“Be the change that you wish to see in the world.”

Mahatma Gandhi

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Synthesis of new cyclic and acyclic biologically relevant amino acid derivatives

Thesis submitted in fulfillment of the requirements for the degree of Doctor (PhD) in Applied Biological Sciences: Chemistry and Bioprocess Technology

Dutch translation of the title: **Synthese van nieuwe cyclische en acyclische biologisch relevante aminozuurderivaten**

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> "And once the storm is over, you won't remember how you made it through, how you managed to survive. You won't even be sure, whether the storm is really over. But one thing is certain. When you come out of the storm, you won't be the same person who walked in. That's what this storm's all about."
>
> *(*Haruki Murakami, *Kafka on the Shore)*

More than four years ago I came to Belgium for the greatest challenge in my life (…so far). I am internally happy and thankful for this priceless experience and knowledge which I got here. I would like to express my gratitude to the many people who have been by my side for all this years; to all those who provided support, who made this journey to be an exciting and beautiful one.

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Elena Semina

Ghent, 2016

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List of abbreviations

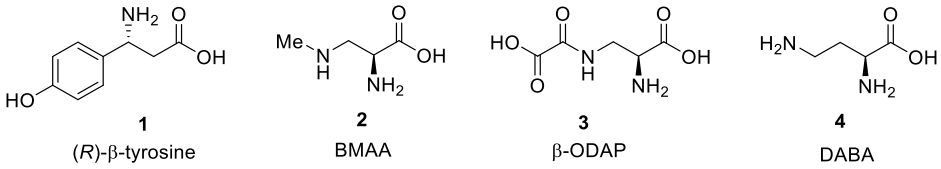
Ac: acetyl
Ala: alanine
ALS-PDC: amyotrophic lateral sclerosis and the parkinsonism-dementia complex
Amyl: pentyl
Aze: azetidine-2-carboxylic acid
β-ODAP: β-*N*-oxalyl-L-α,β-diaminopropionic acid
BINOL: 1,1′-bi(2-naphthol)
BMAA: β-*N*-methylamino-L-alanine
Bn: benzyl
Boc: *tert*-butoxycarbonyl
Bus: *tert*-butoxysulfonyl
CAN: cerium(IV) ammonium nitrate
Cbz: carboxybenzyl
$Cp_2Zr(H)Cl$: bis(cyclopentadienyl)zirconium chloride hydride
DABA: 2,4-diaminobutanoic acid
DBU: 1,8-diazabicyclo[5.4.0]undec-7-ene
DEAD: diethyl azodicarboxylate
DIAD: diisopropyl azodicarboxylate
DIBAL-H: diisobutylaluminium hydride
DIPEA: *N*,*N*-diisopropylethylamine
DMA: *N*,*N*-dimethylacetamide
DMAP: 4-dimethylaminopyridine
DMF: *N*,*N*-dimethylformamide
DMPU: 1,3-dimethyl-3,4,5,6-tetrahydro-2(*1H*)-pyrimidinone
DMSO: dimethyl sulfoxide
DOS: diversity oriented synthesis
dr: diastereomeric excess
DRI: direct renin inhibitor
ee: enantiomeric excess
E^+: electrophile
equiv: equivalent
GABA: γ-aminobutyric acid
HIV: human immunodeficiency virus
HPLC: High-Performance Liquid Chromatography
IBX: 2-iodoxybenzoic acid
KHMDS: potassium bis(trimethylsilyl)amide
LDA: lithium diisopropylamide
LiHMDS: lithium bis(trimethylsilyl)amide
Mbs: *p*-methoxybenzenesulfonyl
*m*CPBA: 3-chloroperoxybenzoic acid
MCR: multicomponent reaction
mGluR5: metabotropic glutamate receptor 5
$MMPP{\cdot}6H_2O$: magnesium monoperoxyphthalate hexahydrate
Ms: methanesulfonyl
MTPA-Cl (Mosher acid chloride): α-methoxy-α-trifluoromethylphenylacetyl chloride
NaHMDS: sodium bis(trimethylsilyl)amide
NBS: *N*-bromosuccinimide
NMDA: *N*-Methyl-D-aspartic acid
NMO: *N*-methylmorpholine *N*-oxide
NPAA: non-proteinogenic amino acid
Ns: 4-nitrobenzenesulfonyl
Nu: nucleophile

PA: picolinamide (2-pyridinecarboxamide)
PE: petroleum ether
PivCl: pivaloyl chloride (trimethylacetyl chloride)
PKC: protein kinase C
PMP: *p*-methoxyphenyl
PPII: polyproline II helix
PPTS: pyridinium *p*-toluenesulfonate
Py: pyridine
r.t.: room temperature
RCM: ring closure metathesis
TAT: tyrosine aminotransferase
TBAc: *tert*-butyl acetate
TBAF: tetra-*n*-butylammonium fluoride
TBAI: tetrabutylammonium iodide
TBDPSCl: tert-butyldiphenylchlorosilane
TBS: *tert*-butyldimethylsilyl
TBTU: *O*-(benzotriazol-1-yl)-*N*,*N*,*N'*,*N'*-tetramethyluronium tetrafluoroborate
TEBAC: benzyltriethylammonium chloride
TEMPO: 2,2,6,6-tetramethyl-1-piperidinyloxyl
Tf: trifluoromethanesulfonyl
TFA: trifluoroacetic acid
TFAA: trifluoroacetic anhydride
THF: tetrahydrofuran
TIPP: triisopropylphenyl
TMEDA: *N*,*N*,*N´*,*N´*-tetramethylethylenediamine
TMS: trimethylsilyl/tetramethylsilane
Tol: *p*-tolyl
Tos/Tosyl: *p*-toluenesulfonyl
Tr (trityl): triphenylmethyl
trans-ACHC: *trans*-2-aminocyclohexanecarboxylic acid
trans-ACPC: *trans*-2-aminocyclopentanecarboxylic acid
TS: transition state
Δ: reflux temperature
4Å MS: molecular sieves 4Å

1 Introduction and goals

Amino acids are classified as non-proteinogenic amino acids (NPAAs) when they are not part of the 22 standard α-amino acids that are translated into proteins by the genetic code.[1] NPAAs occur in nature and can be chemically designed and synthesized as well.[2] Among 700 known NPAAs, around 300 are found in plants. The significant role of NPAA in plants and soil was recently reviewed.[3] Thus, NPAAs could be considered as an important store of organic nitrogen in many ecosystems, as metabolites, as allelopathic substances. For instance, (*R*)-β-tyrosine **1**, a β-amino acid which is enzymatically produced from (*S*)-α-tyrosine, is an interesting allelopathic compound with potential to suppress weeds in rice fields.[4] Moreover, NPAAs are involved in plant defense against insect herbivores.[5]

Since NPAAs, *i.e.* proteomimetic amino acids, were found in proteins, the investigation of the significance of this in drug discovery and peptide synthesis gained close attention as NPAAs can possess interesting biological activity and can substitute the original α-amino acids in polypeptide chains in order to modulate their structure and activity.[6] Moreover, protein misfolding and protein aggregation may cause diseases such as amyotrophic lateral sclerosis, Parkinson's and Alzheimer's diseases and neurodegenerative neurolathyrism.[7] The role of protein aggregation could be accelerated by the incorporation of proteomimetic amino acids into proteins as an environmental factor. Important examples of such toxins are β-*N*-methylamino-L-alanine **2** (BMAA) and β-*N*-oxalyl-L-α,β-diaminopropionic acid **3** (β-ODAP) (Figure 1).[8]



1 (*R*)-β-tyrosine **2** BMAA **3** β-ODAP **4** DABA

Figure 1

BMAA was first isolated from seeds of *Cycas circinalis* and reported as neurotoxic to "higher animals".[9] BMAA is produced by the majority of cyanobacterial isolates,[10] and has been found in cycad seeds, plausibly derived from symbiotic cyanobacteria in coralloid roots (*Cyca micronesica*) as well as in species of free-living marine cyanobacteria, which may bioaccumulate in the marine food web.[11] Moreover, BMAA was recently found in shark fins.[12] This proteomimetic amino acid has the potential to be a major environmental factor capable of causing amyotrophic lateral sclerosis (ALS) and other neurodegenerative diseases.[13] The toxicity of BMAA is connected with amyotrophic lateral sclerosis and the parkinsonism-dementia complex (ALS-PDC), because a high rate of this disease was observed among Chamorro people from Guam.[14] First, it was suggested that consumption of the cycad flour by Chamorro people of Guam is a main source of BMAA, however,

this hypothesis was initially disputed because the level of the neurotoxin in cycad flour after processing is too low to be a cause of neurofibrillary degeneration of nerve cells observed in ALS-PDC of Guam.[15] However, recently the association between BMAA and ALS disease regained attention because it was demonstrated that BMAA can become protein-associated, leading to increases in human BMAA levels and providing a potential mechanism for slow release.[16] Additionally, it was shown that BMAA is biomagnified *via* the food chain from the cyanobacteria symbionts on cycad plants to the flying foxes, which are present in the Chamorro people diet.[17] The univocal mechanism of BMAA toxicity was not established and chronic toxicity might be mechanistically differ from acute toxicity, but several suggestions were made. In the first proposal, the toxicity of BMAA was based on its action as an agonist for glutamate receptors (NMDA, mGluR5).[18] Another suggestion was based on the effect of BMAA on system x_c^- (cystine/glutamate antiporter),[19] inducing oxidative stress and increase of extracellular glutamate.[20] Recently, the Rodgers research group found that BMAA can be misincorporated in place of L-serine in human proteins *in vitro*, with subsequent protein misfolding, what can be a putative explanation of the toxicity of BMAA **2**.[21] Noteworthy, the described misincorporation can be inhibited by L-serine.

