{C}$H$_2$N)$_{major}$); 128.41, 128.44, 129.4 and 129.6 (8×CH$_{arom}$); 132.7 ((C$_{quat,arom}$)$_{minor}$); 132.8 ((C$_{quat,arom}$)$_{major}$); 139.4 (2×C$_{quat,arom}$); 181.3 ((C=N)$_{minor}$); 181.8 ((C=N)$_{major}$). **IR (cm^{-1})**: $v_{C=N}$ = 1638; v_{max} = 2928, 1490, 1456, 1407, 1352, 1298, 1161, 1086, 1014, 965, 805, 665. **MS (70 eV):** *m/z* (%): 277/279 (M$^+$+1, 100). **HRMS (ESI)**: *m/z* calcd for C$_{16}$H$_{22}$ClN$_2$: 277.1466 [*M*+H]$^+$; found: 277.1473.

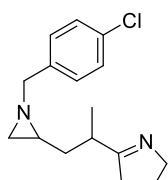### 1-(4-Chlorobenzyl)-2-[2-(1-pyrrolin-2-yl)butyl]aziridine 21f

Spectral data derived from the mixture of diastereomers

Orange oil. R_f = 0,20 (EtOAc/triethylamine 100/5). Yield 66%. *dr* 58/42. **^{1}H NMR** (400 MHz, CDCl$_3$): δ 0.81 (3H, t, *J* = 7.4 Hz, (CH$_3$)$_{minor}$); 0.82 (3H, t, *J* = 7.4 Hz, (CH$_3$)$_{major}$); 1.33-1.37 (2H, m, 2×CH(H̲CH)N); 1.44-1.55 (7H, m, (CH(H̲CH)CH)$_{minor}$, 2×CHN and 2×CH̲$_2$CH$_3$); 1.56-1.67 (4H, m, 2×CH(HCH̲)N and (CHCH̲$_2$CH)$_{major}$); 1.73 (1H, d×d×d, *J* = 13.0, 9.1, 4.1 Hz, (CH(HCH̲)CH)$_{minor}$); 1.81 (2H, ~p, *J* = 7.9 Hz, CH̲$_2$CH$_2$N); 1.83 (2H, ~p, *J* = 7.8 Hz, CH̲$_2$CH$_2$N); 2.18-2.26 (1H, m, (H̲CH)C=N); 2.32-2.41 (2H, m, (HCH̲)C=N and (HCH̲)C=N); 2.43-2.55 (3H, m, (CHC=N)$_{minor}$, (HCH̲)C=N and (CHC=N)$_{major}$); 3.11 (1H, d, *J* = 13.5 Hz, (N(H̲CH)C$_{quat}$)$_{major}$); 3.30 (2H, s, (NCH$_2$C$_{quat}$)$_{minor}$); 3.49 (1H, d, *J* = 13.5 Hz, (N(HCH̲)C$_{quat}$)$_{major}$); 3.77-3.81 (4H, m, 2×CH$_2$CH̲$_2$N); 7.23-7.30 (8H, m, 8×CH$_{arom}$). **^{13}C NMR** (100 MHz, CDCl$_3$): δ 11.6 ((CH$_3$)$_{minor}$); 11.7 ((CH$_3$)$_{major}$); 22.4 (2×CH$_2$CH$_2$N); 25.6 ((CH$_2$CH$_3$)$_{major}$); 25.9 ((CH$_2$CH$_3$)$_{minor}$); 34.06 (CH$_2$CN); 34.09 and 34.3 (2×CHCH$_2$N); 34.9 (CH$_2$CN); 35.7 ((CHCH$_2$CH)$_{minor}$); 36.1 ((CHCH$_2$CH)$_{major}$); 38.0 (2×CHN); 43.8 ((CHCN)$_{minor}$); 44.5 ((CHCN)$_{major}$); 60.4 ((CH$_2$CH$_2$N)$_{major}$); 60.5 ((CH$_2$CH$_2$N)$_{minor}$); 63.7 ((C$_{quat}$CH$_2$N)$_{major}$); 64.1 ((C$_{quat}$CH$_2$N)$_{minor}$); 128.42, 128.43, 129.3 and 129.6 (8×CH$_{arom}$); 132.7 ((C$_{quat,arom}$)$_{major}$); 132.8 and 137.9 (2×(C$_{quat,arom}$)$_{minor}$); 138.0 ((C$_{quat,arom}$)$_{major}$); 180.4 ((C=N)$_{minor}$); 180.9 ((C=N)$_{major}$). **IR (cm^{-1}):** ν$_{C=N}$ = 1637; ν$_{max}$ = 2961, 2868, 1490, 1461, 1406, 1352, 1299, 1238, 1161, 1086, 1014, 966, 805, 665. **MS (70 eV):** *m/z* (%): 291/293 (M$^+$+1, 100). **HRMS (ESI)**: *m/z* calcd for C$_{17}$H$_{24}$ClN$_2$: 291.1623 [*M*+H]$^+$; found: 291.1617.
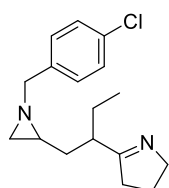
Synthesis of *trans*- and *cis*-pyrrolizidines 13 and 22

As a representative example, the synthesis of *trans*- and *cis*-3-(benzylaminomethyl)pyrrolizidines **13a** is described. To a solution of 1-benzyl-2-[2-(1-pyrrolin-2-yl)ethyl]aziridine **12a** (228 mg, 1 mmol) in dry THF (10 mL) was added In(OTf)$_3$ (169 mg, 0.3 mmol, 0.3 equiv). After one hour, the solution was cooled to 0°C and a solution of LiAlH$_4$ (1 mL, 1 mmol, 1 equiv, 1.0 M in THF) was added via a syringe. Then, the resulting solution was heated under reflux for 1 hour under nitrogen atmosphere. Afterward, the reaction mixture was quenched with brine (10 mL) to neutralize the excess of LiAlH$_4$. The reaction mixture was filtered through a path of Celite® and extracted with Et$_2$O (2 × 10 mL). Drying (MgSO$_4$), filtration of the drying agent and evaporation of the solvent *in vacuo* afforded *trans*- and *cis*-3-(benzylaminomethyl)pyrrolizidines **13a** in a 58/42 ratio. Purification by means of column chromatography on silica gel (CH$_2$Cl$_2$/MeOH 9/1) provided *trans*-3-(benzylaminomethyl)pyrrolizidine **13a** as a yellow oil in a yield of 22% (51 mg, 0.22 mmol).

trans-3-(Benzylaminomethyl)pyrrolizidine (*trans*-13a)

Yellow oil. R_f = 0.08 (CH$_2$Cl$_2$/MeOH 9/1). Yield 22%. **^{1}H NMR** (400 MHz, CDCl$_3$): δ 1.34-1.50 (2H, m, (H̲CH)CH$_2$CHCH$_2$N and (H̲CH)(CH$_2$)$_2$N); 1.53-1.63 (1H, m, CH$_2$(H̲CH)CHCH$_2$N); 1.72-1.94 (3H, m, CH$_2$CH̲$_2$CH$_2$N and (HCH̲)(CH$_2$)$_2$N); 1.96-2.04 (2H, m, (HCH̲)CH$_2$CHCH$_2$N and CH$_2$(HCH̲)CHCH$_2$N); 2.63 (1H, d×d, *J* = 11.5, 5.7 Hz, CH(H̲CH)N); 2.68-2.75 (2H, m, CH(HCH̲)N and (CH$_2$)$_2$(H̲CH)N); 2.85 (1H, d×d×d×d, *J* = 8.8, 6.7, 5.7, 5.7 Hz, CHCH$_2$N); 3.06 (1H, d×t, *J* = 10.7, 6.4 Hz, (CH$_2$)$_2$(HCH̲)N); 3.63 (1H, pe, *J* = 6.8 Hz, CH̲N(CH$_2$)$_3$); 3.79 (1H, d, *J* = 13.3 Hz, N(H̲CH)C$_{quat}$); 3.84 (1H, d, *J* = 13.3 Hz, N(HCH̲)C$_{quat}$); 7.21-7.35 (5H, m, 5×CH$_{arom}$). **^{13}C NMR** (100 MHz, CDCl$_3$): δ 25.8 (CH$_2$CH$_2$CH$_2$N); 31.5 (CH$_2$CHCH$_2$N); 32.0 (CH$_2$(CH$_2$)$_2$N); 32.1 (CH$_2$CH$_2$CHCH$_2$N); 53.6 (NCH$_2$C$_{quat}$); 55.0 (CHCH$_2$N); 55.3 ((CH$_2$)$_2$CH$_2$N); 65.4 (CHN(CH$_2$)$_3$); 67.3 (CHNCH$_2$N); 126.8 (CH$_{arom}$); 128.1
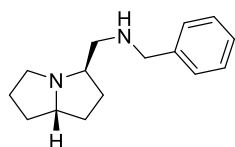
(2×CH$_{arom}$); 128.3 (2×CH$_{arom}$); 140.5 (C$_{quat,arom}$). **IR (cm^{-1})**: v$_{NH}$ = 3304; v$_{max}$ = 2949, 2866, 1574, 1452, 1400, 1218, 1085, 1046, 805, 738, 698. **MS (70 eV)**: *m/z* (%): 231 (M$^+$+1, 100). **HRMS (ESI)**: *m/z* calcd for C$_{15}$H$_{23}$N$_2$: 231.1856 [*M*+H]$^+$; found: 231.1850.

trans-3-[(4-Methylbenzyl)aminomethyl]pyrrolizidine (*trans*-13b)

Yellow oil. R_f = 0.22 (CH$_2$Cl$_2$/MeOH/triethylamine 9/1/0.1). Yield 35%. **^{1}H NMR** (400 MHz, CDCl$_3$): δ 1.51 (1H, d×d×d×d, *J* = 12.6, 10.9, 8.8, 6.9 Hz, (HCH)CH$_2$CHCH$_2$N); 1.59-1.66 (1H, m, (HCH)(CH$_2$)$_2$N); 1.77 (1H, d×d×d×d, *J* = 12.9, 10.9, 9.8, 7.0 Hz, CH$_2$(HCH)CHCH$_2$N); 1.87-2.11 (4H, m, CH$_2$CH$_2$CH$_2$N, CH$_2$(HCH)CHCH$_2$N and (HCH)(CH$_2$)$_2$N); 2.17 (1H, d×d×d×d, *J* = 12.6, 7.0, 7.0, 2.7 Hz, (HCH)CH$_2$CHCH$_2$N); 2.33 (3H, s, CH$_3$); 2.80 (1H, d×d, *J* = 11.8, 8.4 Hz, CH(HCH)N); 2.93-3.11 (3H, m, (CH$_2$)$_2$(HCH)N, CHCH$_2$N and CH(HCH)N); 3.39-3.45 (1H, m, (CH$_2$)$_2$(HCH)N); 3.76 (1H, d, *J* = 13.2 Hz, N(HCH)C$_{quat}$); 3.83 (1H, d, *J* = 13.2 Hz, N(HCH)C$_{quat}$); 4.04-4.11 (1H, m, CHN(CH$_2$)$_3$); 4.31 (1H, s (broad), NH); 7.12 (2H, d, *J* = 7.9 Hz, 2×CH$_{arom}$); 7.20 (2H, d, *J* = 7.9 Hz, 2×CH$_{arom}$). **^{13}C NMR** (100 MHz, CDCl$_3$): δ 21.1 (CH$_3$); 25.4 (CH$_2$CH$_2$CH$_2$N); 31.0 (CH$_2$CHCH$_2$N); 31.1 (CH$_2$(CH$_2$)$_2$N); 31.3 (CH$_2$CH$_2$CHCH$_2$N); 51.4 (CHCH$_2$N); 53.8 (NCH$_2$C$_{quat}$); 55.1 ((CH$_2$)$_2$CH$_2$N); 66.8 (CHN(CH$_2$)$_3$); 69.3 (CHNCH$_2$N); 128.2 and 129.1 (4×CH$_{arom}$); 136.6 and 137.0 (2×C$_{quat,arom}$). **IR (cm^{-1})**: v$_{NH}$ = 3387; v$_{max}$ = 2947, 2868, 2823, 2686, 2600, 2501, 1514, 1455, 1378, 1286, 1197, 1180, 1109, 1036, 804. **MS (70 eV)**: *m/z* (%): 245 (M$^+$+1, 100). **HRMS (ESI)**: *m/z* calcd for C$_{16}$H$_{25}$N$_2$: 245.2012 [*M*+H]$^+$; found: 245.2013.
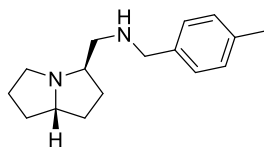
trans-3-[(4-Chlorobenzyl)aminomethyl]pyrrolizidine (*trans*-13c)

Yellow oil. R_f = 0.26 (CH$_2$Cl$_2$/MeOH/triethylamine 9/1/0.1). Yield 22%. **^{1}H NMR** (400 MHz, CDCl$_3$): δ 1.32-1.48 (2H, m, (HCH)CH$_2$CHCH$_2$N and (HCH)(CH$_2$)$_2$N); 1.51-1.60 (1H, m, CH$_2$(HCH)CHCH$_2$N); 1.70-2.02 (5H, m, CH$_2$CH$_2$CH$_2$N, (HCH)(CH$_2$)$_2$N, (HCH)CH$_2$CHCH$_2$N and CH$_2$(HCH)CHCH$_2$N); 2.58 (1H, d×d, *J* = 11.3, 5.7 Hz, CH(HCH)N); 2.65 (1H, d×d, *J* = 11.3, 6.7 Hz, CH(HCH)N); 2.67 (1H, d×t, *J* = 10.9, 6.6 Hz, (CH$_2$)$_2$(HCH)N); 2.82 (1H, d×d×d×d, *J* = 8.5, 6.7, 5.7, 5.7 Hz, CHCH$_2$N); 3.01 (1H, d×t, *J* = 10.6, 6.2 Hz, (CH$_2$)$_2$(HCH)N); 3.56 (1H, p, *J* = 6.8 Hz, CHN(CH$_2$)$_3$); 3.75 (1H, d, *J* = 13.5 Hz, N(HCH)C$_{quat}$); 3.80 (1H, d, *J* = 13.5 Hz, N(HCH)C$_{quat}$); 7.26-7.27 (4H, m, 4×CH$_{arom}$). **^{13}C NMR** (100 MHz, CDCl$_3$): δ 25.8 (CH$_2$CH$_2$CH$_2$N); 31.5 (CH$_2$CHCH$_2$N); 32.0 (CH$_2$(CH$_2$)$_2$N); 32.1 (CH$_2$CH$_2$CHCH$_2$N); 53.6 (NCH$_2$C$_{quat}$); 55.0 (CHCH$_2$N); 55.3 ((CH$_2$)$_2$CH$_2$N); 65.4 (CHN(CH$_2$)$_3$); 67.3 (CHNCH$_2$N); 128.4 and 129.4 (4×CH$_{arom}$); 132.4 and 139.1 (2×C$_{quat,arom}$). **IR (cm^{-1})**: v$_{NH}$ = 3302; v$_{max}$ = 2952, 2864, 2817, 1490, 1449, 1089, 1014, 826, 800. **MS (70 eV)**: *m/z* (%): 265/267 (M$^+$+1, 100). **HRMS (ESI)**: *m/z* calcd for C$_{15}$H$_{22}$ClN$_2$: 265.1466 [*M*+H]$^+$; found: 265.1462.

trans-3-Benzylaminomethyl-1-methylpyrrolizidine (*trans*-22a)

Spectral data derived from the mixture of diastereomers.

Colorless oil. R_f = 0.20 (CH$_2$Cl$_2$/MeOH/triethylamine 9/1/0.1). Yield 26%. *dr* 54/46 (before purification); *dr* 64/36 (after purification). **^{1}H NMR** (400 MHz, CDCl$_3$): δ 0.96 (3H, d, *J* = 7.1 Hz, CH$_3$CH); 1.00 (3H, d, *J* = 6.4 Hz, CH$_3$CH); 1.26-1.35 (1H, m, (HCH)CHCH$_3$); 1.36-1.46 (1H, m, (HCH)(CH$_2$)$_2$N); 1.48-1.90 (12H, m, (HCH)CH$_2$N, (HCH)(CH$_2$)$_2$N, CH$_2$CHCH$_3$, CHCH$_3$, (HCH)(CH$_2$)$_2$N, CH$_2$CH$_2$N, (HCH)CH$_2$N, (HCH)(CH$_2$)$_2$N and 2×NH); 2.06 (1H, d×d×d, *J* = 11.8, 5.8, 5.8 Hz, (HCH)CHCH$_3$); 2.37 (1H, ~septet,
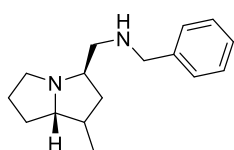
J = 7.1 Hz, CH̲CHCHN); 2.54 (1H, d×d, *J* = 11.3, 5.7 Hz, CH(H̲CH)N); 2.64 (1H, d×d, *J* = 11.3, 7.2 Hz, CH(HCH̲)N); 2.66-2.77 (4H, m, CHCH̲₂N and 2×(CH₂)₂(H̲CH)N); 2.82-2.89 (2H, m, CH̲NCH₂N and CH̲NCH₂N); 3.00 (1H, d×t, *J* = 10.6, 6.6 Hz, (CH₂)₂(HCH̲)N); 3.10-3.19 (2H, m, CH̲NCH and (CH₂)₂(HCH̲)N); 3.44-3.50 (1H, m, CH̲NCH); 3.78 (2×1H, 2×d, *J* = 13.3 Hz, 2×N(H̲CH)C_quat); 3.83 (2×1H, 2×d, *J* = 13.3 Hz, 2×N(HCH̲)C_quat); 7.23-7.34 (10H, m, 10×CH_arom). **¹³C NMR** (100 MHz, CDCl₃): δ 15.8 and 17.3 (2×C̲H₃CH); 25.4 (C̲H₂CH₂N); 25.8 and 26.4 (2×C̲H₂(CH₂)₂N); 30.4 (C̲H₂CH₂N); 34.1 (C̲HCHN); 37.0 (C̲H₂CHCH₃); 40.3 (C̲HCHN); 41.0 (C̲H₂CHCH₃); 54.3 and 54.4 (2×NC̲H₂C_quat); 55.26 ((CH₂)₂C̲H₂N); 55.33 and 55.5 (2×CHC̲H₂N); 56.1 ((CH₂)₂C̲H₂N); 65.9 and 67.6 (2×C̲HNCH₂N); 69.8 and 72.5 (2×C̲HNCH); 126.75, 126.79, 128.12, 128.13, 128.30 and 128.32 (10×C̲H_arom); 140.57 and 140.64 (2×C̲_quat,arom). **IR (cm⁻¹)**: ν_NH = 3304; ν_max = 2953, 2869, 1495, 1453, 1378, 1360, 1200, 1112, 1028, 732, 696. **MS (70 eV)**: *m/z* (%): 245 (M⁺+1, 100). **HRMS (ESI)**: *m/z* calcd for C₁₆H₂₅N₂: 245.2012 [*M*+H]⁺; found: 245.2013.

trans-3-Benzylaminomethyl-1-ethylpyrrolizidine (*trans*-22b)

Spectral data derived from the mixture of diastereomers.

Colorless oil. *R*_f = 0.20 (CH₂Cl₂/MeOH/triethylamine 9/1/0.1). Yield 28%. *dr* 53/47 (before purification); *dr* 56/44 (after purification). **¹H NMR** (400 MHz, CDCl₃): δ 0.90 (3H, t, *J* = 7.2 Hz, CH̲₃CH₂); 0.92 (3H, t, *J* = 7.3 Hz, CH̲₃CH₂); 1.22-1.90 (16H, m, (H̲CH)CHCH₂CH₃, CH₃(H̲CH), CH₃(H̲CH), (H̲CH)(CH₂)₂N, CH₃(HCH̲), CH₃(HCH̲), (H̲CH)CH₂N, CHCHN, (HCH̲)(CH₂)₂N, CH̲₂CHCH₂CH₃, CH̲₂CH₂N, CH̲₂(CH₂)₂N) and (HCH̲)CH₂N); 2.01 (2H, s (broad), 2×NH); 2.11 (1H, d×d×d, *J* = 11.7, 5.8, 5.8 Hz, (HCH̲)CHCH₃); 2.18-2.28 (1H, m, CH̲CHN); 2.51 (1H, d×d, *J* = 11.0, 5.8 Hz, CH(H̲CH)N); 2.58 (1H, d×d, *J* = 11.0, 7.8 Hz, CH(HCH̲)N); 2.61-2.85 (6H, m, CH(H̲CH)N, (CH₂)₂(H̲CH)N, CH(HCH̲)N, (CH₂)₂(HCH̲)N, CH̲NCH₂N and CH̲NCH₂N); 2.93 (1H, d×t, *J* = 10.8, 6.2 Hz, (CH₂)₂(HCH̲)N); 3.07-3.15 (2H, m, (CH₂)₂(HCH̲)N and CH̲NCH); 3.39 (1H, d×t, *J* = 9.5, 6.8 Hz, CH̲NCH); 3.78 (2×1H, 2×d, *J* = 13.3 Hz, 2×N(H̲CH)C_quat); 3.83 (2×1H, 2×d, *J* = 13.3 Hz, 2×N(HCH̲)C_quat); 7.21-7.34 (10H, m, 10×CH_arom). **¹³C NMR** (100 MHz, CDCl₃): δ 12.9 and 13.3 (2×C̲H₃CH₂); 24.1 (C̲H₂CH₃); 25.5 (C̲H₂(CH₂)₂N); 25.9 (C̲H₂CH₂N and C̲H₂(CH₂)₂N); 26.6 (C̲H₂CH₃); 31.6 (C̲H₂CH₂N); 33.9 and 39.1 (2×C̲H₂CHCH₂CH₃); 42.0 and 47.7 (2×C̲HCHN); 54.3 and 54.5 (2×NC̲H₂C_quat); 55.0 ((CH₂)₂C̲H₂N); 55.6 (CHC̲H₂N); 55.9 ((CH₂)₂C̲H₂N); 56.0 (CHC̲H₂N); 65.7 and 67.0 (2×C̲HNCH₂N); 69.1 and 71.2 (2×C̲HNCH); 126.7, 126.8, 128.11, 128.14, 128.30 and 128.32 (10×CH_arom); 140.6 and 140.7 (2×C_quat, arom). **IR (cm⁻¹)**: ν_NH = 3359; ν_max = 3026, 2956, 2870, 1495, 1453, 1359, 1117, 1028, 732, 696. **MS (70 eV)**: *m/z* (%): 259 (M⁺+1, 100). **HRMS (ESI)**: *m/z* calcd for C₁₇H₂₇N₂: 259.2169 [*M*+H]⁺; found: 259.2176.

trans-1-Methyl-3-[(4-methylbenzyl)aminomethyl]pyrrolizidine (*trans*-22c)

Spectral data for one diastereomer resulting from the mixture of *trans*-22c. The relative stereochemistry was secured by 2D-NOESY spectroscopy.

Colorless oil. Purity = 92%. *R*_f = 0.20 (CH₂Cl₂/MeOH/triethylamine 9/1/0.1). **¹H NMR** (400 MHz, CDCl₃): δ 1.03 (3H, d, *J* = 6.5 Hz, CH̲₃CH); 1.40 (1H, d×d×d, *J* = 11.9, 11.6, 11.6 Hz, (H̲CH)CHCH₃); 1.56-1.61 (1H, m, (H̲CH)(CH₂)₂N); 1.66-1.77 (1H, m, CH̲CH₃); 1.78-1.95 (3H, m, CH₂CH̲₂CH₂N and (HCH̲)(CH₂)₂N); 1.98 (1H, s, NH); 2.05 (1H, d×d×d, *J* = 11.9, 5.5, 5.5 Hz, (HCH̲)CHCH₃); 2.33 (3H, s, CH₃,tos); 2.71 (1H, d×d, *J* = 11.8, 4.9 Hz, CH(H̲CH)N); 2.79-2.98 (3H, m, (CH₂)₂(H̲CH)N, CH(HCH̲)N and CH̲CH₂N); 3.20 (1H, d×d×d, *J* = 11.0, 7.9, 6.4 Hz, (CH₂)₂(HCH̲)N); 3.36 (1H, d×d×d, *J* = 9.3, 7.7, 3.5 Hz, CH̲NCHCH₃); 3.74 (1H, d, *J* = 13.2 Hz,
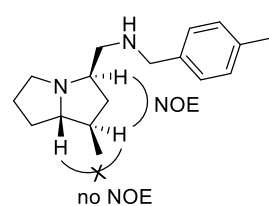
N(H<u>C</u>H)C_{quat}); 3.79 (1H, d, *J* = 13.2 Hz, N(HC<u>H</u>)C_{quat}); 7.12 (2H, 2×d, *J* = 7.9 Hz, 2×CH_{arom}); 7.21 (2H, 2×d, *J* = 7.9 Hz, 2×CH_{arom}). **¹³C NMR** (100 MHz, CDCl₃): δ 17.0 (<u>C</u>H₃CH); 21.1 (CH₃,tos); 25.1 (CH₂<u>C</u>H₂CH₂N); 29.9 (<u>C</u>H₂(CH₂)₂N); 39.9 (<u>C</u>HCH₃); 40.2 (<u>C</u>H₂CHCH₃); 53.2 (CH<u>C</u>H₂N); 54.0 (N<u>C</u>H₂C_{quat}); 54.9 ((CH₂)₂<u>C</u>H₂N); 68.3 (<u>C</u>HNCH₂N); 72.5 (<u>C</u>HNCHCH₃); 128.1 and 129.0 (4×CH_{arom}); 136.4 and 137.2 (2×C_{quat,arom}). **IR (cm⁻¹)**: ν_{NH} = 3294; ν_{max} = 2953, 2870, 1582, 1514, 1454, 1377, 1258, 1094, 1020, 802, 748, 648. **MS (70 eV)**: *m/z* (%): 259 (M⁺+1, 100). **HRMS (ESI)**: *m/z* calcd for C₁₇H₂₇N₂: 259.2169 [*M*+H]⁺; found: 259.2169.
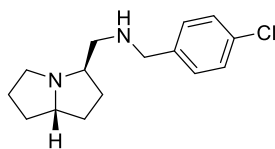
Spectral data derived from the mixture of diastereomers.

Colorless oil. *R*_f = 0.20 (CH₂Cl₂/MeOH/triethylamine 9/1/0.1). Yield 29%. *dr* 58/42 (before purification); *dr* 60/40 (after purification). **¹H NMR** (400 MHz, CDCl₃): δ 0.98 (3H, d, *J* = 7.0 Hz, C<u>H</u>₃CH); 1.04 (3H, d, *J* = 6.5 Hz, C<u>H</u>₃CH); 1.38-1.47 (1H, m, (<u>H</u>CH)CHCH₃); 1.49-1.54 (1H, m, (<u>H</u>CH)(CH₂)₂N); 1.56-1.63 (1H, m, (<u>H</u>CH)CH₂N); 1.65-2.01 (11H, m, (HC<u>H</u>)(CH₂)₂N, C<u>H</u>₂CHCH₃, C<u>H</u>CH₃, C<u>H</u>₂CH₂N, C<u>H</u>₂(CH₂)₂N, (HC<u>H</u>)CH₂N, (HC<u>H</u>)(CH₂)₂N and 2×NH); 2.02-2.08 (1H, m, (HC<u>H</u>)CHCH₃); 2.33 (2×3H, s, 2×CH₃,tos); 2.40-2.51 (1H, m, C<u>H</u>CHN); 2.60 (1H, d×d, *J* = 12.0, 5.2 Hz, CH(<u>H</u>CH)N); 2.71-3.04 (7H, m, CH(H<u>C</u>H)N, (CH₂)₂(<u>H</u>CH)N, CH(HC<u>H</u>)N, (CH₂)₂(<u>H</u>CH)N, CH(HC<u>H</u>)N and 2×C<u>H</u>NCH₂N); 3.23-3.33 (1H, m, (CH₂)₂(H<u>C</u>H)N); 3.38-3.46 (2H, m, (CH₂)₂(HC<u>H</u>)N) and C<u>H</u>NCH); 3.74 (2×1H, 2×d, *J* = 13.3 Hz, 2×N(<u>H</u>CH)C_{quat}); 3.74-3.78 (1H, m, C<u>H</u>NCH); 3.79 (2×1H, 2×d, *J* = 13.3 Hz, 2×N(HC<u>H</u>)C_{quat}); 7.12 (2×2H, 4×d, *J* = 7.9 Hz, 4×CH_{arom}); 7.21 (2×2H, 4×d, *J* = 7.9 Hz, 4×CH_{arom}). **¹³C NMR** (100 MHz, CDCl₃): δ 15.4 and 16.9 (2×<u>C</u>H₃CH); 21.1 (2×CH₃,tos); 25.0 (<u>C</u>H₂CH₂N); 25.6 and 26.2 (2×<u>C</u>H₂(CH₂)₂N); 29.8 (<u>C</u>H₂CH₂N); 33.7 (<u>C</u>HCHN); 36.8 (<u>C</u>H₂CHCH₃); 39.8 (<u>C</u>HCHN); 40.0 (<u>C</u>H₂CHCH₃); 52.6 and 53.4 (2×CH<u>C</u>H₂N); 53.8 and 53.9 (2×N<u>C</u>H₂C_{quat}); 54.8 and 55.7 (2×(CH₂)₂<u>C</u>H₂N); 66.6 and 68.4 (2×<u>C</u>HNCH₂N); 69.4 and 72.5 (2×<u>C</u>HNCH); 128.1, 128.2 and 129.0 (8×CH_{arom}); 136.4, 136.5 and 137.0 (4×C_{quat,arom}).
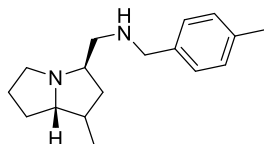
trans-1-Ethyl-3-[(4-methylbenzyl)aminomethyl]pyrrolizidine (*trans*-22d)

Spectral data derived from the mixture of diastereomers.

Colorless oil. *R*_f = 0.20 (CH₂Cl₂/MeOH/triethylamine 9/1/0.1). Yield 25%. *dr* 59/41 (before purification); *dr* 63/37 (after purification). **¹H NMR** (400 MHz, CDCl₃): δ 0.90 and 0.92 (2×3H, 2×t, *J* = 7.3 Hz, 2×C<u>H</u>₃CH₂); 1.21-1.89 (18H, m, (<u>H</u>CH)CHCH₂CH₃, CH₃(<u>H</u>CH), CH₃(<u>H</u>CH), (<u>H</u>CH)(CH₂)₂N, CH₃(HC<u>H</u>), CH₃(HC<u>H</u>), (<u>H</u>CH)CH₂N, C<u>H</u>CHN, (HC<u>H</u>)(CH₂)₂N, C<u>H</u>₂CHCH₂CH₃, C<u>H</u>₂CH₂N, C<u>H</u>₂(CH₂)₂N), (HC<u>H</u>)CH₂N and 2×NH); 2.12 (1H, d×d×d, *J* = 11.7, 5.8, 5.8 Hz, (HC<u>H</u>)CHCH₃); 2.17-2.27 (1H, m, C<u>H</u>CHN); 2.33 (2×3H, 2×s, 2×CH₃); 2.49 (1H, d×d, *J* = 11.1, 5.8 Hz, CH(<u>H</u>CH)N); 2.55-2.84 (7H, m, CH(HC<u>H</u>)N, CH(<u>H</u>CH)N, (CH₂)₂(<u>H</u>CH)N, CH(HC<u>H</u>)N, (CH₂)₂(<u>H</u>CH)N, C<u>H</u>NCH₂N and C<u>H</u>NCH₂N); 2.92 (1H, d×t, *J* = 10.5, 6.3 Hz, (CH₂)₂(HC<u>H</u>)N); 3.06-3.14 (2H, m, (CH₂)₂(HC<u>H</u>)N and C<u>H</u>NCH); 3.38 (1H, d×t, *J* = 9.7, 6.7 Hz, C<u>H</u>NCH); 3.74 (2×1H, 2×d, *J* = 13.1 Hz, 2×N(<u>H</u>CH)C_{quat}); 3.79 (2×1H, 2×d, *J* = 13.1 Hz, 2×N(HC<u>H</u>)C_{quat}); 7.12 (2×2H, 4×d, *J* = 7.9 Hz, 4×CH_{arom}); 7.21 and 7.22 (2×2H, 4×d, *J* = 7.9 Hz, 4×CH_{arom}). **¹³C NMR** (100 MHz, CDCl₃): δ 12.9 and 13.3 (2×<u>C</u>H₃CH₂); 21.1 (2×CH₃); 24.2 (<u>C</u>H₂CH₃); 25.5 (<u>C</u>H₂(CH₂)₂N); 25.9 (<u>C</u>H₂CH₂N and <u>C</u>H₂(CH₂)₂N); 26.6 (<u>C</u>H₂CH₃); 31.6 (<u>C</u>H₂CH₂N); 33.9 and 39.2 (2×<u>C</u>H₂CHCH₂CH₃); 42.0 and 47.7 (2×<u>C</u>HCHN); 54.0 and 54.2 (2×N<u>C</u>H₂C_{quat}); 55.1 ((CH₂)₂<u>C</u>H₂N); 55.7 (CH<u>C</u>H₂N); 55.9 ((CH₂)₂<u>C</u>H₂N); 56.1 (CH<u>C</u>H₂N); 65.7 and 67.0 (2×<u>C</u>HNCH₂N); 69.1 and 71.2 (2×<u>C</u>HNCH); 128.08, 128.10, 128.98 and 129.00 (8×CH_{arom}); 136.26, 136.33, 137.5 and 137.6 (4×C_{quat,arom}). **IR (cm⁻¹)**: ν_{NH} = 3306; ν_{max} = 2954, 2870, 1514, 1454, 1115, 1020, 825, 800, 752. **MS (70 eV)**: *m/z* (%): 273 (M⁺+1, 100). **HRMS (ESI)**: *m/z* calcd for C₁₈H₂₉N₂: 273.2325 [*M*+H]⁺; found: 273.2329.
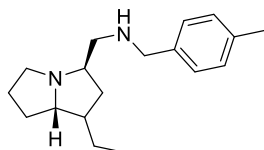
**trans-3-[(4-Chlorobenzyl)aminomethyl]-1-methylpyrrolizidine (trans-22e)**

Spectral data derived from the mixture of diastereomers.

Colorless oil. R_f = 0.20 (CH$_2$Cl$_2$/MeOH/triethylamine 9/1/0.1). Yield 25%. dr 54/46 (before purification); dr 66/34 (after purification). **^{1}H NMR** (400 MHz, CDCl$_3$): δ 0.96 (3H, d, J = 7.0 Hz, CH$_3$CH); 0.99 (3H, d, J = 6.5 Hz, CH$_3$CH); 1.23-1.32 (1H, m, (HCH)CHCH$_3$); 1.34-1.43 (1H, m, (HCH)(CH$_2$)$_2$N); 1.46-1.88 (12H, m, (HCH)CH$_2$N, (HCH)(CH$_2$)$_2$N, CH$_2$CHCH$_3$, CHCH$_3$, (HCH)(CH$_2$)$_2$N, CH$_2$CH$_2$N, (HCH)CH$_2$N, (HCH)(CH$_2$)$_2$N and 2×NH); 2.05 (1H, d×d×d, J = 11.8, 5.8, 5.8 Hz, (HCH)CHCH$_3$); 2.37 (1H, ~septet, J = 7.0 Hz, CHCHN); 2.49 (1H, d×d, J = 11.1, 5.6 Hz, CH(HCH)N); 2.56 (1H, d×d, J = 11.1, 7.6 Hz, CH(HCH)N); 2.58-2.71 (4H, m, CHCH$_2$N and 2×(CH$_2$)$_2$(HCH)N); 2.78-2.85 (2H, m, CHNCH$_2$N and CHNCH$_2$N); 2.92 (1H, d×t, J = 10.5, 6.6 Hz, (CH$_2$)$_2$(HCH)N); 3.04 (1H, d×d×d, J = 9.0, 7.3, 4.1 Hz, CHNCH); 3.11 (1H, d×d×d, J = 10.6, 7.5, 4.7 Hz, (CH$_2$)$_2$(HCH)N); 3.40 (1H, d×t, J = 9.1, 7.0 Hz, CHNCH); 3.74 (1H, d, J = 13.4 Hz, N(HCH)C$_{quat}$); 3.75 (1H, d, J = 13.5 Hz, N(HCH)C$_{quat}$); 3.79 (1H, d, J = 13.4 Hz, N(HCH)C$_{quat}$); 3.80 (1H, d, J = 13.5 Hz, N(HCH)C$_{quat}$); 7.25-7.29 (8H, m, 8×CH$_{arom}$). **^{13}C NMR** (100 MHz, CDCl$_3$): δ 15.8 and 17.4 (2×CH$_3$CH); 25.4 (CH$_2$CH$_2$N); 25.9 and 26.4 (2×CH$_2$(CH$_2$)$_2$N); 30.5 (CH$_2$CH$_2$N); 34.2 (CHCHN); 36.9 (CH$_2$CHCH$_3$); 40.4 (CHCHN); 41.1 (CH$_2$CHCH$_3$); 53.5 and 53.7 (2×NCH$_2$C$_{quat}$); 55.5 ((CH$_2$)$_2$CH$_2$N); 55.7 and 55.8 (2×CHCH$_2$N); 56.2 ((CH$_2$)$_2$CH$_2$N); 65.8 and 67.3 (2×CHNCH$_2$N); 69.8 and 72.5 (2×CHNCH); 128.39, 128.41, 129.42 and 129.44 (8×CH$_{arom}$); 132.38, 132.43, 139.1 and 139.2 (4×C$_{quat,arom}$). **IR (cm^{-1})**: ν$_{NH}$ = 3300; ν$_{max}$ = 2953, 2868, 1489, 1454, 1406, 1088, 1015, 835, 799, 646. **MS (70 eV)**: m/z (%): 279/281 (M$^+$+1, 100). **HRMS (ESI)**: m/z calcd for C$_{16}$H$_{24}$ClN$_2$: 279.1623 [M+H]$^+$; found: 279.1624.
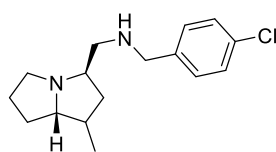
trans-3-[(4-Chlorobenzyl)aminomethyl]-1-ethylpyrrolizidine (trans-22f)

Spectral data derived from the mixture of diastereomers.

Colorless oil. R_f = 0.20 (CH$_2$Cl$_2$/MeOH/triethylamine 9/1/0.1). Yield 31%. dr 56/44 (before purification); dr 55/45 (after purification). **^{1}H NMR** (400 MHz, CDCl$_3$): δ 0.91 and 0.92 (2×3H, 2×t, J = 7.3 Hz, 2×CH$_3$CH$_2$); 1.23-1.90 (18H, m, (HCH)CHCH$_2$CH$_3$, CH$_3$(HCH), CH$_3$(HCH), (HCH)(CH$_2$)$_2$N, CH$_3$(HCH), CH$_3$(HCH), (HCH)CH$_2$N, CHCHN, (HCH)(CH$_2$)$_2$N, CH$_2$CHCH$_2$CH$_3$, CH$_2$CH$_2$N, CH$_2$(CH$_2$)$_2$N), (HCH)CH$_2$N and 2×NH); 2.11 (1H, d×d×d, J = 11.7, 5.8, 5.8 Hz, (HCH)CHCH$_3$); 2.17-2.27 (1H, m, CHCHN); 2.47 (1H, d×d, J = 11.0, 5.6 Hz, CH(HCH)N); 2.54 (1H, d×d, J = 11.0, 7.8 Hz, CH(HCH)N); 2.58-2.84 (6H, m, CH(HCH)N, (CH$_2$)$_2$(HCH)N, CH(HCH)N, (CH$_2$)$_2$(HCH)N, CHNCH$_2$N and CHNCH$_2$N); 2.92 (1H, d×t, J = 10.5, 6.3 Hz, (CH$_2$)$_2$(HCH)N); 3.07-3.15 (2H, m, (CH$_2$)$_2$(HCH)N and CHNCH); 3.39 (1H, d×t, J = 9.7, 6.7 Hz, CHNCH); 3.74 and 3.75 (2×1H, 2×d, J = 13.5 Hz, 2×N(HCH)C$_{quat}$); 3.79 (2×1H, 2×d, J = 13.5 Hz, 2×N(HCH)C$_{quat}$); 7.24-7.29 (8H, m, 8×CH$_{arom}$). **^{13}C NMR** (100 MHz, CDCl$_3$): δ 12.8 and 13.3 (2×CH$_3$CH$_2$); 24.1 (CH$_2$CH$_3$); 25.5 (CH$_2$(CH$_2$)$_2$N); 25.9 (CH$_2$CH$_2$N and CH$_2$(CH$_2$)$_2$N); 26.6 (CH$_2$CH$_3$); 31.6 (CH$_2$CH$_2$N); 33.8 and 39.0 (2×CH$_2$CHCH$_2$CH$_3$); 42.1 and 47.7 (2×CHCHN); 53.5 and 53.7 (2×NCH$_2$C$_{quat}$); 55.1 ((CH$_2$)$_2$CH$_2$N); 55.4 and 55.8 (2×CHCH$_2$N); 56.0 ((CH$_2$)$_2$CH$_2$N); 65.8 and 67.0 (2×CHNCH$_2$N); 69.1 and 71.2 (2×CHNCH); 128.38, 128.40, 129.41 and 129.44 (8×CH$_{arom}$); 132.37, 132.44, 139.1 and 139.19 (4×C$_{quat,arom}$). **IR (cm^{-1})**: ν$_{NH}$ = 3294; ν$_{max}$ = 2957, 2870, 1597, 1489, 1406, 1287, 1117, 1088, 1015, 800, 646. **MS (70 eV)**: m/z (%): 293/295 (M$^+$+1, 100). **HRMS (ESI)**: m/z calcd for C$_{17}$H$_{26}$ClN$_2$: 293.1779 [M+H]$^+$; found: 293.1785.
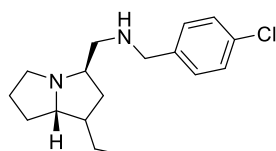
Synthesis of *trans*- and *cis*-3-benzylaminomethyl-7a-cyanopyrrolizidines 33

To a solution of 1-benzyl-2-[2-(1-pyrrolin-2-yl)ethyl]aziridine **12a** (228 mg, 1 mmol) in dry THF (10 mL) was added In(OTf)$_3$ (169 mg, 0.3 mmol, 0.3 equiv). After one hour, the solution was cooled to 0°C and a solution of KCN (65 mg, 1 mmol, 1 equiv) in MeOH (10 mL) was added via a syringe, after which the resulting solution was heated under reflux for 48 hours. Then, the reaction mixture was filtered through a path of Celite® and extracted with Et$_2$O (2 × 10 mL). Drying (MgSO$_4$), filtration of the drying agent and evaporation of the solvent *in vacuo* afforded *trans*- and *cis*-3-benzylaminomethyl-7a-cyanopyrrolizidines **33** in a 79/21 ratio. Purification by means of column chromatography on silica gel (CH$_2$Cl$_2$/MeOH 9/1) provided *trans*-3-benzylaminomethyl-7a-cyanopyrrolizidine **33** as a colorless oil in a 34% yield (87 mg, 0.34 mmol).

trans-3-Benzylaminomethyl-7a-cyanopyrrolizidine (*trans*-33)

Colorless oil. R_f = 0.09 (CH$_2$Cl$_2$/MeOH 9/1). Yield 34%. **^{1}H NMR** (400 MHz, CDCl$_3$): δ 1.69 (1H, s (broad), NH); 1.74-2.09 (6H, m, CHNCH$_2$(H$\underline{C}$H), CH$_2$NCH$_2$(H$\underline{C}$H), CH$_2$N(H$\underline{C}$H)CH$_2$, CHN(H$\underline{C}$H)CH$_2$, CH$_2$N(H$\underline{C}$H)CH$_2$ and CHN(H$\underline{C}$H)CH$_2$); 2.26-2.32 (1H, m, CH$_2$NCH$_2$(HC$\underline{H}$)); 2.38 (1H, d×d×d, *J* = 12.6, 6.5, 3.6 Hz, CHNCH$_2$(HC$\underline{H}$)); 2.60-2.71 (3H, m, C$\underline{H}_2$NCHN and CH$_2$(H$\underline{C}$H)N); 2.91 (1H, d×t×d, *J* = 8.2, 5.9, 5.9 Hz, CHN); 3.16 (1H, d×d×d, *J* = 10.2, 6.0, 5.4 Hz, CH$_2$(HC$\underline{H}$)N); 3.80 (1H, d, *J* = 13.4 Hz, N(H$\underline{C}$H)C$_{quat,arom}$); 3.84 (1H, d, *J* = 13.4 Hz, N(HC$\underline{H}$)C$_{quat,arom}$); 7.22-7.33 (5H, m, 5×CH$_{arom}$). **^{13}C NMR** (100 MHz, CDCl$_3$): δ 26.4 (CH$_2$N$\underline{C}$H$_2$CH$_2$); 30.9 (CHN$\underline{C}$H$_2$CH$_2$); 38.0 (CHNCH$_2$$\underline{C}H_2$); 38.4 (CH$_2NCH_2$$\underline{C}H_2$); 54.0 ($\underline{C}H_2$NCHN); 54.2 (N$\underline{C}H_2C_{quat,arom}$); 55.2 (CH$_2$$\underline{C}H_2$N); 67.8 (CHN); 124.7 (CN); 126.9 (CH$_{arom}$); 128.0 (2×CH$_{arom}$); 128.4 (2×CH$_{arom}$); 140.5 (C$_{quat,arom}$). **IR (cm^{-1})**: ν_{CN} = 2230; ν_{max} = 2967, 2941, 2868, 2818, 1495, 1452, 1182, 1109, 1028, 827, 735, 696, 669, 598. **MS (70 eV)**: *m/z* (%): 256 (M$^+$+1, 100). **HRMS (ESI)**: *m/z* calcd for C$_{16}$H$_{22}$N$_3$: 256.1808 [*M*+H]$^+$; found: 256.1817.
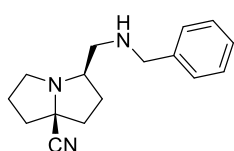
PART IV

LiAlH₄-induced thia-aza-Payne rearrangement of functionalized 2-(thiocyanatomethyl)aziridines into 2-(aminomethyl)thiiranes as an entry to 5-(chloromethyl)thiazolidin-2-ones

Abstract

Non-activated 2-(thiocyanatomethyl)aziridines with diverse substitution patterns were deployed as substrates to effect a LiAlH₄-promoted thia-aza-Payne rearrangement, providing access to functionalized 2-(aminomethyl)thiiranes in good to excellent yields (78-94%). The developed strategy is based on a hydride reduction of the thiocyanato moiety followed by intramolecular aziridine ring opening. Subsequent exposure of the obtained 2-(aminomethyl)episulfide intermediates to triphosgene resulted in the formation of 5-(chloromethyl)thiazolidin-2-ones.

Graphical abstract
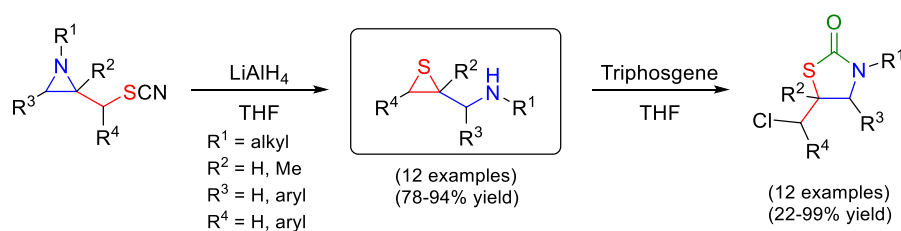
Reference

Dolfen, J.; Van Hecke, K.; D'hooghe, M. "LiAlH₄-induced thia-aza-Payne rearrangement of functionalized 2-(thiocyanatomethyl)aziridines into 2-(aminomethyl)thiiranes as an entry to 5-(chloromethyl)thiazolidin-2-ones". *Eur. J. Org. Chem* **2017**, 3229-3233 (I.F. 3.07).

1. Introduction

Since Payne's comprehensive research on the reorganization of 2,3-epoxy alcohols into their isomeric counterparts in 1962,[136] the 'Payne rearrangement' has evolved to a powerful reaction in organic chemistry. Moreover, due to its broad applicability, this elegant interconversion has become a widely used method in natural product synthesis.[137] Although the involved intramolecular ring-opening reactions occur in a stereospecific S_N2 fashion with inversion of configuration at the more-substituted carbon atom, the reversible character of the isomerization process still represents a significant drawback.

The 'aza-Payne rearrangement', however, implying the conversion of a 2-(hydroxymethyl)aziridine into its isomeric oxirane or vice versa,[138] and the 'thia-Payne rearrangement', referring to the equilibrium between a 2-(hydroxymethyl)thiirane and an epoxide,[139] can be tuned and controlled to a certain extent depending on the applied reaction conditions. Despite the numerous papers in the literature reporting on epoxide-aziridine and/or epoxide-thiirane migrations, only one article dealing with an aziridine-to-thiirane rearrangement has been published so far.[140] Moreover, the transformations in that particular study appeared to induce the formation of side products as well, as treatment of a variety of polysubstituted 1-tosyl-2-(tosyloxymethyl)aziridines with an excess of benzyltriethylammonium tetrathiomolybdate ([BnEt$_3$N]$_2$MoS$_4$) in CH$_3$CN afforded the corresponding thiiranes as the major products (75-80%) and cyclic disulfides as the minor compounds (20-25%).

In continuation of the research efforts concerning the LiAlH$_4$-induced regioselective ring rearrangement of (2-cyanoethyl)aziridines to either 2-(aminomethyl)pyrrolidines or 3-aminopiperidines,[25] and in light of the growing interest in sulfur-containing heterocycles,[141] the deployment of 2-(thiocyanatomethyl)aziridines as substrates for a hydride-promoted thia-aza-Payne rearrangement was envisaged in the present chapter. The feasibility of the premised aziridine-to-thiirane interconversion was assessed starting from non-activated 2-(thiocyanatomethyl)aziridines **1**. These aziridines, bearing an electron-donating group at nitrogen and differing in substitution pattern, can be prepared from either the corresponding monosubstituted 2-(bromomethyl)aziridines **2**, 2,2-disubstituted aziridines **3** or 2,3-disubstituted aziridines **4**, which have amply proven to be versatile precursors for further synthetic elaboration (Figure 1).[30,45,142]
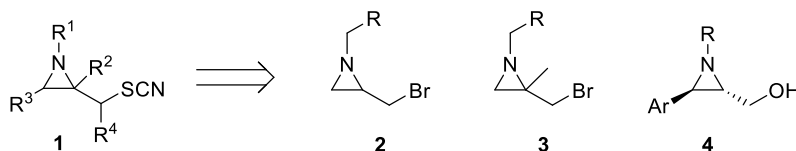
Figure 1

2. Thia-aza-Payne rearrangement of monosubstituted 2-(thiocyanatomethyl)-aziridines

In the outset of this study, 2-(bromomethyl)aziridine **2a** was converted into 2-(thiocyanatomethyl)aziridine **5a** in 90% isolated yield upon treatment with KSCN (2 equiv) in DMF at 70 °C,[142g] which was then used as a model substrate for the premised thia-aza-Payne rearrangement (Scheme 1). The formation of 2-(thiocyanatomethyl)aziridine **5a** can be rationalized by a direct displacement of the bromide leaving group in 2-(bromomethyl)aziridine **2a**. Although the thiocyanate anion represents an ambident nucleophile, the nucleophilic attack across the exocyclic carbon atom in aziridine **2a** occurred via the sulfur atom in a kinetically controlled way,[143] as infrared spectroscopic analysis of the crude reaction mixture indicated the presence of a thiocyanate group (v_{SCN} = 2153 cm^{-1}).[144] Then, in a first attempt, aziridine **5a** was treated with 2 equiv of LiAlH$_4$ and 0.3 equiv of In(OTf)$_3$ at reflux temperature,[25] but these reaction conditions resulted in intermolecular dimer formation instead of intramolecular ring rearrangement (Table 1, Entry 1). Next, an equimolar amount of LiAlH$_4$ and In(OTf)$_3$ was used, which led to complete conversion to the desired thiirane **6a** (Table 1, Entry 2). However, upon standing for a few hours, the reaction product appeared to be unstable, probably due to the presence of residual In(OTf)$_3$. Lowering the reaction temperature from reflux temperature to 0 °C in the absence of In(OTf)$_3$ again resulted in dimer formation (Table 1, Entry 3), whereas increasing the amount of LiAlH$_4$ (1.7 equiv) in combination with a reaction temperature of -78 °C afforded the desired thiirane **6a** in an acceptable yield of 78% (Table 1, Entry 4). As the isolated 2-(aminomethyl)thiirane **6a** still appeared to be unstable upon standing for a few days, it was trapped through treatment with triphosgene (1 equiv) in THF to furnish 5-(chloromethyl)thiazolidin-2-one **7a** in 85% yield.
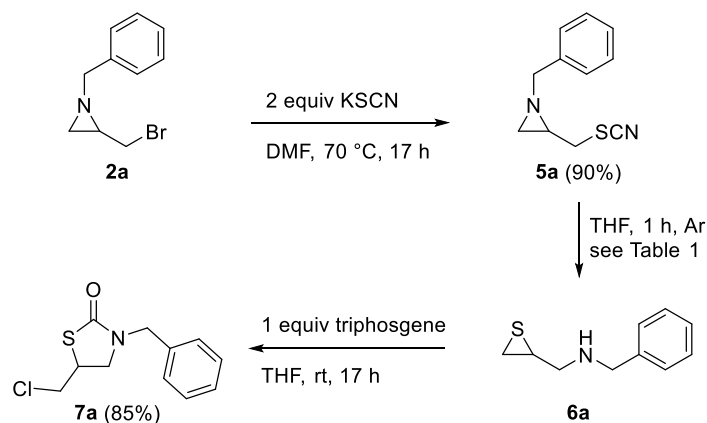
Scheme 1

Table 1. Optimization of the reaction conditions for the thia-aza-Payne rearrangement of 1-benzyl-2-(thiocyanatomethyl)aziridine 5a.

Entry	LiAlH$_4$ (equiv)	In(OTf)$_3$ (equiv)	Temp (°C)	Compound 6a (yield [%])
1	2	0.3	Δ	-[a]
2	1	1	Δ	45[b]
3	1.2	0	0	-[a]
4	1.7	0	-78 °C	78

[a] Dimer formation.

[b] Thiirane 6a appeared to be unstable in the presence of residual In(OTf)$_3$.

Mechanistically, the thia-aza-Payne rearrangement of 2-(thiocyanatomethyl)aziridine 5a can be rationalized by hydride addition across the thiocyanato moiety with concomitant release of HCN (Scheme 2). The *in situ* formed sulfide anion effects an intramolecular aziridine ring opening, resulting in 2-(aminomethyl)thiirane 6a after aqueous work-up. Although non-activated aziridines generally require activation of the ring system prior to ring opening (in contrast to activated aziridines),[14b,145] the ring opening of 1-benzylaziridine 5a can be attributed to the Lewis acid activity of LiAlH$_4$ (through coordination of aluminum with nitrogen).[146] Subsequent treatment of the obtained 2-(aminomethyl)thiirane 6a with triphosgene results in *N*-acylation toward carbamate 8a, followed by regioselective chloride-induced ring opening of the thiirane core at the less-substituted carbon atom[141d,147] and ring transformation toward the corresponding 5-(chloromethyl)thiazolidin-2-one 7a. The initial attack of the amino group in 6a across triphosgene was corroborated by reaction of thiirane 6a with methyl chloroformate and Boc$_2$O on an analytical scale, affording the *N*-acylated products without thiirane ring opening.
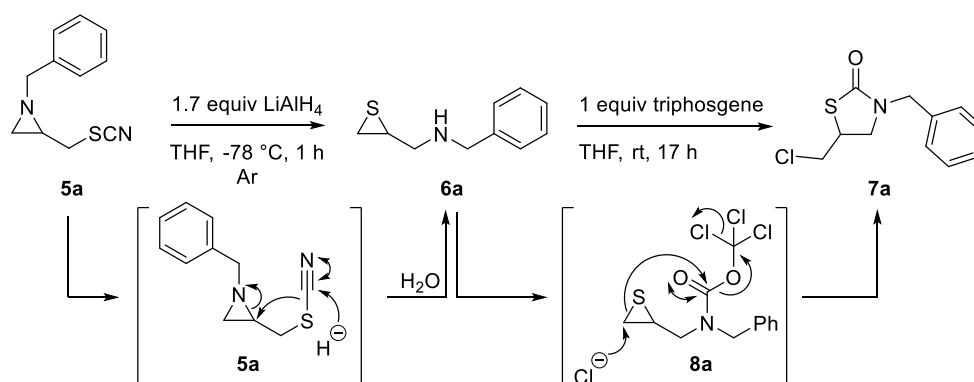
Scheme 2

Having the optimal reaction conditions for the conversion of aziridine 5a into thiirane 6a in hand, other monosubstituted 2-(thiocyanatomethyl)aziridines were prepared next to trigger the observed thia-aza-Payne rearrangement. To that end, 2-(thiocyanatomethyl)aziridines 5b-e were synthesized from the

corresponding 2-(bromomethyl)aziridines **2b-e** (2 equiv KSCN, DMF, 70 °C, 17 h), which were subsequently confronted with LiAlH$_4$ (1.7 equiv) at -78 °C under Ar-atmosphere to furnish 2-(aminomethyl)thiiranes **6b-e** in good to excellent yields (79-92%) (Table 2). Due to the unstable nature of the obtained thiiranes **6b-e** upon storing and purification on silica gel, these intermediates were immediately treated with triphosgene (1 equiv) in THF, producing stable 5-(chloromethyl)thiazolidin-2-ones **7b-e** in 81-99% yield.
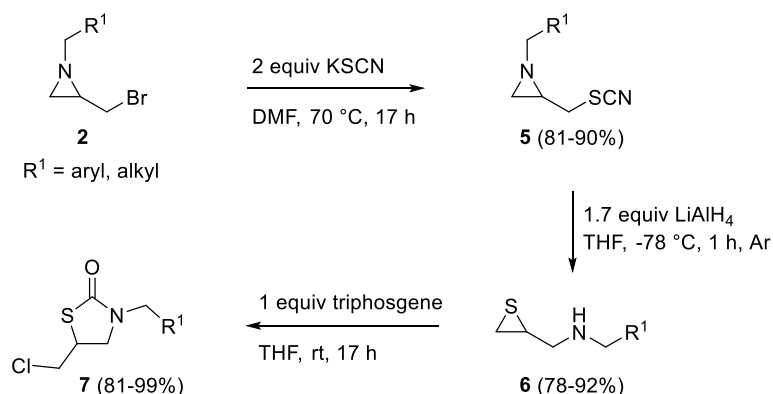
Scheme 3

Table 2. Synthesis of aziridines 5, thiiranes 6 and thiazolidin-2-ones 7.

R^1	Aziridines **5** (yield [%])	Thiiranes **6** (yield [%])	Thiazolidin-2-ones **7** (yield [%])
Ph	**5a** (90)	**6a** (78)	**7a** (85)
4-MeC$_6$H$_4$	**5b** (87)	**6b** (82)	**7b** (89)
4-ClC$_6$H$_4$	**5c** (95)	**6c** (79)	**7c** (81)
*i*Pr	**5d** (83)	**6d** (92)	**7d** (85)
*c*Hex	**5e** (81)	**6e** (86)	**7e** (99)

3. Thia-aza-Payne rearrangement of 2-methyl-2-(thiocyanatomethyl)aziridines

The effect of an additional substituent at the aziridine C2-position on the thia-aza-Payne rearrangement was investigated next. In that respect, 2-methyl-2-(thiocyanatomethyl)aziridines **9** were synthesized in excellent yields (86-96%) starting from 2-bromomethyl-2-methylaziridines **3** upon treatment with an equimolar amount of KSCN in DMF at 65 °C (Scheme 4, Table 3).[45] Subsequent addition of an excess of LiAlH$_4$ (1.7 equiv) in THF at -78 °C induced the desired aziridine-to-thiirane reorganization, and 2-(aminomethyl)thiiranes **10** were isolated in high yields (91-94%). As a consequence, it can be concluded that the presence of a quaternary carbon center in aziridines **9** does not have a negative impact on the thia-aza-Payne rearrangement. On the contrary, 2-aminomethyl-2-methylthiiranes **10** were isolated in slightly higher yields (91-94%) with respect to 2-(aminomethyl)thiiranes **6** (78-92%) and appeared to be more stable upon prolonged storage at 4 °C and purification on silica gel. Subsequently, the obtained 2,2-disubstituted thiiranes **10** were treated with triphosgene (1 equiv) in THF at room temperature,

affording the corresponding 5-chloromethyl-5-methylthiazolidin-2-ones **11** in almost quantitative yields (92-99%) (Table 3). It should be noted that also in the case of *gem*-disubstituted thiiranes **10**, ring opening of the thiirane core by chloride proceeded regioselectively at the less-substituted carbon atom.[148] The regioselective thiirane-ring opening toward thiazolidin-2-ones **11** was confirmed by means of ^{13}C NMR spectroscopy, as ^{13}C NMR chemical shifts of 51.3 ppm (CDCl$_3$) indicated an exocyclic CH$_2$Cl carbon atom instead of an endocyclic CH$_2$S carbon atom (δ_{CH2S} = 29-32 ppm) in the case of the regioisomeric thiazinan-2-ones.[142g,149]
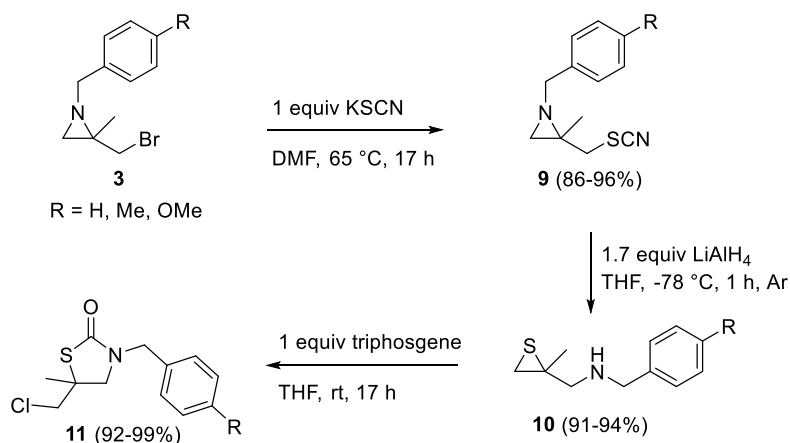
Scheme 4

Table 3. Synthesis of aziridines 9, thiiranes 10 and thiazolidin-2-ones 11.

R	Aziridines **9** (yield [%])	Thiiranes **10** (yield [%])	Thiazolidin-2-ones **11** (yield [%])
H	**9a** (86)	**10a** (94)	**11a** (97)
Me	**9b** (96)	**10b** (91)	**11b** (99)
OMe	**9c** (91)	**10c** (93)	**11c** (92)

4. Thia-aza-Payne rearrangement of 2-aryl-3-(thiocyanatomethyl)aziridines

The deployment of aziridine substrate class **4**, featuring a *vic*-disubstitution pattern, for the developed thia-aza-Payne rearrangement commenced with the preparation of 3-(thiocyanatomethyl)aziridine **12** in a two-step reaction sequence (Scheme 5). Tosylation of 2-(4-chlorophenyl)-3-(hydroxymethyl)aziridine **4a** with TsCl (1.05 equiv) in the presence of DMAP (0.1 equiv) and Et$_3$N (1.1 equiv) in CH$_2$Cl$_2$, followed by nucleophilic substitution upon addition of KSCN (1 equiv) in DMF at 65 °C, afforded 3-(thiocyanatomethyl)aziridine **12** in 52% yield as a single reaction product. It should be mentioned that NMR analysis (CDCl$_3$) of intermediate **12** appeared to be impossible due to unclear resolutions of the corresponding peaks. Aziridine **12** was then treated with LiAlH$_4$ (1.7 equiv) in THF at -78 °C, evoking a thia-aza-Payne rearrangement to afford thiirane **13** in 88% yield with inversion of configuration, and subsequent reaction with an equimolar amount of triphosgene afforded the corresponding *cis*-thiazolidin-2-one **14** in 71% yield.
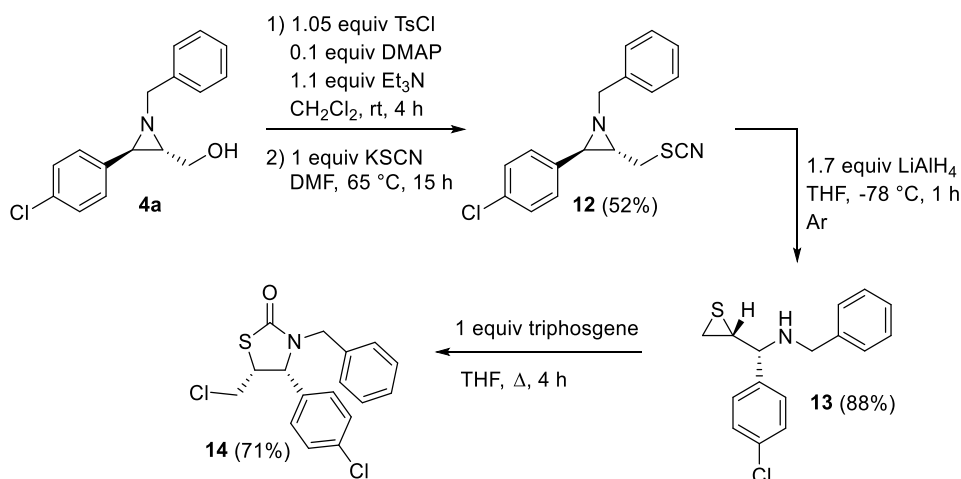
Scheme 5

Surprisingly, tosylation of 2-phenyl-3-(hydroxymethyl)aziridine **4b** (1.05 equiv TsCl, 0.1 equiv DMAP, 1.1 equiv Et$_3$N, CH$_2$Cl$_2$, rt, 4 h), and subsequent treatment with KSCN (1 equiv) in DMF at 65 °C afforded 3-(thiocyanatomethyl)aziridine **16** and 2-[phenyl(thiocyanato)methyl]aziridine **17** in a 55/45 ratio (Scheme 6). Based on the obtained experimental results, addition of KSCN to *in situ* formed 3-(tosyloxymethyl)aziridine **15** seems to provoke a competition between ring opening at the benzylic position (route a) and the expected direct tosyloxy group displacement (route b).[30] The difference in regioselectivity of the nucleophilic attack across (tosylated) aziridines **4a** and **4b** might be attributed to an electron withdrawal by induction of the 4-chlorophenyl substituent in **4a** with respect to a phenyl substituent in **4b**, hence destabilizing the transition state by p-π conjugation toward the aziridine-ring-opening product in case of substrate **4a**. Despite intensive efforts, structural isomers **16** and **17** could not be separated and, as a consequence, this mixture was used as such in the next step. To that end, treatment of the obtained aziridine mixture with LiAlH$_4$ (1.7 equiv) in THF at -78 °C afforded thiiranes **18** and **19** in a combined yield of 93%. Separation of thiiranes **18** and **19** appeared to be inconvenient and, as a consequence, the mixture was used as such in the ring-transformation reaction with triphosgene (1 equiv) in THF. After 4 hours at reflux temperature, the corresponding thiazolidin-2-ones **20** and **21** were produced, which could eventually be separated and isolated by means of preparative TLC (SiO$_2$) in 33% and 22% yield, respectively. Again, NMR analysis (CDCl$_3$) of aziridine **16** appeared to be impossible due to unclear resolutions of the corresponding peaks. The relative *cis*-stereochemistry of thiazolidin-2-ones **14** and **20** was confirmed by the vicinal coupling constants between the 4H and 5H protons on the thiazolidin-2-one ring (J_{cis} = 7.8 Hz), which is in accordance with the literature.[37]
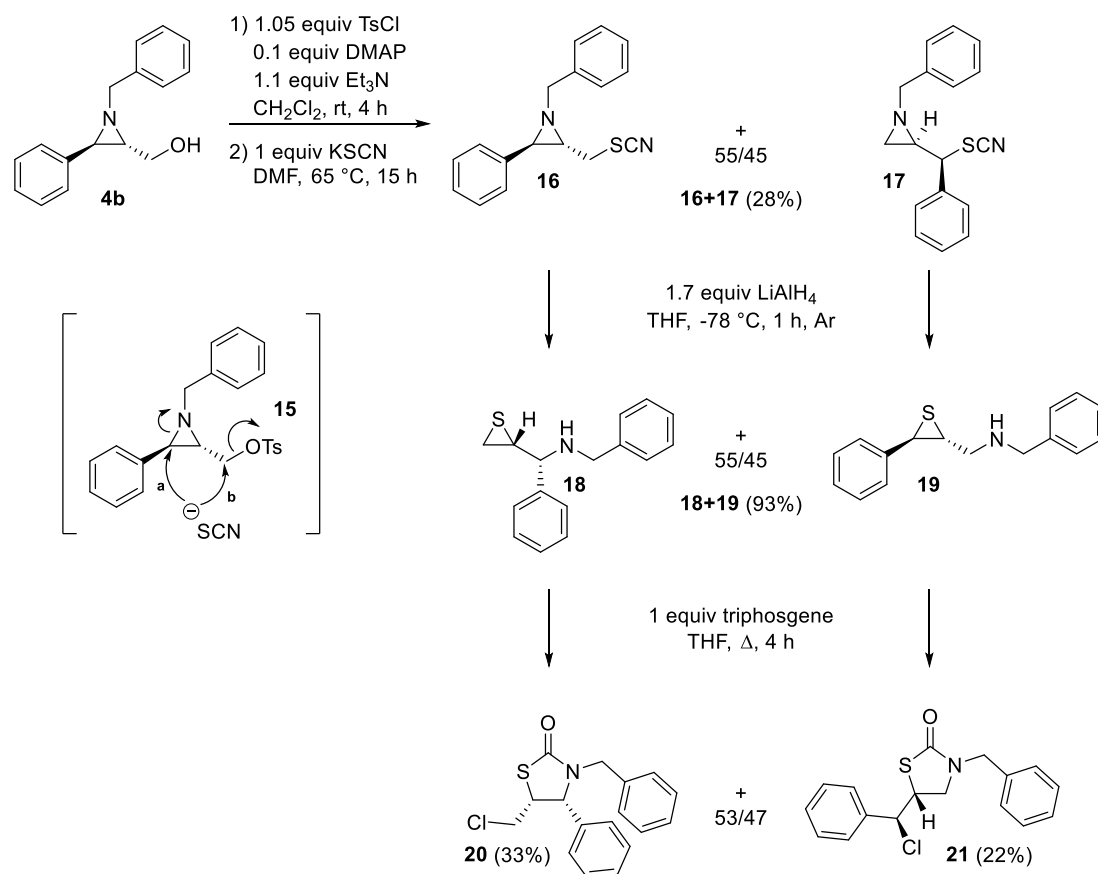
Scheme 6

In addition to the unexpected influence of the 2-aryl substituent on the thiocyanate-induced tosyloxy displacement, the effect of the *N*-substituent in *vic*-disubstituted aziridines **4** was also studied via tosylation and subsequent thiocyanatomethylation of 1-isopropyl-2-phenylaziridine **4c**. Again, a mixture of two isomers **22** and **23** was obtained in a ratio of 30/70, although in favor of 2-[phenyl(thiocyanato)methyl]aziridine **23** in this case (Scheme 7). Subsequent column chromatographic purification (SiO$_2$) of the reaction mixture allowed the isolation of the major **23** in 44% yield. Then, aziridine **23** was treated with LiAlH$_4$ (1.7 equiv) in THF at -78 °C, affording *trans*-thiirane **24** in 90% yield. The relative *trans*-stereochemistry of thiiranes **19** and **24** was confirmed by the vicinal coupling constants between the 2H and 3H protons on the thiirane ring (J_{trans} = 5.2-5.4 Hz), which is in accordance with the literature.[150] In contrast, *cis*-thiiranes have typical vicinal coupling constants of 6.4-6.8 Hz between the 2H and 3H protons.[151] Aminomethylated thiirane **24** was treated with triphosgene (1 equiv) in THF at reflux conditions, affording 5-(chloromethyl)thiazolidin-2-one **25** in 95% yield.
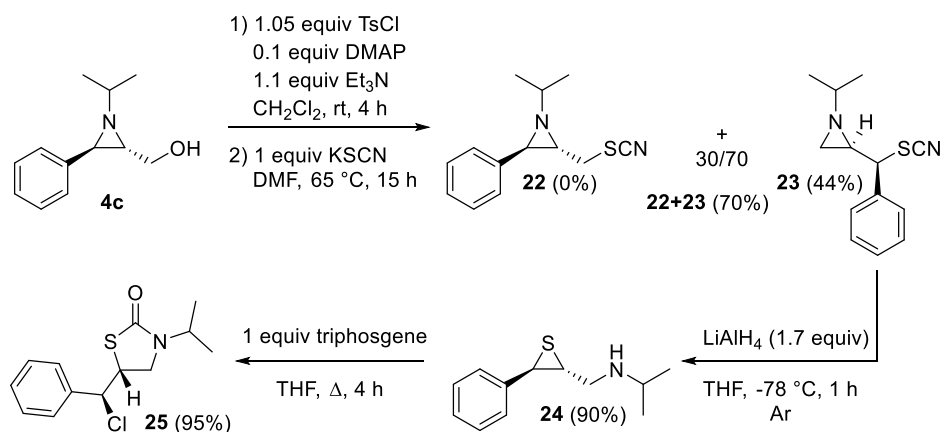
Scheme 7

The molecular identity of thiazolidin-2-one **25** was unequivocally established by means of a single crystal X-ray analysis (Figure 2), providing clear evidence for the regioselective chloride-induced ring opening of thiiranes **19** and **24** at the benzylic position.[147b,147d]
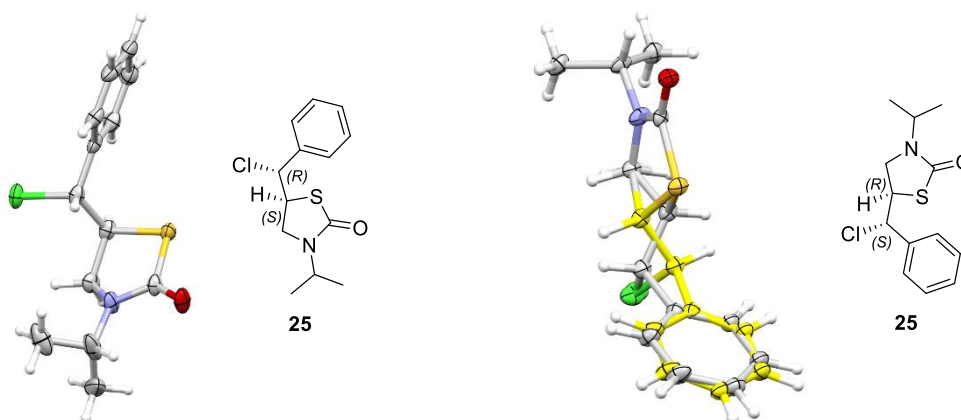
Figure 2

From the above-described results, it is clear that non-activated 2-(thiocyanatomethyl)aziridines **1**, derived from the corresponding aziridines **2-4**, represent valuable substrates for an unprecedented and efficient thia-aza-Payne rearrangement, as shown by the synthesis and characterization of 12 new 2-(aminomethyl)thiiranes. Furthermore, the involved experiments showed that the aziridine-to-thiirane migrations are irreversible and occur with inversion at the stereogenic center. Moreover, subsequent treatment of the obtained 2-(aminomethyl)thiiranes with triphosgene resulted in the formation of chloromethyl-substituted thiazolidin-2-ones via regioselective thiirane ring opening by chloride at the less-substituted or benzylic position, which is in accordance with the literature concerning the ring opening of thiiranes.[141d,147-148] It should be noted that this report discloses the first method for an aziridine-to-thiirane conversion in a selective and straightforward manner, which should therefore be considered as a powerful strategy in modern organic chemistry.