Another neurotoxin, β-ODAP **3**, was found in the seeds of grass peas (*Lathyrus sativus* L. family *Fabaceae* syn. *Leguminosae*) and was proposed to be responsible for the neurodegenerative disease neurolathyrism.[22] The clinical syndrome of the latter disease is attributed to the excessive consumption of grass pea seeds as survival food in some regions of Africa and Asia due to the hardy and drought tolerant nature of the plants.[23] Albeit numerous studies were performed in order to establish the mechanism of initiation of neurolathyrism by β-ODAP, understanding the precise mechanism of toxicity remains challenging.[24] Moreover, β-ODAP was reported as an inhibitor of tyrosine aminotransferase (TAT) and as activator of protein kinase C (PKC).[25] Another example of a NPAA is α,γ-diaminobutyric acid **4** (DABA, or 2,4-diaminobutanoic acid) which was found in *Lathyrus* species.[26] DABA is highly toxic and, as β-ODAP, could cause a type of neurolathyrism (Figure 1).[27]

An important example of a cyclic NPAA is azetidine-2-carboxylic acid (Aze) **5** (Figure 2) which mimics proline and could be incorporated into polypeptides promoting irreversible abnormal protein conformation, which could also result in neurodegeneration, multiple sclerosis and autoimmune disorders.[28] Additionally, derivatives of Aze **5** are known as active pharmaceutical ingredients, as for example the withdrawn thrombin inhibitor melagatran **6** (Figure 2).[29]

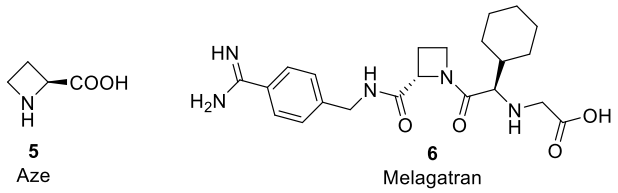


Figure 2

The design and synthesis of new peptides with discrete and predictable folding propensities ("foldamers") is one of the essential topics both in academia and in the pharmaceutical industry.[30] Peptides, constructed of α-amino acids, have some disadvantages such as low bioavailability and susceptibility to enzymatic degradation as well as flexibility of the peptide backbone, hampering the definition of the bioactive conformation. One of the possible solutions to these problems is the use of β-amino acids instead for the synthesis of oligomers (so called β-peptides).[31] The most interesting properties of β-peptides are folding in a predictable way and stability to cleavage by peptidases. The conformationally restricted alicyclic analogues of β-amino acids represent even more advantages for the chemistry of β-peptides.[32] Thus, *trans*-2-aminocyclohexanecarboxylic acid **7** (*trans*-ACHC) and *trans*-2-aminocyclopentanecarboxylic acid **8** (*trans*-ACPC) formed predictable peptide 14- and 12-helices, respectively, what is unprecedented among α-peptides (Figure 3).[33]

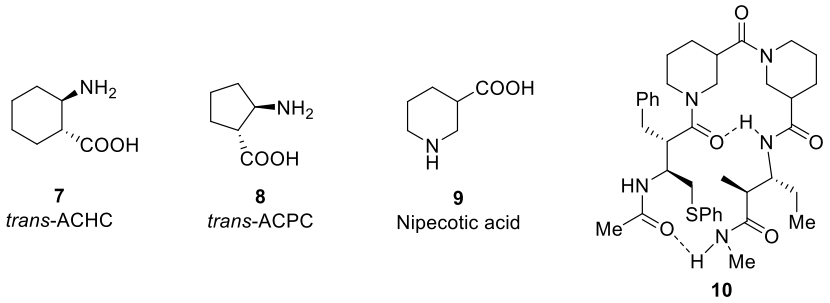


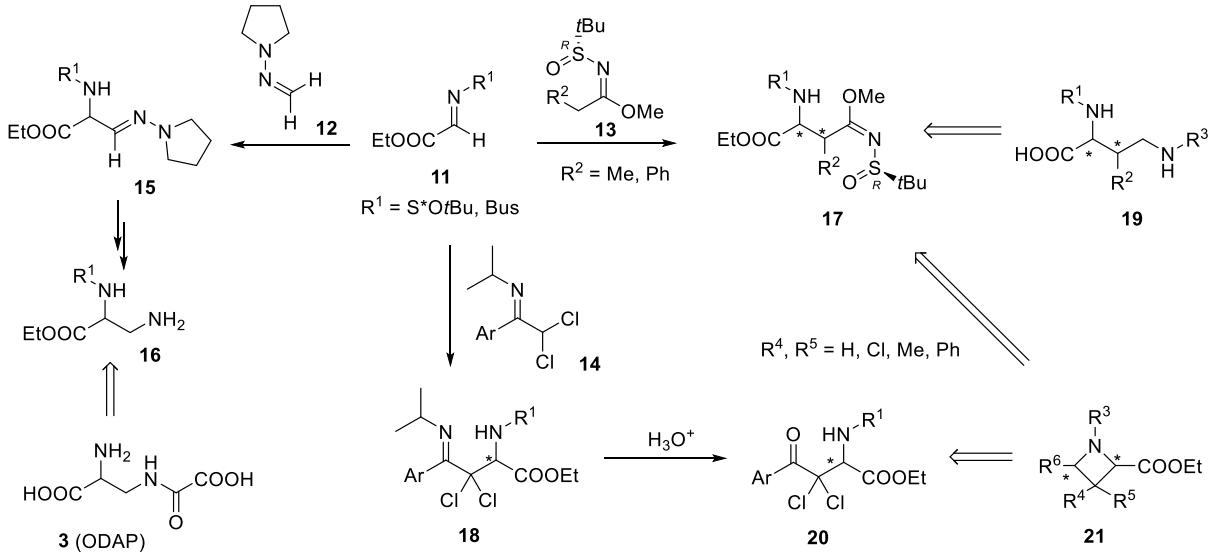
Figure 3

On the other hand, azacyclic β-amino acids allowed to generate peptides with sheet conformation. For instance, nipecotic acid **9** was incorporated in a short peptide **10** that appeared to adopt well-defined conformations (Figure 3).[34] It was suggested that dinipecotic acid segments are useful for the development of β-turn mimics for biological application[35] and for the creation of hairpin-shaped catalysts for asymmetric reactions.[36] Moreover, homooligomers of (*S*)-nipecotic acid are able to adopt non-hydrogen-bonded secondary structures such as the polyproline II helix (PPII).[37]

In view of the importance of the aforementioned classes of non-proteinogenic amino acids in different fields of biological study, the aim of the present PhD-work is to expand on the synthesis of some of these amino acids and their analogues *via* different new pathways, involving diversity oriented synthesis (DOS) as major approach. Initially, (chiral) building blocks will be prepared which

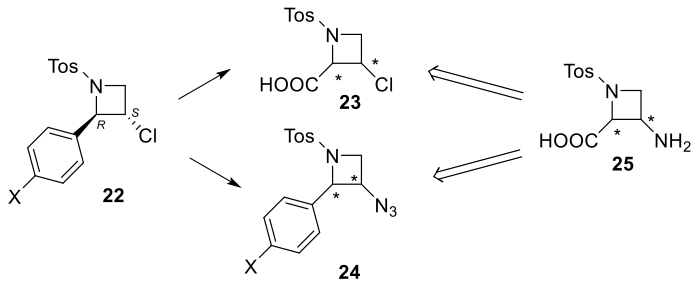
are suited for subsequent (stereoselective) coupling reactions and final functional group transformations or cyclization. The focus of DOS is on efficient synthesis of collections of small molecules with skeletal and stereochemical diversity.[38] Both acyclic and cyclic α- and β-amino acid derivatives functionalized with diverse groups will be prepared. Such compounds can serve as analytical or biological tools in research regarding NPAAs or as building blocks in functional peptidomimetic foldamers.

In the first part, it is envisioned that the addition of 1-(methylenamino)pyrrolidine **12**, which possesses nucleophilic properties associated to its aza-enamine character,[39] across *N*-sulfinyl- or *N*-sulfonyliminoesters **11** would lead to the formation of adducts **15** (Scheme 1). The *N*-sulfinylimino ester **11** (R = S*O*t*Bu) was previously represented as a versatile reagent for the asymmetric synthesis of α- amino acids.[40] The *N*-sulfinyl substituent in iminoacetate **11** exerts a powerful stereodirecting effect and activates the C=N bond for nucleophilic addition and could be easily deprotected as well by simple acid hydrolysis.[41] *N*-sulfonyl imines **11** (R = Bus) also proved to be useful synthons in organic chemistry, including cycloadditions and nucleophilic reactions.[42] Adducts **15** could be foreseen as precursors for the synthesis of α,β-diamino acid derivatives. Thus, reduction of the C=N bond in **15** and subsequent N-N cleavage (for example, with BH_3·THF)[43] could provide the diaminopropanoic acid derivatives **16** which could be elaborated towards ODAP **3** (Scheme 1). Noteworthy, this synthetic pathway would provide an advantageous chiral synthesis of diamino acid **3** as opposed to the previously described methods. The latter were mainly based on chiral pool synthesis, having a lack of efficiency or requiring harsh reaction conditions.[22a, 44] Additionally, the chiral *N*-sulfinyl iminoacetate **11** (R = S^RO*t*Bu) will be explored as electrophilic substrate in addition reactions of imidates **13** or α,α- dichloroketimines **14** in order to obtain the adducts **17** and **18**, respectively. Adducts **17** could serve as precursor for the synthesis of enantiomerically pure α,γ-diamino acid derivatives **19**. Moreover, substrates **17** and **18** could be transformed into substituted azetidine-2-carboxylic acid derivatives **21** *via* elaboration of the imino and imidate moiety towards possible leaving groups. 3,3-Dichloroazetidines **21** (R^5 = R^6 = Cl) form a rather unknown class of strained azaheterocycles and their synthesis is rarely reported in the literature.[45] Moreover, the asymmetric synthesis of these dichloroazetidines was not previously described. The 3,3-dichlorinated azetidines **11** represent valuable substrates towards a broad range of reactivities, including formation of 2-azetines and its further transformations (*i.e.* ring constructions or ring opening).[45b, 46]



Scheme 1

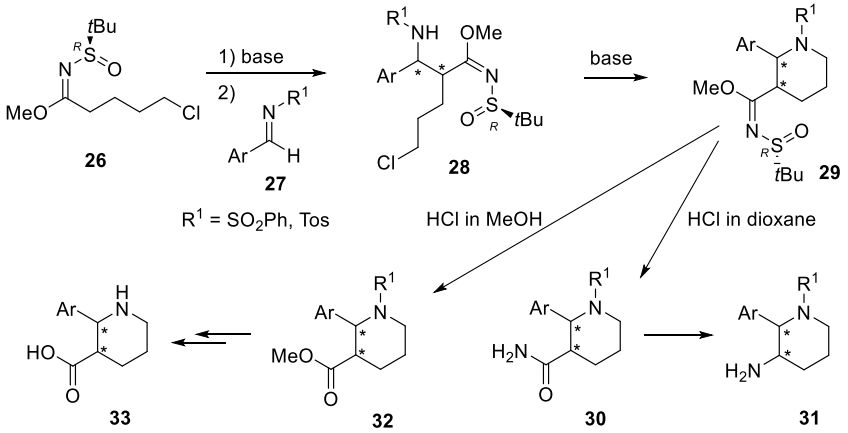
Previous research at the Department of Sustainable Organic Chemistry and Technology (UGent) has shown that the addition of α-chloro *N*-sulfinyl imidates across *N*-tosyl aldimines proceeds with high *anti*-diastereoselectivity, affording enantiomerically pure imidates, which were elaborated towards chiral 3-chloro-2-arylazetidines **22**.[47] In the present research, further transformations of those azetidines **22** (Scheme 2), involving oxidation of aromatic C-2 substituent and nucleophilic substitution of the chloride at C-3, will be attempted in order to synthesize the 3-aminoazetidine-2-carboxylic acid derivative **25**. The latter azetidine **25** can be used as azacyclic β-amino acid derivative for the synthesis of β-peptides or to develop functional chemical probes for use in the study the relevance of azetidine-2-carboxylic acid **5** in neurodegenerative diseases.[32a]



Scheme 2

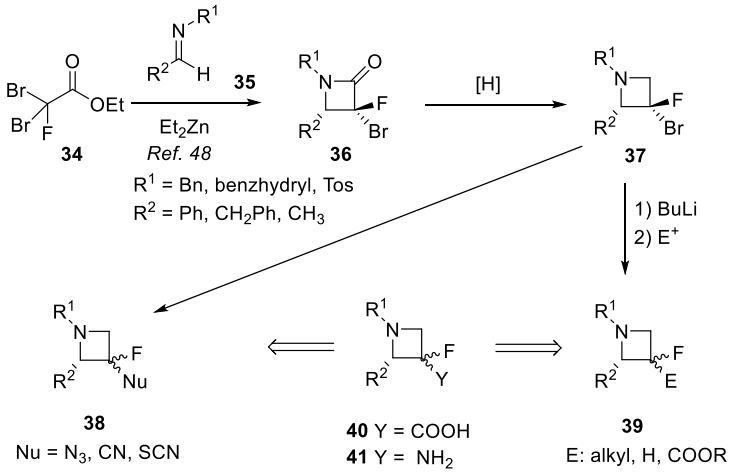
Moreover, it is envisioned that the use of δ-chloro-*N*-sulfinyl imidates **26** in the addition reaction across aromatic aldimines **27** could afford the new chiral β-aryl-δ-chloro-substituted β-amino acid derivatives **28** as potential building blocks for the synthesis of enantiopure 2,3-difunctionalized piperidines **29**-**33** (Scheme 3). The latter piperidines and their derivatives are a well-known class of

organic compounds due to their natural occurrence and their presence in pharmacologically active compounds (*vide infra*).