5. Evaluation of the reactivity of a representative 5-(chloromethyl)thiazolidin-2-one

In a final stage, additional synthetic efforts were made to explore the reactivity of the obtained 5-chloromethyl-substituted thiazolidin-2-one building blocks. To that end, treatment of thiazolidin-2-one **7c** as a representative example with KOtBu (1.02 equiv) in DMSO afforded 5-methylthiazolin-2-one **27** in 91% yield after 2 days at 100 °C via base-induced dehydrochlorination and subsequent prototrophic rearrangement toward a more stable endocyclic double bond (Scheme 8).[142g]

Scheme 8
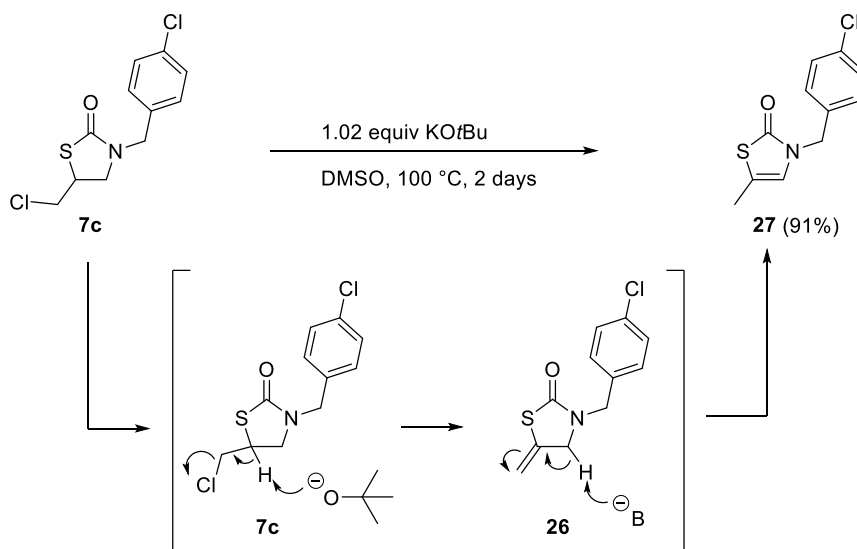
Apart from the above-described dehydrochlorination of thiazolidin-2-one **7c**, the substitution aptitude of the chloro atom was also investigated. To that end, reaction of the same thiazolidin-2-one **7c** with KSCN (2 equiv) in DMF or NaI (4 equiv) in acetone under microwave irradiation resulted in the formation of substitution products **28** and **29**, both in 87% yield (Scheme 9).

Scheme 9
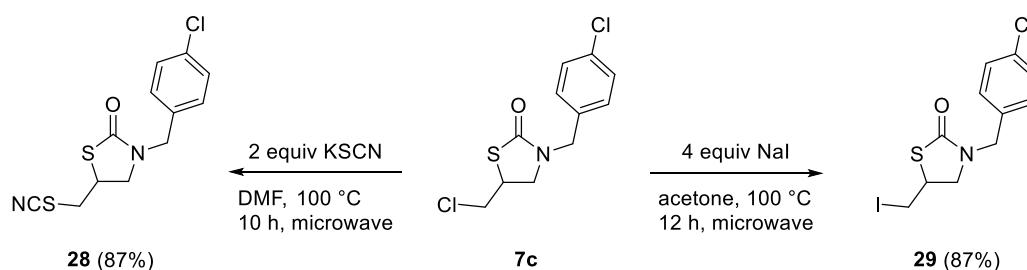
The use of benzylamine, NaOAc and KCN, however, appeared to be less straightforward and resulted in more complex reaction mixtures. Also, the deployment of 5-(iodomethyl)thiazolidin-2-one **30** (X = I) as substrate did not yield the desired substitution products (Scheme 10, Table 4).
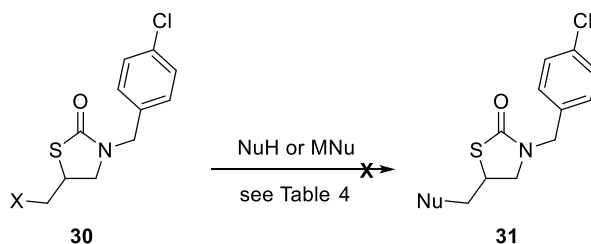
Scheme 10

Table 4. Attempts toward the substitution of thiazolidin-2-ones 30 with benzylamine, NaOAc and KCN.

X	NuH or MNu	Reaction conditions	Conversion
Cl	5 equiv BnNH$_2$	CH$_3$CN, Δ, 4 h	No reaction
Cl	5 equiv BnNH$_2$	CH$_3$CN, 100 °C, 20 h, pressure vial	No reaction
Cl	10 equiv BnNH$_2$	1 equiv K$_2$CO$_3$, DMF, 110 °C, 10 h, microwave	Complex reaction mixture
Cl	10 equiv BnNH$_2$	1 equiv NaI, DMF, 110 °C, 12 h, microwave	Complex reaction mixture
I	5 equiv BnNH$_2$	CH$_3$CN, rt, 20 h	No reaction
I	5 equiv BnNH$_2$	CH$_3$CN, 50 °C, 20 h	Complex reaction mixture
I	5 equiv BnNH$_2$	DMF, 50 °C, 2 h, microwave	Complex reaction mixture
I	5 equiv BnNH$_2$	DMF, 110 °C, 1 h, microwave	Complex reaction mixture
Cl	2 equiv NaOAc	EtOH, 110 °C, 13 h, microwave	Complex reaction mixture
I	2 equiv NaOAc	EtOH, 110 °C, 2 h, microwave	Complex reaction mixture
Cl	2 equiv NaOAc	DMSO, 50 °C, 13 h, microwave	Complex reaction mixture
Cl	2 equiv NaOAc	DMSO, 80 °C, 13 h	Complex reaction mixture
Cl	2 equiv NaOAc	DMSO, 110 °C, 1 h, microwave	Complex reaction mixture
Cl	2 equiv KCN	DMF, 100 °C, 10 h, microwave	Complex reaction mixture
Cl	4 equiv KCN	DMF, 140 °C, 2 h, microwave	No reaction
I	2 equiv KCN	DMF, 100 °C, 5 h, microwave	Complex reaction mixture

Finally, treatment of 5-(chloromethyl)thiazolidin-2-one **7c** with an equimolar amount of LiAlH$_4$ was evaluated while varying the applied reaction temperature. Apparently, increasing the reaction temperature (from -78 °C to room temperature) changed the ratio of thiazolidine **32** with respect to thiirane **33** in favor of thiirane **33**, and both isomers **32** and **33** could be isolated in 20% and 53% yield, respectively (Scheme 11, Table 5).
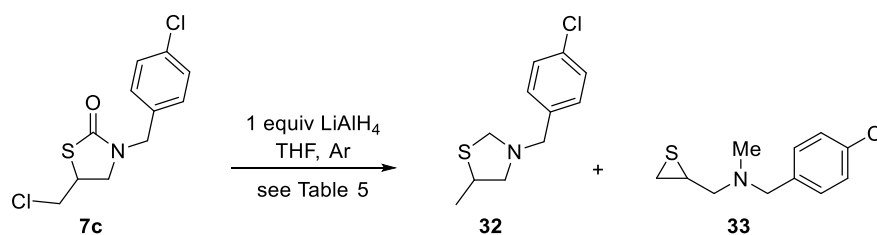
Scheme 11

Table 5. Reactivity of 5-(chloromethyl)thiazolidin-2-one 7c with respect to LiAlH₄.

Entry	Temperature	Time	Conversion[a]	
			Thiazolidine **32**	Thiirane **33**
1	-78 °C	3 h	30 (20% yield)	70
2	0 °C	1 h	24	76
3	rt	1 h	18	82 (53% yield)

[a] Based on ^{1}H NMR analysis (CDCl₃) of the crude reaction mixture.

6. Conclusion

In conclusion, an efficient and reliable thia-aza-Payne rearrangement of non-activated 2-(thiocyanatomethyl)aziridines toward 2-(aminomethyl)thiiranes was developed. The deployment of different classes of aziridine substrates showed that the diverse substitution patterns did not impose any restrictions on the desired aziridine-to-thiirane migrations. In addition, the obtained 2-(aminomethyl)thiiranes were easily converted into 5-(chloromethyl)thiazolidin-2-one building blocks, pointing to a regioselective thiirane ring opening by chloride.

7. Experimental details

General methods

^{1}H NMR spectra were recorded at 400 MHz on a Bruker Advance III-400 with solvents as indicated and tetramethylsilane as internal standard. ^{13}C NMR spectra were recorded at 100 MHz on a Bruker Advance III-400 with solvents as indicated. IR spectra were measured with a Spectrum One FT-IR spectrometer or a IRAffinity-1S FT-IR spectrophotometer. Electron spray (ES) mass spectra were obtained with an Agilent 1100 Series MS (ES, 4000V) mass spectrometer. High resolution electron spray (ES-TOF) mass spectra were obtained with an Agilent Technologies 6210 Series time-of-flight mass spectrometer. Melting points were determined on a Kofler bench, type WME Heizbank of Wagner & Munz and were corrected. Tetrahydrofuran was distilled over sodium benzophenone ketyl, while dichloromethane was distilled from calcium hydride before use. All other solvents and reagents were used as received from the supplier.

Microwave reactions were performed in a CEM Focused Microwave™ Synthesis System, Model Discover, with a continuous power output from 0 to 300 Watt and a self-adjusting, single mode MW cavity. The reactions were performed in 10 mL thick-walled Pyrex reaction vessels, closed with a 'snap-on' septa cap and equipped with a small stirring bar. A ramp time of maximum five minutes was used whereby the temperature was increased from room temperature to the desired one. This temperature was maintained during the course of the reaction for the indicated time. The temperature control system used a non-contact infrared sensor to measure the temperature on the bottom of the vessel and was used in a feedback loop with the on-board computer to regulate the temperature from 25 to 250 °C by adjusting the power output (1 Watt increments). The pressure control, IntelliVent™ Pressure Control system, used an indirect measurement of the pressure by sensing changes in the external deflection of the septa on the top on the sealed pressure vessel. Stirring was performed by a rotating magnetic plate, located below the floor of the microwave cavity. When the reaction was done, cooling of the vial was performed by a stream of clean air onto the vial, which decreased the temperature of a 2 mL solution from approximately 150 °C to 40 °C in less than 120 seconds.

Safety

General safety aspects

The practical work in this chapter was performed according to the SynBioC Research Group Internal Guidelines and with the aid of the internal safety document "Safety Instructions: How to work with chemicals". Wherever possible, hazardous or toxic reagents were avoided and/or substituted by safer or greener alternatives.

Specific safety aspects

A list of risks associated with each chemical and recommendations for safe use is available in the corresponding material safety data sheet (MSDS), which can be found on the website of the supplier. A brief overview of the most hazardous chemicals employed in this work will be given below, along with the potential hazards and precautions.

Bromine (Br$_2$): skin corrosion, acute aquatic toxicity. Avoid inhalation, wear protective gloves and clothing, avoid release in the environment.

Chloroform: specific target organ toxicity following repeated exposure. Avoid inhalation and wear protective gloves and clothing.

Chloroacetylchloride: skin corrosion, specific target organ toxicity following repeated exposure. Avoid contact with water. Avoid inhalation and release in the environment. Wear protective gloves and clothing.

Cyanides (KCN): corrosive to metals, acute toxicity after inhalation, skin contact and oral intake, specific target organ toxicity following repeated and acute exposure, acute and chronic aquatic toxicity. Avoid dust formation and inhalation. Wear protective gloves and clothing. Avoid release in the environment.

LiAlH$_4$ solution: flammable liquid, substances and mixtures which in contact with water emit flammable gases, skin corrosion. Avoid contact with air or water and work under an inert atmosphere. Avoid inhalation of vapors. Wear protective gloves and clothing. Keep away from heat, fire, hot surfaces, sparks and ignition sources.

Organic bases (Et$_3$N, KO*t*Bu): skin corrosion. Keep away from heat, fire, hot surfaces, sparks and ignition sources. Avoid inhalation and wear protective gloves and clothing.

Solvents in general: acute toxicity after inhalation, specific target organ toxicity following single or repeated exposure. Keep away from heat, fire, hot surfaces, sparks and ignition sources. Avoid inhalation and wear protective gloves and clothing..

Triphosgene: acute toxicity after inhalation, skin corrosion. Avoid dust formation and inhalation. Wear protective gloves and clothing.

Synthesis of 2-(bromomethyl)aziridines 2, 2-bromomethyl-2-methylaziridines 3 and 2-aryl-3-(hydroxymethyl)aziridines 4

2-(Bromomethyl)aziridines **2** were prepared according to literature procedures, and spectral data corresponded with those reported in the literature.[43,142f,152]

2-Bromomethyl-2-methylaziridines **3** were prepared according to a literature procedure, and spectral data corresponded with those reported in the literature.[44]

2-Aryl-3-(hydroxymethyl)aziridines **4** were prepared according to a literature procedure, and spectral data corresponded with those reported in the literature.[30]

Synthesis of 2-(thiocyanatomethyl)aziridines 5

As a representative example, the synthesis of 1-benzyl-2-(thiocyanatomethyl)aziridine **5a** is described here. To a solution of 1-benzyl-2-(bromomethyl)aziridine **2a** (2.25 g, 10 mmol) in dimethylformamide (30 mL), potassium thiocyanate (1.94 g, 20 mmol, 2 equiv) was added at room temperature, and the resulting solution was stirred for 17 hours at 70 °C. The cooled reaction mixture was poured into brine (50 mL) and extracted with diethyl ether (3 × 40 mL). The combined organic phases were washed with a LiCl-solution (1M in H$_2$O, 3 × 20 mL) and dried with MgSO$_4$. Filtration of the drying agent and evaporation of the solvent *in vacuo* afforded 1-benzyl-2-(thiocyanatomethyl)aziridine **5a** in 90% yield (1.85 g, 9 mmol). Because of the high purity of the obtained aziridines **5** (purity > 95%, ^{1}H NMR), these compounds were used as such in the next step.

Spectral data of 1-benzyl-2-(thiocyanatomethyl)aziridine **5a** correspond with those reported in the literature.[142g]

1-(4-Methylbenzyl)-2-(thiocyanatomethyl)aziridine 5b

Yellow oil. Yield 87%. **^{1}H NMR** (400 MHz, CDCl$_3$): δ 1.66 (1H, d, J = 6.1 Hz, (HCH)CHN); 1.87 (1H, d, J = 3.1 Hz, (HCH)CHN); 1.91-1.96 (1H, m, CHN); 2.35 (3H, s, CH$_3$); 2.87 (1H, d×d, J = 13.2 Hz, 7.0 Hz, (HCH)S); 3.08 (1H, d×d, J = 13.2 Hz, 5.3 Hz, (HCH)S); 3.43 (1H, d, J = 12.9 Hz, N(HCH)C$_{quat}$); 3.51 (1H, d, J = 12.9 Hz, N(HCH)C$_{quat}$); 7.15 (2×1H, 2×d, J = 7.9 Hz, 2 × CH$_{arom}$); 7.21 (2×1H, 2×d, J = 7.9 Hz, 2 × CH$_{arom}$). **^{13}C NMR** (100 MHz, ref = CDCl$_3$): δ 21.1 (CH$_3$); 34.6 (CHCH$_2$N); 37.57 (CH$_2$S); 37.60 (CH); 64.0 (NCH$_2$C$_{quat}$); 112.2 (SCN); 128.3 and 129.2 (4×CH$_{arom}$); 135.2 and 137.1 (2×C$_{quat,arom}$). **IR (cm^{-1})**: ν$_{SCN}$ = 2153; ν$_{max}$ = 2982, 2922, 2834, 1515, 1446, 1353, 1247, 1155, 1058, 1020, 854, 799, 752, 697, 669. **MS (70 eV)**: m/z (%): 219 (M$^+$+1, 100).
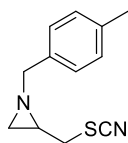
1-(4-Chlorobenzyl)-2-(thiocyanatomethyl)aziridine 5c

Yellow oil. Yield 95%. **^{1}H NMR** (400 MHz, CDCl$_3$): δ 1.67 (1H, d, J = 6.2 Hz, (HCH)CHN); 1.90 (1H, d, J = 3.2 Hz, (HCH)CHN); 1.93-1.98 (1H, m, CHN); 2.84 (1H, d×d, J = 13.3 Hz, 7.1 Hz, (HCH)S); 3.11 (1H, d×d, J = 13.3 Hz, 5.1 Hz, (HCH)S); 3.41 (1H, d, J = 13.2 Hz, N(HCH)C$_{quat}$); 3.54 (1H, d, J = 13.2 Hz, N(HCH)C$_{quat}$); 7.28 (2×1H, 2×d, J = 8.5 Hz, 2 × CH$_{arom}$); 7.32 (2×1H, 2×d, J = 8.5 Hz, 2 × CH$_{arom}$). **^{13}C NMR** (100 MHz, ref = CDCl$_3$): δ 34.8 (CHCH$_2$N); 37.4 (CH$_2$S); 37.8 (CH); 63.5 (NCH$_2$C$_{quat}$); 112.1 (SCN); 128.7 and 129.6 (4×CH$_{arom}$); 133.3 and 136.8 (2×C$_{quat,arom}$). **IR (cm^{-1})**: ν$_{SCN}$ = 2153; ν$_{max}$ = 3051, 2983, 2836, 1597, 1490, 1408, 1351, 1247, 1155, 1086, 1060, 1014, 855, 804, 765, 697, 665. **MS (70 eV)**: m/z (%): 239/241 (M$^+$+1, 100).
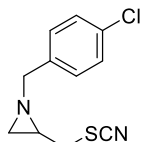
1-Isobutyl-2-(thiocyanatomethyl)aziridine 5d

Colorless oil. Yield 83%. **^{1}H NMR** (400 MHz, CDCl$_3$): δ 0.94 and 0.99 (2×3H, 2×d, J = 6.6 Hz, (CH$_3$)$_2$CH); 1.49 (1H, d, J = 6.1 Hz, (HCH)CHN); 1.71-1.76 (1H, m, CHN); 1.79-1.89 (1H, m, CH(CH$_3$)$_2$); 1.82 (1H, d, J = 3.1 Hz, (HCH)CHN); 2.11 (1H, d×d, J = 11.8, 7.8 Hz, N(HCH)CH(CH$_3$)$_2$); 2.16 (1H, d×d, J = 11.8, 6.5 Hz, N(HCH)CH(CH$_3$)$_2$); 2.86 (1H, d×d, J = 13.2, 7.0 Hz, (HCH)S); 3.13 (1H, d×d, J = 13.2, 5.3 Hz, (HCH)S). **^{13}C NMR** (100 MHz, ref = CDCl$_3$): δ 20.8 and 20.9 ((CH$_3$)$_2$CH); 29.1 (CH(CH$_3$)$_2$); 34.9 (CHCH$_2$N); 37.5 (CHN); 37.8 (CH$_2$S); 69.1 (NCH$_2$C$_{quat}$), 112.2 (SCN). **IR (cm^{-1})**: ν$_{SCN}$ = 2154; ν$_{max}$ = 2955, 2930, 2872, 2820, 1470, 1385, 1246, 1169, 1061, 1028, 824, 704. **MS (70 eV)**: m/z (%): 171 (M$^+$+1, 100).
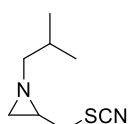
1-Cyclohexylmethyl-2-(thiocyanatomethyl)aziridine 5e

Colorless oil. Yield 81%. **^{1}H NMR** (400 MHz, CDCl$_3$): δ 0.89-1.00 (2H, m, (CH$_2$)$_5$CH); 1.11-1.32 (3H, m, (CH$_2$)$_5$CH); 1.48 (1H, d, J = 6.1 Hz, (HCH)CHN); 1.50 (1H, m, CH(CH$_2$)$_5$); 1.66-1.75 (5H, m, 4×(CH$_2$)$_5$CH and CHN); 1.81 (1H, d, J = 3.1 Hz, (HCH)CHN); 1.89-1.93 (1H, m, (CH$_2$)$_5$CH); 2.14 (1H, d×d, J = 11.7, 7.3 Hz, N(HCH)CH(CH$_2$)$_5$); 2.18 (1H, d×d, J = 11.7, 6.3 Hz, N(HCH)CH(CH$_2$)$_5$); 2.87 (1H, d×d, J = 13.2, 7.0 Hz, (HCH)S); 3.12 (1H, d×d, J = 13.2, 5.3 Hz, (HCH)S). **^{13}C NMR** (100 MHz, ref = CDCl$_3$): δ 25.96, 26.01, 26.6, 31.5 and 31.6 ((CH$_2$)$_5$CH); 35.1 (CHNCH$_2$N); 37.5 (CHN); 37.8 (CH$_2$S); 38.6 (CH(CH$_2$)$_5$); 67.9 (NCH$_2$CH(CH$_2$)$_5$); 112.2 (SCN). **IR (cm^{-1})**: ν$_{SCN}$ = 2154; ν$_{max}$ = 2920, 2849, 1449, 1362, 1244, 1055, 1024, 843, 702. **MS (70 eV)**: m/z (%): 211 (M$^+$+1, 100).
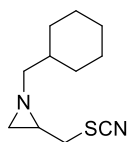
Synthesis of 2-methyl-2-(thiocyanatomethyl)aziridines 9

2-Methyl-2-(thiocyanatomethyl)aziridines **9** were prepared from the corresponding 2-bromomethyl-2-methylaziridines **3** according to a literature procedure, and spectral data corresponded with those reported in the literature.[45]

Synthesis of 2-(aminomethyl)thiiranes 6 and 10

As a representative example, the synthesis of 2-(benzylaminomethyl)thiirane **6a** is described here. A solution of 1-benzyl-2-(thiocyanatomethyl)aziridine **5a** (408 mg, 2 mmol) was dissolved in dry THF (10 mL) at -78 °C and placed under argon atmosphere. Next, a solution of $LiAlH_4$ (3.4 mL, 3.4 mmol, 1.7 equiv, 1M in THF) was added dropwise through a syringe. Then, the resulting solution was stirred at -78 °C for 1 hour under argon atmosphere. Afterward, the reaction mixture was quenched with a minimum amount of brine to neutralize the excess of $LiAlH_4$. Then, an excess of $MgSO_4$ was added and the reaction mixture was filtered through a path of Celite®. Subsequently, the remaining solids on the filter were washed intensively with EtOAc (5 × 10 mL). Evaporation of the combined organic phases *in vacuo* afforded 2-(benzylaminomethyl)thiirane **6a** in a yield of 78% (279 mg, 1.56 mmol) as a yellow oil in high purity (> 90% based on ^1H NMR spectroscopy). Due to the unstable nature of the obtained thiiranes **6** upon preservation and purification on silica gel, these compounds were used as such in the next step. 2-Aminomethyl-2-methylthiiranes **10** were purified by means of preparative TLC (SiO_2) to provide analytically pure samples.

2-(Benzylaminomethyl)thiirane 6a

Yellow oil. Yield 78%. **^1H NMR** (400 MHz, $CDCl_3$): δ 1.73 (1H, s (broad), NH); 2.25 (1H, d×d, *J* = 5.3, 1.0 Hz, (HCH)S); 2.50 (1H, d×d, *J* = 6.0, 1.0 Hz, (HCH)S); 2.63 (1H, d×d, *J* = 12.1, 6.7 Hz, CH(HCH)N); 3.09 (1H, d×d, *J* = 12.1, 4.9 Hz, CH(HCH)N); 3.11-3.16 (1H, m, CHS); 3.83 (1H, d, *J* = 13.2 Hz, N(HCH)C_quat); 3.87 (1H, d, *J* = 13.2 Hz, N(HCH)C_quat); 7.23-7.34 (5H, m, 5 × CH_arom). **^{13}C NMR** (100 MHz, ref = $CDCl_3$): δ 24.3 (CH_2S); 35.2 (CHS); 53.6 (NCH_2C_quat); 54.4 (CHCH_2N); 127.1 (CH_arom); 128.1 and 128.5 (4×CH_arom); 140.0 (C_quat,arom). **IR (cm⁻¹)**: ν_max = 2991, 2831, 1753, 1489, 1448, 1407, 1087, 1042, 1014, 907, 835, 797, 729. **MS** (70 eV): *m/z* (%): 359 (2*M⁺+1, 100).
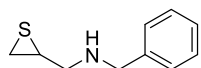
2-(4-Methylbenzylaminomethyl)thiirane 6b

Yellow oil. Yield 82%. **^1H NMR** (400 MHz, $CDCl_3$): δ 1.73 (1H, s (broad), NH); 2.25 (1H, d×d, *J* = 5.4, 0.9 Hz, (HCH)S); 2.33 (3H, s, CH_3); 2.50 (1H, d×d, *J* = 6.2, 0.9 Hz, (HCH)S); 2.62 (1H, d×d, *J* = 12.2, 6.7 Hz, CH(HCH)N); 3.08 (1H, d×d, *J* = 12.2, 5.0 Hz, CH(HCH)N); 3.09-3.16 (1H, m, CHS); 3.79 (1H, d, *J* = 13.1 Hz, N(HCH)C_quat); 3.83 (1H, d, *J* = 13.1 Hz, N(HCH)C_quat); 7.13 (2×1H, 2×d, *J* = 7.9 Hz, 2 × CH_arom); 7.21 (2×1H, 2×d, *J* = 7.9 Hz, 2 × CH_arom). **^{13}C NMR** (100 MHz, ref = $CDCl_3$): δ 21.1 (CH_3); 24.3 (CH_2S); 35.2 (CHS); 53.3 (NCH_2C_quat); 54.3 (CHCH_2N); 128.0 and 129.1 (4×CH_arom); 136.7 and 136.9 (2×C_quat,arom). **IR (cm⁻¹)**: ν_NH = 3311; ν_max = 2921, 2822, 1754, 1612, 1514, 1450, 1356, 1116, 1040, 1021, 844, 804. **MS (70 eV)**: *m/z* (%): 194 (M⁺+1, 100).
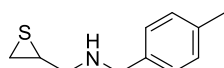
2-(4-Chlorobenzylaminomethyl)thiirane 6c

Yellow oil. Yield 79%. **^{1}H NMR** (400 MHz, CDCl$_3$): δ 1.68 (1H, s (broad), NH); 2.25 (1H, d×d, J = 5.4, 1.0 Hz, (HCH)S); 2.50 (1H, d×d, J = 6.1, 1.0 Hz, (HCH)S); 2.56-2.63 (1H, m, CH(HCH)N); 3.06-3.14 (2H, m, CH(HCH)N and CHS); 3.79 (1H, d, J = 13.9 Hz, N(HCH)C$_{quat}$); 3.83 (1H, d, J = 13.9 Hz, N(HCH)C$_{quat}$); 7.23-7.30 (4H, m, 4 × CH$_{arom}$). **^{13}C NMR** (100 MHz, ref = CDCl$_3$): δ 24.2 (CH$_2$S); 35.2 (CHS); 52.8 (NCH$_2$C$_{quat}$); 54.2 (CHCH$_2$N); 128.6 and 129.4 (4×CH$_{arom}$); 132.7 and 138.5 (2×C$_{quat,arom}$). **IR (cm^{-1})**: ν$_{NH}$ = 3308; ν$_{max}$ = 2826, 1597, 1489, 1454, 1407, 1353, 1087, 1042, 1014, 799. **MS (70 eV)**: m/z (%): 214/216 (M$^+$+1, 100).
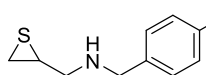
2-(Isobutylaminomethyl)thiirane 6d

Colorless oil. Yield 92%. **^{1}H NMR** (400 MHz, CDCl$_3$): δ 0.92 (2×3H, 2×d, J = 6.7 Hz, (CH$_3$)$_2$CH); 1.18 (1H, s (broad), NH); 1.74 (1H, septet, J = 6.7 Hz, CH(CH$_3$)$_2$); 2.26 (1H, ~d, J = 5.4 Hz, (HCH)S); 2.37-2.51 (2H, m, CH$_2$NCH(CH$_3$)$_2$); 2.52 (1H, ~d, J = 6.1 Hz, (HCH)S); 2.61 (1H, d×d, J = 12.4, 7.0 Hz, CHS(HCH)N); 3.05 (1H, d×d, J = 12.4, 4.4 Hz, CHS(HCH)N); 3.09-3.15 (1H, m, CHS). **^{13}C NMR** (100 MHz, ref = CDCl$_3$): δ 20.6 ((CH$_3$)$_2$CH); 24.4 (CH$_2$S); 28.4 (CH(CH$_3$)$_2$); 35.4 (CHS); 55.4 (CHSCH$_2$N); 57.7 (NCH$_2$CH(CH$_3$)$_2$). **IR (cm^{-1})**: ν$_{max}$ = 2953, 2870, 2816, 1462, 1385, 1366, 1125, 1049, 725. **MS** (70 eV): m/z (%): 291 (2*M$^+$+1, 50).
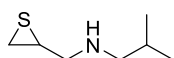
2-(Cyclohexylmethylaminomethyl)thiirane 6e

Colorless oil. Yield 86%. **^{1}H NMR** (400 MHz, CDCl$_3$): δ 0.86-0.96 (2H, m, (CH$_2$)$_5$CH); 1.11-1.30 (4H, m, 3×(CH$_2$)$_5$CH and NH); 1.40-1.49 (1H, m, CH(CH$_2$)$_5$); 1.65-1.76 (5H, m, (CH$_2$)$_5$CH); 2.25 (1H, d×d, J = 5.5, 0.9 Hz, (HCH)S); 2.44-2.54 (3H, m, CH$_2$NCH(CH$_2$)$_5$ and (HCH)S); 2.60 (1H, d×d, J = 12.5, 7.0 Hz, CHS(HCH)N); 3.03 (1H, d×d, J = 12.5, 5.1 Hz, CHS(HCH)N); 3.09-3.15 (1H, m, CHS). **^{13}C NMR** (100 MHz, ref = CDCl$_3$): δ 24.4 (CH$_2$S); 26.0, 26.7, 31.41, 31.43 (5×(CH$_2$)$_5$CH); 35.4 (CHS); 38.0 (CH(CH$_3$)$_2$); 55.4 (CHSCH$_2$N); 56.5 (NCH$_2$CH(CH$_3$)$_2$). **IR (cm^{-1})**: ν$_{NH}$ = 3308; ν$_{max}$ = 2918, 2849, 1447, 1126, 1042, 891, 843, 746, 648. **MS (70 eV)**: m/z (%): 371 (2*M$^+$+1, 100).
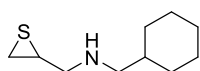
2-Benzylaminomethyl-2-methylthiirane 10a

Colorless oil. R_f = 0.39 (Hexane/EtOAc 1/1). Yield 94%. **^{1}H NMR** (400 MHz, CDCl$_3$): δ 1.51 (1H, s (broad), NH); 1.66 (3H, s, CH$_3$); 2.35 (1H, s, (HCH)S); 2.53 (1H, s, (HCH)S); 2.73 (1H, d, J = 12.3 Hz, C$_{quat}$S(HCH)N); 2.98 (1H, d, J = 12.4 Hz, C$_{quat}$S(HCH)N); 3.82 (2H, s, NCH$_2$C$_{quat,arom}$); 7.22-7.27 (1H, m, CH$_{arom}$); 7.31-7.32 (4H, m, 4×CH$_{arom}$). **^{13}C NMR** (100 MHz, ref = CDCl$_3$): δ 24.9 (CH$_3$); 32.6 (CH$_2$S); 46.1 (C$_{quat}$S); 53.6 (NCH$_2$C$_{quat,arom}$); 57.6 (NCH$_2$C$_{quat}$S); 126.9 (CH$_{arom}$); 128.0 and 128.4 (4×CH$_{arom}$); 140.3 (C$_{quat,arom}$). **IR (cm^{-1})**: ν$_{NH}$ = 3302; ν$_{max}$ = 2980, 2916, 2826, 1495, 1452, 1123, 1053, 735, 698. **MS (70 eV)**: m/z (%): 194 (M$^+$+1, 100).
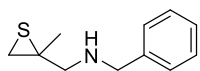
2-Methyl-2-(4-methylbenzylaminomethyl)thiirane 10b

Colorless oil. R_f = 0.36 (Hexane/EtOAc 3/2). Yield 91%. **^{1}H NMR** (400 MHz, CDCl$_3$): δ 1.53 (1H, s (broad), NH); 1.66 (3H, s, CH$_3$); 2.34 (3H, s, CH$_{3,tos}$); 2.35 (1H, s, (HCH)S); 2.53 (1H, s, (HCH)S); 2.72 (1H, d, J = 12.3 Hz, C$_{quat}$S(HCH)N); 2.97 (1H, d, J = 12.3 Hz, C$_{quat}$S(HCH)N); 3.78 (2H, s, NCH$_2$C$_{quat,arom}$); 7.13 (2×1H, 2×d, J = 7.9 Hz, 2×CH$_{arom}$); 7.20 (2×1H, 2×d, J = 7.9 Hz, 2×CH$_{arom}$). **^{13}C NMR** (100 MHz, ref = CDCl$_3$): δ 21.1 (CH$_{3,tos}$);
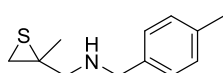
24.9 (CH$_3$); 32.6 (CH$_2$S); 46.1 (C$_{quat}$S); 53.3 (NCH$_2$C$_{quat,arom}$); 57.5 (NCH$_2$C$_{quat}$S); 127.9 and 129.1 (4×CH$_{arom}$); 136.5 and 137.2 (2×C$_{quat,arom}$). **IR (cm^{-1})**: ν$_{NH}$ = 3304; ν$_{max}$ = 2980, 2918, 2826, 1514, 1445, 1377, 1115, 1051, 1020, 843, 802, 719, 638, 611. **MS (70 eV)**: *m/z* (%): 208 (M$^+$+1, 100).

2-(4-Methoxybenzylaminomethyl)-2-methylthiirane 10c

Colorless oil. *R*$_f$ = 0.29 (Hexane/EtOAc 3/2). Yield 93%. **^{1}H NMR** (400 MHz, CDCl$_3$): δ 1.52 (1H, s (broad), NH); 1.66 (3H, s, CH$_3$); 2.36 (1H, s, (HCH)S); 2.53 (1H, s, (HCH)S); 2.72 (1H, d, *J* = 12.3 Hz, C$_{quat}$S(HCH)N); 2.97 (1H, d, *J* = 12.3 Hz, C$_{quat}$S(HCH)N); 3.76 (2H, s, NCH$_2$C$_{quat,arom}$); 3.80 (3H, s, CH$_3$O); 6.86 (2×1H, 2×d, *J* = 8.6 Hz, 2×CH$_{arom}$); 7.23 (2×1H, 2×d, *J* = 8.6 Hz, 2×CH$_{arom}$). **^{13}C NMR** (100 MHz, ref = CDCl$_3$): δ 24.9 (CH$_3$); 32.6 (CH$_2$S); 46.1 (C$_{quat}$S); 53.0 (NCH$_2$C$_{quat,arom}$); 55.3 (CH$_3$O); 57.5 (NCH$_2$C$_{quat}$S); 113.8 and 129.1 (4×CH$_{arom}$); 132.4 and 158.6 (2×C$_{quat,arom}$). **IR (cm^{-1})**: ν$_{NH}$ = 3310; ν$_{max}$ = 2911, 2833, 1611, 1510, 1441, 1300, 1244, 1173, 1107, 1034, 816. **MS (70 eV)**: *m/z* (%): 224 (M$^+$+1, 100).
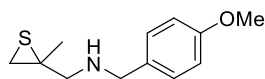
Synthesis of 5-(chloromethyl)thiazolidin-2-ones 7 and 11

As a representative example, the synthesis of 3-benzyl-5-(chloromethyl)thiazolidin-2-one **7a** is described here. To a solution of 2-(benzylaminomethyl)thiirane **6a** (358 mg, 2 mmol) in dry THF (10 mL), triphosgene (594 mg, 2 mmol, 1 equiv) was added at room temperature. Then, the resulting solution was stirred for 17 hours at room temperature. Afterward, the reaction mixture was quenched with sat. NaHCO$_3$ (10 mL) and the aqueous phase was extracted with EtOAc (3 × 20 mL). Drying (MgSO$_4$), filtration of the drying agent, and evaporation of the solvent *in vacuo* afforded 3-benzyl-5-(chloromethyl)thiazolidin-2-one **7a** in 85% yield (410 mg, 1.70 mmol) as a white powder. Purification by means of column chromatography on silica gel provided an analytically pure sample.

3-Benzyl-5-(chloromethyl)thiazolidin-2-one 7a

White powder. Mp 51 °C. *R*$_f$ = 0.26 (Hexane/EtOAc 5/1). Yield 85%. **^{1}H NMR** (400 MHz, CDCl$_3$): δ 3.52 (1H, d×d, *J* = 10.9, 3.0 Hz, CH(HCH)N); 3.56 (1H, d×d, *J* = 10.9, 10.5 Hz, (HCH)Cl); 3.63 (1H, d×d, *J* = 10.9, 7.1 Hz, CH(HCH)N); 3.66 (1H, d×d, *J* = 10.9, 4.4 Hz, (HCH)Cl); 3.75 (1H, d×d×d×d, *J* = 10.5, 7.1, 4.4, 3.0 Hz, CHS); 4.48 (1H, d, *J* = 15.3 Hz, N(HCH)C$_{quat}$); 4.52 (1H, d, *J* = 15.3 Hz, N(HCH)C$_{quat}$); 7.25-7.39 (5H, m, 5×CH$_{arom}$). **^{13}C NMR** (100 MHz, ref = CDCl$_3$): δ 42.1 (CHS); 45.8 (CH$_2$Cl); 48.7 (NCH$_2$C$_{quat}$); 50.4 (CHCH$_2$N); 128.1 (CH$_{arom}$); 128.2 and 129.0 (4×CH$_{arom}$); 135.5 (C$_{quat,arom}$); 169.8 (C$_{quat}$O). **IR (cm^{-1})**: ν$_{C=O}$ = 1660; ν$_{max}$ = 2943, 1485, 1431, 1409, 1348, 1276, 1257, 1214, 1200, 1177, 1081, 969, 932, 893, 755, 702, 691, 662, 617. **MS (70 eV)**: *m/z* (%): 242/244 (M$^+$+1, 100). **HRMS (ESI)**: *m/z* calcd for C$_{11}$H$_{13}$ClNOS: 242.0401 [*M*+H]$^+$; found: 242.0389.
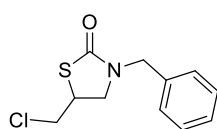
5-Chloromethyl-3-(4-methylbenzyl)thiazolidin-2-one 7b

White powder. Mp 65 °C. *R*$_f$ = 0.23 (Hexane/EtOAc 5/1). Yield 89%. **^{1}H NMR** (400 MHz, CDCl$_3$): δ 2.35 (3H, s, CH$_3$); 3.49 (1H, d×d, *J* = 11.1, 3.0 Hz, CH(HCH)N); 3.56 (1H, d×d, *J* = 11.0, 10.7 Hz, (HCH)Cl); 3.61 (1H, d×d, *J* = 11.1, 7.5 Hz, CH(HCH)N); 3.65 (1H, d×d, *J* = 11.0, 4.7 Hz, (HCH)Cl); 3.70-3.77 (1H, m, CHS); 4.43 (1H, d, *J* = 14.7 Hz, N(HCH)C$_{quat}$); 4.48 (1H, d, *J* = 14.7 Hz, N(HCH)C$_{quat}$); 7.13-7.18 (4H, m, 4×CH$_{arom}$). **^{13}C NMR** (100 MHz, ref = CDCl$_3$): δ 21.1 (CH$_3$); 42.1 (CHS); 45.8 (CH$_2$Cl); 48.5 (NCH$_2$C$_{quat}$);
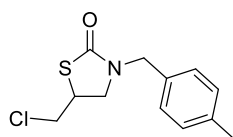
50.4 (CH$\underline{C}$H$_2$N); 128.2 and 129.6 (4×CH$_{arom}$); 132.5 and 137.9 (2×C$_{quat,arom}$); 169.8 (C$_{quat}$O). **IR (cm^{-1})**: $v_{C=O}$ = 1668; v_{max} = 2923, 1515, 1475, 1436, 1405, 1356, 1257, 1195, 971, 906, 804, 752, 728, 694, 660, 644, 611. **MS (70 eV)**: *m/z* (%): 256/258 (M$^+$+1, 73). **HRMS (ESI)**: *m/z* calcd for C$_{12}$H$_{15}$ClNOS: 256.0557 [*M*+H]$^+$; found: 256.0546.

3-(4-Chlorobenzyl)-5-(chloromethyl)thiazolidin-2-one 7c

White powder. Mp 78 °C. R_f = 0.18 (Hexane/EtOAc 5/1). Yield 81%. **^{1}H NMR** (400 MHz, CDCl$_3$): δ 3.51 (1H, d×d, *J* = 10.8, 3.1 Hz, CH($\underline{H}$CH)N); 3.56 (1H, d×d, *J* = 10.9, 10.5 Hz, ($\underline{H}$CH)Cl); 3.62 (1H, d×d, *J* = 10.8, 7.1 Hz, CH(HC$\underline{H}$)N); 3.67 (1H, d×d, *J* = 10.9, 4.3 Hz, (HC$\underline{H}$)Cl); 3.77 (1H, d×d×d×d, *J* = 10.5, 7.1, 4.3, 3.1 Hz, CHS); 4.44 (1H, d, *J* = 14.9 Hz, N($\underline{H}$CH)C$_{quat}$); 4.49 (1H, d, *J* = 14.9 Hz, N(HC$\underline{H}$)C$_{quat}$); 7.21 (2×1H, 2×d, *J* = 8.4 Hz, 2×CH$_{arom}$); 7.34 (2×1H, 2×d, *J* = 8.4 Hz, 2×CH$_{arom}$). **^{13}C NMR** (100 MHz, ref = CDCl$_3$): δ 42.0 (CHS); 45.7 (CH$_2$Cl); 48.0 (NCH$_2$C$_{quat}$); 50.4 (CH$\underline{C}$H$_2$N); 129.2 and 129.5 (4×CH$_{arom}$); 134.0 and 134.1 (2×C$_{quat,arom}$); 170.0 (C$_{quat}$O). **IR (cm^{-1})**: $v_{C=O}$ = 1658; v_{max} = 2939, 1595, 1485, 1437, 1404, 1349, 1278, 1256, 1213, 1198, 1176, 1094, 1017, 974, 897, 844, 800, 728, 720, 690. **MS (70 eV)**: *m/z* (%): 276/278/280 (M$^+$+1, 100). **HRMS (ESI)**: *m/z* calcd for C$_{11}$H$_{12}$Cl$_2$NOS: 276.0011 [*M*+H]$^+$; found: 276.0001.
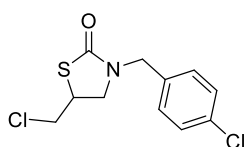
5-Chloromethyl-3-isobutylthiazolidin-2-one 7d

Colorless oil. R_f = 0.26 (Hexane/EtOAc 5/1). Yield 85%. **^{1}H NMR** (400 MHz, CDCl$_3$): δ 0.93 (2×3H, 2×d, *J* = 6.7 Hz, (C$\underline{H}_3$)$_2$CH); 1.87-2.00 (1H, m, C$\underline{H}$(CH$_3$)$_2$); 3.05 (1H, d×d, *J* = 13.6, 7.4 Hz, ($\underline{H}$CH)NCH(CH$_3$)$_2$); 3.23 (1H, d×d, *J* = 13.6, 7.6 Hz, (HC$\underline{H}$)NCH(CH$_3$)$_2$); 3.61-3.80 (5H, m, CH$_2$Cl, CH$_2$NCHS and CHS). **^{13}C NMR** (100 MHz, ref = CDCl$_3$): δ 19.9 and 20.0 (($\underline{C}$H$_3$)$_2$CH); 27.1 ($\underline{C}$H(CH$_3$)$_2$); 42.1 (CHS); 45.8 (CH$_2$Cl); 51.4 ($\underline{C}$H$_2$NCHS); 52.3 (N$\underline{C}$H$_2$CH(CH$_3$)$_2$); 169.7 (C$_{quat}$O). **IR (cm^{-1})**: $v_{C=O}$ = 1668; v_{max} = 2959, 2872, 1466, 1437, 1412, 1339, 1261, 1204, 1117, 974, 922, 725, 696, 662, 661. **MS (70 eV)**: *m/z* (%): 208/210 (M$^+$+1, 100). **HRMS (ESI)**: *m/z* calcd for C$_8$H$_{15}$ClNOS: 208.0557 [*M*+H]$^+$; found: 208.0559.
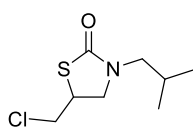
5-Chloromethyl-3-(cyclohexylmethyl)thiazolidin-2-one 7e

Colorless oil. R_f = 0.35 (Hexane/EtOAc 5/1). Yield 99%. **^{1}H NMR** (400 MHz, CDCl$_3$): δ 0.93-1.01 (2H, m, (C$\underline{H}_2$)$_5$CH); 1.11-1.28 (3H, m, (C$\underline{H}_2$)$_5$CH); 1.57-1.77 (6H, m, C$\underline{H}$(CH$_2$)$_5$ and (C$\underline{H}_2$)$_5$CH); 3.10 (1H, d×d, *J* = 13.8, 7.1 Hz, ($\underline{H}$CH)NCH(CH$_3$)$_2$); 3.22 (1H, d×d, *J* = 13.8, 7.1 Hz, (HC$\underline{H}$)NCH(CH$_3$)$_2$); 3.59-3.79 (5H, m, CH$_2$Cl, CH$_2$NCHS and CHS). **^{13}C NMR** (100 MHz, ref = CDCl$_3$): δ 25.7, 26.3, 30.6 and 30.7 (($\underline{C}$H$_2$)$_5$CH); 36.3 ($\underline{C}$H(CH$_2$)$_5$); 42.1 (CHS); 45.8 (CH$_2$Cl); 51.1 (N$\underline{C}$H$_2$CH(CH$_2$)$_5$); 51.6 ($\underline{C}$H$_2$NCHS); 169.6 (C$_{quat}$O). **IR (cm^{-1})**: $v_{C=O}$ = 1670; v_{max} = 2920, 2851, 1476, 1449, 1412, 1260, 1207, 1126, 1078, 976, 955, 905, 725, 696, 660, 604. **MS (70 eV)**: *m/z* (%): 248/250 (M$^+$+1, 100). **HRMS (ESI)**: *m/z* calcd for C$_{11}$H$_{19}$ClNOS: 248.0870 [*M*+H]$^+$; found: 248.0880.
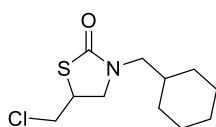
3-Benzyl-5-chloromethyl-5-methylthiazolidin-2-one 11a

Colorless oil. R_f = 0.34 (Hexane/EtOAc 4/1). Yield 97%. **¹H NMR** (400 MHz, CDCl₃): δ 1.55 (3H, s, CH₃); 3.20 and 3.56 (2×1H, 2×d, *J* = 10.8 Hz, CH(HCH)N); 3.61 and 3.77 (2×1H, 2×d, *J* = 11.1 Hz, (HCH)Cl); 4.47 and 4.52 (2×1H, 2×d, *J* = 14.8 Hz, N(HCH)C$_{quat,arom}$); 7.26-7.38 (5H, m, 5×CH$_{arom}$). **¹³C NMR** (100 MHz, ref = CDCl₃): δ 23.5 (CH₃); 48.7 (NCH₂C$_{quat}$); 50.9 (C$_{quat}$S); 51.3 (CH₂Cl); 56.1 (CH₂NC$_{quat}$S); 128.1 (CH$_{arom}$); 128.2 and 128.9 (4×CH$_{arom}$); 135.6 (C$_{quat,arom}$); 170.1 (C$_{quat}$O). **IR (cm⁻¹)**: ν$_{C=O}$ = 1682; ν$_{max}$ = 2967, 2932, 2876, 1454, 1410, 1213, 702. **MS (70 eV)**: *m/z* (%): 256/258 (M⁺+1, 100). **HRMS (ESI)**: *m/z* calcd for C₁₂H₁₅ClNOS: 256.0557 [*M*+H]⁺; found: 256.0553.
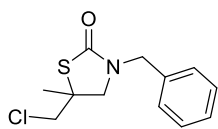
5-Chloromethyl-5-methyl-3-(4-methylbenzyl)thiazolidin-2-one 11b

Colorless oil. R_f = 0.26 (Hexane/EtOAc 4/1). Yield 99%. **¹H NMR** (400 MHz, CDCl₃): δ 1.55 (3H, s, CH₃); 2.35 (3H, s, CH$_{3,tos}$); 3.18 and 3.54 (2×1H, 2×d, *J* = 10.8 Hz, CH(HCH)N); 3.61 and 3.77 (2×1H, 2×d, *J* = 11.1 Hz, (HCH)Cl); 4.42 and 4.49 (2×1H, 2×d, *J* = 14.6 Hz, N(HCH)C$_{quat,arom}$); 7.13-7.18 (4H, m, 4×CH$_{arom}$). **¹³C NMR** (100 MHz, ref = CDCl₃): δ 21.2 (CH$_{3,tos}$); 23.5 (CH₃); 48.4 (NCH₂C$_{quat}$); 50.8 (C$_{quat}$S); 51.3 (CH₂Cl); 56.0 (CH₂NC$_{quat}$S); 128.2 and 129.6 (4×CH$_{arom}$); 132.6 and 137.9 (2×C$_{quat,arom}$); 170.0 (C$_{quat}$O). **IR (cm⁻¹)**: ν$_{C=O}$ = 1672; ν$_{max}$ = 2922, 2870, 1514, 1474, 1449, 1433, 1404, 1287, 1233, 1209, 1194, 964, 802, 754, 716, 662, 644, 600. **MS (70 eV)**: *m/z* (%): 270/272 (M⁺+1, 100). **HRMS (ESI)**: *m/z* calcd for C₁₃H₁₇ClNOS: 270.0714 [*M*+H]⁺; found: 270.0724.
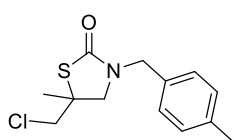
5-Chloromethyl-3-(4-methoxybenzyl)-5-methylthiazolidin-2-one 11c

Colorless oil. R_f = 0.19 (Hexane/EtOAc 4/1). Yield 92%. **¹H NMR** (400 MHz, CDCl₃): δ 1.54 (3H, s, CH₃); 3.18 and 3.54 (2×1H, 2×d, *J* = 10.8 Hz, CH(HCH)N); 3.60 and 3.76 (2×1H, 2×d, *J* = 11.1 Hz, (HCH)Cl); 3.81 (3H, s, CH₃O); 4.40 and 4.46 (2×1H, 2×d, *J* = 14.6 Hz, N(HCH)C$_{quat,arom}$); 6.88 (2×1H, 2×d, *J* = 8.6 Hz, 2×CH$_{arom}$); 6.19 (2×1H, 2×d, *J* = 8.6 Hz, 2×CH$_{arom}$). **¹³C NMR** (100 MHz, ref = CDCl₃): δ 23.5 (CH₃); 48.1 (NCH₂C$_{quat}$); 50.8 (C$_{quat}$S); 51.3 (CH₂Cl); 55.3 (CH₃O); 56.0 (CH₂NC$_{quat}$S); 114.3 (2×CH$_{arom}$); 127.7 (C$_{quat,arom}$); 129.6 (2×CH$_{arom}$); 159.4 (C$_{quat,arom}$); 170.0 (C$_{quat}$O). **IR (cm⁻¹)**: ν$_{C=O}$ = 1676; ν$_{max}$ = 2934, 2837, 1611, 1512, 1408, 1296, 1248, 1213, 1200, 1175, 1034, 818, 664, 602. **MS (70 eV)**: *m/z* (%): 286/288 (M⁺+1, 100). **HRMS (ESI)**: *m/z* calcd for C₁₃H₁₇ClNO₂S: 286.0663 [*M*+H]⁺; found: 286.0673.
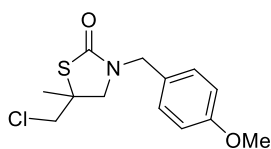
Synthesis of *trans*-1-benzyl-2-(4-chlorophenyl)-3-(thiocyanatomethyl)aziridine 12

To an ice-cooled solution of *trans*-1-benzyl-2-(4-chlorophenyl)-3-(hydroxymethyl)aziridine **4a** (819 mg, 3 mmol) in dry CH₂Cl₂ (30 mL), 4-(dimethylamino)pyridine (37 mg, 0.3 mmol, 0.1 equiv), Et₃N (333 mg, 3.3 mmol, 1.1 equiv) and tosylchloride (602 mg, 3.15 mmol, 1.05 equiv) were added, after which the mixture was stirred for 4 hours at room temperature. Afterward, the reaction mixture was washed with brine (2 × 10 mL) and a saturated NaHCO₃ solution (2 × 10 mL). The aqueous phase was extracted with CH₂Cl₂ (3 × 10 mL), after which the organic fraction was dried (MgSO₄), followed by removal of the drying agent and evaporation of the solvent *in vacuo*. In the next step, the crude reaction mixture was dissolved in dimethylformamide (20 mL), and potassium thiocyanate (292 mg, 3 mmol, 1 equiv) was added at room temperature, after which the resulting solution was stirred for 15 hours at 65 °C. The

cooled reaction mixture was poured into brine (50 mL) and extracted with diethyl ether (3 × 40 mL). The combined organic phases were washed with a LiCl-solution (1M in H_2O, 3 × 20 mL) and dried with $MgSO_4$. Filtration of the drying agent and evaporation of the solvent afforded *trans*-1-benzyl-2-(4-chlorophenyl)-3-(thiocyanatomethyl)aziridine **12**. Reversed phase column chromatographic separation isolated the pure compound in 52% yield (490 mg, 1.56 mmol) as a yellow oil (CH_3CN/H_2O: 3 CV 45% CH_3CN, 30 CV 45-70% CH_3CN). NMR analysis ($CDCl_3$) of aziridine **12** appeared to be impossible due to unclear resolutions of the corresponding signals.
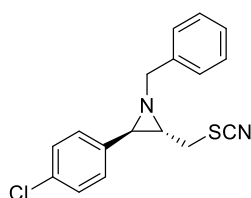
IR (cm⁻¹): 3028, 2980, 2845, 2153, 1493, 1452, 1429, 1395, 1356, 1242, 1090, 1015, 835, 783, 733, 696, 606. **MS (70 eV)**: *m/z* (%): 315/317 (M⁺+1, 100).

Synthesis of *trans*-1-benzyl-2-phenyl-3-(thiocyanatomethyl)aziridine 16 and (2*R**,1'*S**)-1-benzyl-2-[phenyl(thiocyanato)methyl]aziridine 17

To an ice-cooled solution of *trans*-1-benzyl-3-hydroxymethyl-2-phenylaziridine **4b** (717 mg, 3 mmol) in dry CH_2Cl_2 (30 mL), 4-(dimethylamino)pyridine (37 mg, 0.3 mmol, 0.1 equiv), Et_3N (333 mg, 3.3 mmol, 1.1 equiv) and tosylchloride (602 mg, 3.15 mmol, 1.05 equiv) were added, after which the mixture was stirred for 4 hours at room temperature. Afterward, the reaction mixture was washed with brine (2 × 10 mL) and a saturated $NaHCO_3$ solution (2 × 10 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL), after which the organic fraction was dried ($MgSO_4$), followed by removal of the drying agent and evaporation of the solvent *in vacuo* to afford *trans*-1-benzyl-2-phenyl-3-(tosyloxymethyl)aziridine **15**. In the next step, *trans*-1-benzyl-2-phenyl-3-(tosyloxymethyl)aziridine **15** (1.18 g, 3 mmol, 1 equiv) was dissolved in dimethylformamide (20 mL), and potassium thiocyanate (292 mg, 3 mmol, 1 equiv) was added at room temperature, after which the resulting solution was stirred for 15 hours at 65 °C. The cooled reaction mixture was poured into brine (50 mL) and extracted with diethyl ether (3 × 40 mL). The combined organic phases were washed with a LiCl-solution (1M in H_2O, 3 × 20 mL) and dried with $MgSO_4$. Filtration of the drying agent and evaporation of the solvent afforded *trans*-1-benzyl-2-phenyl-3-(thiocyanatomethyl)aziridine **16** and (2*R**,1'*S**)-1-benzyl-2-[phenyl(thiocyanato)methyl]aziridine **17** in a 55/45 ratio. Column chromatographic separation on silica gel was not successful, and both aziridines **16** and **17** were isolated as a mixture in a combined yield of 28% yield (235 mg, 0.84 mmol) and used as such in the next step. NMR analysis ($CDCl_3$) of aziridine **16** appeared to be impossible due to unclear resolutions of the corresponding signals.
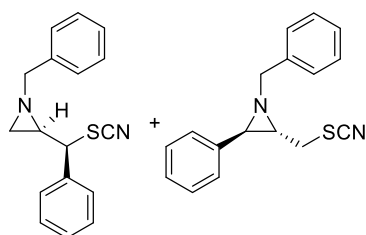
Yellow oil. R_f = 0.27 (Hexane/EtOAc 2/1). Yield 28%. Ratio of 55/45. **IR (cm⁻¹)**: 3063, 3030, 2986, 2849, 2154, 1497, 1454, 1028, 737, 700. **MS (70 eV)**: *m/z* (%): 281 (M⁺+1, 100).

Spectral data for (2*R**,1'*S**)-1-benzyl-2-[phenyl(thiocyanato)methyl]aziridine **17**:
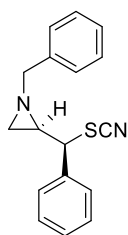
¹H NMR (400 MHz, CDCl₃): δ 1.78 (1H, d, *J* = 6.1 Hz, (HCH)CHN); 2.05 (1H, d, *J* = 3.2 Hz, (HCH)CHN); 2.24-2.29 (1H, m, CHN); 3.31 (1H, d, *J* = 13.2 Hz, N(HCH)C$_{quat,arom}$); 3.59 (1H, d, *J* = 13.2 Hz, N(HCH)C$_{quat,arom}$); 4.16 (1H, d, *J* = 7.8 Hz, CHS); 7.13-7.38 (10H, m, 10×CH$_{arom}$). **¹³C NMR** (100 MHz, ref = CDCl₃): δ 34.6 (CHCH₂N); 42.3 (CHN); 55.4 (CHS); 64.2 (NCH₂C$_{quat,arom}$); 111.4 (SCN); 127.19, 127.23, 127.9, 128.1, 128.3, 128.4, 128.9 and 129.0 (10×CH$_{arom}$); 136.0 (C$_{quat,arom}$); 138.0 (C$_{quat,arom}$).

Synthesis of *trans*-1-isopropyl-2-phenyl-3-(thiocyanatomethyl)aziridine 22 and (2*R**,1'*S**)-1-isopropyl-2-[phenyl(thiocyanato)methyl]aziridine 23

To an ice-cooled solution of *trans*-1-isopropyl-3-hydroxymethyl-2-phenylaziridine **4c** (573 mg, 3 mmol) in dry CH₂Cl₂ (30 mL), 4-(dimethylamino)pyridine (37 mg, 0.3 mmol, 0.1 equiv), Et₃N (333 mg, 3.3 mmol, 1.1 equiv) and tosylchloride (602 mg, 3.15 mmol, 1.05 equiv) were added, after which the mixture was stirred for 4 hours at room temperature. Afterward, the reaction mixture was washed with brine (2 × 10 mL) and a saturated NaHCO₃ solution (2 × 10 mL). The aqueous phase was extracted with CH₂Cl₂ (3 × 10 mL), after which the organic fraction was dried (MgSO₄), followed by removal of the drying agent and evaporation of the solvent *in vacuo*. In the next step, the crude reaction mixture was dissolved in dimethylformamide (20 mL), and potassium thiocyanate (292 mg, 3 mmol, 1 equiv) was added at room temperature, after which the resulting solution was stirred for 15 hours at 65 °C. The cooled reaction mixture was poured into brine (50 mL) and extracted with diethyl ether (3 × 40 mL). The combined organic phases were washed with a LiCl-solution (1M in H₂O, 3 × 20 mL) and dried with MgSO₄. Filtration of the drying agent and evaporation of the solvent afforded the corresponding isomeric *trans*-1-isopropyl-2-phenyl-3-(thiocyanatomethyl)aziridine **22** and (2*R**,1'*S**)-1-isopropyl-2-[phenyl(thiocyanato)methyl]aziridine **23** in a 30/70 ratio. Subsequent column chromatographic purification on silica gel afforded (2*R**,1'*S**)-1-isopropyl-2-[phenyl(thiocyanato)methyl]aziridine **23** only in 44% yield (306 mg, 1.32 mmol) as a white-yellow powder.

(2*R**,1'*S**)-1-Isopropyl-2-[phenyl(thiocyanato)methyl]aziridine 23

White-yellow powder. Mp 61 °C. R_f = 0.14 (Petroleumether/EtOAc 3/1). Yield 44%. **¹H NMR** (400 MHz, CDCl₃): δ 0.69 (3H, d, *J* = 6.2 Hz, CH₃CHCH₃); 1.04 (3H, d, *J* = 6.2 Hz, CH₃CHCH₃); 1.48 (1H, septet, *J* = 6.2 Hz, CH(CH₃)₂); 1.62 (1H, d, *J* = 6.1 Hz, (HCH)CHN); 1.96 (1H, d, *J* = 3.0 Hz, (HCH)CHN); 2.04-2.08 (1H, m, CHNCHS); 4.04 (1H, d, *J* = 8.5 Hz, CHS); 7.34-7.43 (5H, m, 5×CH$_{arom}$). **¹³C NMR** (100 MHz, ref = CDCl₃): δ 21.7 (CH₃CHCH₃); 21.9 (CH₃CHCH₃); 33.8 (CHCH₂N); 43.1 (CHNCHS); 55.9 (CHS); 60.7 (CH(CH₃)₂); 111.4 (SCN); 128.0 (2×CH$_{arom}$); 129.0 (2×CH$_{arom}$); 129.1 (CH$_{arom}$); 136.7 (C$_{quat,arom}$). **IR (cm⁻¹)**: ν$_{SCN}$ = 2154; ν$_{max}$ = 2968, 2930, 2870, 1495, 1454, 1383, 1367, 1341, 1180, 1001, 752, 698. **MS (70 eV)**: *m/z* (%): 233 (M⁺+1, 100).
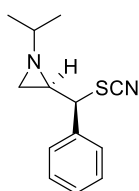
Synthesis of (2*R**,1'*R**)-2-[benzylamino(4-chlorophenyl)methyl]thiirane 13

A solution of *trans*-1-benzyl-2-(4-chlorophenyl)-3-(thiocyanatomethyl)aziridine **12** (628 mg, 2 mmol) was dissolved in dry THF (10 mL) at -78 °C and placed under argon atmosphere. Next, a solution of LiAlH$_4$ (3.4 mL, 3.4 mmol, 1.7 equiv, 1M in THF) was added dropwise through a syringe. Then, the resulting solution was stirred at -78 °C for 1 hour under argon atmosphere. Afterward, the reaction mixture was quenched with a minimum amount of brine to neutralize the excess of LiAlH$_4$. Then, an excess of MgSO$_4$ was added and the reaction mixture was filtered through a path of Celite®. Subsequently, the remaining solids on the filter were washed intensively with EtOAc (5 × 10 mL). Evaporation of the combined organic phases *in vacuo* afforded (2*R**,1'*R**)-2-[benzylamino(4-chlorophenyl)methyl]thiirane **13** in a yield of 88% (509 mg, 1.76 mmol) as a colorless oil. Purification by means of column chromatography on silica gel provided an analytically pure sample.

Colorless oil. R_f = 0.32 (Hexane/EtOAc 3/1). Yield 88%. **^{1}H NMR** (400 MHz, CDCl$_3$): δ 1.84 (1H, s (broad), NH); 2.42 (2H, d, J = 5.9 Hz, CH$_2$S); 3.13 (1H, d×d, J = 5.9, 5.8 Hz, CHS); 3.54 (1H, d, J = 13.4 Hz, N(HCH)C$_{quat,arom}$); 3.66 (1H, d, J = 5.8 Hz, CHN); 3.70 (1H, d, J = 13.4 Hz, N(HCH)C$_{quat,arom}$); 7.22-7.27 (1H, m, CH$_{arom}$); 7.22-7.37 (9H, m, 9×CH$_{arom}$). **^{13}C NMR** (100 MHz, ref = CDCl$_3$): δ 23.3 (CH$_2$S); 40.1 (CHS); 51.1 (NCH$_2$C$_{quat,arom}$); 63.8 (CHN); 127.1, 128.0, 128.5, 128.7 and 129.0 (9×CH$_{arom}$); 133.4, 140.0 and 140.1 (3×C$_{quat,arom}$). **IR (cm^{-1})**: v_{NH} = 3289; v_{max} = 3028, 2916, 2833, 1491, 1452, 1090, 1015, 826, 698, 611. **MS (70 eV)**: m/z (%): 290/292 (M$^+$+1, 100).
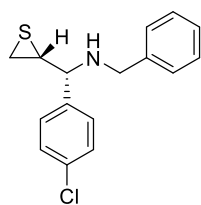
Synthesis of (2*R**,1'*R**)-2-[benzylamino(phenyl)methyl]thiirane 18 and *trans*-3-benzylaminomethyl-2-phenylthiirane 19

A solution of *trans*-1-benzyl-2-phenyl-3-(thiocyanatomethyl)aziridine **16** and (2*R**,1'*S**)-1-benzyl-2-[phenyl(thiocyanato)methyl]aziridine **17** in a 55/45 ratio (560 mg, 2 mmol) was dissolved in dry THF (10 mL) at -78 °C and placed under argon atmosphere. Next, a solution of LiAlH$_4$ (3.4 mL, 3.4 mmol, 1.7 equiv, 1M in THF) was added dropwise through a syringe. Then, the resulting solution was stirred at -78 °C for 1 hour under argon atmosphere. Afterward, the reaction mixture was quenched with a minimum amount of brine to neutralize the excess of LiAlH$_4$. Then, an excess of MgSO$_4$ was added and the reaction mixture was filtered through a path of Celite®. Subsequently, the remaining solids on the filter were washed intensively with EtOAc (5 × 10 mL). Evaporation of the combined organic phases *in vacuo* afforded (2*R**,1'*R**)-2-[benzylamino(phenyl)methyl]thiirane **18** and *trans*-3-benzylaminomethyl-2-phenylthiirane **19** in a 55/45 ratio and in a combined yield of 93% (474 mg, 1.96 mmol) as a colorless oil. Attempted purification by means of column chromatography on silica gel did not result in separation of the isomeric thiiranes and, as a consequence, the obtained mixture (without further purification) was used as such in the next step.

Spectral data for (2*R**,1'*R**)-2-[benzylamino(phenyl)methyl]thiirane **18**:
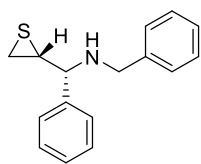
¹H NMR (400 MHz, CDCl₃): δ 1.79 (1H, s (broad), NH); 2.42-2.44 (1H, m, (H̲CH)S); 2.48 (1H, ~d, *J* = 5.6 Hz, (HCH̲)S); 3.17-3.22 (1H, m, CHS); 3.57 (1H, d, *J* = 13.2 Hz, N(H̲CH)C$_{quat,arom}$); 3.70 (1H, d, *J* = 5.7 Hz, CHN); 3.71 (1H, d, *J* = 13.2 Hz, N(HCH̲)C$_{quat,arom}$); 7.22-7.43 (10H, m, 10×CH$_{arom}$).

Spectral data for *trans*-3-benzylaminomethyl-2-phenylthiirane **19**:
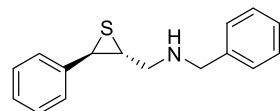
¹H NMR (400 MHz, CDCl₃): δ 1.79 (1H, s (broad), NH); 2.83 (1H, d×d, *J* = 12.6, 6.6 Hz, CHS(H̲CH)N); 3.17-3.22 (1H, m, CHS(HCH̲)N); 3.31-3.35 (1H, m, C̲HSCH₂N); 3.73 (1H, d, *J* = 5.4 Hz, CHPh); 3.85 (1H, d, *J* = 13.2 Hz, N(H̲CH)C$_{quat,arom}$); 3.89 (1H, d, *J* = 13.2 Hz, N(HCH̲)C$_{quat,arom}$); 7.24-7.35 (10H, m, 10×CH$_{arom}$).

Spectral data for the mixture of (2*R**,1'*R**)-2-[benzylamino(phenyl)methyl]thiirane **18** and *trans*-3-benzylaminomethyl-2-phenylthiirane **19**:

Yellow oil. Yield 93%. Ratio of 55/45. **¹³C NMR** (100 MHz, ref = CDCl₃): δ 23.4 (CH₂S); 40.4 (C̲HSCH₂S); 42.5 (CH(S)Ph); 44.1 (C̲HSCH(S)Ph); 51.2 (NC̲H₂C$_{quat,arom}$); 53.5 (NC̲H₂C$_{quat,arom}$); 53.8 (C̲H₂NCHS); 64.3 (CH(N)Ph); 126.9, 127.0, 127.1, 127.6, 127.7, 127.8, 128.06, 128.07, 128.4, 128.55 and 128.59 (20×CH$_{arom}$); 138.7, 140.0, 140.2 and 141.7 (4×C$_{quat,arom}$). **IR (cm⁻¹)**: v_{NH} = 3296; v_{max} = 3024, 2920, 2826, 1601, 1493, 1450, 1198, 1155, 1117, 1072, 1028, 966, 912, 735, 694. **MS (70 eV)**: *m/z* (%): 256 (M⁺+1, 100), 224 (46).

Synthesis of *trans*-3-isopropylaminomethyl-2-phenylthiirane 24

A solution of (2*R**,1'*S**)-1-isopropyl-2-[phenyl(thiocyanato)methyl]aziridine **23** (464 mg, 2 mmol) was dissolved in dry THF (10 mL) at -78 °C and placed under argon atmosphere. Next, a solution of LiAlH₄ (3.4 mL, 3.4 mmol, 1.7 equiv, 1M in THF) was added dropwise through a syringe. Then, the resulting solution was stirred at -78 °C for 1 hour under argon atmosphere. Afterward, the reaction mixture was quenched with a minimum amount of brine to neutralize the excess of LiAlH₄. Then, an excess of MgSO₄ was added and the reaction mixture was filtered through a path of Celite®. Subsequently, the remaining solids on the filter were washed intensively with EtOAc (5 × 10 mL). Evaporation of the combined organic phases *in vacuo* afforded *trans*-3-isopropylaminomethyl-2-phenylthiirane **24** in a yield of 90% (373 mg, 1.80 mmol) as a colorless oil in acceptable purity (> 80%, based on ¹H NMR). Further purification by means of column chromatography on silica gel was not succesfull and, as a consequence, the obtained thiirane **24** was used as such in the next step.

Colorless oil. Purity > 80%. Yield 90%. **¹H NMR** (400 MHz, CDCl₃): δ 1.08 (2×3H, 2×d, *J* = 6.2 Hz, (CH₃)₂CH); 2.89 (1H, septet, *J* = 6.2 Hz, CH̲(CH₃)₂); 2.73 (1H, d×d, *J* = 12.4, 7.0 Hz, CHS(H̲CH)N); 3.24 (1H, d×d, *J* = 12.4, 5.0 Hz, CHS(HCH̲)N); 3.33 (1H, d×d×d, *J* = 7.0, 5.2, 5.0 Hz, C̲HSCH₂N); 3.73 (1H, d, *J* = 5.2 Hz, CHPh); 7.24-7.35 (5H, m, 5×CH$_{arom}$). **¹³C NMR** (100 MHz, ref = CDCl₃): δ 22.9 (C̲H₃CHCH₃); 23.1 (CH₃CHC̲H₃); 42.6 (CHPh); 44.5 (C̲HSCH₂N); 48.3 (C̲H(CH₃)₂); 52.2 (CH₂N); 126.9 (2×CH$_{arom}$); 127.7

(CH$_{arom}$); 128.6 (2×CH$_{arom}$); 138.7 (C$_{quat,arom}$). **IR (cm^{-1})**: ν$_{NH}$ = 3287; ν$_{max}$ = 2963, 1454, 1379, 1366, 1337, 1175, 1126, 1070, 1026, 760, 694, 665, 644, 610. **MS (70 eV)**: *m/z* (%): 176 (100), 208 (M$^+$+1, 36).