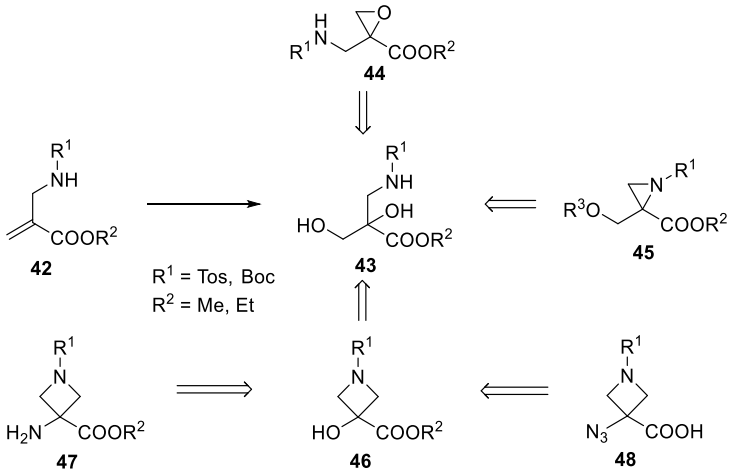
Scheme 3

Fluorinated analogues of bioactive compounds find increasing interest since fluorine often improves the bioactivity and bioavailability of drug molecules.[48] Recently, the diastereoselective synthesis *cis*-α-bromo-α-fluoro-β-lactams **36** (Scheme 4) was reported using the diethylzinc-promoted Reformatsky-type reaction of ethyl dibromofluoroacetate **34** with aromatic aldimines **35**.[49] The β-lactams **36** are envisioned as attractive precursors for the synthesis of new 2-aryl-3-bromo-3-fluoroazetidines **37** *via* reduction of the carbonyl functionality. Because of incorporation of bromide and fluoride at the C-3 position of the azetidine ring, the investigation of the reactivity of azetidines **37** is in the focus of the following research. Indeed, the nucleophilic substitution of bromide with functional groups such as azide or cyanide would provide valuable precursors **38** towards fluorinated 3-aminoazetidines **40** or azetidine-3-carboxylic acid derivatives **41**. Additionally, the elaboration of azetidines **37** *via* a halogen-exchange strategy will be attempted pursuing the synthesis of cyclic amino acid derivatives **41**. Moreover, the scope of the Reformatsky-type reaction will be extended towards the use of a broad range of aldimines, including aliphatic aldimines and aldimines bearing an electron-withdrawing group on nitrogen.



Scheme 4

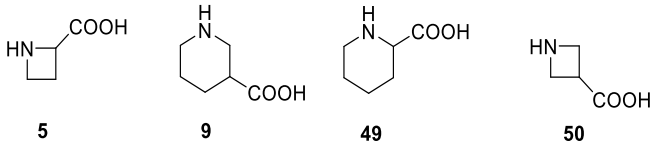
In the last part of this thesis, the research will further elaborate on a preliminary study of the reactivity of alkyl *N*-tosyl-2-(aminomethyl)acrylate.[50] The pool of *N*-substituted alkyl 2-(aminomethyl)acrylates **42** (Scheme 5) will be extended and their transformations towards a diverse range of α- and β-amino acid derivatives, including of alkyl 2-(aminomethyl)oxirane-2-carboxylates **44**, alkyl aziridine-2-carboxylates **45** and alkyl azetidine-3-carboxylates **46**, will be investigated. Elaboration of the azetidines **46** towards the 3-aminoazetidine-3-carboxylates **47** and 3-azidoazetidine-3-carboxylic acids **48** would provide new C^{α}-tetrasubstituted amino acid derivatives. The latter have great potential for the design of peptidomimetic drugs.[51]



Scheme 5

2 Literature overview

The objective of this literature overview is to give a general summary concerning the azacyclic non-proteinogenic α- and β-amino acid derivatives, their significance and synthesis. The present research is mainly devoted to the synthesis of cyclic amino acid derivatives, in particular, with a four- and six-membered heterocyclic core. Therefore, the latter amino acids **5**, **9**, **49**, **50** and their derivatives are the focus of the present report (Figure 4). The synthetic approaches of the last years (2010-2015) are highlighted. The earlier work was summarized in previous reviews.[52]



5 **9** **49** **50**

Figure 4

2.1 Significance of α- and β-amino acids with a piperidine and azetidine skeleton

2.1.1 Pipecolic acid and its derivatives

Pipecolic acid **49** is a naturally occurring non-proteinogenic amino acid which can be found in plants.[53] Numerous natural or synthetic derivatives of pipecolic acid **49** possess interesting biological activity, including anesthetic,[54] NMDA antagonistic, antibiotic,[55] or glycosidase and dehydrogenase inhibition.[56] Furthermore, the pipecolic acid core is a part of complex biologically active molecules. For instance, a pipecolic acid derivative is part of the structure of compounds such as *anti*-tumor antibiotic tetrazomine **51**,[57] rapamycin **52**, which was originally identified as antifungal agent and later recognized as a potent immunosuppressant,[58] allosteric modulator PNU-69176E **53** of the serotonine (5-HT) 5-HT_{2C} receptor (5-HT_{2C}R),[59] and palinavir **54** or its analogue (nelfinavir), as a potent HIV protease inhibitor (Figure 5).[60]

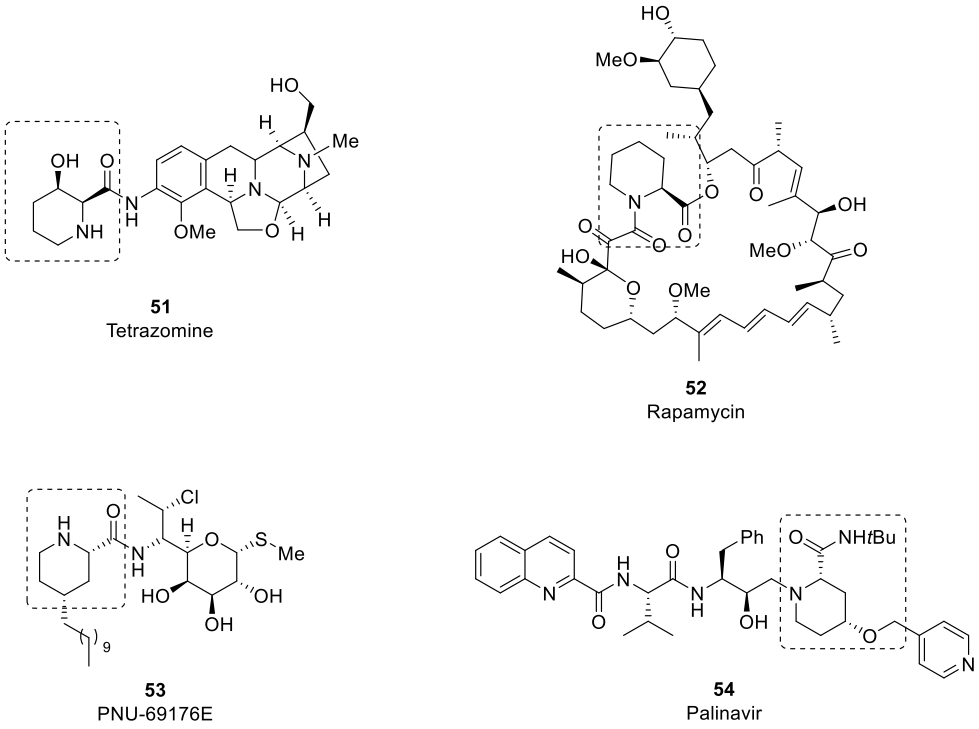


Figure 5

Moreover, pipecolic acid has been used in peptide chemistry.[61] Additionally, *anti*-HIV cyclodepsipeptide, homophymine A **55**, isolated from a New Caledonian collection of the marine sponge *Homophymia sp*, contains a pipecolic acid moiety in the structure (Figure 6).[62]

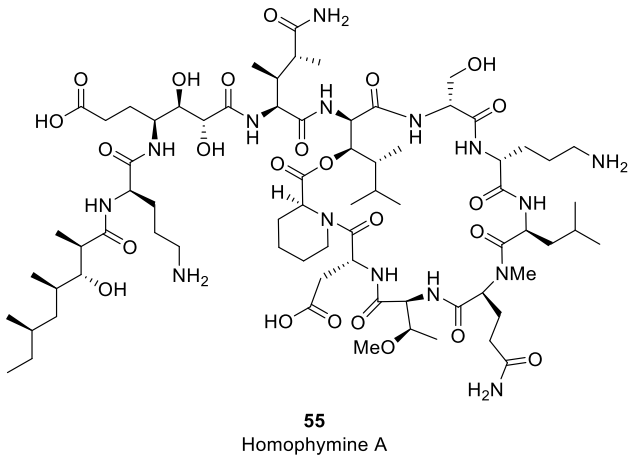


Figure 6

Addtionally, L-pipecolic acid derived *N*-formamides were applied as basic organocatalysts for enantioselective synthesis.[63] Some metal complexes of racemic pipecolic acid exhibit anticancer activity.[64]

2.1.2 Nipecotic acid and its derivatives

Recently, the development of a new series of piperidine-base renin inhibitors **56** and its analogues has gained close attention due to high *in vitro* potency toward human renin with good off-target selectivity and dose-depended blood pressure lowering effects (Figure 7).[65] A necessity for the design of new renin inhibitors, different from direct renin inhibitors (DRIs), is the lack of oral bioactivity of the DRIs. Also, nipecotic acid can be considered as a conformationally restricted γ-aminobutyric acid (GABA) analogue, as exemplified by Tiagabine **57** (Gabitril®).[66]