Synthesis of (4*R**,5*R**)-3-benzyl-5-chloromethyl-4-(4-chlorophenyl)thiazolidin-2-one 14

To a solution of (2*R**,1'*R**)-2-[benzylamino(4-chlorophenyl)methyl]thiirane **13** (578 mg, 2 mmol) in dry THF (10 mL), triphosgene (594 mg, 2 mmol, 1 equiv) was added at room temperature. Then, the resulting solution was stirred for 4 hours at reflux temperature. Afterward, the cooled reaction mixture was quenched with sat. NaHCO$_3$ (10 mL) and the aqueous phase was extracted with EtOAc (3 × 20 mL). Drying (MgSO$_4$), filtration of the drying agent, and evaporation of the solvent *in vacuo* afforded the crude product, which was purified by means of column chromatography on silica gel to afford (4*R**,5*R**)-3-benzyl-5-chloromethyl-4-(4-chlorophenyl)thiazolidin-2-one **14** in 71% yield (498 mg, 1.42 mmol) as a colorless oil.

Colorless oil. *R*$_f$ = 0.17 (Hexane/EtOAc 6/1). Yield 71%. **¹H NMR** (400 MHz, CDCl$_3$): δ 3.12 (1H, d×d, *J* = 11.3, 8.2 Hz, (<u>H</u>CH)Cl); 3.33 (1H, d×d, *J* = 11.3, 6.6 Hz, (HC<u>H</u>)Cl); 3.48 (1H, d, *J* = 14.9 Hz, N(<u>H</u>CH)C$_{quat,arom}$); 4.40 (1H, d×d×d, J = 8.2, 7.8, 6.6 Hz, CHS); 4.65 (1H, d, *J* = 7.8 Hz, CHN); 5.13 (1H, d, *J* = 14.9 Hz, N(HC<u>H</u>)C$_{quat,arom}$); 7.11-7.15 (2H, m, 2×CH$_{arom}$); 7.21-7.41 (7H, m, 7×CH$_{arom}$). **¹³C NMR** (100 MHz, ref = CDCl$_3$): δ 42.6 (CH$_2$Cl); 47.1 (N<u>C</u>H$_2$C$_{quat}$); 48.1 (CHS); 63.3 (CHN); 128.1, 128.3, 128.9 and 129.3 (9×CH$_{arom}$); 131.6, 135.50 and 135.54 (3×C$_{quat,arom}$); 170.3 (C$_{quat}$O). **IR (cm^{-1})**: ν$_{C=O}$ = 1676; ν$_{max}$ = 3030, 2953, 2918, 1491, 1393, 1215, 1198, 1092, 1015, 841, 702. **MS (70 eV)**: *m/z* (%): 352/354/356 (M$^+$+1, 100). **HRMS (ESI)**: *m/z* calcd for C$_{17}$H$_{16}$Cl$_2$NOS: 352.0324 [*M*+H]$^+$; found: 352.0325.
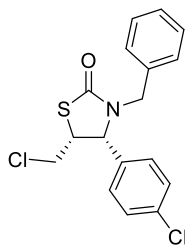
Synthesis of (4*R**,5*R**)-3-benzyl-5-chloromethyl-4-phenylthiazolidin-2-one 20 and (5*R**,1'*S**)-3-benzyl-5-[chloro(phenyl)methyl]thiazolidin-2-one 21

To a solution of (2*R**,1'*R**)-2-[benzylamino(phenyl)methyl]thiirane **18** and *trans*-3-benzylaminomethyl-2-phenylthiirane **19** in a 55/45 ratio (255 mg, 1 mmol) in dry THF (5 mL), triphosgene (297 mg, 1 mmol, 1 equiv) was added at room temperature. Then, the resulting solution was stirred for 4 hours at reflux temperature. Afterward, the cooled reaction mixture was quenched with sat. NaHCO$_3$ (5 mL) and the aqueous phase was extracted with EtOAc (3 × 10 mL). Drying (MgSO$_4$), filtration of the drying agent, and evaporation of the solvent *in vacuo* afforded (4*R**,5*R**)-3-benzyl-5-chloromethyl-4-phenylthiazolidin-2-one **20** and (5*R**,1'*S**)-3-benzyl-5-[chloro(phenyl)methyl]thiazolidin-2-one **21** in a 53/47 ratio. Purification and isolation by means of preparative TLC (SiO$_2$) afforded thiazolidin-2-one **20** as a colorless oil and thiazolidin-2-one **21** as a white powder, in respective yields of 33% (105 mg, 0.33 mmol) and 22% (70 mg, 0.22 mmol).

(4*R**,5*R**)-3-Benzyl-5-chloromethyl-4-phenylthiazolidin-2-one 20

Colorless oil. R_f = 0.26 (Hexane/EtOAc 6/1). Yield 33%. **¹H NMR** (400 MHz, CDCl₃): δ 3.16 (1H, d×d, J = 11.2, 7.7 Hz, (HCH)Cl); 3.26 (1H, d×d, J = 11.2, 7.3 Hz, (HCH)Cl); 3.49 (1H, d, J = 14.8 Hz, N(HCH)C_quat,arom); 4.37-4.43 (1H, m, CHS); 4.67 (1H, d, J = 7.8 Hz, CHN); 5.14 (1H, d, J = 14.8 Hz, N(HCH)C_quat,arom); 7.12-7.16 (2H, m, 2×CH_arom); 7.27-7.43 (8H, m, 8×CH_arom). **¹³C NMR** (100 MHz, ref = CDCl₃): δ 43.1 (CH₂Cl); 47.0 (NCH₂C_quat); 48.5 (CHS); 64.0 (CHN); 126.4, 128.0, 128.3, 128.4, 128.86, 128.94, 129.1, 129.3 and 129.5 (10×CH_arom); 133.1 (C_quat,arom); 135.7 (C_quat,arom); 170.6 (C_quat O). **IR (cm⁻¹)**: ν_C=O = 1665; ν_max = 3026, 2920, 2826, 1601, 1493, 1452, 1196, 1117, 1074, 1028, 910, 733, 694. **MS (70 eV)**: m/z (%): 318/320 (M⁺+1, 100). **HRMS (ESI)**: m/z calcd for C₁₇H₁₇ClNOS: 318.0714 [*M*+H]⁺; found: 318.0715.
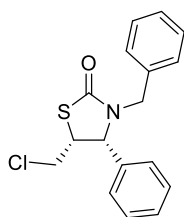
(5*R**,1'*S**)-3-Benzyl-5-[chloro(phenyl)methyl]thiazolidin-2-one 21

White powder. Mp 74 °C. R_f = 0.16 (Hexane/EtOAc 6/1). Yield 22%. **¹H NMR** (400 MHz, CDCl₃): δ 3.69 (1H, d×d, J = 10.9, 5.2 Hz, (HCH)N); 3.76 (1H, d×d, J = 10.9, 7.3 Hz, (HCH)N); 4.14 (1H, d×d×d, J = 10.7, 7.3, 5.2 Hz, CHS); 4.45 (1H, d, J = 14.7 Hz, N(HCH)C_quat,arom); 4.57 (1H, d, J = 14.7 Hz, N(HCH)C_quat,arom); 4.83 (1H, d, J = 10.7 Hz, CHCl); 7.34-7.38 (5H, m, 5×CH_arom). **¹³C NMR** (100 MHz, ref = CDCl₃): δ 48.3 (CHS); 48.7 (NCH₂C_quat,arom); 51.7 (CH₂NCHS); 64.6 (CHCl); 127.6 (2×CH_arom); 128.1 (CH_arom); 128.2 (2×CH_arom); 128.9 (2×CH_arom); 129.0 (2×CH_arom); 129.4 (CH_arom); 135.6 (C_quat,arom); 138.5 (C_quat,arom); 170.0 (C_quat O). **IR (cm⁻¹)**: ν_C=O = 1665; ν_max = 3032, 1632, 1495, 1412, 1356, 1217, 1196, 1163, 934, 764, 694, 681, 635, 606. **MS (70 eV)**: m/z (%): 318/320 (M⁺+1, 100). **HRMS (ESI)**: m/z calcd for C₁₇H₁₇ClNOS: 318.0714 [*M*+H]⁺; found: 318.0711.
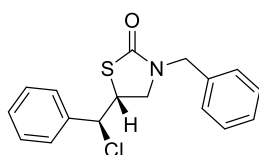
Synthesis of (5*R**,1'*S**)-3-isopropyl-5-[chloro(phenyl)methyl]thiazolidin-2-one 25

To a solution of *trans*-3-isopropylaminomethyl-2-phenylthiirane **24** (207 mg, 1 mmol) in dry THF (5 mL), triphosgene (297 mg, 1 mmol, 1 equiv) was added at room temperature. Then, the resulting solution was stirred for 4 hours at reflux temperature. Afterward, the cooled reaction mixture was quenched with sat. NaHCO₃ (5 mL) and the aqueous phase was extracted with EtOAc (3 × 10 mL). Drying (MgSO₄), filtration of the drying agent, and evaporation of the solvent *in vacuo* afforded (5*R**,1'*S**)-3-isopropyl-5-[chloro(phenyl)methyl]thiazolidin-2-one **25** in 95% yield (256 mg, 0.95 mmol) as a white powder. Purification by means of column chromatography on silica gel provided an analytically pure sample.

White powder. Mp 101 °C. R_f = 0.12 (Hexane/EtOAc 6/1). Yield 95%. **¹H NMR** (400 MHz, CDCl₃): δ 1.21 (3H, d, J = 6.8 Hz, CH₃CHCH₃); 1.23 (3H, d, J = 6.8 Hz, CH₃CHCH₃); 3.82 (2H, d, J = 5.7 Hz, CH₂N); 4.38 (1H, septet, J = 6.8 Hz, CH(CH₃)₂); 4.14 (1H, d×t, J = 10.9, 5.7 Hz, CHS); 4.86 (1H, d, J = 10.9 Hz, CHCl); 7.34-7.38 (5H, m, 5×CH_arom). **¹³C NMR** (100 MHz, ref = CDCl₃): δ 19.8 (CH₃CHCH₃); 20.1 (CH₃CHCH₃); 45.5 (CHS); 47.2 (CH₂N); 48.5 (CHN); 64.4 (CHCl); 127.7 (2×CH_arom); 128.9 (2×CH_arom); 129.3 (CH_arom); 138.6 (C_quat,arom); 169.1 (C_quat O). **IR (cm⁻¹)**: ν_C=O = 1672; ν_max = 2974, 2934, 2876, 1456, 1412, 1368, 1204, 698. **MS (70 eV)**: m/z (%): 270/272 (M⁺+1, 100). **HRMS (ESI)**: m/z calcd for C₁₃H₁₇ClNOS: 270.0714 [*M*+H]⁺; found: 270.0710.
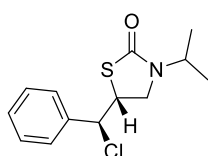
Synthesis of 3-(4-chlorobenzyl)-5-methylthiazolin-2-one 27

A mixture of 3-(4-chlorobenzyl)-5-(chloromethyl)thiazolidin-2-one **7c** (275 mg, 1 mmol) and potassium *tert*-butoxide (110 mg, 1.02 mmol, 1.02 equiv) in DMSO (15 mL) was heated for 2 days at 100 °C. The cooled reaction mixture was poured into brine (20 mL) and extracted with diethyl ether (3 × 30 mL). The combined organic extracts were washed with a LiCl-solution (1M in H_2O, 3 × 20 mL) and dried ($MgSO_4$). Filtration of the drying agent and removal of the solvent *in vacuo* afforded 3-(4-chlorobenzyl)-5-methylthiazolin-2-one **27** in 91% yield (217 mg, 0.91 mmol) as a white powder. Purification by means of preparative TLC (SiO_2) provided an analytically pure sample.

White powder. Mp 103 °C. R_f = 0.12 (Hexane/EtOAc 9/1). Yield 91%. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.10 (3H, d, *J* = 1.4 Hz, CH_3); 4.78 (2H, s, CH_2); 6.14 (1H, q, *J* = 1.4 Hz, CHN); 7.20 (2×1H, 2×d, *J* = 8.4 Hz, 2×CH_{arom}); 7.32 (2×1H, 2×d, *J* = 8.4 Hz, 2×CH_{arom}). **^{13}C NMR** (100 MHz, ref = $CDCl_3$): δ 13.9 (CH_3); 47.6 (CH_2); 114.6 ($\underline{C}_{quat}CH_3$); 119.4 (CHN); 129.1 and 129.2 (4×CH_{arom}); 134.0 and 134.7 (2×$C_{quat,arom}$); 171.9 ($C_{quat}O$). **IR (cm^{-1})**: $v_{C=O}$ = 1655, 1622; v_{max} = 3084, 2947, 2920, 1493, 1437, 1335, 1223, 1142, 1096, 1020, 847, 802, 731, 665, 610. **MS (70 eV)**: *m/z* (%): 240/242 (M$^+$+1, 100). **HRMS (ESI)**: *m/z* calcd for $C_{11}H_{11}ClNOS$: 240.0244 [*M*+H]$^+$; found: 240.0250.
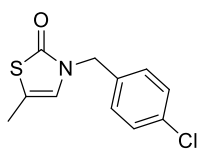
Synthesis of 3-(4-chlorobenzyl)-5-(thiocyanatomethyl)thiazolidin-2-one 28

A mixture of 3-(4-chlorobenzyl)-5-(chloromethyl)thiazolidin-2-one **7c** (275 mg, 1 mmol) and potassium thiocyanate (194 mg, 2 mmol, 2 equiv) in DMF (5 mL) was placed in a 10 mL sealed glass vessel, provided with an appropriate stirring bar and subjected to microwave conditions (100 °C, 10 hours). Afterward, the cooled reaction mixture was poured into brine (10 mL) and extracted with diethyl ether (3 × 20 mL). The combined organic extracts were washed with LiCl-solution (1M in H_2O, 3 × 20 mL) and dried ($MgSO_4$). Filtration of the drying agent and removal of the solvent *in vacuo* afforded 3-(4-chlorobenzyl)-5-(thiocyanatomethyl)thiazolidin-2-one **28** in 87% yield (259 mg, 0.87 mmol) as a colorless oil. Purification by means of preparative TLC (SiO_2) provided an analytically pure sample.

Colorless oil. R_f = 0.07 (Hexane/EtOAc 5/1). Yield 87%. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 3.51 (1H, d×d, *J* = 10.8, 3.1 Hz, CH($\underline{H}$CH)N); 3.56 (1H, d×d, *J* = 10.9, 10.5 Hz, ($\underline{H}$CH)Cl); 3.62 (1H, d×d, *J* = 10.8, 7.1 Hz, CH(HC$\underline{H}$)N); 3.67 (1H, d×d, *J* = 10.9, 4.3 Hz, (HC$\underline{H}$)Cl); 3.77 (1H, d×d×d×d, *J* = 10.5, 7.1, 4.3, 3.1 Hz, CHS); 4.44 (1H, d, *J* = 14.9 Hz, N($\underline{H}$CH)C_{quat}); 4.49 (1H, d, *J* = 14.9 Hz, N(HC$\underline{H}$)C_{quat}); 7.21 (2×1H, 2×d, *J* = 8.4 Hz, 2×CH_{arom}); 7.34 (2×1H, 2×d, *J* = 8.4 Hz, 2×CH_{arom}). **^{13}C NMR** (100 MHz, ref = $CDCl_3$): δ 42.0 (CHS); 45.7 (CH_2Cl); 48.0 (N$\underline{C}H_2C_{quat}$); 50.4 (CH$\underline{C}H_2$N); 129.2 and 129.5 (4×CH_{arom}); 134.0 and 134.1 (2×$C_{quat,arom}$); 170.0 ($C_{quat}O$). **IR (cm^{-1})**: v_{SCN} = 2154; $v_{C=O}$ = 1665; v_{max} = 2928, 2876, 1491, 1474, 1402, 1248, 1194, 1092, 1015, 800, 727, 646. **MS (70 eV)**: *m/z* (%): 299/301 (M$^+$+1, 100). **HRMS (ESI)**: *m/z* calcd for $C_{12}H_{12}ClN_2OS_2$: 299.0074 [*M*+H]$^+$; found: 299.0075.
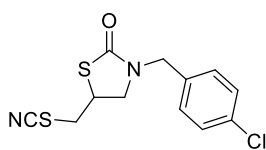
Synthesis of 3-(4-chlorobenzyl)-5-(iodomethyl)thiazolidin-2-one 29

A mixture of 3-(4-chlorobenzyl)-5-(chloromethyl)thiazolidin-2-one **7c** (138 mg, 0.50 mmol) and sodium iodide (300 mg, 2 mmol, 4 equiv) in acetone (5 mL) was placed in a 10 mL sealed glass vessel, provided with an appropriate stirring bar and subjected to microwave conditions (100 °C, 12 hours). Afterward, the cooled reaction mixture was poured into brine (10 mL) and extracted with ethyl acetate (3 × 20 mL). The combined organic extracts were dried (MgSO₄), and filtration of the drying agent and removal of the solvent *in vacuo* afforded 3-(4-chlorobenzyl)-5-(iodomethyl)thiazolidin-2-one **29** in 87% yield (160 mg, 0.44 mmol) as a white solid. Purification by means of preparative TLC (SiO₂) provided an analytically pure sample.

White powder. Mp 87 °C. R_f = 0.28 (Petroleumether/EtOAc 4/1). Yield 87%. **¹H NMR** (400 MHz, CDCl₃): δ 3.28 (1H, d×d, *J* = 10.8, 10.2 Hz, (HCH)I); 3.41 (1H, d×d, *J* = 10.7, 3.8 Hz, CH(HCH)N); 3.42 (1H, d×d, *J* = 10.2, 4.2 Hz, (HCH)I); 3.61 (1H, d×d, *J* = 10.7, 7.1 Hz, CH(HCH)N); 3.84 (1H, d×d×d×d, *J* = 10.8, 7.1, 4.2, 3.8 Hz, CHS); 4.46 (2H, s, NCH₂Cquat); 7.21 (2×1H, 2×d, *J* = 8.4 Hz, 2×CHarom); 7.34 (2×1H, 2×d, *J* = 8.4 Hz, 2×CHarom). **¹³C NMR** (100 MHz, ref = CDCl₃): δ 8.0 (CH₂I); 42.2 (CHS); 48.1 (NCH₂Cquat); 53.3 (CHCH₂N); 129.2 and 129.6 (4×CHarom); 134.0 and 134.1 (2×Cquat,arom); 170.2 (CquatO). **IR (cm⁻¹)**: νC=O = 1667; νmax = 3028, 2926, 2876, 1491, 1402, 1263, 1213, 1196, 1092, 1015, 800, 646. **MS (70 eV)**: *m/z* (%): 368/370 (M⁺+1, 100). **HRMS (ESI)**: *m/z* calcd for C₁₁H₁₂ClINOS: 367.9367 [*M*+H]⁺; found: 367.9371.
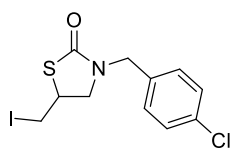
Synthesis of 3-(4-chlorobenzyl)-5-methylthiazolidine 32 and 2-[4-chlorobenzyl(methyl)aminomethyl]thiirane 33

A solution of 3-(4-chlorobenzyl)-5-(chloromethyl)thiazolidin-2-one **7c** (138 mg, 0.5 mmol) was dissolved in dry THF (10 mL) at -78 °C and placed under argon atmosphere. Next, a solution of LiAlH₄ (0.5 mL, 0.5 mmol, 1 equiv, 1M in THF) was added dropwise through a syringe. Then, the resulting solution was stirred at -78 °C for 3 hours under argon atmosphere. Afterward, the reaction mixture was quenched with a minimum amount of brine to neutralize the excess of LiAlH₄. Then, an excess of MgSO₄ was added and the reaction mixture was filtered through a path of Celite®. Subsequently, the remaining solids on the filter were washed intensively with EtOAc (5 × 10 mL). Evaporation of the combined organic phases *in vacuo* afforded 3-(4-chlorobenzyl)-5-methylthiazolidine **32** and 2-[4-chlorobenzyl(methyl)aminomethyl]thiirane **33** in a 30/70 ratio. Purification of the crude reaction mixture by means of preparative TLC (SiO₂) afforded 3-(4-chlorobenzyl)-5-methylthiazolidine **32** in 20% yield (24 mg, 0.10 mmol) as a colorless oil. When the applied reaction temperature was increased to room temperature (instead of -78 °C), 3-(4-chlorobenzyl)-5-methylthiazolidine **32** and 2-[4-chlorobenzyl(methyl)aminomethyl]thiirane **33** were obtained after 1 hour in a ratio of 18/82. Purification of the crude reaction mixture by means of preparative TLC (SiO₂) afforded 2-[4-chlorobenzyl(methyl)aminomethyl]thiirane **33** in 53% yield (64 mg, 0.27 mmol) as a colorless oil.

3-(4-Chlorobenzyl)-5-methylthiazolidine 32

Colorless oil. R_f = 0.26 (Hexane/EtOAc 9/1). Yield 20%. **^{1}H NMR** (400 MHz, CDCl$_3$): δ 1.38 (d, J = 6.5 Hz, CH$_3$); 2.48 (1H, d×d, J = 12.0, 8.8 Hz, CH(HC<u>H</u>)N); 3.26 (1H, d×d×d, J = 12.0, 6.0 Hz, J_{long} = 1.6 Hz, CH(HC<u>H</u>)N); 3.60 (1H, d, J = 13.2 Hz, N(<u>H</u>CH)C$_{quat}$); 3.64-3.71 (2H, m, N(HC<u>H</u>)C$_{quat}$ and CHS); 3.93 (1H, d×d, J = 9.2 Hz, J_{long} = 1.6 Hz, S(<u>H</u>CH)N); 4.19 (1H, d, J = 9.2 Hz, S(HC<u>H</u>)N); 7.28-7.34 (4H, m, 4×CH$_{arom}$). **^{13}C NMR** (100 MHz, ref = CDCl$_3$): δ 20.6 (CH$_3$); 42.0 (CHS); 57.1 (N<u>C</u>H$_2$C$_{quat}$); 60.3 (SCH$_2$N); 65.3 (CH<u>C</u>H$_2$N); 128.6 (2×CH$_{arom}$); 130.2 (2×CH$_{arom}$); 133.1 (C$_{quat,arom}$); 137.2 (C$_{quat,arom}$). **IR (cm^{-1})**: v_{max} = 2955, 2920, 2862, 2801, 1489, 1443, 1227, 1088, 1045, 1015, 862, 841, 800, 689, 664. **MS (70 eV)**: m/z (%): 228/230 (M$^+$+1, 100).
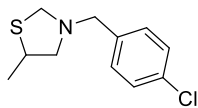
2-[4-Chlorobenzyl(methyl)aminomethyl]thiirane 33

Colorless oil. R_f = 0.14 (Hexane/EtOAc 9/1). Yield 53%. **^{1}H NMR** (400 MHz, CDCl$_3$): δ 2.12 (1H, d×d, J = 5.5, 1.1 Hz, (<u>H</u>CH)S); 2.33 (3H, s, CH$_3$); 2.51-2.56 (2H, m, (HC<u>H</u>)S and CH(<u>H</u>CH)N); 2.75 (1H, d×d, J = 13.2, 5.6 Hz, CH(HC<u>H</u>)N); 2.95-3.01 (1H, m, CHS); 3.55 (1H, d, J = 13.4 Hz, N(<u>H</u>CH)C$_{quat}$); 3.58 (1H, d, J = 13.4 Hz, N(HC<u>H</u>)C$_{quat}$); 7.25-7.30 (4H, m, 4 × CH$_{arom}$). **^{13}C NMR** (100 MHz, ref = CDCl$_3$): δ 24.7 (CH$_2$S); 31.8 (CHS); 42.5 (CH$_3$N); 61.5 (N<u>C</u>H$_2$C$_{quat}$); 63.1 (CH<u>C</u>H$_2$N); 128.4 (2×CH$_{arom}$); 130.2 (2×CH$_{arom}$); 132.7 (C$_{quat,arom}$); 137.3 (C$_{quat,arom}$). **IR (cm^{-1})**: v_{max} = 2843, 2791, 1489, 1454, 1406, 1086, 1043, 1013, 860, 835, 800, 619, 615. **MS (70 eV)**: m/z (%): 228/230 (M$^+$+1, 100).
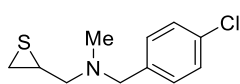
Single crystal X-ray diffraction

X-ray analysis was performed by Prof. Kristof Van Hecke (XStruct, Department of Inorganic and Physical Chemistry, Faculty of Sciences, Ghent University).

For the structure of (5R*,1'S*)-3-isopropyl-5-[chloro(phenyl)methyl]thiazolidin-2-one **25**, X-ray intensity data were collected at 100 K on an Agilent Supernova Dual Source (Cu at zero) diffractometer equipped with an Atlas CCD detector using ω scans and CuKα (λ = 1.54184 Å) radiation. The images were interpreted and integrated with the program CrysAlisPro. Using Olex2, the structure was solved by direct methods using the ShelXS structure solution program and refined by full-matrix least-squares on F^2 using the ShelXL program package. Non-hydrogen atoms were anisotropically refined and the hydrogen atoms in the riding mode and isotropic temperature factors fixed at 1.2 times U(eq) of the parent atoms (1.5 times for methyl groups).

The asymmetric unit contains two crystallographic independent molecules, which show opposite chirality at C7 (R), C8 (S) and C20A (S), C21A (R) for the first and second molecule, respectively. But obviously, because of the centro-symmetric space group, also the inverse configuration is present in the crystal structure. Additionally, the second molecule in the asymmetric unit shows a positional disorder with the inverse configuration at C20B (R), C21B (S). The disorder could be modeled in two parts with refined occupancy factors of 0.715(3) and 0.285(3).

CCDC 1536450 contains the supplementary crystallographic data for this paper and can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic

Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44-1223-336033; or deposit@ccdc.cam.ac.uk).

Crystal data for compound 25:

$C_{13}H_{16}ClNOS$, $M = 269.78$, monoclinic, space group $P2_1/c$ (No. 14), $a = 10.36538(10)$ Å, $b = 11.83391(9)$ Å, $c = 21.70290(17)$ Å, $\beta = 90.4084(8)°$, $V = 2662.08(4)$ Å^3, $Z = 8$, $T = 100$ K, $\rho_{calc} = 1.346$ g cm^{-3}, μ(Cu-Kα) = 3.867 mm^{-1}, $F(000) = 1136$, 28357 reflections measured, 5364 unique ($R_{int} = 0.0481$) which were used in all calculations. The final $R1$ was 0.0473 ($I > 2\sigma (I)$) and $wR2$ was 0.1294 (all data). The asymmetric unit contains two crystallographic independent molecules.

PERSPECTIVES

The ring rearrangement of non-activated aziridines, in which the aziridine nucleus is deployed as an electrophilic moiety and subjected to intramolecular ring opening upon reaction with an *in situ* generated nucleophilic heteroatom at a remote position, covered the major part of this PhD thesis. From the obtained results, it is clear that the synthetic potential of this underexplored ring-expansion methodology is very promising and, as a consequence, further elaboration of this strategy toward the construction of novel classes of heterocyclic systems is desirable.

In this doctoral thesis, 2-(2-cyanoethyl)aziridines were used as substrates in a $LiAlH_4$-induced ring rearrangement, providing a selective access to either 2-(aminomethyl)pyrrolidines or 3-aminopiperidines. Based on the same methodology, the potential use of 2-(ω-cyanoalkyl)azetidines **2** as the higher homologues of 2-(2-cyanoethyl)aziridines can be envisaged toward the preparation of pyrrolidines **3a** and piperidines **3b** (Scheme 1). In concreto, 2-(ω-cyanoalkyl)azetidines **2** can be prepared in a four-step protocol from the corresponding β-lactams **1**, obtained via Staudinger reaction between an alkoxyketene and the appropriate imine,[20c] followed by $LiAlH_4$-promoted rearrangement in the presence of $In(OTf)_3$ to afford novel 2-(2-aminoethyl)pyrrolidines **3a** and 2-(2-aminoethyl)piperidines **3b**. The pyrrolidine and piperidine systems are of paramount value to medicinal chemistry, and new approaches toward functionalized representatives will continue to attract the attention of the chemical society.
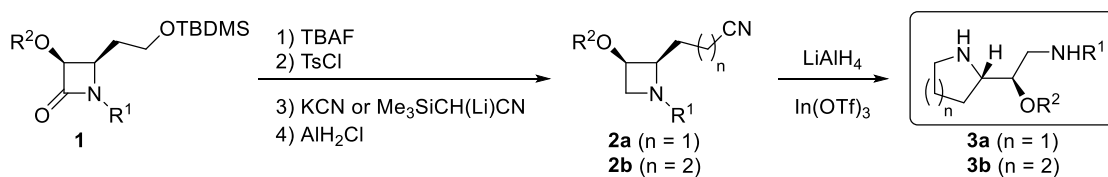
Scheme 1

The general ring-rearrangement concept can also be extended toward the construction of the oxygen counterparts of 2-(aminoalkyl)pyrrolidines and 3-amino(alkyl)-substituted piperidines. In that respect, 2-(2-cyanoethyl)aziridines **4** and 2-(ω-cyanoalkyl)azetidines **2** can be transformed into the corresponding aldehydes **5** (R^2 = H) and **10** (R^3 = H) via selective DIBAL-H-induced reduction of the cyano moiety on the one hand, or into ketones **5** (R^2 = alkyl, aryl) and **10** (R^3 = alkyl, aryl) via Grignard additions across the cyano group on the other hand (Scheme 2). Further $LiAlH_4$-induced ring rearrangement of 2-(3-oxoalkyl)aziridines **5** in the presence of $In(OTf)_3$ can lead to the formation of intermediate oxygen anions **6**, which might be rearranged into 2-(aminomethyl)oxolanes **7** or 3-aminooxanes **8** depending on the aziridine substitution pattern. 2-(Aminomethyl)oxolanes represent important substructures of S-adenosylmethionine (SAM) analogues, which have proven to be more stable than the natural co-factor SAM.[153] Moreover, desoxymuscarine **9**, accommodating a 2-(aminomethyl)tetrahydrofuran scaffold, is known to be a muscarine-receptor agonist.[154] Finally, 3-aminooxanes comprise valuable building blocks in the synthesis of aminoglycosides (e.g. streptomycine), which function as antibiotics against several bacteria.[155] In addition, the same ring-expansion strategy can be evaluated from azetidines **10**, providing access to either biologically interesting 2-(2-aminoethyl)-substituted tetrahydrofurans **11a** or

tetrahydropyrans **11b** depending on the substrate. 2,5-Disubstituted tetrahydrofurans **11a** (and **7**) have for example been reported in the literature as selective serotonin re-uptake inhibitors.[156]
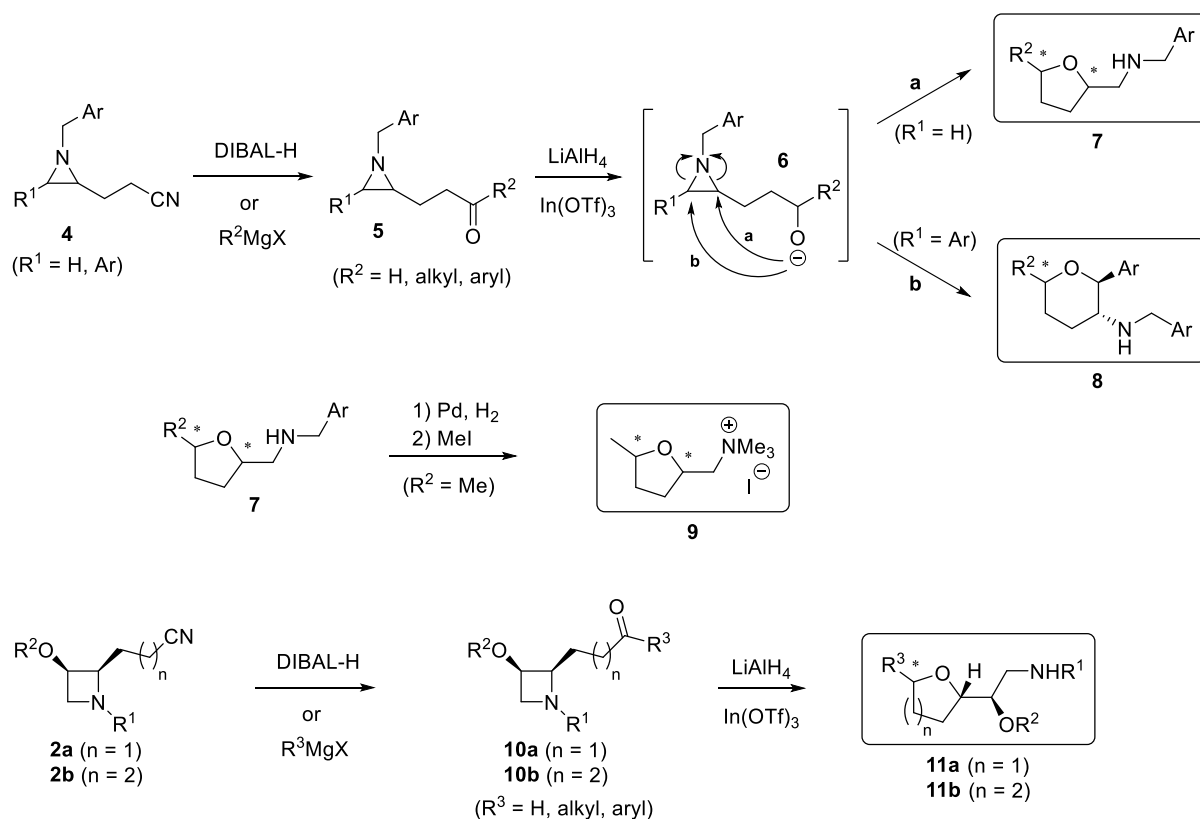
Scheme 2

Next to the presence of nitrogen and oxygen atoms in a wide variety of drugs, integration of sulfur atoms in therapeutic agents has also become an important challenge in medicinal chemistry[157] and, as a consequence, new entries toward thiaheterocyclic systems should be strongly aspired. To that end, the construction of amino(alkyl)-substituted thiolanes and thianes **14**, **15** and **17** starting from a variety of 2-(thioxoalkyl)aziridines **12** and -azetidines **16** can be envisaged (Scheme 3). Treatment of 2-(3-oxoalkyl)aziridines **5** and 2-(oxoalkyl)azetidines **10** with the Lawesson's reagent might lead to the synthesis of the corresponding 2-thioxoalkyl derivatives **12** and **16**, respectively. Subsequent addition of LiAlH$_4$ in the presence of In(OTf)$_3$ can finally lead to novel classes of functionalized thiaheterocycles **14**, **15** and **17**.

LR = Lawesson's reagent
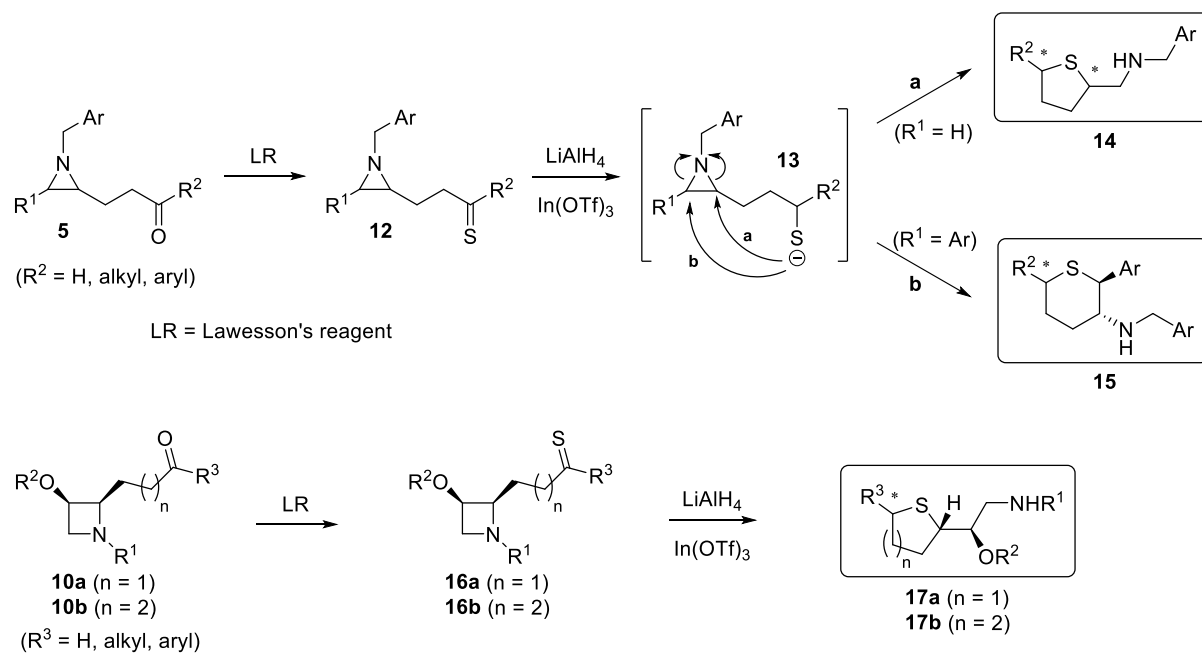
Scheme 3

SUMMARY

Efficient and selective syntheses of nitrogen-containing heterocycles (azaheterocycles) have attracted considerable attention from many synthetic and medicinal chemists due to their particular interest within the realm of organic and medicinal chemistry. Among many possible routes for their preparation, the strategy involving ring expansion of a small-ring system comprises an attractive way with many advantages. In that respect, the aziridine and azetidine moieties, both characterized by a high strain energy associated with the three- and four-membered ring system, have been widely recognized as valuable synthons toward the construction of a variety of azaheterocyclic target compounds. Depending on the nature of the *N*-substituent, *i.e.* an electron-withdrawing or electron-donating group, these small-ring substrates are classified into activated or non-activated aziridines/azetidines, according to whether or not nucleophilic ring-opening reactions require the activation toward an aziridinium/azetidinium intermediate.