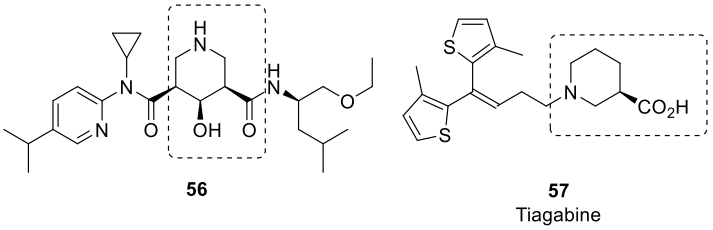


Figure 7

As pipecolic acid **49**, nipecotic acid **9** presents great potential in peptide chemistry.[31c] Functionalized piperidine-3-carboxylic acids are conformationally restricted azacyclic analogues of β-amino acids, which are known to be useful building blocks for the synthesis of peptides with modified and improved biological activities such as stability to metabolization, slow microbial degradation, stability to proteases and peptidases.[32c, 32d, 33e, 58a, 67] It has also been established that nipecotic acid can be incorporated into short homochiral peptides that appear to adopt well-defined conformations. Nipecotic acid-containing heterochiral dipeptides also strongly stabilize reverse-turn formation.[32e, 34, 37] Additionally, piperidine-3-carboxylic acid derivatives were envisioned as potent activators of TrkB receptors in mammalian neurons,[68] as inhibitors of Rho/MKL1/SRF-mediated gene transcription that inhibits invasion of PC-3 prostate cancer cells,[69] and as *anti*-diabetic[70] and *anti*-staphyloccocal agents.[71]

2.1.3 Azetidine-2-carboxylic acid and its derivatives

L-Azetidine-2-carboxylic acid (Aze) **5** is a naturally occurring plant non-proteinogenic amino acid and can be regarded as the lower homolog of proline.[28e] Aze is readily misincorporated in proteins in place of proline in different species, including humans, and causes toxic effects as well as congenital malformations.[28a, 28d, 72] Aze **5** is also a valuable building block for peptide synthesis.[73] Azetidine-2-carboxylic acid derivatives are incorporated in a wide range of biologically and pharmacologically important natural products and synthetic compounds.

Natural products with an Aze moiety in their structure were isolated, including nicotianamine **58**,[74] mugineic acid **59**,[75] 2-deoxymugineic acid **60**,[76] isomugineic acid **61**,[75b] and medicanine **62**[77] (Figure 8).

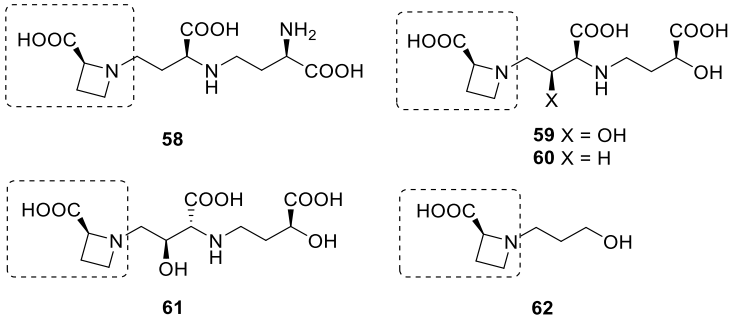


Figure 8

Among the bioactive compounds, the Aze **5** part can be found in hepatitis C virus NS3 protease inhibitors **63**,[78] in agonist **64** of Takeda G-protein receptors (TGR5) associated with diabetes, metabolic syndrome, and autoimmune disease,[79] and in the withdrawn thrombin inhibitors melagatran® **6** or exanta® **65** (Figure 9).[80]

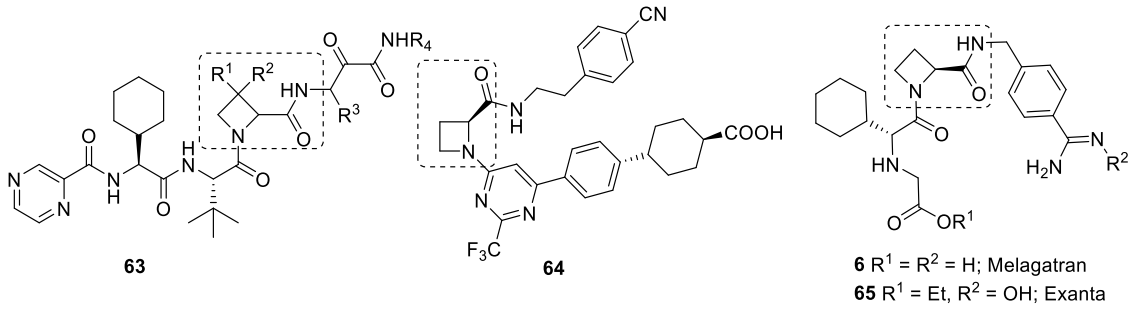
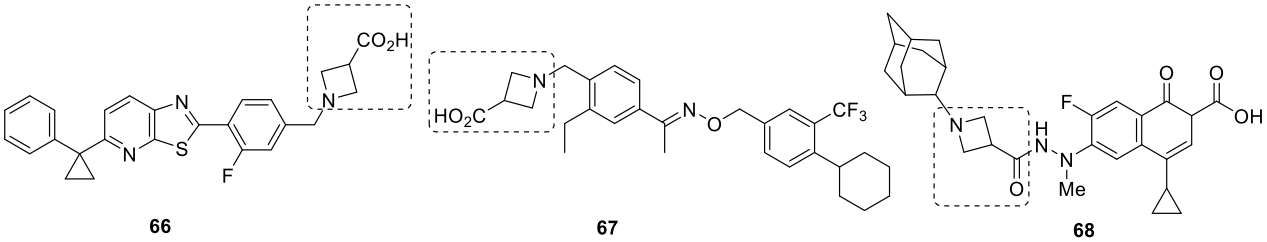


Figure 9

Additionally, enantiopure azetidine-2-carboxylic acid derivatives could be used as organocatalysts for asymmetric reactions.[81]

2.1.4 Azetidine-3-carboxylic acid and its derivatives

Azetidine-3-carboxylic acid **50** (Figure 4) is a non-proteinogenic azacyclic β-amino acid which is, similar to its 6-membered analogue **9**, of interest for use in peptide chemistry (*vide supra*). Since β-peptides possess higher metabolic stability, they could be applied in some cases where the use of azetidine-2-carboxylic acid derivatives failed due to lack of stability.[82] Azetidine-3-carboxylic acid **50** is used for the preparation of biologically and pharmaceutically valuable compounds. For instance, AMG 369 **66**[83] and BAF312 **67**[84] and their analogues,[83, 85] were discovered as agonists of $S1P_1$ and $S1P_5$ (Figure 10). Compound **68** showed antibacterial and anticancer properties comparable to the marketed drugs Linezolid and Ciprofloxacin (Figure 10).[86]



66
AMG 369

67
BAF312 (Siponimod)

68

Figure 10

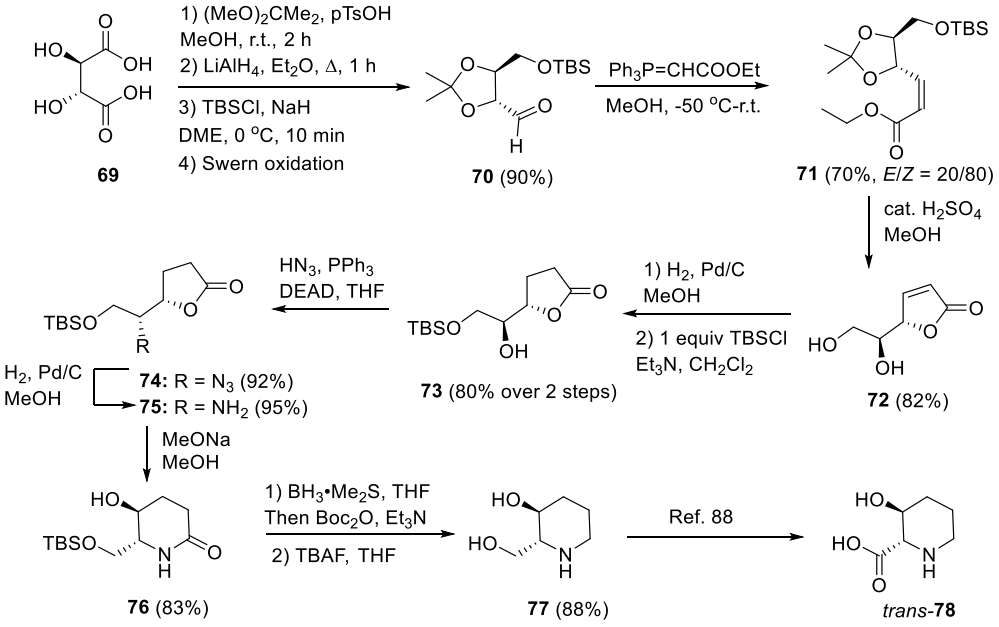
2.2 Synthesis of pipecolic acid and its derivatives

2.2.1 Chiral pool synthesis

Recently, the synthesis of pipecolic acid derivatives based on chiral pool synthesis, using chiral starting materials such as serine, phenylglycinol, glutamic acid, proline, glyceraldehyde, glucose, mandelic acid and 1,2-amino alcohols was well reviewed.[52d] Therefore, the following overview will be focused on the most relevant new synthesis of piperidine-2-carboxylic acid derivatives.