The main part of known transformations of non-activated aziridines/azetidines into other (aza)heterocyclic systems is based on the nucleophilic interaction of the aziridine/azetidine nitrogen atom with an electrophilic moiety at a remote position. This results in the generation of strained 1-azabicyclo[m.n.0]alkane intermediates, which makes them very prone to nucleophilic attack toward ring-expanded products. On the other hand, the elaboration of an alternative approach, in which the aziridine/azetidine ring is considered as an electrophilic moiety suitable to undergo ring opening by a nucleophilic heteroatom present at a remote position within the same substrate, has been investigated to a far lesser extent in the chemical literature. In that respect, the feasibility of both ring-rearrangement strategies was considered in this PhD thesis starting from a broad variety of non-activated aziridines and azetidines.
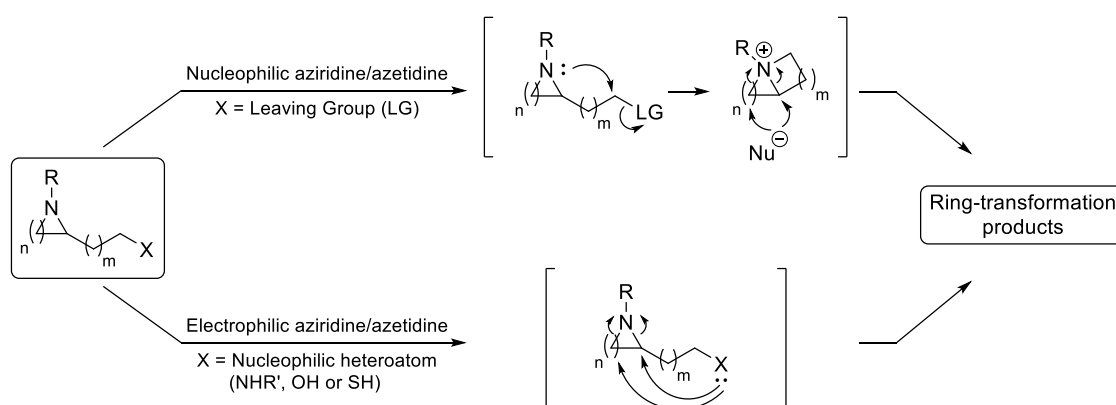
The preparation and synthetic utilization of bicyclic aziridinium salts was covered in a comprehensive literature overview in this work. Inspired by the versatile potential of these strained intermediates toward the construction of a broad library of polysubstituted azaheterocycles, efforts were devoted in a first part of this thesis to the deployment of enantiopure 2-(2,2,2-trifluoro-1-hydroxyethyl)azetidines **ii** and **iii** as substrates for this ring-expansion strategy. Azetidines **ii** and **iii** were easily accessible in a two-step protocol from the corresponding 4-formyl-β-lactams **i**, involving initial trifluoromethylation of the aldehyde moiety, followed by monochloroalane-induced selective removal of the carbonyl group. Importantly, the

addition of the CF₃ group across the aldehyde motif in 4-formyl-β-lactams **i** proceeded in a diastereoselective manner, as the (1'*S*)-azetidines **ii** were isolated as the major isomers. Subsequent sulfonylation of the hydroxyl group afforded the corresponding triflate-activated azetidines **iv** and **ix**, and remarkably, the ring-rearrangement aptitude of these azetidines appeared to be dependent on the stereochemistry of the exocyclic CF₃-substituted carbon atom. Whereas the major (1'*S*)-azetidines **iv** were easily converted to 3,4-disubstituted 2-(trifluoromethyl)pyrrolidines **v** with high diastereoselectivity upon reaction with a variety of nitrogen, oxygen, sulfur and fluorine nucleophiles, their diastereomeric counterparts (epimeric at 1' position) were not able to act as substrates for this type of ring rearrangement. Theoretical calculations performed at the Center for Molecular Modeling (UGent) suggested that the major (1'*S*)-azetidines **iv** are less stable than the minor (1'*R*)-azetidines **ix**. Also, the activation barrier toward the corresponding bicyclic aziridinium intermediates was higher in case of the minor (1'*R*)-azetidines **ix**. Representative pyrrolidines **v** were *N,O*-debenzylated in a selective way and used for further synthetic elaboration to produce e.g. a CF₃-substituted 2-oxa-4,7-diazabicyclo[3.3.0]octan-3-one system **viii**.
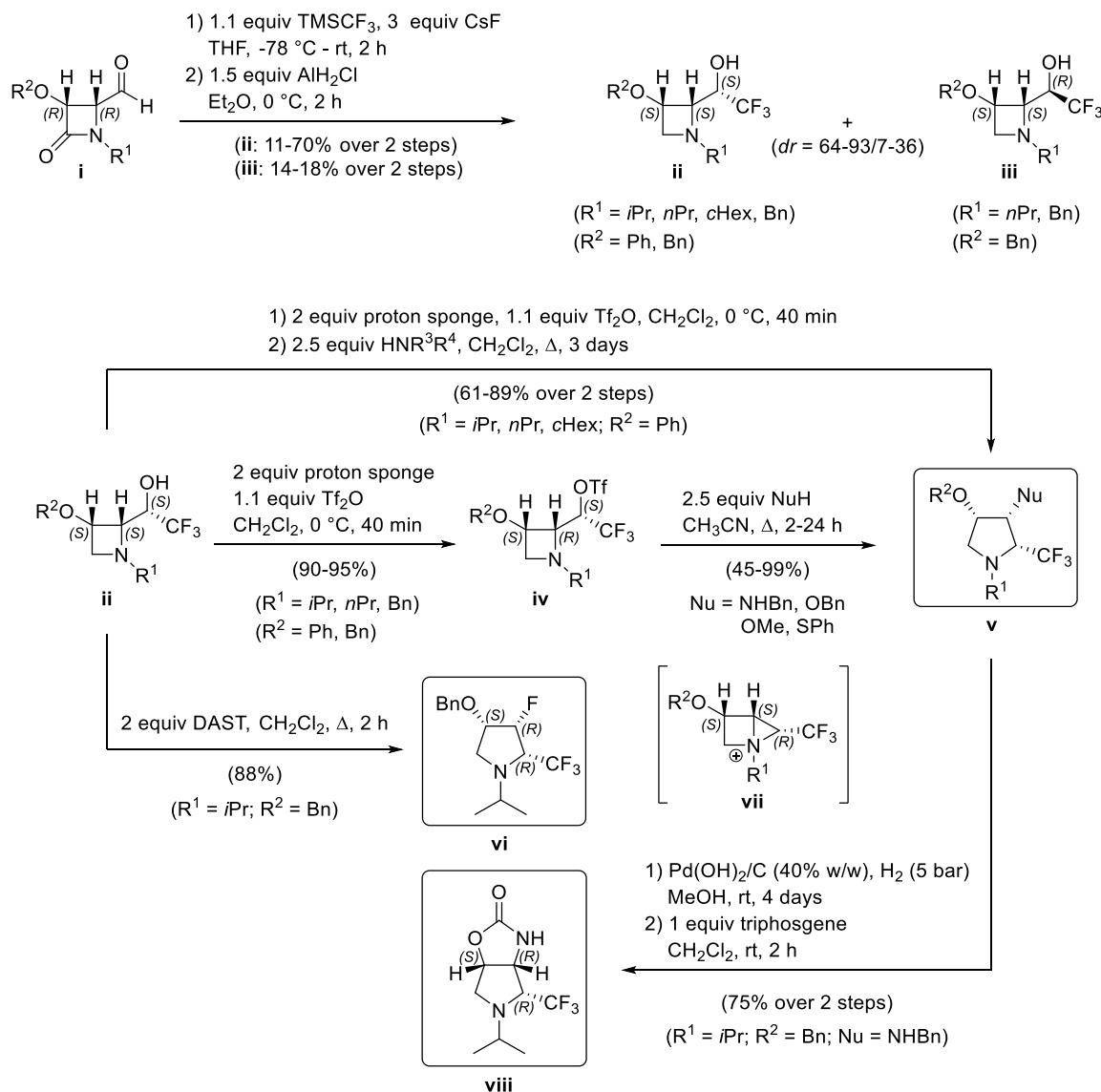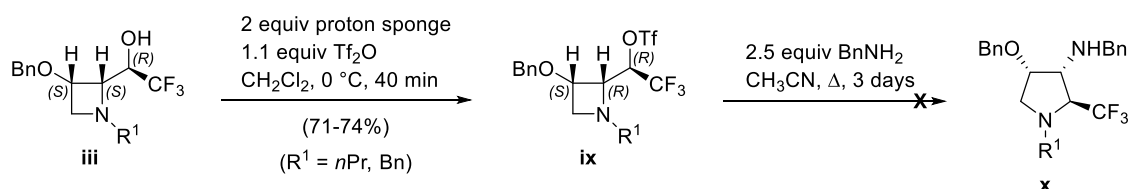
In the major part of this PhD thesis, the 'reversed' ring-expansion strategy was studied, involving the deployment of the aziridine/azetidine core as an electrophilic moiety. This alternate ring-rearrangement methodology was contemplated using three different classes of non-activated aziridines, *i.e.* 2-(2-cyanoethyl)aziridines **xiv**, 2-[2-(1-pyrrolin-2-yl)ethyl]aziridines **xv** and 2-(thiocyanatomethyl)aziridines **xvi**, which were prepared from the corresponding 2-(bromomethyl)aziridines **xi**, 2-bromomethyl-2-methylaziridines **xii** or 3-(tosyloxymethyl)aziridines **xiii** via displacement with the appropriate nucleophile (lithium trimethylsilylacetonitrile, lithiated 1-methyl-2-pyrroline or potassium thiocyanate).
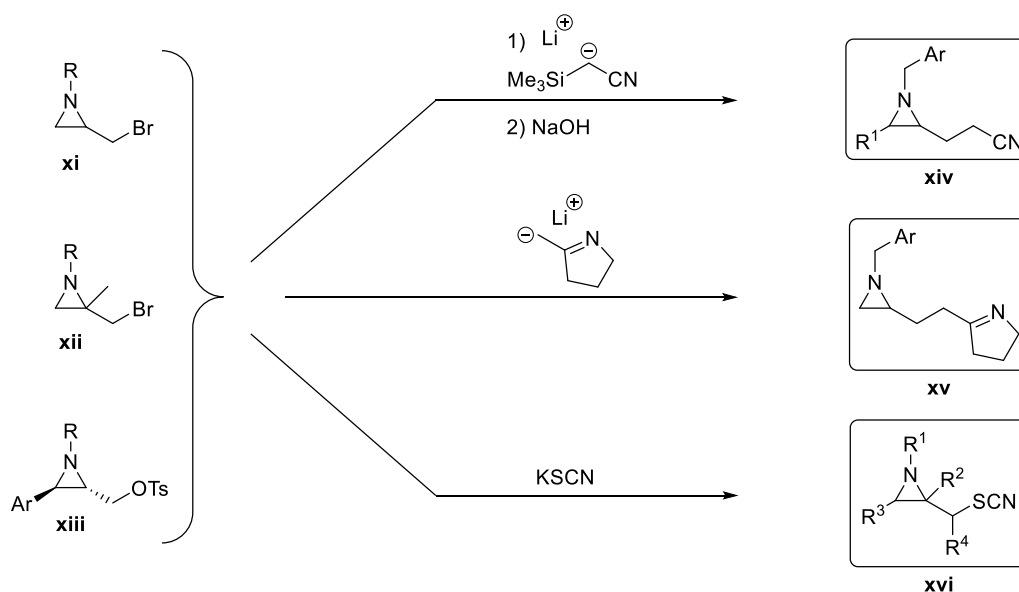
In a first objective of this alternative approach, 2-(2-cyanoalkyl)aziridines **xvii**, **xviii** and 3-(2-cyanoethyl)aziridines **xxi** were deployed for a LiAlH₄-promoted ring rearrangement. To that end, 2-(2-cyanoethyl)aziridines **xvii** were first mono- and dialkylated via deprotonation with LDA, followed by neutralization with an alkyl iodide toward 2-(2-cyanoalkyl)aziridines **xviii**. After a systematic screening of different Lewis acids to trigger the premised ring transformation, aziridines **xvii** and **xviii** were successfully converted into 2-(aminomethyl)pyrrolidines **xx** upon treatment with LiAlH₄ in the presence of In(OTf)₃. From a mechanistic point of view, the formation of 2-(aminomethyl)pyrrolidines **xx** is rationalized by initial hydride addition across the cyano moiety in 2-(2-cyanoalkyl)aziridines **xvii** and **xviii** providing iminyl anions **xix**, followed by ring opening of the aziridine core at the more-hindered carbon atom and hydride reduction of the corresponding cyclic intermediates. Importantly, the intramolecular ring opening of aziridines **xix** occurred in a regioselective way, which is in accordance

with the Baldwin's rules, *i.e.* a 5-*exo-tet* ring closure is favored whereas a 6-*endo-tet* is disfavored. Importantly, the introduction of an aromatic substituent on the aziridine moiety had a profound effect on the regioselectivity of the aziridine ring opening, as treatment of 2-aryl-3-(2-cyanoethyl)aziridines **xxi** with the same reaction conditions (LiAlH₄, In(OTf)₃) resulted in the generation of 3-aminopiperidines **xxiii**. The influence of the aryl group on the regioselectivity of the aziridine ring-opening process is explainable by the stabilization of the developing benzylic carbenium ion at C2, which surpasses the Baldwin's rules. As a consequence, the ring rearrangement of (2-cyanoethyl)aziridines can be controlled in a regioselective way, as 2-(2-cyanoethyl)aziridines **xvii** and **xviii** were converted into pyrrolidine scaffolds **xx** and 2-aryl-3-(2-cyanoethyl)aziridines **xxi**, bearing an aromatic substituent on the aziridine core, were transformed into piperidine skeletons **xxiii**.
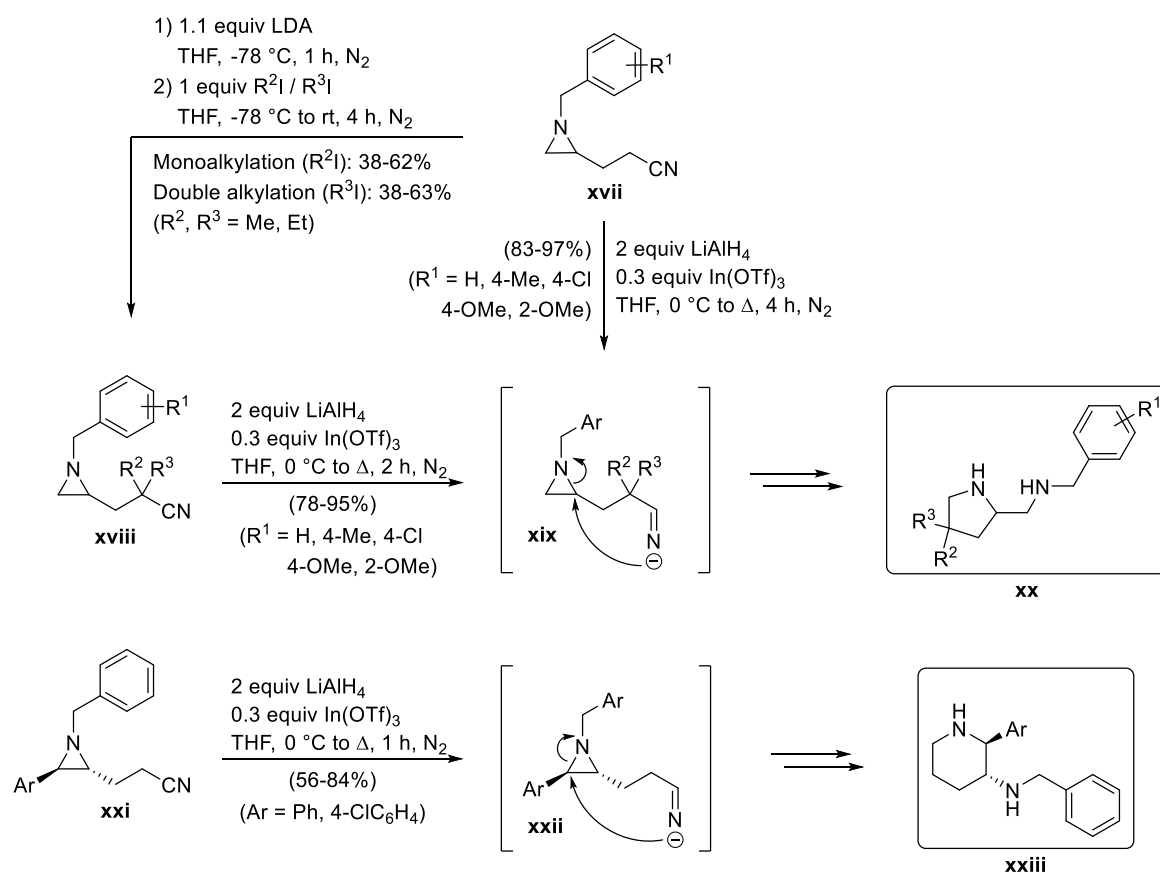
In a next step, the reactivity of the 1,2-diamino unit in the obtained azaheterocycles **xx** and **xxiii** was explored toward different coupling reagents. Therefore, a selection of 2-(aminomethyl)pyrrolidines **xx** and 3-aminopiperidines **xxiii** were transformed into bicyclic imidazolidinones **xxiv**, **xxvi** and diketopiperazines **xxv**, **xxvii** upon treatment with triphosgene, CDI, oxalylchloride or oxalyldiimidazole.
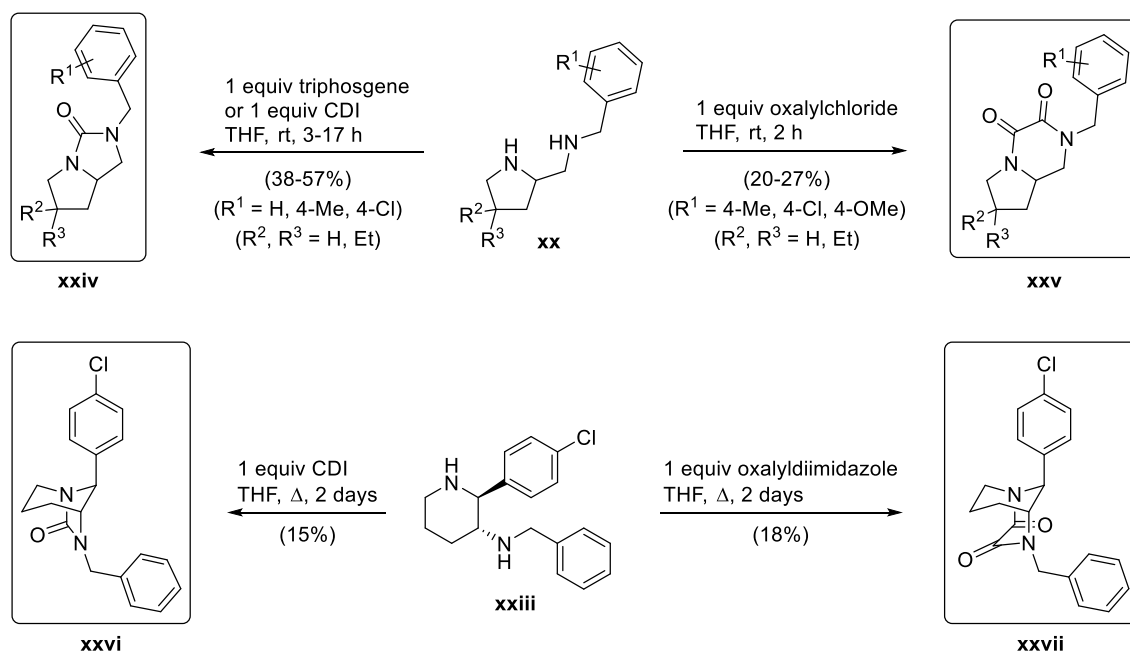
In a third part of this work, the developed ring rearrangement of (2-cyanoethyl)aziridines was further elaborated toward the construction of 1-azabicyclo[3.3.0]octanes, as these scaffolds represent important structural units in natural products and biologically active compounds. In that respect, 2-[2-(1-pyrrolin-2-yl)ethyl]aziridines **xv** and 2-[2-(1-pyrrolin-2-yl)alkyl]aziridines **xxxi** (obtained via alkylation of aziridinyl pyrrolines **xv** upon treatment with LDA, followed by quenching with an alkyl iodide) were transformed into *trans*- and *cis*-pyrrolizidines **xxviii** and **xxxii**. Column chromatographic purification allowed the isolation of the major *trans* isomers, exclusively. Mechanistically, In(OTf)$_3$-mediated regioselective ring opening of aziridines **xxix** affords bicyclic intermediates **xxx**, and consecutive nucleophilic attack across these *in situ* generated pyrrolizidinium salts gives rise to the formation of *trans*- and *cis*-pyrrolizidines **xxviii** and **xxxii**.
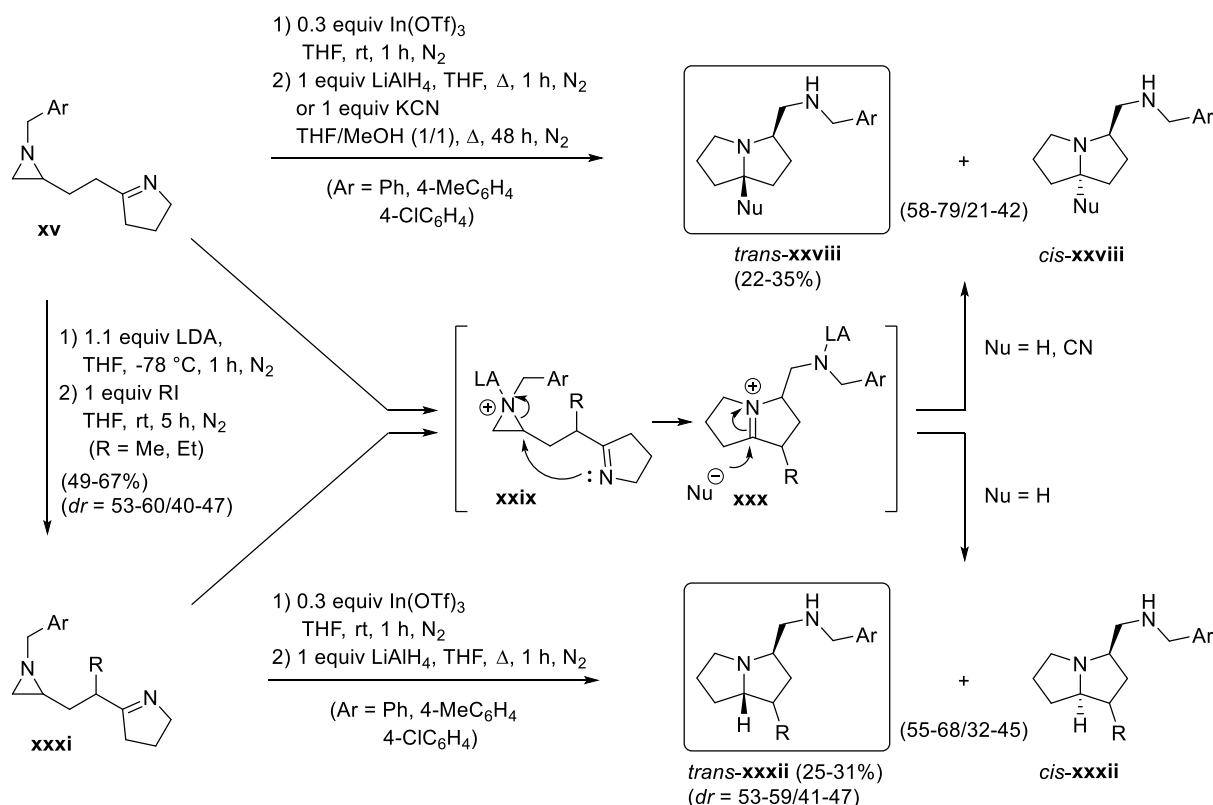
In a final part of this PhD thesis, non-activated 2-(thiocyanatomethyl)aziridines with diverse substitution patterns were deployed as synthons to effect a LiAlH$_4$-promoted ring rearrangement. To that end, monosubstituted 2-(thiocyanatomethyl)aziridines **xxxiii**, *gem*-disubstituted 2-methyl-2-(thiocyanatomethyl)aziridines **xxxvi** and *vic*-disubstituted *trans*-2-aryl-3-(thiocyanatomethyl)aziridines **xxxix** were converted via an unprecedented thia-aza-Payne rearrangement into new functionalized 2-(aminomethyl)thiiranes in a stereospecific way. The developed strategy is based on a hydride reduction of the thiocyanato moiety followed by intramolecular aziridine ring opening. Subsequent exposure of the obtained 2-(aminomethyl)episulfide intermediates **xxxiv**, **xxxvii** and **xl** to triphosgene resulted in the regioselective formation of 5-(chloromethyl)thiazolidin-2-ones **xxxv**, **xxxviii** and **xli**, respectively. In addition, the reactivity of 3-(4-chlorobenzyl)-5-(chloromethyl)thiazolidinone **xxxv** (R^1 = 4-ClC$_6$H$_4$CH$_2$, R^2 = H), as a representative example within the class of synthesized 5-(chloromethyl)thiazolidin-2-ones, was explored by application of substitution, elimination and reductive reaction procedures.

(R¹ = Bn, 4-MeC$_6$H$_4$CH$_2$, 4-ClC$_6$H$_4$CH$_2$, *i*Pr, *i*Bu, *c*HexCH$_2$)
(R² = H, Ph)

(R = H, Me, MeO)

(Ar = Ph, 4-ClC$_6$H$_4$)
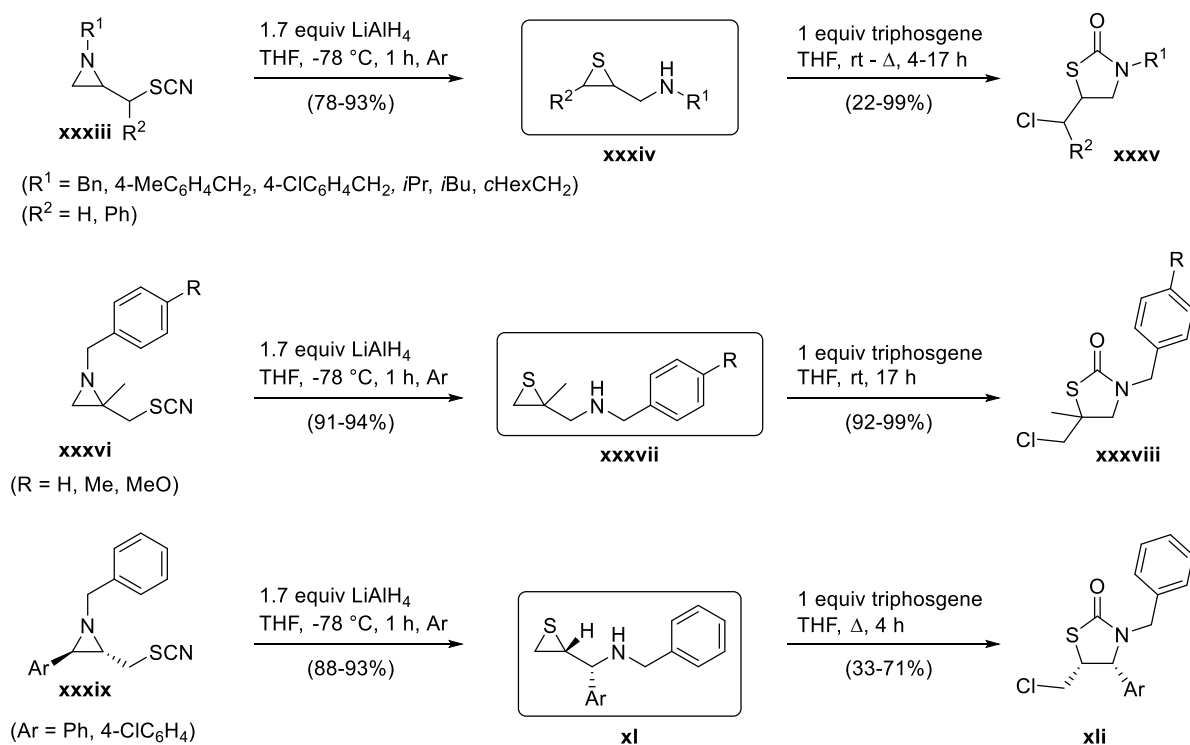
In this PhD thesis, a variety of functionalized non-activated aziridines and azetidines has successfully been deployed as fruitful synthons in different ring-expansion strategies toward the preparation of novel classes of five- and six-membered azaheterocycles. On the one hand, the use of 1-azabicyclo[m.n.0]alkanes has been illustrated by means of the elaboration of azetidines toward a vast number of enantiopure trifluoromethylated pyrrolidines. On the other hand, the 'reversed' ring-rearrangement methodology, in which the strain-loaded small ring is deployed as an electrophilic moiety, has been demonstrated by the conversion of polysubstituted aziridines into a broad library of interesting nitrogen-containing compounds. It is clear that the latter ring-transformation strategy should be recognized as a powerful method in modern organic chemistry, and that only a small part of its capacity has been uncovered in this thesis, making this an intriguing and promising area of research for further elaboration in the future.

SAMENVATTING

Efficiënte en selectieve synthesen van stikstofbevattende heterocyclische verbindingen hebben de aandacht van vele chemici getrokken omwille van hun bijzondere interesse binnen het domein van de organische en medicinale chemie. Onder de vele mogelijke routes voor hun aanmaak biedt de strategie met ringexpansie van een klein ringsysteem vele voordelen. In dat opzicht zijn aziridinen en azetidinen algemeen bekend als waardevolle bouwstenen voor de constructie van verscheidene azaheterocyclische doelverbindingen. Op basis van de aard van de *N*-substituent, dat wil zeggen een elektronenzuigende of elektronengevende groep, worden deze kleine ringsubstraten ingedeeld in geactiveerde of niet-geactiveerde aziridinen/azetidinen, afhankelijk of nucleofiele ringopeningsreacties al dan niet de activatie tot een aziridinium-/azetidiniumintermediair vereisen.