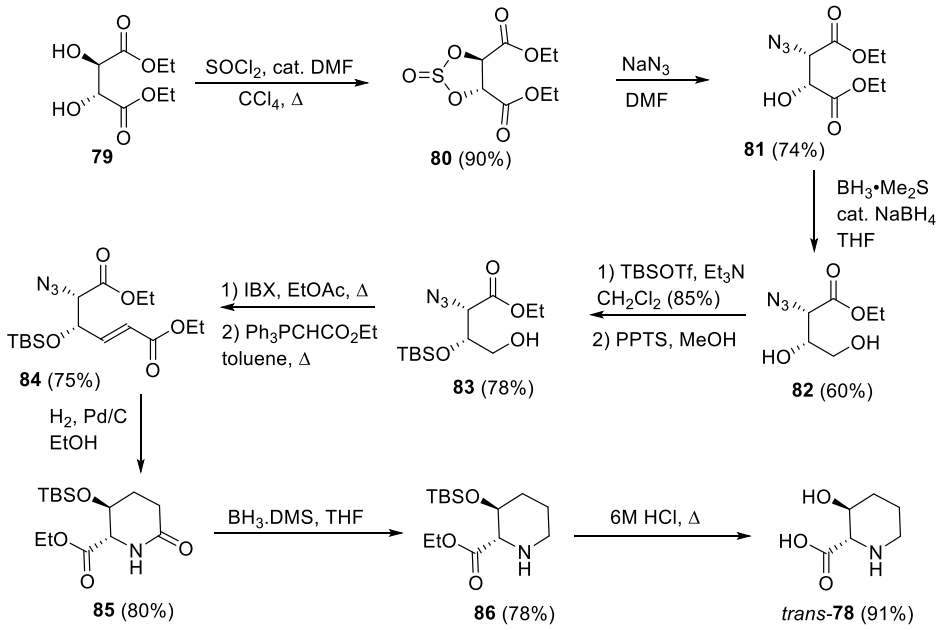
2.2.1.1 Synthesis from L-(+)-tartaric acid

L-(+)-Tartaric acid **69** is a naturally abundant and cheap starting material. Chavan *et al.* reported two pathways applying L-(+)-tartaric acid **69**.[87] In the first route, aldehyde **70** was prepared from tartaric acid **69** *via* a known procedure[88] and was subsequently used for Wittig olefination (Scheme 6). Alkene **71** was transformed to five-membered butyrolactone **72** *via* deprotection of the acetonide and TBS group. The reduction of the double bond and further selective protection of the primary alcohol with TBSCl led to formation of lactone **73**. Furthermore, azido functionality was introduced using Mitsunobu reaction conditions to furnish azide **74**. After the reduction of azide **74**, the obtained compound **75** was treated with sodium methoxide to accomplish the cyclization towards lactam **76**. Following reduction, the TBS-deprotection was carried out using TBAF in THF, affording the intermediate **77**, which could be easily oxidized to (*2S,3S*)-3-hydroxypipecolic acid *trans*-**78**.[89]



Scheme 6

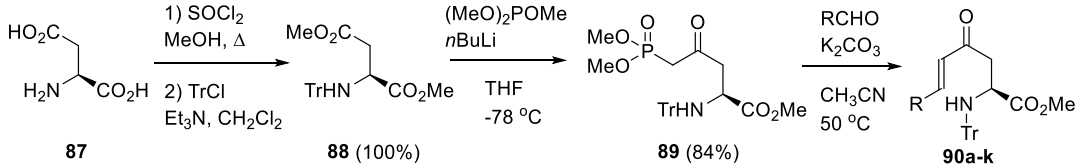
A second approach, reported by the same author, towards the synthesis of pipecolic acid derivatives based on tartaric acid **69** included less steps and was more convenient (Scheme 7).[90] Esterification of tartrate **69** afforded ethyl tartrate **79**, which was treated with thionyl chloride to furnish sulfite **80**. Opening of sulfite **80** with sodium azide and subsequent selective reduction of the ester group of substrate **81** gave β,γ-diol **82**. The protection of diol **82** with a TBS group and further selective primary TBS deprotection furnished azido alcohol **83** which was oxidized using 2-iodobenzoic acid (IBX). The aldehyde was used for Wittig reaction, affording α,β-unsaturated ester **84**. The reductive lactamization was performed by using hydrogen and Pd/C as catalyst, affording 6-oxopiperidine **85**. The latter was subjected to selective reduction of the amide group to provide amino ester **86**, which was hydrolyzed towards the target (*2S*,*3S*)-3-hydroxypipecolic acid *trans*-**78**.



Scheme 7

2.2.1.2 Synthesis from L-aspartic acid

The direct synthesis of *cis*- and *trans*-2,6-disubstituted-4-oxo-L-pipecolic acid derivatives from L-aspartic acid, where the stereochemical outcome depended on the presence or absence of a *N*-protective group, was reported.[91] The starting enones **90** were prepared from L-aspartic acid **87** (Scheme 8). The latter was converted to *N*-trityl L-aspartate dimethyl ester **88** under standard conditions. The phosphonate ester **89** was prepared by reaction of ester **88** with the anion of dimethyl methylphosphonate. Horner-Wadsworth-Emmons reaction of ester **89** with different aldehydes gave exclusively *E*-enones **90**.

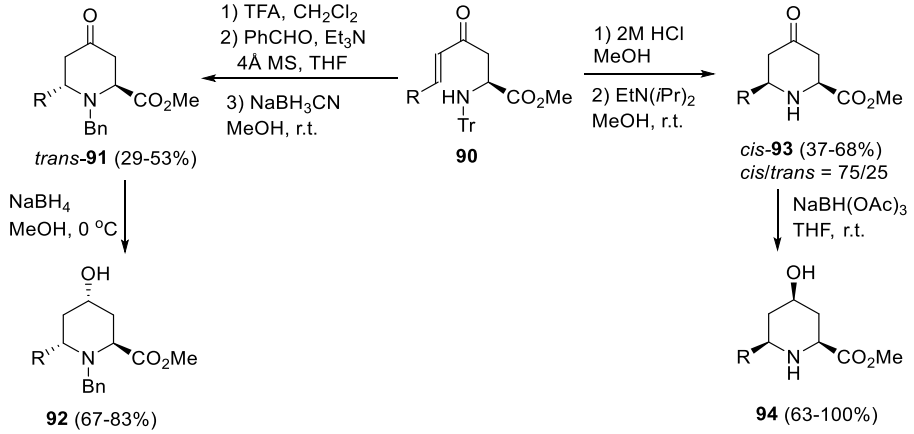


90a R = Ph, 95%
90b R = $(CH_3)_2CHCH_2$, 58%
90c R = $CH_3CH_2CH_2$, 59%
90d R = $PhCH_2CH_2$, 93%
90e R = 4-$NO_2C_6H_4$, 69%
90f R = 4-BrC_6H_4, 95%
90g R = 4-$MeOC_6H_4$, 66%
90h R = 3-$(H_2C{=}CH)C_6H_4$, 61%
90i R = 2-Naphthyl, 80%
90j R = 3-Pyridyl, 95%
90k R = 4-(3'-$NO_2C_6H_4$)C_6H_4, 84%

Scheme 8

The synthesis of *trans*-2,6-disubstituted-4-oxo-L-pipecolic acid derivatives **91** was achieved from enones **90** *via* tandem reductive amination/*6-endo-trig* cyclization mediated by sodium cyanoborohydride (Scheme 9).[91a] In turn, the synthesis of *cis*-2,6-disubstituted-4-oxo-L-pipecolic acid derivatives **93** was synthesized *via* one-pot, two-step procedure, which included the *N*-

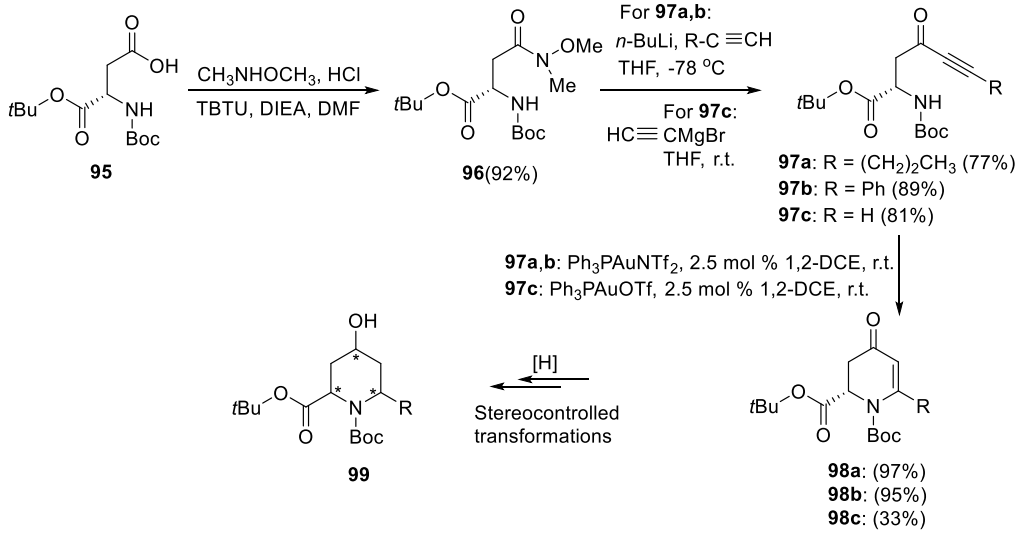
deprotection of enone **90** prior to the base-mediated *6-endo-trig* cyclization.[91b] The optimal results were obtained using Hunig's base (Scheme 9). Noteworthy, the second approach led to formation of minor product *trans*-**91** in a *cis*-**93**/*trans*-**91** ratio of 75/25 and the main isomer could be easily isolated *via* column chromatography.



Scheme 9

Subsequent stereoselective reduction of the keto functionality of the 4-piperidones **91** and **93** using sodium borohydride (for **91**) or sodium triacetoxyborohydride (for **93**) afforded methyl 4,6-disubstituted piperidine-2-carboxylates **92** and **94**, respectively, in good yield (Scheme 9).

The Gouault research group also reported the synthesis of pipecolic acid derivatives based on (*S*)- aspartic acid (Scheme 10).[92] As key step of their method, the gold-catalyzed cyclization of ynone-containing α-amino esters **97** was accomplished. Weinreb amide **96**, obtained from protected (*S*)- aspartic acid **95**, was treated with lithium propylacetylide and lithium phenylacetylide, affording ynones **97a,b**. The treatment of amide **96** with ethynylmagnesium bromide furnished **97c**. Subsequent cyclization towards compounds **98** was performed using (triphenylphosphane)gold(I) bis(trifluoromethanesulfonyl)imide (for **98a** and **98b**) and using (triphenylphosphane)gold(I) triflate (for **98c**).

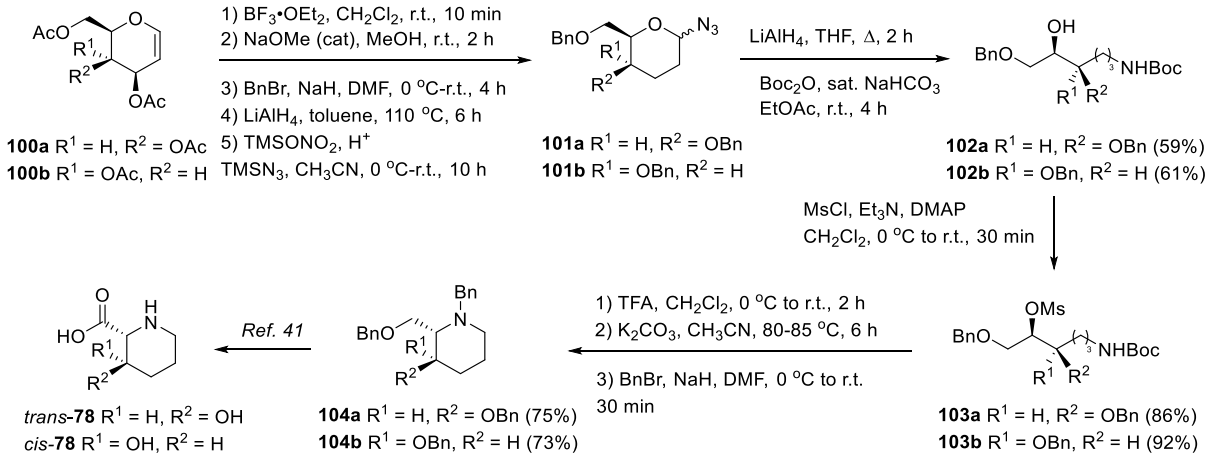


Scheme 10

The enantiopure dihydropyridone-2-carboxylates **98** were revealed as key intermediates to undergo conversions into various 6-substituted 4-hydroxypipecolic acid derivatives **99**.