Het grootste deel van bekende transformaties van niet-geactiveerde aziridinen/azetidinen tot andere (stikstofbevattende) heterocyclische systemen is gebaseerd op de nucleofiele interactie van het aziridine-/azetidinestikstofatoom met een elektrofiele groep op een verdere positie. Dit resulteert in de vorming van gespannen en geladen 1-azabicyclo[m.n.0]alkaanintermediairen, waardoor ze zeer gevoelig zijn voor nucleofiele aanval met ringexpansieproducten tot gevolg. Anderzijds is de uitwerking van een alternatieve aanpak, waarbij de aziridine-/azetidinering wordt beschouwd als een elektrofiele groep die geschikt is om ringopening te ondergaan door een nucleofiel heteroatoom aanwezig op een verdere positie binnen hetzelfde substraat, in veel mindere mate onderzocht in de chemische literatuur. In dat opzicht werd de haalbaarheid van beide ringomleggingsstrategieën in dit proefschrift onderzocht, vertrekkende van een breed gamma aan niet-geactiveerde aziridinen en azetidinen.
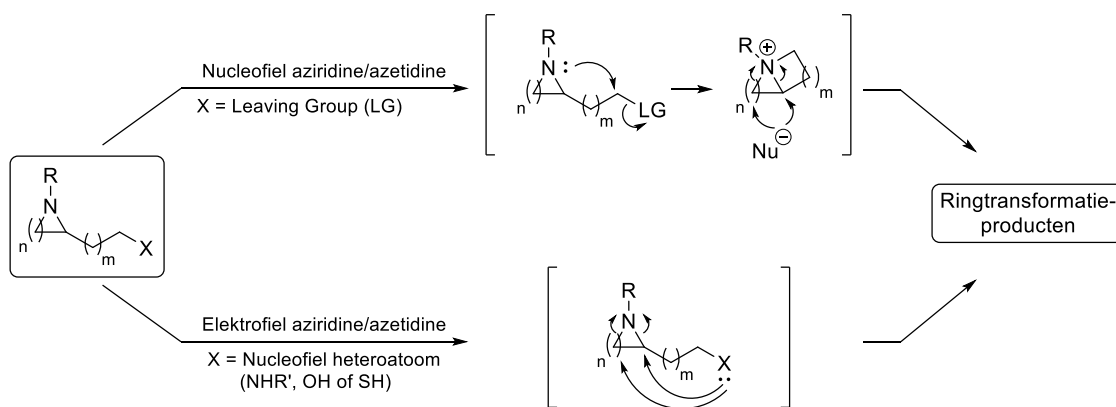
De aanmaak en het synthetisch gebruik van bicyclische aziridiniumzouten werd in een uitgebreid literatuuroverzicht in dit werk behandeld. Geïnspireerd door het veelzijdige potentieel van deze gespannen intermediairen voor de opbouw van een grote bibliotheek aan polygesubstitueerde stikstofbevattende verbindingen, werden in een eerste deel van dit proefschrift inspanningen geleverd met betrekking tot de inzet van enantiomeer zuivere 2-(2,2,2-trifluor-1-hydroxyethyl)azetidinen **ii** en **iii** als substraten voor deze ringexpansiestrategie. Azetidinen **ii** en **iii** waren gemakkelijk te bereiden via een tweestapsprotocol uit de overeenkomstige 4-formyl-β-lactamen **i**, waarbij initiële trifluormethylering van de aldehydegroep gevolgd werd door monochlooralaan-geïnduceerde selectieve verwijdering van de carbonylgroep. De additie van de CF$_3$-groep in 4-formyl-β-lactamen **i** gebeurde op een

diastereoselectieve manier, aangezien de (1'*S*)-azetidinen **ii** als hoofdisomeren werden geïsoleerd. De daaropvolgende sulfonylering van de hydroxylgroep leverde de overeenkomstige triflaat-geactiveerde azetidinen **iv** en **ix** op, en de geschiktheid tot ringomlegging van deze azetidinen bleek onverwacht afhankelijk te zijn van de stereochemie van het exocyclische CF₃-gesubstitueerde koolstofatoom. Terwijl (1'*S*)-azetidinen **iv** gemakkelijk werden omgezet tot 3,4-digesubstitueerde 2-(trifluormethyl)pyrrolidinen **v** met hoge diastereoselectiviteit na reactie met verscheidene stikstof-, zuurstof-, zwavel- en fluornucleofielen, konden hun diastereomere tegenhangers (epimeren ten opzichte van de 1'-positie) niet fungeren als substraten voor dit type van ringomlegging. Theoretische berekeningen uitgevoerd aan het Centrum voor Moleculaire Modellering (UGent) stelden dat de (1'*S*)-azetidinen **iv** minder stabiel zijn dan de (1'*R*)-azetidinen **ix**. Ook was de activatiebarrière tot de overeenkomstige bicyclische aziridiniumintermediairen hoger in het geval van de (1'*R*)-azetidinen **ix**. Representatieve pyrrolidinen **v** werden op een selectieve wijze *N*,*O*-gedebenzyleerd en gebruikt voor verdere synthetische uitwerking om bijvoorbeeld een CF₃-gesubstitueerd 2-oxa-4,7-diazabicyclo[3.3.0]octaan-3-onsysteem **viii** te produceren.
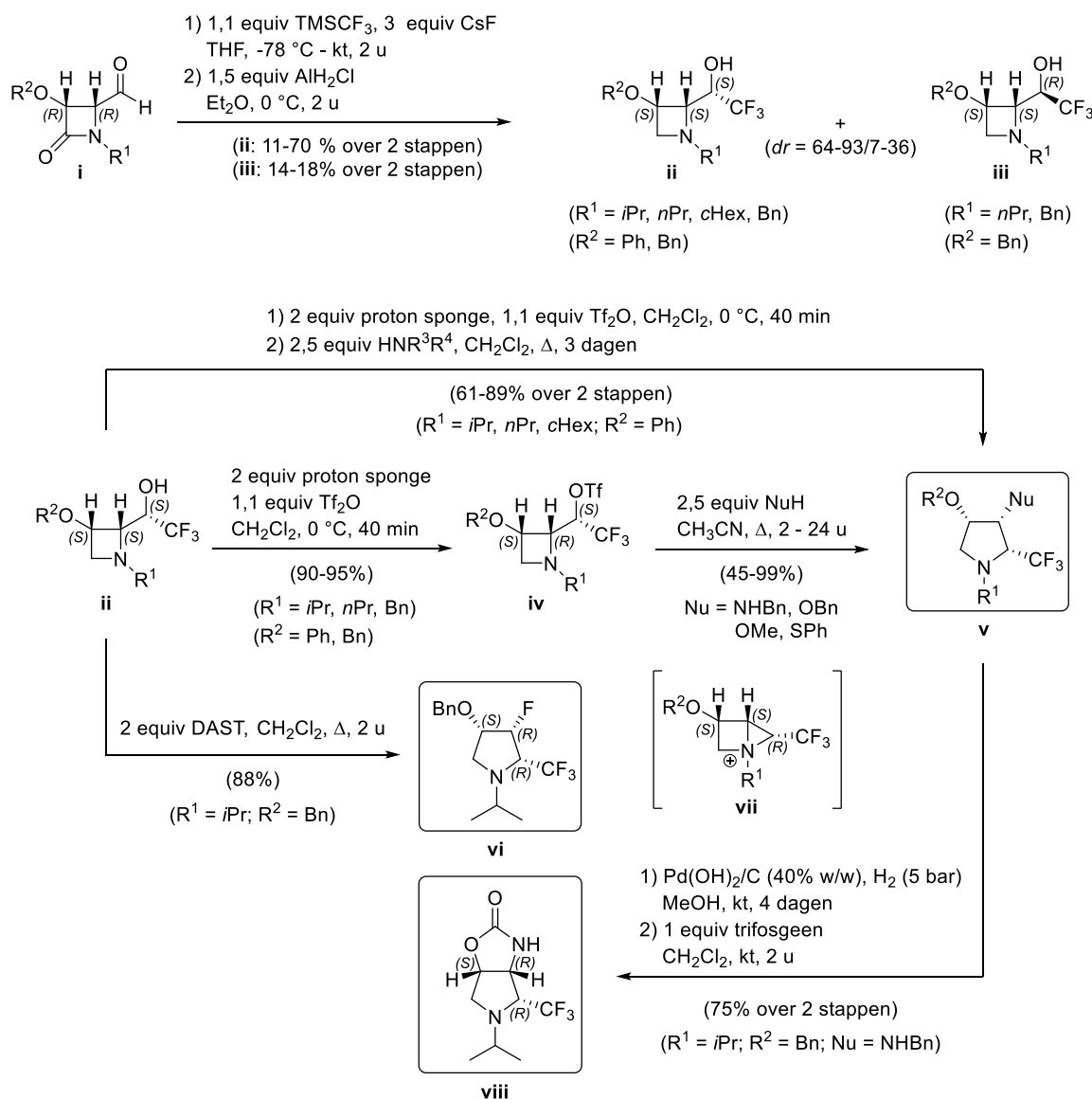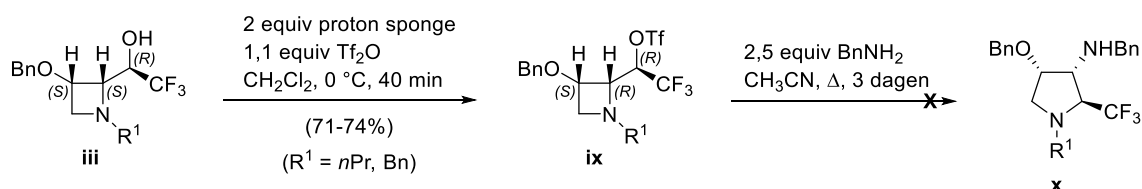
In het grootste deel van dit proefschrift werd de 'omgekeerde' ringexpansiestrategie bestudeerd, waarbij de aziridine-/azetidinekern als elektrofiel wordt beschouwd. Deze alternatieve ringomleggingsmethode werd geëvalueerd door gebruik te maken van drie verschillende klassen van niet-geactiveerde aziridinen, namelijk 2-(2-cyaanethyl)aziridinen **xiv**, 2-[2-(1-pyrrolin-2-yl)ethyl]aziridinen **xv** en 2-(thiocyaanmethyl)aziridinen **xvi**, die werden bereid uit de overeenkomstige 2-(broommethyl)aziridinen **xi**, 2-broommethyl-2-methylaziridinen **xii** of 3-(tosyloxymethyl)aziridinen **xiii** door middel van een substitutiereactie met het geschikte nucleofiel (lithiumtrimethylsilylacetonitril, gelithieerd 1-methyl-2-pyrroline of kaliumthiocyanaat).
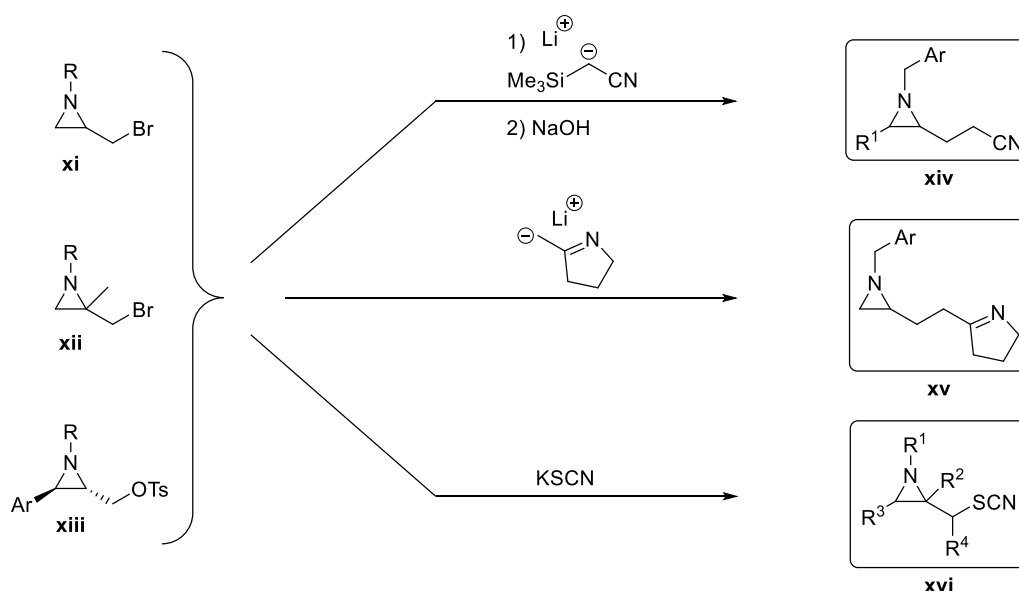
In een eerste doelstelling van deze alternatieve aanpak werden 2-(2-cyaanalkyl)aziridinen **xvii**, **xviii** en 3-(2-cyaanethyl)aziridinen **xxi** ingezet voor een LiAlH$_4$-geïnduceerde ringomlegging. Hiertoe werden 2-(2-cyaanethyl)aziridinen **xvii** eerst gemono- en gedialkyleerd tot 2-(2-cyaanalkyl)aziridinen **xviii** door middel van deprotonering met behulp van LDA gevolgd door neutralisatie met een alkyljodide. Na een systematische screening van verschillende Lewiszuren om de beoogde ringtransformaties uit te lokken, werden aziridinen **xvii** en **xviii** succesvol omgezet tot 2-(aminomethyl)pyrrolidinen **xx** na behandeling met LiAlH$_4$ in aanwezigheid van In(OTf)$_3$. Vanuit mechanistisch standpunt kan de synthese van 2-(aminomethyl)pyrrolidinen **xx** verklaard worden door initiële hydride additie aan de cyaangroep in 2-(2-cyaanalkyl)aziridinen **xvii** en **xviii** met vorming van iminylanionen **xix**, gevolgd door ringopening van de aziridinekern op het meest gehinderde koolstofatoom en hydride reductie van de overeenkomstige

cyclische tussenproducten. Hierbij gebeurde de intramoleculaire ringopening op een regioselectieve wijze, hetgeen in overeenstemming is met de regels van Baldwin, nl. een 5-*exo-tet* ringsluiting is gunstig in tegenstelling tot een 6-*endo-tet* ringsluiting, dewelke ongunstig is. De introductie van een aromatische substituent op de aziridinekern had een belangrijk effect op de regioselectiviteit van de ringopening, aangezien behandeling van 2-aryl-3-(2-cyaanethyl)aziridinen **xxi** met dezelfde reactieomstandigheden (LiAlH$_4$, In(OTf)$_3$) resulteerde in de vorming van 3-aminopiperidinen **xxiii**. De invloed van de arylgroep op de regioselectiviteit van het ringopeningsproces is te wijten aan de stabilisatie van het ontwikkelende benzylisch carbeniumion op C2, hetgeen de regels van Baldwin overtreft. De ringomlegging van (2-cyaanethyl)aziridinen kan dus op een regioselectieve manier gecontroleerd worden, aangezien 2-(2-cyaanethyl)aziridinen **xvii** en **xviii** werden omgezet tot pyrrolidinen **xx** en 2-aryl-3-(2-cyaanethyl)aziridinen **xxi**, met een aromatische substituent op de aziridinekern, werden getransformeerd tot piperidinen **xxiii**.
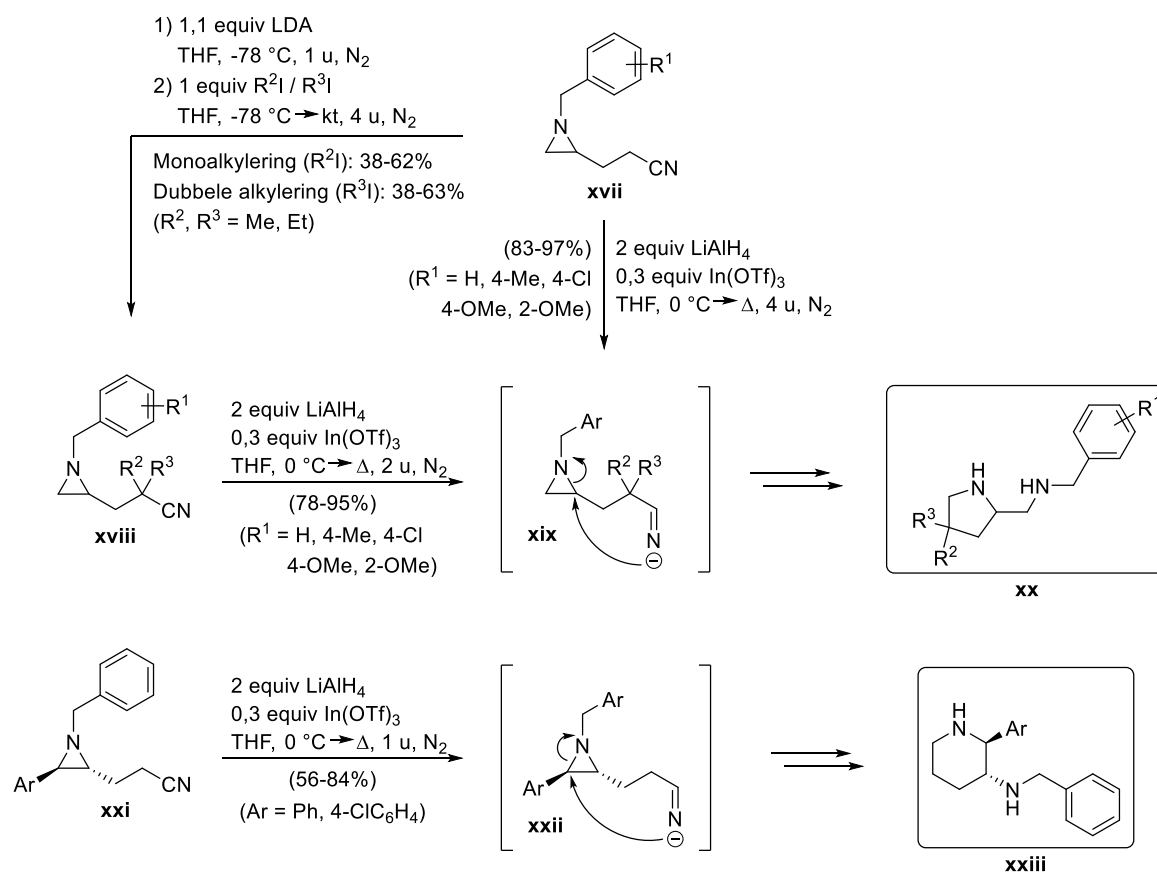
In een volgende stap werd de reactiviteit van de 1,2-diaminestructuur in de verkregen stikstofbevattende verbindingen **xx** en **xxiii** onderzocht ten opzichte van verschillende koppelingsreagentia. Hiervoor werd een selectie van 2-(aminomethyl)pyrrolidinen **xx** en 3-aminopiperidinen **xxiii** omgezet tot bicyclische imidazolidinonen **xxiv**, **xxvi** en diketopiperazinen **xxv**, **xxvii** na behandeling met trifosgeen, CDI, oxalylchloride of oxalyldiimidazool.
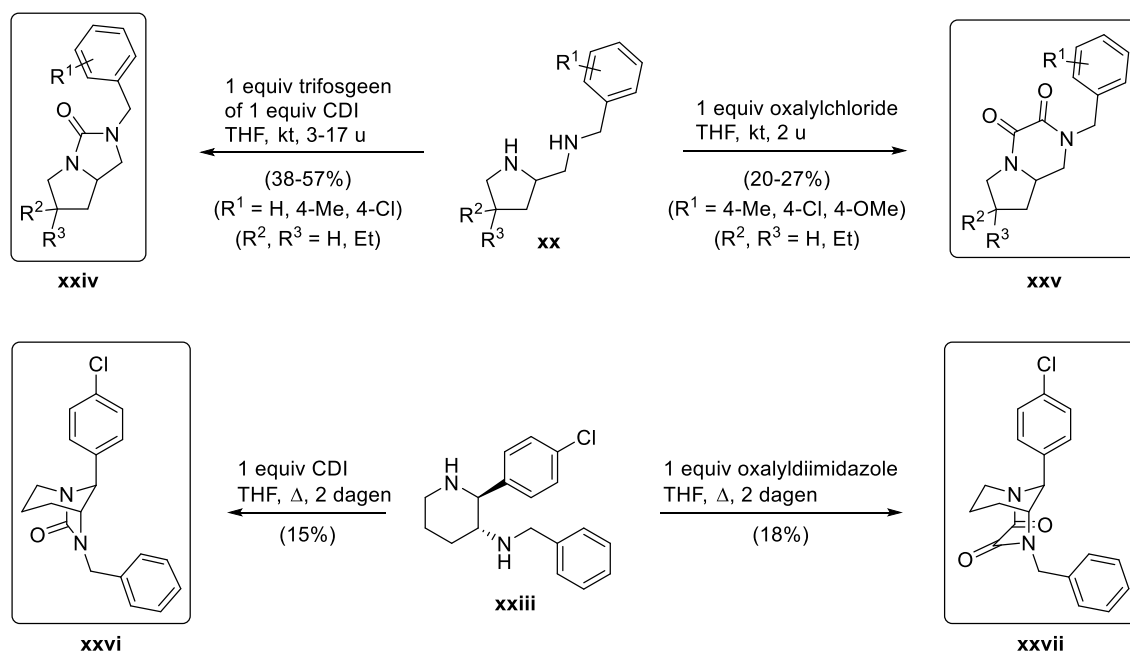
In een derde deel van dit werk werd de ontwikkelde ringomlegging van (2-cyaanethyl)aziridinen verder uitgewerkt voor de constructie van 1-azabicyclo[3.3.0]octanen, aangezien deze kernen belangrijke structurele éénheden voorstellen in natuurproducten en biologisch actieve verbindingen. In dit opzicht werden 2-[2-(1-pyrrolin-2-yl)ethyl]aziridinen **xv** en 2-[2-(1-pyrrolin-2-yl)alkyl]aziridinen **xxxi** (verkregen door middel van alkylering van verbindingen **xv** na behandeling met LDA, gevolgd door quenchen met behulp van een alkyljodide) omgevormd tot *trans*- en *cis*-pyrrolizidinen **xxviii** en **xxxii**. Zuivering door middel van kolomchromatografie liet enkel de isolatie van de major *trans*-isomeren toe. Mechanistisch gezien levert de In(OTf)$_3$-gemedieerde regioselectieve ringopening van aziridinen **xxix** bicyclische intermediairen **xxx** op, en opeenvolgende nucleofiele aanval geeft vervolgens aanleiding tot de vorming van *trans*- en *cis*-pyrrolizidinen **xxviii** en **xxxii**.

1) 0,3 equiv In(OTf)$_3$
   THF, kt, 1 u, N$_2$
2) 1 equiv LiAlH$_4$, THF, Δ, 1 u, N$_2$
   OF 1 equiv. KCN
   THF/MeOH (1/1), Δ, 48 u, N$_2$

(Ar = Ph, 4-MeC$_6$H$_4$
4-ClC$_6$H$_4$)

xv

1) 1,1 equiv. LDA,
   THF, -78 °C, 1 u, N$_2$
2) 1 equiv. RI
   THF, kt, 5 u, N$_2$
   (R = Me, Et)

(49-67%)
(*dr* = 53-60/40-47)

xxxi

1) 0,3 equiv In(OTf)$_3$
   THF, kt, 1 u, N$_2$
2) 1 equiv LiAlH$_4$, THF, Δ, 1 u, N$_2$

(Ar = Ph, 4-MeC$_6$H$_4$
4-ClC$_6$H$_4$)

xxix   **xxx**   Nu = H, CN   Nu = H

trans-**xxviii**   (58-79/21-42)   *cis*-**xxviii**
(22-35%)

trans-**xxxii** (25-31%)   (55-68/32-45)   *cis*-**xxxii**
(*dr* = 53-59/41-47)
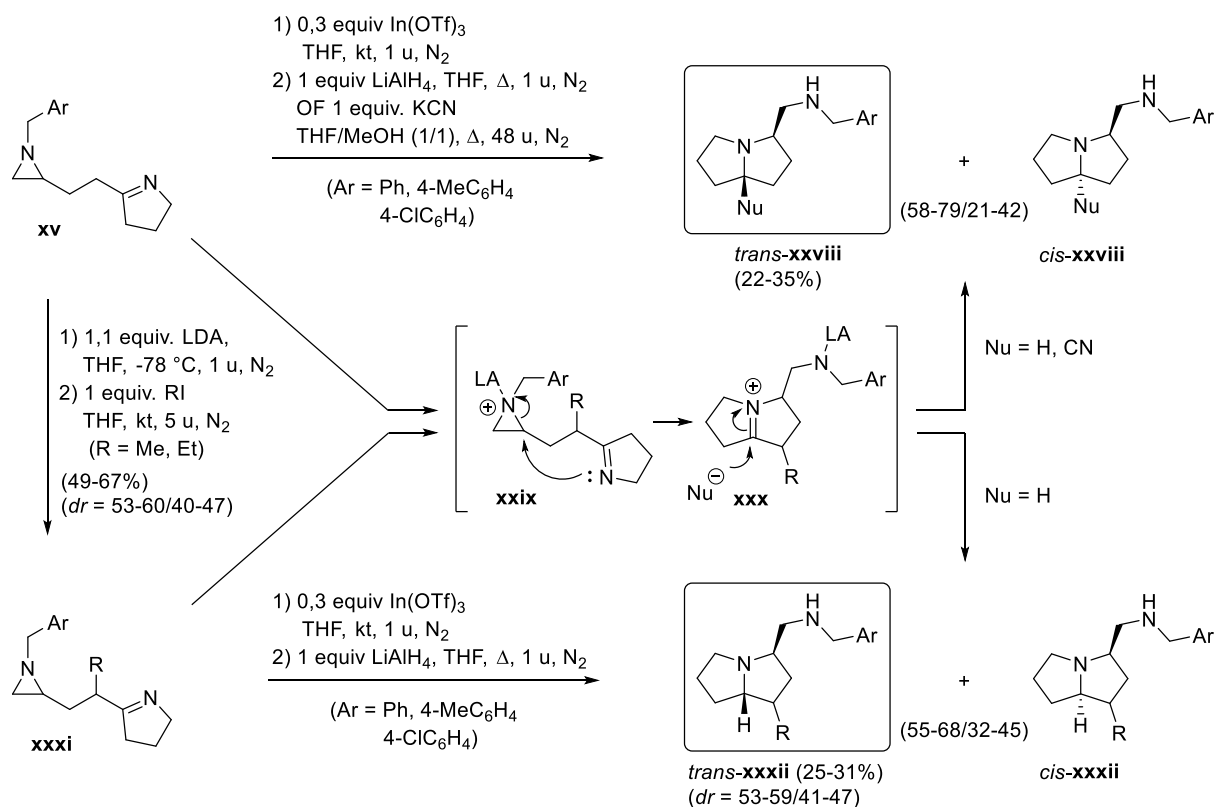
In een finaal deel van deze doctoraatsthesis werden niet-geactiveerde 2-(thiocyaanmethyl)aziridinen met diverse substitutiepatronen ingezet als synthons om een LiAlH$_4$-geïnduceerde ringomlegging te bewerkstelligen. Hiertoe werden monogesubstitueerde 2-(thiocyaanmethyl)aziridinen **xxxiii**, *gem*-digesubstitueerde 2-methyl-2-(thiocyaanmethyl)aziridinen **xxxvi** en *vic*-digesubstituteerde *trans*-2-aryl-3-(thiocyaanmethyl)aziridinen **xxxix** op een stereospecifieke wijze omgezet tot nieuwe gefunctionaliseerde 2-(aminomethyl)thiiranen door middel van een ongekende thia-aza-Payne-omlegging. De ontwikkelde strategie is gebaseerd op een hydride reductie van de thiocyaangroep gevolgd door intramoleculaire aziridine ringopening. Opeenvolgende blootstelling van de verkregen 2-(aminomethyl)episulfide-intermediairen **xxxiv**, **xxxvii** en **xl** aan trifosgeen resulteerde in de regioselectieve vorming van respectievelijk 5-(chloormethyl)thiazolidin-2-onen **xxxv**, **xxxviii** en **xli**. Aanvullend werd de reactiviteit van 3-(4-chloorbenzyl)-5-(chloormethyl)thiazolidin-2-on **xxxv** (R^1 = 4-ClC$_6$H$_4$CH$_2$, R^2 = H), als representatief voorbeeld binnen de klasse van gesynthetiseerde 5-(chloormethyl)thiazolidin-2-onen, onderzocht door toepassing van substitutie, eliminatie en reductieve reactieprocedures.

(R^1 = Bn, 4-MeC$_6$H$_4$CH, 4-ClC$_6$H$_4$CH$_2$, *i*Pr, *i*Bu, *c*HexCH$_2$)
(R^2 = H, Ph)

(R = H, Me, MeO)

(Ar = Ph, 4-ClC$_6$H$_4$)
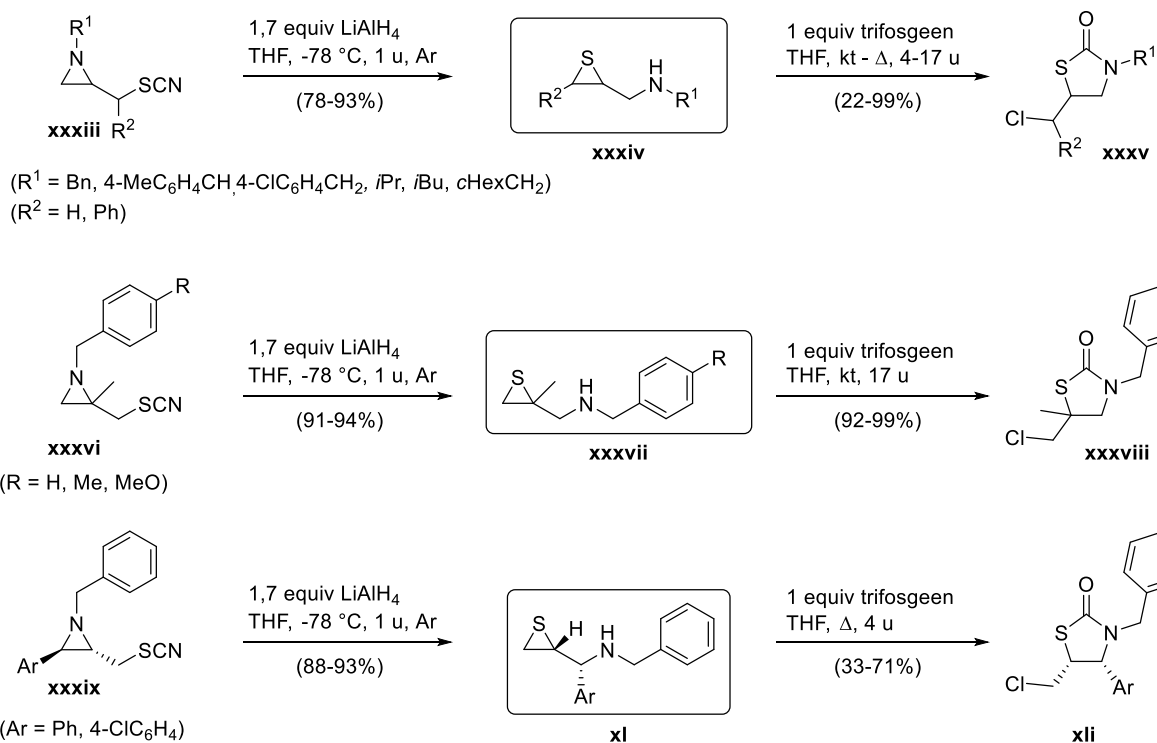
In dit doctoraat werd een variëteit aan gefunctionaliseerde niet-geactiveerde aziridinen en azetidinen succesvol ingezet als productieve synthons in verschillende ringexpansiestrategieën voor de aanmaak van nieuwe klassen van stikstofbevattende vijf- en zesringen. Enerzijds werd het gebruik van intermediaire 1-azabicyclo[m.n.0]alkanen geïllustreerd aan de hand van transformaties van azetidinen tot een groot aantal enantiomeer zuivere trifluormethyl-gesubstitueerde pyrrolidinen. Anderzijds werd de omgekeerde ringomleggingsmethodologie, waarbij de met ringspanning beladen kleine ring ingezet wordt als een elektrofiel deeltje, gedemonstreerd door middel van de omzetting van polygesubstitueerde aziridinen tot een brede bibliotheek van interessante stikstofbevattende verbindingen. Het is duidelijk dat deze laatste ringexpansiestrategie moet erkend worden als een zeer krachtige strategie in de moderne organische chemie en dat slechts een klein stuk van zijn capaciteit in deze thesis werd ontdekt, hetgeen dit een intrigerend en veelbelovend onderzoeksgebied maakt voor verder onderzoek in de toekomst.

REFERENCES

REFERENCES

1. (a) Patil, B.; Banerjee, S. *J. Pharm. Res.* **2012**, *5*, 5496-5509. (b) Haider, S.; Saify, Z. S.; Begum, N.; Ashraf, S.; Zarreen, T.; Saeed, S. M. G. *World J. Pharm. Res.* **2014**, *3*, 987-1024.
2. Gunasekara, N. S.; Noble, S.; Benfield, P. *Drugs* **1998**, *55*, 85-120.
3. Zimmer, L. *Trends Pharmacol. Sci.* **2017**, *38*, 608-620.
4. Niemegeers, C. J. E.; Colpaert, F. C.; Awouters, F. H. L. *Drug Dev. Res.* **1981**, *1*, 1-20.
5. Chaudhry, S. A.; Koren, G. *Reprod. Toxicol.* **2014**, *46*, 40-45.
6. Hoy, S. M. *CNS drugs* **2016**, *30*, 761-772.
7. Smieja, M. *Can. J. Infect. Dis.* **1998**, *9*, 22-28.
8. D'hooghe, M.; Ha, H.-J., *Synthesis of 4-to 7-membered Heterocycles by Ring Expansion: Aza-, oxa- and thiaheterocyclic small-ring systems*. Springer: 2016; Vol. 41.
9. De Rycke, N.; David, O.; Couty, F. *Org. Lett.* **2011**, *13*, 1836-1839.
10. Tymoshenko, D. O. *Arkivoc* **2011**, *1*, 329-345.
11. (a) Singh, G. S.; D'hooghe, M.; De Kimpe, N. *Chem. Rev.* **2007**, *107*, 2080-2135. (b) Sweeney, J. B. *Chem. Soc. Rev.* **2002**, *31*, 247-258.
12. Hu, X. E. *Tetrahedron* **2004**, *60*, 2701-2743.
13. (a) Ghorai, M. K.; Tiwari, D. P. *J. Org. Chem.* **2010**, *75*, 6173-6181. (b) Ghorai, M. K.; Kumar, A.; Tiwari, D. P. *J. Org. Chem.* **2009**, *75*, 137-151.
14. (a) Métro, T.-X.; Duthion, B.; Gomez Pardo, D.; Cossy, J. *Chem. Soc. Rev.* **2010**, *39*, 89-102. (b) Stanković, S.; D'hooghe, M.; Catak, S.; Eum, H.; Waroquier, M.; Van Speybroeck, V.; De Kimpe, N.; Ha, H.-J. *Chem. Soc. Rev.* **2012**, *41*, 643-665.
15. Catak, S.; D'hooghe, M.; Verstraelen, T.; Hemelsoet, K.; Van Nieuwenhove, A.; Ha, H.-J.; Waroquier, M.; De Kimpe, N.; Van Speybroeck, V. *J. Org. Chem.* **2010**, *75*, 4530-4541.
16. Dudev, T.; Lim, C. *J. Am. Chem. Soc.* **1998**, *120*, 4450-4458.
17. (a) Bott, T. M.; West, F. *Heterocycles* **2012**, *84*, 223-264. (b) Couty, F.; Evano, G. *Org. Prep. Proced. Int.* **2006**, *38*, 427-465.
18. Vervisch, K.; D'hooghe, M.; Törnroos, K. W.; De Kimpe, N. *J. Org. Chem.* **2010**, *75*, 7734-7744.
19. Dolfen, J.; Yadav, N. N.; De Kimpe, N.; D'hooghe, M.; Ha, H.-J. *Adv. Synth. Catal.* **2016**, *358*, 3485-3511.
20. (a) Mollet, K.; D'hooghe, M.; Broeckx, L.; Danneels, B.; Desmet, T.; De Kimpe, N. *Tetrahedron* **2013**, *69*, 2603-2607. (b) De Kimpe, N.; D'hooghe, M.; Mollet, K.; Broeckx, L. *Heterocycles* **2012**, *84*, 431-447. (c) Mollet, K.; Catak, S.; Waroquier, M.; Van Speybroeck, V.; D'hooghe, M.; De Kimpe, N. *J. Org. Chem.* **2011**, *76*, 8364-8375. (d) Van Brabandt, W.; Van Landeghem, R.; De Kimpe, N. *Org. Lett.* **2006**, *8*, 1105-1108.
21. Berson, J. A. *Angew. Chem. Int. Ed.* **2006**, *45*, 4724-4729.
22. (a) Campanini, L.; Duréault, A.; Depezay, J.-C. *Tetrahedron Lett.* **1996**, *37*, 5095-5098. (b) Capriati, V.; Florio, S.; Luisi, R.; Musio, B. *Org. Lett.* **2005**, *7*, 3749-3752. (c) Concellón, J. M.; Riego, E.; Rivero, I. A.; Ochoa, A. *J. Org. Chem.* **2004**, *69*, 6244-6248. (d) Dammacco, M.; Degennaro, L.; Florio, S.; Luisi, R.; Musio, B.; Altomare, A. *J. Org. Chem.* **2009**, *74*, 6319-6322. (e) de Ceglie, M. C.; Musio, B.; Affortunato, F.; Moliterni, A.; Altomare, A.; Florio, S.; Luisi, R. *Chem. Eur. J.* **2011**, *17*, 286-296. (f) Tanner, M. E.; Miao, S. *Tetrahedron Lett.* **1994**, *35*, 4073-4076. (g) Vervisch, K.; D'hooghe, M.; Rutjes, F. P.; De Kimpe, N. *Org. Lett.* **2012**, *14*, 106-109.
23. Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734-736.
24. D'hooghe, M.; Vervisch, K.; Törnroos, K. W.; Verhaeghe, T.; Desmet, T.; Lategan, C.; Smith, P. J.; Chibale, K.; De Kimpe, N. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 1507-1510.
25. Dolfen, J.; Vervisch, K.; De Kimpe, N.; D'hooghe, M. *Chem. Eur. J.* **2016**, *22*, 4945-4951.
26. (a) Alcaide, B.; Almendros, P. *Chem. Soc. Rev.* **2001**, *30*, 226-240. (b) Alcaide, B.; Almendros, P.; Aragoncillo, C.; Callejo, R.; Ruiz, M. P. *J. Org. Chem.* **2013**, *78*, 10154-10165. (c) Alcaide, B.; Almendros, P.; Cabrero, G.; Ruiz, M. P. *J. Org. Chem.* **2007**, *72*, 7980-7991. (d) Alcaide, B.; Almendros, P.; Martín-Montero, R.; Ruiz, M. P. *Adv. Synth. Catal.* **2016**, *358*, 1469-1477. (e) Dekeukeleire, S.; D'hooghe, M.; Vanwalleghem, M.; Van Brabandt, W.; De Kimpe, N. *Tetrahedron* **2012**, *68*, 10827-10834. (f) Van Brabandt, W.; Vanwalleghem, M.; D'hooghe, M.; De Kimpe, N. *J. Org. Chem.* **2006**, *71*, 7083-7086.

27. (a) Charpentier, J.; Früh, N.; Togni, A. *Chem. Rev.* **2015**, *115*, 650-682. (b) Dilman, A. D.; Levin, V. V. *Eur. J. Org. Chem.* **2011**, 831-841. (c) Prieto, A.; Baudoin, O.; Bouyssi, D.; Monteiro, N. *Chem. Commun.* **2016**, *52*, 869-881. (d) Rubiales, G.; Alonso, C.; de Marigorta, E. M.; Palacios, F. *Arkivoc* **2014**, *2*, 362-405. (e) Wang, S.-M.; Han, J.-B.; Zhang, C.-P.; Qin, H.-L.; Xiao, J.-C. *Tetrahedron* **2015**, *71*, 7949-7976. (f) Zhang, C. *Org. Biomol. Chem.* **2014**, *12*, 6580-6589. (g) Zhu, W.; Wang, J.; Wang, S.; Gu, Z.; Aceña, J. L.; Izawa, K.; Liu, H.; Soloshonok, V. A. *J. Fluorine Chem.* **2014**, *167*, 37-54.

28. Rioton, S.; Orliac, A.; Antoun, Z.; Bidault, R.; Gomez Pardo, D.; Cossy, J. *Org. Lett.* **2015**, *17*, 2916-2919.

29. D'hooghe, M.; Vervisch, K.; De Kimpe, N. *J. Org. Chem.* **2007**, *72*, 7329-7332.

30. Mollet, K.; Decuyper, L.; Vander Meeren, S.; Piens, N.; De Winter, K.; Desmet, T.; D'hooghe, M. *Org. Biomol. Chem.* **2015**, *13*, 2716-2725.

31. (a) Endoh, K.; Akamatsu, K.; Matsumoto, T.; Morikawa, K.; Honda, M.; Mitsui, H.; Koizumi, M.; Koizumi, K.; Matsuno, T. *Anticancer Res.* **1988**, *9*, 987-991. (b) Fujiwara, Y.; Nakamura, M.; Yokoo, S. *Br. J. Cancer* **1993**, *67*, 1285-1292.

32. Cox, J. M.; Harper, B.; Mastracchio, A.; Leiting, B.; Sinha Roy, R.; Patel, R. A.; Wu, J. K.; Lyons, K. A.; He, H.; Xu, S.; Zhu, B.; Thornberry, N. A.; Weber, A. E.; Edmondson, S. D. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 4579-83.

33. Koerber, J.; Goodman, D.; Barnes, J. L.; Grimm, J. W. *Behav Pharmacol.* **2013**, *24*, 633-639.

34. (a) Li, J. J.; Sutton, J. C.; Nirschl, A.; Zou, Y.; Wang, H.; Sun, C.; Pi, Z.; Johnson, R.; Krystek, S. R.; Seethala, R. *J. Med. Chem.* **2007**, *50*, 3015-3025. (b) Overman, L. E.; Shin, Y. *Org. Lett.* **2007**, *9*, 339-341. (c) Seya, H.; Nozawa, K.; Udagawa, S.-I.; Nakajima, S.; Kawai, K.-I. *Chem. Pharm. Bull.* **1986**, *34*, 2411-2416. (d) Sun, C.; Robl, J. A.; Wang, T. C.; Huang, Y.; Kuhns, J. E.; Lupisella, J. A.; Beehler, B. C.; Golla, R.; Sleph, P. G.; Seethala, R. *J. Med. Chem.* **2006**, *49*, 7596-7599.

35. (a) Bhat, C.; Tilve, S. G. *RSC Adv.* **2014**, *4*, 5405-5452. (b) Michael, J. P. *Nat. Prod. Rep.* **2008**, *25*, 139-165.

36. (a) Casida, J. E.; Gulevich, A. G.; Sarpong, R.; Bunnelle, E. M. *Bioorg. Med. Chem.* **2010**, *18*, 1942-1947. (b) Wei, Z.-L.; Kozikowski, A. P. *J. Org. Chem.* **2003**, *68*, 9116-9118. (c) Camerano, J. A.; Casado, M. A.; Ciriano, M. A.; Lahoz, F. J.; Oro, L. A. *Organometallics* **2005**, *24*, 5147-5156.

37. Noh, H.-Y.; Kim, S.-W.; Paek, S. I.; Ha, H.-J.; Yun, H.; Lee, W. K. *Tetrahedron* **2005**, *61*, 9281-9290.

38. Higgins, R. H.; Kidd, B. *J. Phys. Org. Chem.* **1998**, *11*, 763-773.

39. Ikee, Y.; Hashimoto, K.; Kamino, M.; Nakashima, M.; Hayashi, K.; Sano, S.; Shiro, M.; Nagao, Y. *Chem. Pharm. Bull.* **2008**, *56*, 346-356.

40. Mlostoń, G.; Celeda, M. *Helv. Chim. Acta* **2005**, *88*, 1658-1663.

41. (a) Woznicka, M.; Urbaniak, K.; Mloston, G.; Heimgartnerb, H. *Heterocycles* **2006**, *69*, 351-364. (b) Mlostoń, G.; Woźnicka, M.; Drabowicz, J.; Linden, A.; Heimgartner, H. *Helv. Chim. Acta* **2008**, *91*, 1419-1429.

42. Hortmann, A. G.; Robertson, D. A. *J. Am. Chem. Soc.* **1972**, *94*, 2758-2765.

43. De Kimpe, N.; De Smaele, D.; Szakonyi, Z. *J. Org. Chem.* **1997**, *62*, 2448-2452.

44. Stanković, S.; Catak, S.; D'hooghe, M.; Goossens, H.; Abbaspour Tehrani, K.; Bogaert, P.; Waroquier, M.; Van Speybroeck, V.; De Kimpe, N. *J. Org. Chem.* **2011**, *76*, 2157-2167.

45. Stanković, S.; Goossens, H.; Catak, S.; Tezcan, M.; Waroquier, M.; Van Speybroeck, V.; D'hooghe, M.; De Kimpe, N. *J. Org. Chem.* **2012**, *77*, 3181-3190.

46. Žukauskaitė, A.; Mangelinckx, S.; Buinauskaitė, V.; Šačkus, A.; De Kimpe, N. *Amino Acids* **2011**, *41*, 541-558.

47. Stanković, S.; D'hooghe, M.; Abbaspour Tehrani, K.; De Kimpe, N. *Tetrahedron Lett.* **2012**, *53*, 107-110.

48. Van Driessche, B.; Van Brabandt, W.; D'hooghe, M.; Dejaegher, Y.; De Kimpe, N. *Tetrahedron* **2006**, *62*, 6882-6892.

49. Van Brabandt, W.; Mangelinckx, S.; D'hooghe, M.; Van Driessche, B.; De Kimpe, N. *Curr. Org. Chem.* **2009**, *13*, 827-851.

50. Okutani, T.; Masuda, K. *Chem. Pharm. Bull.* **1974**, *22*, 1498-1505.

51. Dejaegher, Y.; Mangelinckx, S.; De Kimpe, N. *J. Org. Chem.* **2002**, *67*, 2075-2081.
52. Joucla, M.; Fouchet, B.; Hamelin, J. *Tetrahedron* **1985**, *41*, 2707-2715.
53. Banks, H. D. *J. Org. Chem.* **2006**, *71*, 8089-8097.
54. D'hooghe, M.; Aelterman, W.; De Kimpe, N. *Org. Biomol. Chem.* **2009**, *7*, 135-141.
55. (a) Couty, F.; Durrat, F.; Prim, D. *Tetrahedron Lett.* **2003**, *44*, 5209-5212. (b) Durrat, F.; Sanchez, M. V.; Couty, F.; Evano, G.; Marrot, J. *Eur. J. Org. Chem.* **2008**, 3286-3297.
56. Couty, F.; Drouillat, B.; David, O.; Evano, G.; Marrot, J. *Synlett* **2008**, 1345-1348.
57. Anxionnat, B.; Robert, B.; George, P.; Ricci, G.; Perrin, M. A.; Gomez Pardo, D.; Cossy, J. *J. Org. Chem.* **2012**, *77*, 6087-6099.
58. Dekeukeleire, S.; D'hooghe, M.; Törnroos, K. W.; De Kimpe, N. *J. Org. Chem.* **2010**, *75*, 5934-5940.
59. (a) Feula, A.; Dhillon, S. S.; Byravan, R.; Sangha, M.; Ebanks, R.; Salih, M. A. H.; Spencer, N.; Male, L.; Magyary, I.; Deng, W.-P.; Müller, F.; Fossey, J. S. *Org. Biomol. Chem.* **2013**, *11*, 5083-5093. (b) Feula, A.; Male, L.; Fossey, J. S. *Org. Lett.* **2010**, *12*, 5044-5047.
60. Couty, F.; Kletskii, M. *J. Mol. Struc.: Theochem* **2009**, *908*, 26-30.
61. Hammer, C. F.; Heller, S. R.; Craig, J. H. *Tetrahedron* **1972**, *28*, 239-253.
62. Hayashi, K.; Kujime, E.; Katayama, H.; Sano, S.; Shiro, M.; Nagao, Y. *Chem. Pharm. Bull.* **2009**, *57*, 1142-1146.
63. Ji, M.-K.; Hertsen, D.; Yoon, D.-H.; Eum, H.; Goossens, H.; Waroquier, M.; Van Speybroeck, V.; D'hooghe, M.; De Kimpe, N.; Ha, H.-J. *Chem. Asian. J.* **2014**, *9*, 1060-1067.
64. Eum, H.; Choi, J.; Cho, C. G.; Ha, H.-J. *Asian J. Org. Chem.* **2015**, *4*, 1399-1409.
65. Brain, E. G.; Doyle, F. P.; Mehta, M. D. *J. Chem. Soc.* **1961**, 633-639.
66. Gomez Pardo, D.; Cossy, J. *Chem. Eur. J.* **2014**, *20*, 4516-4525.
67. Cossy, J.; Déchamps, I.; Gomez Pardo, D. *Synlett* **2007**, 263-267.
68. (a) Davies, S. G.; Figuccia, A. L. A.; Fletcher, A. M.; Roberts, P. M.; Thomson, J. E. *Org. Lett.* **2013**, *15*, 2042-2045. (b) Davies, S. G.; Figuccia, A. L. A.; Fletcher, A. M.; Roberts, P. M.; Thomson, J. E. *Tetrahedron* **2014**, *70*, 3601-3607. (c) Davies, S. G.; Nicholson, R. L.; Price, P. D.; Roberts, P. M.; Russell, A. J.; Savory, E. D.; Smith, A. D.; Thomson, J. E. *Tetrahedron: Asymmetry* **2009**, *20*, 758-772.
69. Bilke, J. L.; Moore, S. P.; O'Brien, P.; Gilday, J. *Org. Lett.* **2009**, *11*, 1935-1938.
70. Feraldi-Xypolia, A.; Gomez Pardo, D.; Cossy, J. *Chem. Eur. J.* **2015**, *21*, 12876-12880.
71. Abbaspour Tehrani, K.; Van Syngel, K.; Boelens, M.; Contreras, J.; De Kimpe, N. *Tetrahedron Lett.* **2000**, *41*, 2507-2510.
72. Graham, M. A.; Thornton-Pett, M.; Rayner, C. M.; Wadsworth, A. H. *Chem. Commun.* **2001**, 966-967.
73. (a) De Kimpe, N.; Boelens, M.; Contreras, J. *Tetrahedron Lett.* **1996**, *37*, 3171-3174. (b) De Kimpe, N.; Boelens, M.; Piqueur, J.; Baele, J. *Tetrahedron Lett.* **1994**, *35*, 1925-1928.
74. Rosas Alonso, E.; Abbaspour Tehrani, K.; Boelens, M.; De Kimpe, N. *Synlett* **2005**, 1726-1730.
75. Shinkevich, E. Y.; Novikov, M. S.; Khlebnikov, A. F. *Synthesis* **2007**, 225-230.
76. Lee, K. M.; Kim, J. C.; Kang, P.; Lee, W. K.; Eum, H.; Ha, H.-J. *Tetrahedron* **2012**, *68*, 883-893.
77. Zhou, J.; Yeung, Y.-Y. *Org. Lett.* **2014**, *16*, 2134-2137.
78. Bowen, E. G.; Wardrop, D. J. *Org. Lett.* **2010**, *12*, 5330-5333.
79. Chong, H.-s.; Ganguly, B.; Broker, G. A.; Rogers, R. D.; Brechbiel, M. W. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2080-2086.
80. Bagal, S. K.; Davies, S. G.; Lee, J. A.; Roberts, P. M.; Russell, A. J.; Scott, P. M.; Thomson, J. E. *Org. Lett.* **2009**, *12*, 136-139.
81. Böhm, H. J.; Banner, D.; Bendels, S.; Kansy, M.; Kuhn, B.; Muller, K.; Obst-Sander, U.; Stahl, M. *ChemBioChem* **2004**, *5*, 637-643.
82. Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320-330.
83. Wang, J.; Sanchez-Rosello, M.; Acena, J. L.; del Pozo, C.; Sorochinsky, A. E.; Fustero, S.; Soloshonok, V. A.; Liu, H. *Chem. Rev.* **2014**, *114*, 2432-2506.

84. (a) Yang, X.; Wu, T.; Phipps, R. J.; Toste, F. D. *Chem. Rev.* **2015**, *115*, 826-870. (b) Zhi, Y.; Zhao, K.; Liu, Q.; Wang, A.; Enders, D. *Chem. Commun.* **2016**, *52*, 14011-14014.

85. Liu, X.; Xu, C.; Wang, M.; Liu, Q. *Chem. Rev.* **2015**, *115*, 683-730.

86. Mollet, K.; Goossens, H.; Piens, N.; Catak, S.; Waroquier, M.; Törnroos, K. W.; Van Speybroeck, V.; D'hooghe, M.; De Kimpe, N. *Chem. Eur. J.* **2013**, *19*, 3383-3396.

87. Ojima, I.; Zhao, M.; Yamato, T.; Nakahashi, K. *J. Org. Chem.* **1991**, *56*, 5263-5277.

88. Dao Thi, H.; Decuyper, L.; Mollet, K.; Kenis, S.; De Kimpe, N.; Van Nguyen, T.; D'hooghe, M. *Synlett* **2016**, *27*, 1100-1105.

89. Déchamps, I.; Gomez Pardo, D.; Cossy, J. *Eur. J. Org. Chem.* **2007**, 4224-4234.

90. (a) Crabtree, E. V.; Martinez, R. F.; Nakagawa, S.; Adachi, I.; Butters, T. D.; Kato, A.; Fleet, G. W.; Glawar, A. F. *Org. Biomol. Chem.* **2014**, *12*, 3932-3943. (b) Curtis, K. L.; Evinson, E. L.; Handa, S.; Singh, K. *Org. Biomol. Chem.* **2007**, *5*, 3544-3553. (c) Pohl, R.; Slavetinska, L. P.; Eng, W. S.; Keough, D. T.; Guddat, L. W.; Rejman, D. *Org. Biomol. Chem.* **2015**, *13*, 4693-4705. (d) Rejman, D.; Panova, N.; Klener, P.; Maswabi, B.; Pohl, R.; Rosenberg, I. *J. Med. Chem.* **2012**, *55*, 1612-1621. (e) Scatena, C. D.; Kumer, J. L.; Arbitrario, J. P.; Howlett, A. R.; Hawtin, R. E.; Fox, J. A.; Silverman, J. A. *Cancer Chemother. Pharmacol.* **2010**, *66*, 881-888.

91. (a) Bianchi, P.; Roda, G.; Riva, S.; Danieli, B.; Zabelinskaja-Mackova, A.; Griengl, H. *Tetrahedron* **2001**, *57*, 2213-2220. (b) Schmid, C. R.; Bryant, J. D. *Org. Synth.* **1993**, *72*, 6-12.

92. Alcaide, B.; Aly, M. F.; Rodrıguez, C.; Rodriguez-Vicente, A. *J. Org. Chem.* **2000**, *65*, 3453-3459.

93. Jayaraman, M.; Deshmukh, S. *J. Org. Chem.* **1994**, *59*, 932-934.

94. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, J. A., Jr.; Peralta, J. E.; Ogliaro, F.; Bearpark, M. J.; Heyd, J.; Brothers, E. N.; Kudin, K. N.; Staroverov, V. N.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A. P.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, N. J.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, O.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J., *Gaussian09*; Gaussian, Inc.: Wallingford, CT, USA, 2009.

95. Zhao, Y.; Truhlar, D. G. *Theor. Chem. Acc.* **2008**, *120*, 215-241.

96. (a) Hohenstein, E. G.; Chill, S. T.; Sherrill, C. D. *J. Chem. Theory Comput.* **2008**, *4*, 1996-2000. (b) Xu, X.; Alecu, I. M.; Truhlar, D. G. *J. Chem. Theory Comput.* **2011**, *7*, 1667-1676.

97. Gonzalez, C.; Schlegel, H. B. *J. Chem. Phys.* **1989**, *90*, 2154-2161.

98. Barone, V.; Cossi, M. *J. Phys. Chem. A* **1998**, *102*, 1995-2001.

99. Lynch, B. J.; Fast, P. L.; Harris, M.; Truhlar, D. G. *J. Phys. Chem. A* **2000**, *104*, 4811-4815.

100. Chai, J.-D.; Head-Gordon, M. *Phys. Chem. Chem. Phys.* **2008**, *10*, 6615-6620.

101. Adamo, C.; Barone, V. *J. Chem. Phys.* **1999**, *110*, 6158-6170.

102. Burns, L.; Vazquez-Mayagoitia, A.; Sumpter, B. G.; Sherrill, C. D. *J. Chem. Phys.* **2011**, *134*, 084107.

103. (a) Callebaut, G.; Meiresonne, T.; De Kimpe, N.; Mangelinckx, S. *Chem. Rev.* **2014**, *114*, 7954-8015. (b) Ohno, H. *Chem. Rev.* **2014**, *114*, 7784-7814. (c) Padwa, A.; Murphree, S. S. *Arkivoc* **2006**, *3*, 6-33. (d) Pearson, W. H.; Lian, B. W.; Bergmeier, S. C., Aziridines and azirines: monocyclic. In *Comprehensive Heterocyclic Chemistry II*, Padwa, A., Ed. Pergamon: Oxford, 1996; Vol. 1, 1-60. (e) Tanner, D. *Angew. Chem. Int. Ed.* **1994**, *33*, 599-619.

104. (a) Lindström, U. M.; Somfai, P. *Synthesis* **1998**, 109-117. (b) McCoull, W.; Davis, F. A. *Synthesis* **2000**, 1347-1365. (c) Osborn, H. M. I.; Sweeney, J. *Tetrahedron: Asymmetry* **1997**, *8*, 1693-1715. (d) Tsang, D. S.; Yang, S.; Alphonse, F.-A.; Yudin, A. K. *Chem. Eur. J.* **2008**, *14*, 886-894. (e) Watson, I. D.; Yu, L.; Yudin, A. K. *Chem. Res.* **2006**, *39*, 194-206. (f) Zwanenburg, B.; ten Holte, P. *Top. Curr. Chem.* **2001**, 93-124.

105. (a) Barrelle, M.; Apparu, M. *Tetrahedron* **1977**, *33*, 1309-1319. (b) Giovine, A.; Musio, B.; Degennaro, L.; Falcicchio, A.; Nagaki, A.; Yoshida, J.; Luisi, R. *Chem. Eur. J.* **2013**, *19*, 1872-1876. (c) Vervisch, K.; D'hooghe, M.; Törnroos, K. W.; De Kimpe, N. *Org. Biomol. Chem.* **2012**, *10*, 3308-3314. (d) Yoon, H.; Cho, K. S.; Sim, T. *Tetrahedron: Asymmetry* **2014**, *25*, 497-502.

106. Beesley, R. M.; Ingold, C. K.; Thorpe, J. F. *J. Chem. Soc, Trans.* **1915**, *107*, 1080-1106.

107. Yadav, J. S.; Reddy, B. V. S.; Rao, R. S.; Veerendhar, G.; Nagaiah, K. *Tetrahedron Lett.* **2001**, *42*, 8067-8070.

108. Fu, N. Y.; Zhao, X. M.; Yuan, Y. F.; Wang, J. T. *Chin. Chem. Lett.* **2003**, *14*, 1018-1020.

109. Mineno, T.; Tsukagoshi, R.; Iijima, T.; Watanabe, K.; Miyashita, H.; Yoshimitsu, H. *Tetrahedron Lett.* **2014**, *55*, 3765-3767.

110. Sakai, N.; Asama, S.; Anai, S.; Konakahara, T. *Tetrahedron* **2014**, *70*, 2027-2033.

111. (a) Akahane, Y.; Inomata, K.; Endo, Y. *Heterocycles* **2009**, *77*, 1065-1078. (b) Amedjkouh, M.; Ahlberg, P. *Tetrahedron: Asymmetry* **2002**, *13*, 2229-2234. (c) Hashimoto, K.; Saito, B.; Miyamoto, N.; Oguro, Y.; Tomita, D.; Shiokawa, Z.; Asano, M.; Kakei, H.; Taya, N.; Kawasaki, M.; Sumi, H.; Yabuki, M.; Iwai, K.; Yoshida, S.; Yoshimatsu, M.; Aoyama, K.; Kosugi, Y.; Kojima, T.; Morishita, N.; Dougan, D. R.; Snell, G. P.; Imamura, S.; Ishikawa, T. *J. Med. Chem.* **2013**, *56*, 1228-1246.

112. D'hooghe, M.; Mollet, K.; Dekeukeleire, S.; De Kimpe, N. *Org. Biomol. Chem.* **2010**, *8*, 607-615.

113. Ahari, M.; Perez, A.; Menant, C.; Vasse, J.-L.; Szymoniak, J. *Org. Lett.* **2008**, *10*, 2473-2476.

114. Kokotos, C. G.; Aggarwal, V. K. *Org. Lett.* **2007**, *9*, 2099-2102.

115. Cai, X.-F.; Chen, M.-W.; Ye, Z.-S.; Guo, R.-N.; Shi, L.; Li, Y.-Q.; Zhou, Y.-G. *Chem. Asian J.* **2013**, *8*, 1381-1385.

116. Vervisch, K. *Synthesis of 2-(2-cyanoethyl)aziridines and their transformation into a variety of novel cyclic amino nitriles*. PhD thesis, UGent, 2011.

117. Pearson, W. H.; Hines, J. V. *J. Org. Chem.* **2000**, *65*, 5785-5793.

118. Lim, W.; Rhee, Y. H. *Tetrahedron* **2015**, *71*, 5939-5945.

119. Senges, J.; Ehe, L. *Arch. Pharmacol.* **1973**, *280*, 265-274.

120. (a) Bartwal, A.; Mall, R.; Lohani, P.; Guru, S. K.; Arora, S. *J. Plant Growth Regul.* **2012**, *32*, 216-232. (b) Irchhaiya, R.; Kumar, A.; Yadav, A.; Gupta, N.; Kumar, S.; Gupta, N.; Kumar, S.; Yadav, V.; Prakash, A.; Gurjar, H. *World J. Pharm. Pharmaceut. Sci.* **2015**, *4*, 287-305. (c) Kliebenstein, D. J. *Annu. Rev. Phytopathol.* **2012**, *50*, 155-173. (d) Schoonhoven, L. M.; Van Loon, J. J. A.; Dicke, M., *Insect-plant biology*. 2nd ed.; Oxford University Press on Demand: Oxford, 2005; . (e) Silva, L. N.; Zimmer, K. R.; Macedo, A. J.; Trentin, D. S. *Chem. Rev.* **2016**, *116*, 9162-9236.

121. (a) Cogni, R.; Trigo, J. R. *Neotrop. Entomol.* **2016**, *45*, 252-257. (b) Joosten, L.; van Veen, J. A. *Phytochem. Rev.* **2011**, *10*, 127-136. (c) Narberhaus, I.; Zintgraf, V.; Dobler, S. *Chemoecology* **2005**, *15*, 121-125. (d) Nuringtyas, T. R.; Verpoorte, R.; Klinkhamer, P. G.; van Oers, M. M.; Leiss, K. A. *J. Chem. Ecol.* **2014**, *40*, 609-616. (e) Thoden, T. C.; Boppré, M.; Hallmann, J. *Nematology* **2007**, *9*, 343-349. (f) Trigo, J. R. *Phytochem. Rev.* **2010**, *10*, 83-98.

122. (a) Kim, H. Y.; Stermitz, F. R.; Molyneux, R. J.; Wilson, D. W.; Taylor, D.; Coulombe, R. A. *Toxicol. Appl. Pharmacol.* **1993**, *122*, 61-69. (b) Liddell, J. R. *Nat. Prod. Rep.* **2000**, *17*, 455-462. (c) Mattocks, A. R. *Nature* **1968**, *217*, 723-728. (d) Robertson, J.; Stevens, K. *Nat. Prod. Rep.* **2014**, *31*, 1721-1788. (e) Wiedenfeld, H.; Edgar, J. *Phytochem. Rev.* **2010**, *10*, 137-151.

123. (a) Broggini, G.; Zecchi, G. *Synthesis* **1999**, 905-917. (b) Ikeda, M.; Sato, T.; Ishibashi, H. *Heterocycles* **1988**, *27*, 1465-1487. (c) Martinez, S. T.; Belouezzane, C.; Pinto, A. C.; Glasnov, T. *Org. Prep. Proc. Int.* **2016**, *48*, 223-253. (d) Pyne, S. G.; Tang, M. *Curr. Org. Chem.* **2005**, *9*, 1393-1418.

124. Salunke, R. V.; Ramesh, N. G. *Eur. J. Org. Chem.* **2016**, 654-657.

125. Crabb, T. A.; Newton, R. F.; Jackson, D. *Chem. Rev.* **1971**, *71*, 109-126.

126. Abbaspour Tehrani, K.; D'hooghe, M.; De Kimpe, N. *Tetrahedron* **2003**, *59*, 3099-3108.

127. Gademann, K.; Kerschgens, I. *Synthesis* **2015**, *47*, 3153-3160.

128. Hirner, J. J.; Roth, K. E.; Shi, Y.; Blum, S. A. *Organometallics* **2012**, *31*, 6843-6850.

129. De Smaele, D.; Bogaert, P.; De Kimpe, N. *Tetrahedron Lett.* **1998**, *39*, 9797-9800.

130. Toma, Y.; Kunigami, M.; Watanabe, K.-j.; Higashi, M.; Arimitsu, S. *J. Fluorine Chem.* **2016**, *189*, 22-32.

131. Manjappa, K. B.; Peng, Y.-T.; Jhang, W.-F.; Yang, D.-Y. *Tetrahedron* **2016**, *72*, 853-861.

132. Mancebo-Aracil, J.; Nájera, C.; Castelló, L. M.; Sansano, J. M.; Larrañaga, O.; de Cózar, A.; Cossío, F. P. *Tetrahedron* **2015**, *71*, 9645-9661.

133. Nguyen Van, T.; De Kimpe, N. *Tetrahedron* **2000**, *56*, 7969-7973.

134. (a) Opatz, T. *Synthesis* **2009**, 1941-1959. (b) Otto, N.; Opatz, T. *Chem. Eur. J.* **2014**, *20*, 13064-13077.

135. Bergner, I.; Wiebe, C.; Meyer, N.; Opatz, T. *J. Org. Chem.* **2009**, *74*, 8243-8253.

136. Payne, G. B. *J. Org. Chem.* **1962**, *27*, 3819-3822.

137. Hanson, R. M., *Epoxide Migration (Payne Rearrangement) and Related Reactions*. John Wiley & Sons, Inc.: 2002; Vol. 60.

138. (a) Bilke, J. L.; Dzuganova, M.; Fröhlich, R.; Würthwein, E.-U. *Org. Lett.* **2005**, *7*, 3267-3270. (b) Bouyacoub, A.; Volatron, F. *Eur. J. Org. Chem.* **2002**, 4143-4150. (c) Ibuka, T. *Chem. Soc. Rev.* **1998**, *27*, 145-154. (d) Kulshrestha, A.; Salehi Marzijarani, N.; Dilip Ashtekar, K.; Staples, R.; Borhan, B. *Org. Lett.* **2012**, *14*, 3592-3595. (e) Schomaker, J. M.; Bhattacharjee, S.; Yan, J.; Borhan, B. *J. Am. Chem. Soc.* **2007**, *129*, 1996-2003. (f) Xichun, F.; Guofu, Q.; Shucai, L.; Hanbing, T.; Lamei, W.; Xianming, H. *Tetrahedron: Asymmetry* **2006**, *17*, 1394-1401. (g) Xu, W.; Zhang, J.; Guo, H.; Zhu, Q.; Hu, X. *Lett. Org. Chem.* **2009**, *6*, 412-415.

139. (a) Rayner, C. M. *Contemp. Org. Synth.* **1996**, *3*, 499-533. (b) Rayner, C. M. *Synlett* **1997**, 11-21.

140. Sureshkumar, D.; Koutha, S.; Ganesh, V.; Chandrasekaran, S. *J. Org. Chem.* **2010**, *75*, 5533-5541.

141. (a) Grzelak, P.; Mlostoń, G. *Chem. Heterocycl. Compd.* **2016**, *52*, 282-284. (b) Kaur, N.; Kishore, D. *Synth. Commun.* **2014**, *44*, 2615-2644. (c) O'Leary, E. M.; Jones, D. J.; O'Donovan, F. P.; O'Sullivan, T. P. *J. Fluorine Chem.* **2015**, *176*, 93-120. (d) Xu, J., Synthesis of Four- to Seven-Membered Heterocycles by Ring Expansion: Ring Expansions of Thiiranes and Thietanes. In *Synthesis of 4- to 7-membered Heterocycles by Ring Expansion* D'hooghe, M.; Ha, H.-J., Eds. Springer International Publishing: Switzerland, 2016; Vol. 41, 311-361.

142. (a) Andersson, P. G.; Guijarro, D.; Tanner, D. *J. Org. Chem.* **1997**, *62*, 7364-7375. (b) Davoli, P.; Forni, A.; Moretti, I.; Prati, F.; Torre, G. *Tetrahedron* **2001**, *57*, 1801-1812. (c) D'hooghe, M.; De Kimpe, N. *Chem. Commun.* **2007**, 1275-1277. (d) D'hooghe, M.; Kenis, S.; Vervisch, K.; Lategan, C.; Smith, P. J.; Chibale, K.; De Kimpe, N. *Eur. J. Med. Chem.* **2011**, *46*, 579-587. (e) D'hooghe, M.; Vandekerckhove, S.; Mollet, K.; Vervisch, K.; Dekeukeleire, S.; Lehoucq, L.; Lategan, C.; Smith, P. J.; Chibale, K.; De Kimpe, N. *Beilstein J. Org. Chem.* **2011**, *7*, 1745-1752. (f) D'hooghe, M.; Vanlangendonck, T.; Törnroos, K. W.; De Kimpe, N. *J. Org. Chem.* **2006**, *71*, 4678-4681. (g) D'hooghe, M.; Waterinckx, A.; De Kimpe, N. *J. Org. Chem.* **2005**, *70*, 227-232. (h) Manaka, T.; Nagayama, S. I.; Desadee, W.; Yajima, N.; Kumamoto, T.; Watanabe, T.; Ishikawa, T.; Kawahata, M.; Yamaguchi, K. *Helv. Chim. Acta* **2007**, *90*, 128-142. (i) Pak, C. S.; Kim, T. H.; Ha, S. J. *J. Org. Chem.* **1998**, *63*, 10006-10010.

143. Loos, R.; Kobayashi, S.; Mayr, H. *J. Am. Chem. Soc.* **2003**, *125*, 14126-14132.

144. Bertini, I.; Sabatini, A. *Inorg. Chem.* **1966**, *5*, 1025-1028.

145. Lu, P. *Tetrahedron* **2010**, *66*, 2549-2560.

146. (a) Stanković, S.; D'hooghe, M.; De Kimpe, N. *Org. Biomol. Chem.* **2010**, *8*, 4266-4273. (b) Vilhelmsen, M. H.; Ostergaard, L. F.; Nielsen, M. B.; Hammerum, S. *Org. Biomol. Chem.* **2008**, *6*, 1773-1778.

147. (a) Huang, J.; Wang, F.; Du, D.-M.; Xu, J. *Synthesis* **2005**, 2122-2128. (b) Li, X.; Xu, J. *Tetrahedron* **2011**, *67*, 1681-1688. (c) Silvestri, M. G.; Wong, C.-H. *J. Org. Chem.* **2001**, *66*, 910-914. (d) Xu, J.; Yu, H.; Cao, S.; Zhang, L.; Liu, G. *Synthesis* **2009**, 2205-2209.

148. Xu, J.; Huang, J.; Du, D.-M. *Synthesis* **2006**, 315-319.

149. (a) Ram, R. N.; Gupta, D. K.; Soni, V. K. *Eur. J. Org. Chem.* **2016**, 3434-3440. (b) Dong, C.; Alper, H. *Org. Lett.* **2004**, *6*, 3489-3492.

150. Gay, J.; Scherowsky, G. *Synth. Commun.* **1995**, *25*, 2665-2672.

151. Carlier, P. R.; Liu, G.; Peter Lam, H. Y. *Phosphorus, Sulfur Silicon Relat. Elem.* **1997**, *126*, 223-234.

152. (a) De Kimpe, N.; De Smaele, D.; Bogaert, P. *Synlett* **1994**, 287-288. (b) De Kimpe, N.; Jolie, R.; De Smaele, D. *J. Chem. Soc., Chem. Commun.* **1994**, 1221-1222.

153. (a) Joce, C.; Caryl, J.; Stockley, P. G.; Warriner, S.; Nelson, A. *Org. Biomol. Chem.* **2009**, *7*, 635-638. (b) Joce, C.; White, R.; Stockley, P. G.; Warriner, S.; Turnbull, W. B.; Nelson, A. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 278-284.

154. (a) Conti, P.; Dallanoce, C.; De Amici, M.; De Micheli, C.; Carrea, G.; Zambianchi, F. *Tetrahedron: Asymmetry* **1998**, *9*, 657-665. (b) De Amici, M.; Dallanoce, C.; De Micheli, C.; Angeli, P.; Marucci, G.; Cantalamessa, F.; Sparapassi, L. *Life Sci.* **2000**, *67*, 317-326.

155. Jackson, J.; Chen, C.; Buising, K. *Curr. Opin. Infect. Dis.* **2013**, *26*, 516-525.

156. Voelker, T.; Xia, H.; Fandrick, K.; Johnson, R.; Janowsky, A.; Cashman, J. R. *Bioorg. Med. Chem.* **2009**, *17*, 2047-2068.

157. Fenga, M.; Tanga, B.; Liangb, S. H.; Xuefeng Jiang, X. *Curr. Top. Med. Chem.* **2016**, *16*, 1200-1216.

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EDUCATION

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	PhD thesis	"New strategies for the construction of heterocyclic systems through ring transformation of aziridines and azetidines"
	Promoter	Prof. dr. ir. Matthias D'hooghe
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2011-2013   Master of Science in Bioscience Engineering: Chemistry and Bioprocess Technology (graduated with greatest distinction)

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	Master thesis	"Synthese van gefunctionaliseerde pyrrolidinen en piperidinen uitgaande van 1-tosyl-2-(trifluormethyl)aziridine"
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2008-2011   Bachelor of Science in Bioscience Engineering: Chemistry and Food technology (graduated with greatest distinction)

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2002-2008   Sint-Aloysiuscollege, Diksmuide

	Third grade	Latin-Mathematics
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SCIENTIFIC PUBLICATIONS IN INTERNATIONAL PEER-REVIEWED JOURNALS (A1)

1) **Dolfen, J.**; Kenis, S.; Van Hecke, K; De Kimpe, N.; D'hooghe, M. "Selective synthesis of functionalized trifluoromethylated pyrrolidines, piperidines, and azepanes starting from 1-tosyl-2-(trifluoromethyl)aziridine". *Chem. Eur. J.* **2014**, *20*, 10650-10653 (I.F. 5.73).

2) **Dolfen, J.**; Vervisch, K.; De Kimpe, N.; D'hooghe, M. "LiAlH₄-induced selective ring rearrangement of 2-(2-cyanoethyl)aziridines toward 2-(aminomethyl)pyrrolidines and 3-aminopiperidines as eligible heterocyclic building blocks". *Chem. Eur. J.* **2016**, *22*, 4945-4951 (I.F. 5.77).

3) **Dolfen, J.**; De Kimpe, N.; D'hooghe, M. "Deployment of small-ring azaheterocycles as building blocks for the synthesis of organofluorine compounds". *Synlett* **2016**, *27*, 1486-1510 (I.F. 2.32).

4) **Dolfen, J.**; Yadav, N. N.; De Kimpe, N.; D'hooghe, M.; Ha, H.-J. "Bicyclic aziridinium ions in azaheterocyclic chemistry – Preparation and synthetic application of 1-azoniabicyclo[n.1.0]alkanes". *Adv. Synth. Catal.* **2016**, *358,* 3485-3511 (I.F. 6.45).

5) **Dolfen, J.**; D'hooghe, M. "Concise synthesis of 3-(aminomethyl)pyrrolizidines via an In(OTf)₃-mediated ring rearrangement of 2-[2-(1-pyrrolin-2-yl)alkyl]aziridines". *Synthesis* **2017**, *49*, 2215-2222 (I.F. 2.65).

6) **Dolfen, J.**; Van Hecke, K.; D'hooghe, M. "LiAlH₄-induced thia-aza-Payne rearrangement of functionalized 2-(thiocyanatomethyl)aziridines into 2-(aminomethyl)thiiranes as an entry to 5-(chloromethyl)thiazolidin-2-ones". *Eur. J. Org. Chem.* **2017**, 3229-3233 (I.F. 3.07).

7) **Dolfen, J.**; Boydas, E. B.; Van Speybroeck, V.; Catak, S.; Van Hecke, K.; D'hooghe, M. "Asymmetric synthesis of 3,4-disubstituted 2-(trifluoromethyl)pyrrolidines through rearrangement of chiral 2-(2,2,2-trifluoro-1-hydroxyethyl)azetidines". *J. Org. Chem.* **2017**, DOI: 10.1021/acs.joc.7b01241 (I.F. 4.85).

ACTIVE PARTICAPATIONS AT CONFERENCES

1) **Dolfen, J.**; Kenis, S.; Van Hecke, K; De Kimpe, N.; D'hooghe, M. "Selective synthesis of functionalized trifluoromethylated pyrrolidines, piperidines, and azepanes starting from 1-tosyl-2-(trifluoromethyl)aziridine" (poster P-085), *14th Belgian Organic Synthesis Symposium* (July 13-18, **2014**, Louvain-la-Neuve, Belgium).

2) **Dolfen, J.**; Kenis, S.; Van Hecke, K; De Kimpe, N.; D'hooghe, M. "Selective synthesis of functionalized trifluoromethylated pyrrolidines, piperidines, and azepanes starting from 1-tosyl-

2-(trifluoromethyl)aziridine" (poster P-37), *18th Sigma-Aldrich Organic Synthesis Meeting* (December 4-5, **2014**, Blankenberge, Belgium).

3)   **Dolfen, J.**; Vervisch, K.; De Kimpe, N.; D'hooghe, M. "LiAlH$_4$-induced selective ring rearrangement of 2-(2-cyanoethyl)aziridines toward 2-(aminomethyl)pyrrolidines and 3-aminopiperidines as eligible heterocyclic building blocks". (poster P-091), *15th Belgian Organic Synthesis Symposium* (July 10-15, **2016**, Antwerp, Belgium).

4)   **Dolfen, J.**; D'hooghe, M. "Concise synthesis of 3-(aminomethyl)pyrrolizidines via an In(OTf)$_3$-mediated ring rearrangement of 2-[2-(1-pyrrolin-2-yl)alkyl]aziridines" (poster P-71), *20th Sigma-Aldrich Organic Synthesis Meeting* (December 8-9, **2016**, Blankenberge, Belgium).

TUTORING OF MASTER THESIS STUDENTS

1)   Quintens, D. "Onderzoek naar de bereiding van 1-azabicyclo[2.2.1]heptaan-aminochinoline-hybriden als potentiële antimalariamiddelen" (2015-2016).

2)   Bultinck, M. "Synthesis and cytotoxic assessment of azaheteroaromatic curcumin analogues" (2016-2017).