2.2.1.3 Synthesis from D-glycals

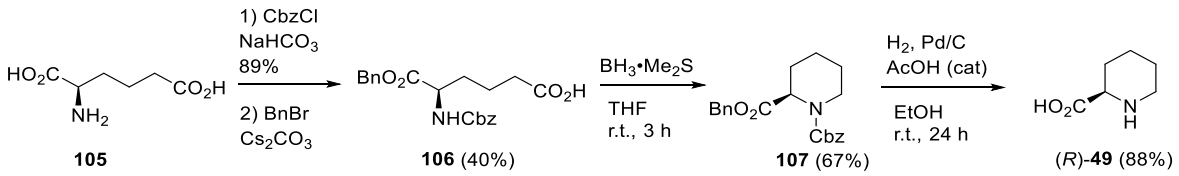
The recent application of D-glycals for the formal synthesis of functionalized compounds with a piperidine core was reported by Mallick *et al.* (Scheme 11).[93] The synthesis of functionalized *cis*-/*trans*-pipecolic acids **78** started from 3,4,6-tri-*O*-acetyl- D-glycals **100a,b**, which were converted to azido derivatives **101a,b**.[94] Reduction of **101a,b** with lithium aluminum hydride followed by *N*-Boc protection of acyclic amino alcohols led to formation of derivatives **102a,b**. Furthermore, the free hydroxyl groups were converted into the corresponding mesylates **103a,b**. Because the direct cyclization of the latter substrates failed, the *N*-deprotection was performed in first instance followed by base-mediated cyclization towards functionalized piperidines **104a,b**. Finally, target molecules *trans*- and *cis*-**78** could be obtained *via* simple transformations of piperidines **104a** and **104b**, including *N*-debenzylation and oxidation of the hydroxymethyl substituent at C-2.



Scheme 11

2.2.1.4 Synthesis from (*R*)-α-aminoadipic acid

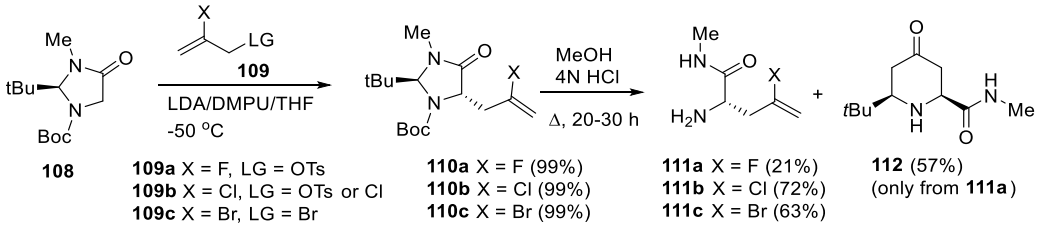
The Sewald research group provided a simple asymmetric synthesis of (*R*)-pipecolic acid **49** starting from (*R*)-α-aminoadipic acid **105** (Scheme 12).[95] Protection of the amino moiety with the benzyloxycarbonyl group followed by selective esterification at the α-position afforded compound **106**.[96] The reductive cyclization of intermediate **106** using BH_3·Me_2S afforded the protected pipecolic acid **107**. Simple hydrogenation of piperidine **107** gave the target (*R*)-pipecolic acid **49**.



Scheme 12

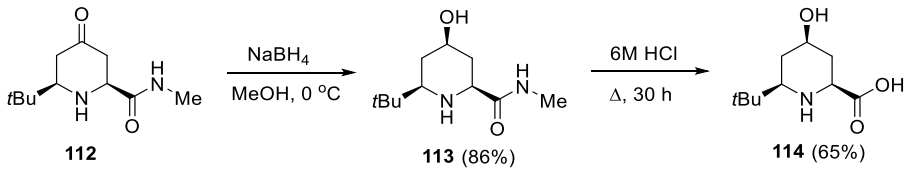
2.2.2 Ring transformation

The Haufe research group reported an acid-catalyzed cascade reaction starting from the fluorovinylic compound **110a** leading to the rearranged 4-oxopipecolic acid derivate **112** (Scheme 13).[97] The starting *tert*-butyl 2-*tert*-butyl-5-(2-haloallyl)-3-methyl-4-oxoimidazolidine-1-carboxylates **110a-c** were prepared *via* asymmetric alkylation of Boc-protected imidazolidinone **108** with different electrophiles **109a-c**. Treatment of substrate **110a** with 4M HCl in methanol afforded the fluorinated amino acid derivative **111a** and 4-oxopipecolic acid derivative **112**. Noteworthy, the use of the chloro- or bromovinyl compounds **110b,c** exclusively led to formation of the halogenated amino acid derivatives **111b,c**. This supported the idea that the presence of a fluorovinyl group in **110a** promoted the molecular rearrangement towards the formation of six-membered heterocycle **112**.



Scheme 13

Product **112** was converted into (*2S,4R,6R*)-6-*tert*-butyl-4-hydroxypiperidine-2-carboxylic acid **114** in two steps, including selective reduction with sodium borohydride and subsequent hydrolysis with HCl (Scheme 14).

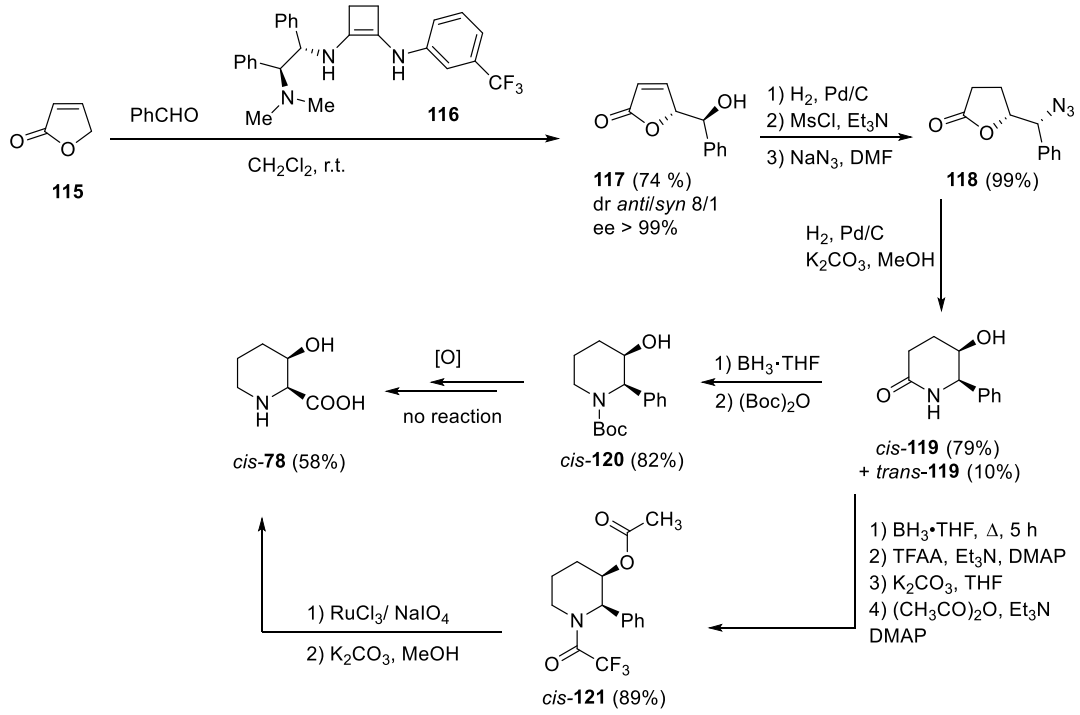


Scheme 14

2.2.3 Enantioselective organocatalytic synthesis

2.2.3.1 Enantioselective organocatalytic vinylogous aldol reaction

The direct vinylogous aldol reaction of commercially available γ-crotonolactone **115** and benzaldehyde in the presence of aminosquaramide **116** as catalyst afforded aldol product **117** as a diastereomeric mixture of *anti*/*syn* in a ratio of 8/1 (Scheme 15).[98] Hydrogenation of the latter, subsequent mesylation of the secondary alcohol and substitution of the mesylate by azide (with inversion of configuration) yielded the azidobutyrolactone **118**. Reduction of the azide **118** in the presence of a base (K_2CO_3) accomplished the rearrangement towards the piperidone **119**. The major *cis*-isomer was easily separated *via* column chromatography and was used in further transformations. Reduction of the piperidone *cis*- **119** with borane and further *N*-Boc protection of the obtained piperidine afforded derivative **120**, which was used as substrate for the synthesis of pipecolic acid derivative *cis*-**78** *via* oxidative cleavage of the 2-aryl group. Noteworthy, the changing of the *N*-substituent in piperidine **120** had a crucial effect on the oxidation of the 2-aryl substituent with $RuCl_3/NaIO_4$. The oxidation of the *N*-Boc protected piperidine **120** failed whereas the reaction of *N*-trifluoroacetyl substituted piperidine **121** proceeded smoothly to provide, after methanolysis of the trifluoroacetamide, the corresponding carboxylic acid **78**. In order to synthesize substrate **121**, (*2R,3R*)-2-phenyl-3-hydroxypiperidine **120** was first converted to the *N*,O-*bis* trifluoroacetyl derivative and the trifluoroacetate ester was replaced with an acetate group to afford *cis*-**121**.

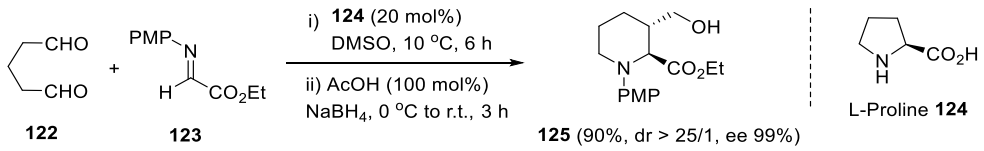


Scheme 15

2.2.3.2 Proline-catalyzed cascade reaction

Proline and its derivatives have been proven to be efficient catalysts in asymmetric synthesis.[99]

An efficient one-pot cascade reaction towards the synthesis of functionalized piperidine **125** involved a proline **124**-catalyzed Mannich reaction of glutaraldehyde **122** with imine **123** and acid-mediated intramolecular reductive cyclization towards pipecolic acid derivative **125** as one-pot cycloaddition (Scheme 16).[100]

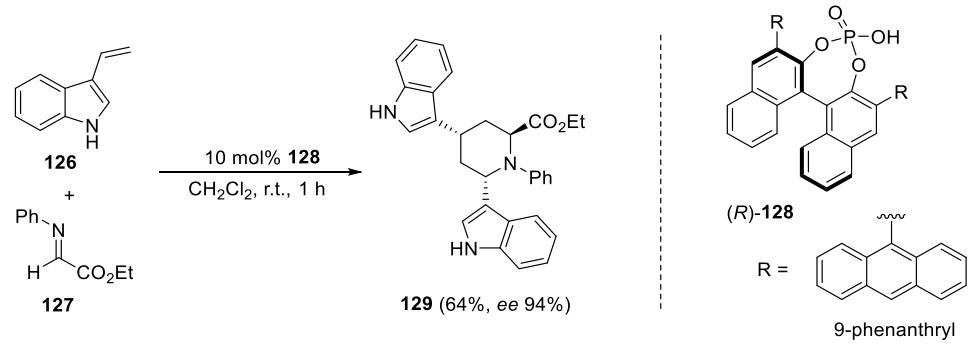


Scheme 16

2.2.3.3 Chiral phosphonic acid catalysis

Chiral phosphonic acids **128** are a catalyst class widely used in organic chemistry.[101]

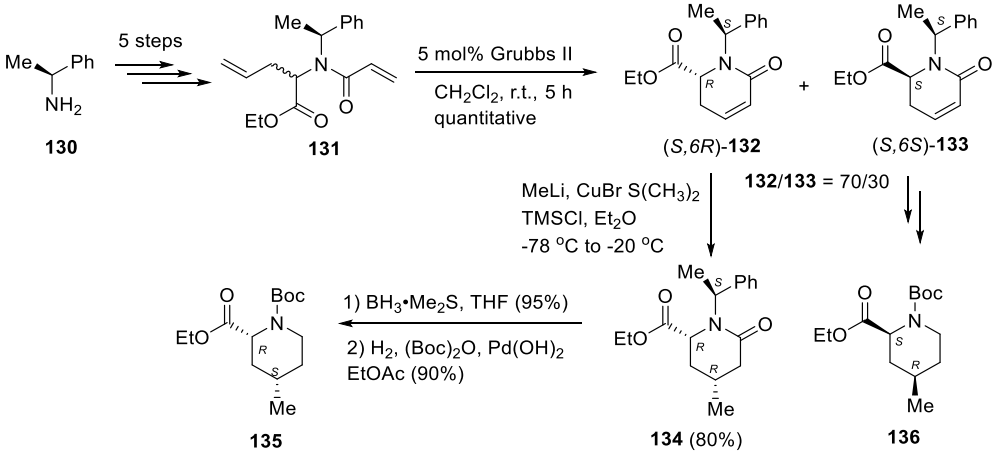
Recently, an enantioselective organocatalytic synthesis of 4,6-bis(1*H*-indole-3-yl)piperidine-2-carboxylate **129**, using 3-vinylindole **126** and imino ester **127** in the presence of the chiral phosphoric acid **128** as catalyst, was reported (Scheme 17).[102] The product **129** was obtained under mild reaction conditions in good yield (64%) and high enantiomeric excess (94%).



Scheme 17

2.2.4 Ring closure metathesis

The diastereoselective synthesis of 4-methylpipecolic esters **135** and **136** based on ring closure metathesis (RCM) reaction and conjugate Michael addition was described *via* precursor **131** which was obtained as diastereomeric mixture from (*S*)-(-)-phenylethylamine **130** in 5 steps (Scheme 18).[103] This mixture was subjected to a RCM reaction, giving a diastereomeric mixture of unsaturated esters **132** and **133** in diastereomeric ratio of 70/30. The diastereomeric mixture was separated and the absolute configuration of C-6 atom of the piperidine core was determined as (*R*) for **132** and (*S*) for **133**. Furthermore, the conjugate addition of methylcuprate to the major (*R*)-**132** afforded the desired *cis*-4-methylpiperidine-2-on-6-carboxylate **134** as major diastereomer. The reduction/*N*-deprotection/*N*-protection sequence afforded pipecolic acid derivative **135**. The minor isomer (*S*)-**133** was subjected to the same transformations as **132** in order to obtain the 1,3-disubstituted piperidine **136**.



Scheme 18

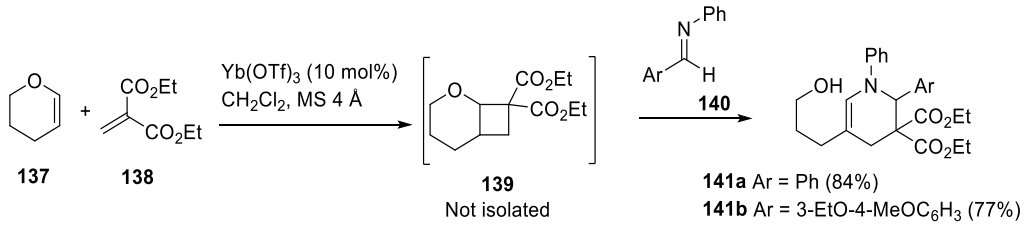
2.3 Synthesis of nipecotic acid derivatives

In this part, the methods to synthesize piperidine-3-carboxylic acid derivatives, mainly based on one-pot/cascade reactions, were reviewed. In the past decade, one-pot multicomponent reactions have

drawn considerable attention due to their efficiency towards the preparation of complex molecules, in particular, polysubstituted piperidines.

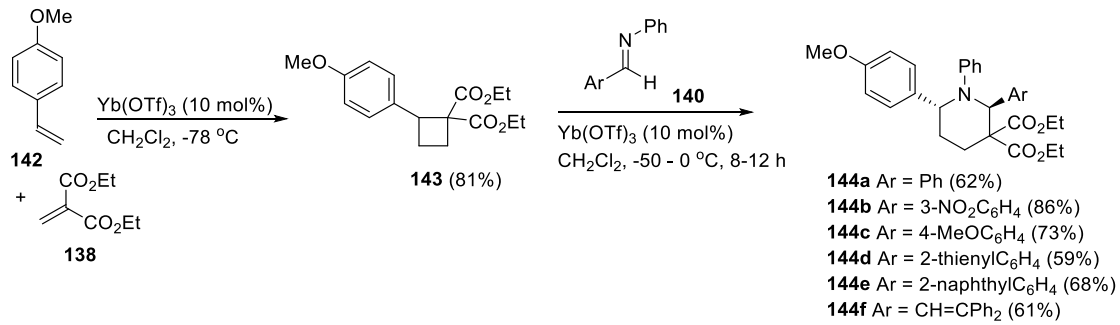
2.3.1 Formal [4+2]-cycloaddition of donor-acceptor cyclobutanes with imines

The Pagenkopf research group has reported ytterbium triflate-catalyzed stereoselective synthesis of donor-acceptor cyclobutane **139** and its [4+2]-cycloaddition with imines **140** (Scheme 1).[104] The [2+2] reaction of ethyl methylidene malonate **138** with dihydropyran **137** in the presence of 10 mol% of ytterbium triflate afforded the intermediate cyclobutane **139**. Although the synthesis of this class of cyclobutanes was reported in 1986,[105] the use of these substrates in dipolar cycloaddition was not investigated. Subsequently, a CH_2Cl_2 solution of Schiff bases **140** was added to a concentrated solution of the *in situ* formed cyclobutane **139** and adducts **141** were formed in yields ranging from 77 to 84%. The obtained dihydropyridines **141** could serve as versatile precursors for the synthesis of piperidine-3,3-dicarboxylic acid derivatives.



Scheme 19

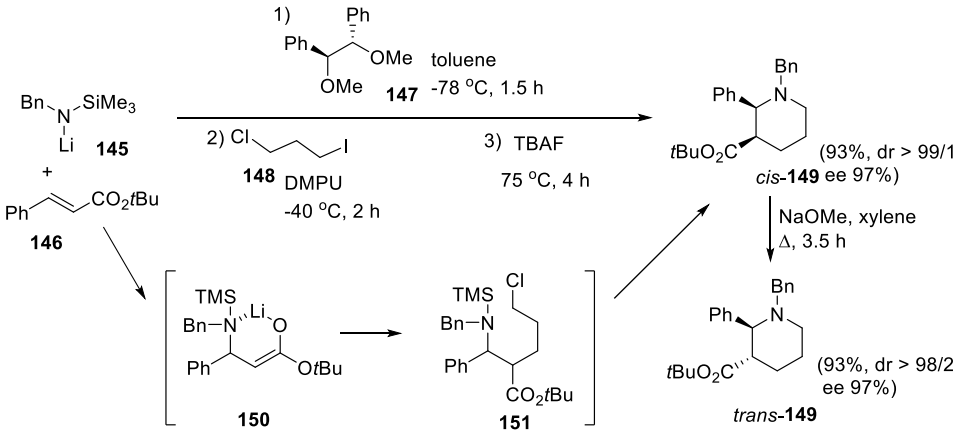
Moreover, this methodology was applied for different substrates. Thus, the ability of $Yb(OTf)_3$ to catalyze the synthesis of cyclobutanes with carbon-donating groups was demonstrated. The reaction of methylidene malonate **138** with *p*-vinylanisol **142** gave cyclobutane **143** (Scheme 20). Noteworthy, the adducts **143** could be isolated in good yield. Further addition of the obtained cyclobutane **143** across imines **140** afforded the highly substituted piperidine-3,3-dicarboxylates **144** in good yields (59-86%) and exclusively as the *trans*-diastereomers.



Scheme 20

2.3.2 [*N*+2+3]-cyclization strategy

Harada *et al*. reported an asymmetric one-pot [*N*+2+3] cyclization strategy towards the synthesis of six membered azaheterocycles.[106] The procedure started with the chiral diether **147**-controlled asymmetric conjugate addition reaction of lithium amide **145** across *tert*-butyl cinnamate **146** in toluene, followed by treatment with 1-chloro-3-iodopropane **148** in DMPU for 2 hours and then with tetrabutylammonium fluoride giving *cis*-2,3-disubstituted piperidine *cis*-**149** in good yield (dr >99/1, ee 97%) (Scheme 21). Noteworthy, the *trans*-isomer *trans*-**149** was easily obtained from *cis*-isomer by heating in xylene in the presence of sodium methoxide.

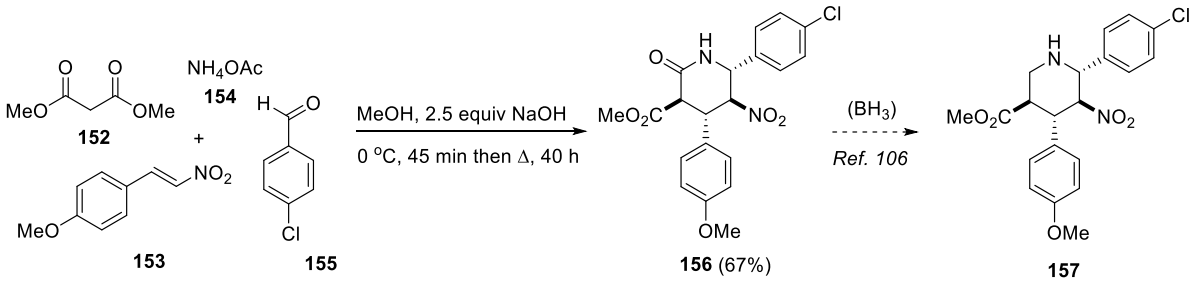


Scheme 21

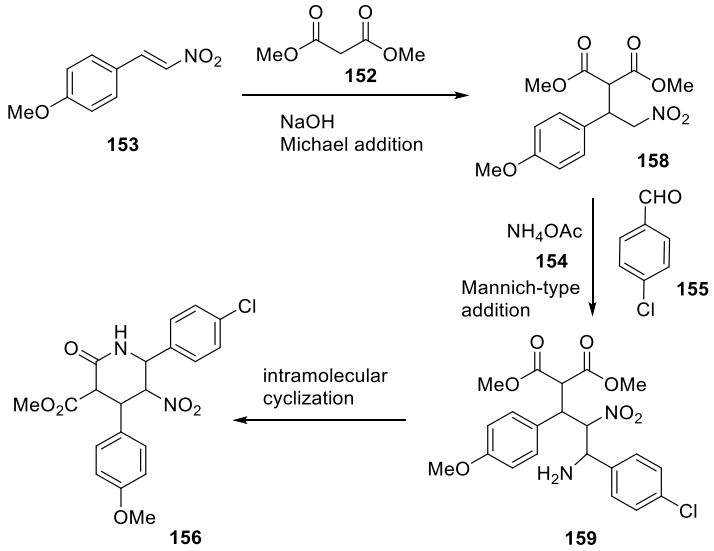
2.3.3 Multicomponent reactions (MCRs)

Multicomponent reactions (MCRs) starting from simple starting materials are interesting approaches due to their practical value and accessibility.[107]

In a first study, the four-component one-pot reaction between substituted nitrostyrenes **153**, aromatic aldehydes **155**, dialkyl malonates **152** and ammonium acetate **154** led to formation of a wide range of polysubstituted piperidinone derivatives (only one example **156** is presented) (Scheme 22).[108] The proposed pathway includes three steps, namely: the Michael addition of dimethyl malonate **152** to the substituted nitrostyrene **153** to form 2-(1-aryl-2-nitroethyl)malonate **158**, followed by nitro-Mannich nucleophilic addition to afford intermediate **159**, and finally, intramolecular cyclization with elimination of methanol to give the cyclic amide **156** (Scheme 23). The piperidinone **156** could be foreseen as precursor for the synthesis of polysubstituted piperidine-3-carboxylic acid derivatives **157**, which could be obtained *via* selective reduction of the amide **156** under mild conditions (Scheme 22).[109]

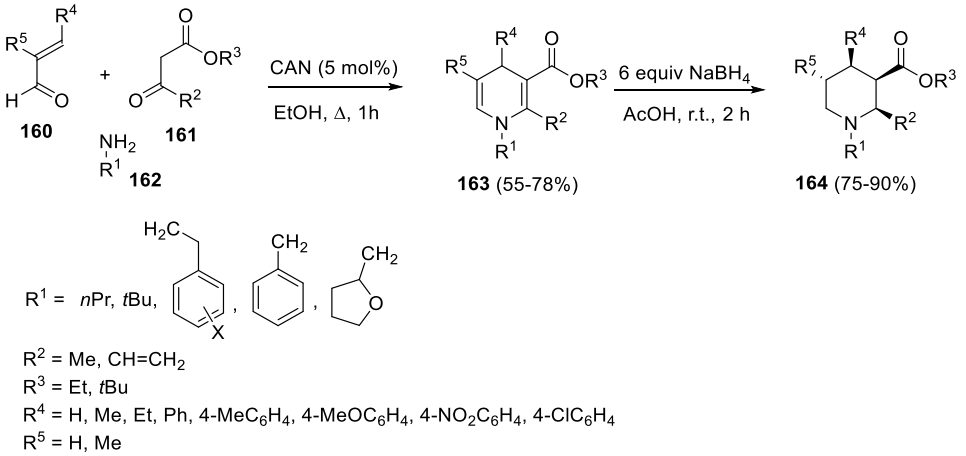


Scheme 22

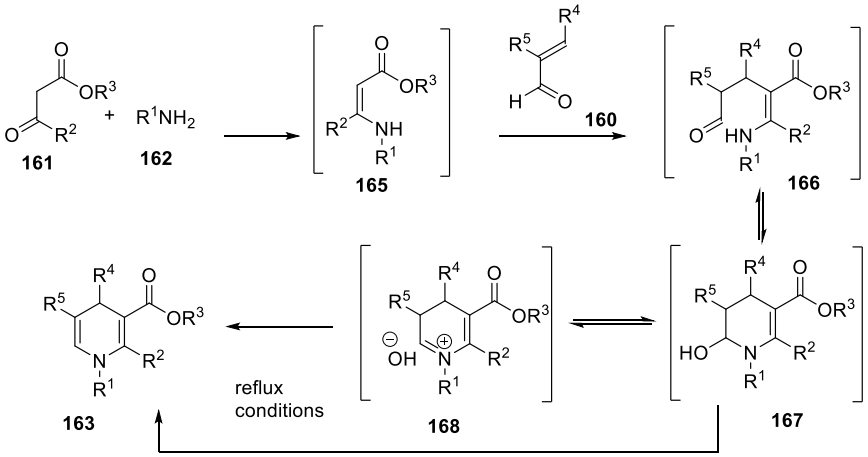


Scheme 23

Another multicomponent synthesis of functionalized piperidines concerned the reaction between primary amines **162**, α,β-unsaturated aldehydes **160**, β-dicarbonyl compounds **161** and alcohols in the presence of cerium(IV) ammonium nitrate (CAN) as a Lewis acid affording the 1,4-dihydropyridine-3-carboxylates **163** which were subsequently reduced towards functionalized nipecotic acid derivatives **164** (Scheme 24).[110] The reaction mechanism was explained. *via* β-enaminone **165** which underwent Michael addition across α,β-unsaturated aldehyde **160** to give intermediate **166** (Scheme 25). The *6-exo-trig* cyclization of the latter afforded enaminoester **167**, presumably in equilibrium with iminium ion **168** which was deprotonated to dehydropyridine **163**. More than 20 derivatives of **163** were prepared *via* this cascade reaction in 55-78% yields.

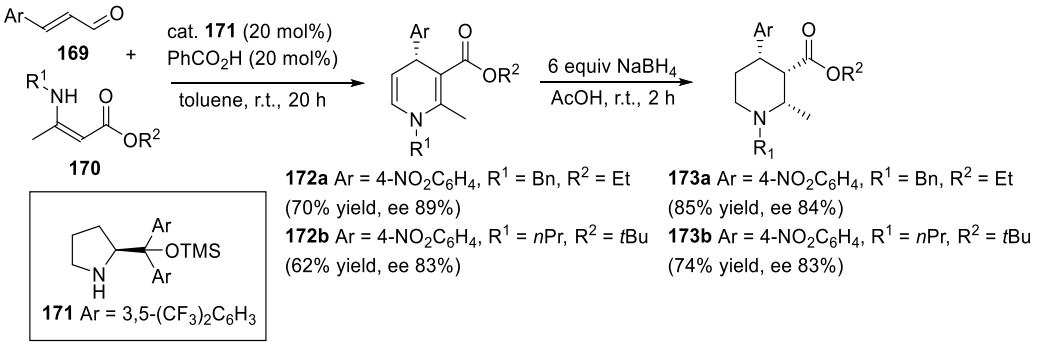


Scheme 24



Scheme 25

Asymmetric synthesis of piperidines **173a,b** was accomplished *via* reduction of enantiomerically enriched 1,4-dihydropyridines **172** (Scheme 26). The latter were prepared *via* an organocatalytic asymmetric aza-ene-type cascade reaction, developed by Noole et al.[111] The conjugate addition of β-enamino esters **170** across α,β-unsaturated aldehydes **169** (cinnamaldehyde derivatives) in the presence of (*S*)-diarylprolinol-TMS ether **171** and benzoic acid afforded the 1,4-dihydropyridines **172a,b** in good yields (62-70%) and enantiomeric excess of 83-89%. Subsequently, these dihydropyridine derivatives **172** were subjected to reduction with $NaBH_4$, giving highly functionalized piperidine-3-carboxylates **173** in 74-85% yield and enantiomeric excess of 83-84%.



Scheme 26

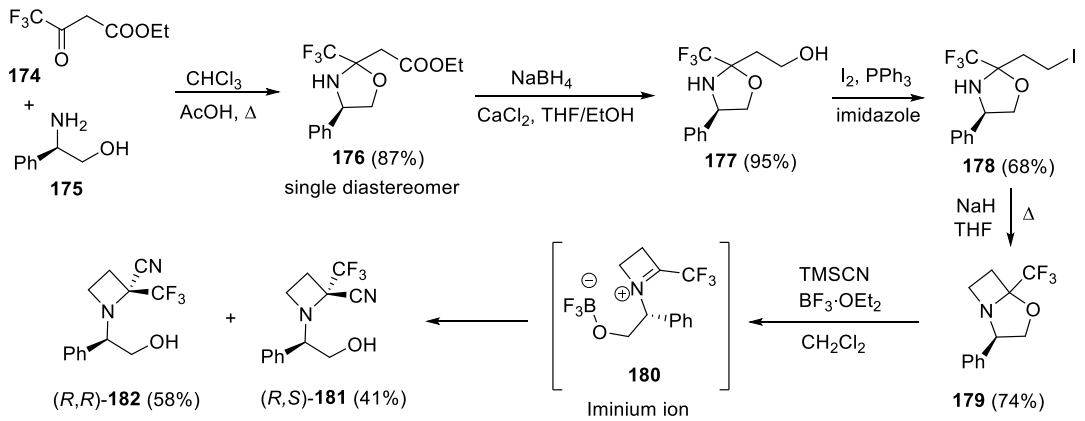
2.4 Synthesis of azetidine-2-carboxylic acid derivatives

An overview of the latest synthetic approaches was prepared below with main focus on asymmetric synthesis of azetidine-2-carboxylic acid derivatives.

2.4.1 Synthesis starting from chiral substrates

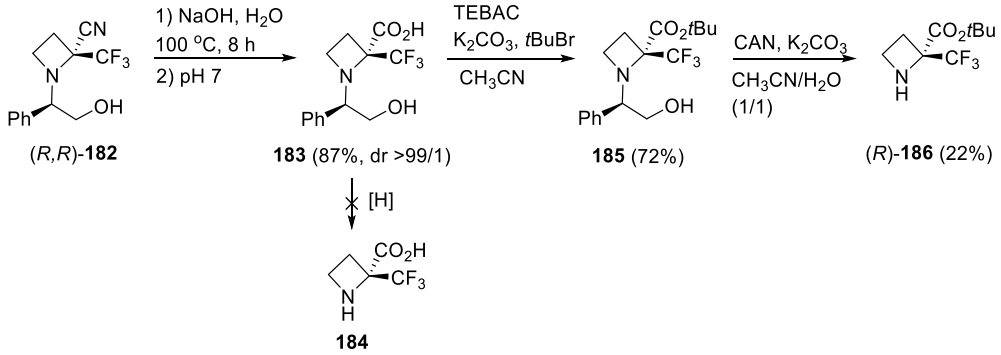
2.4.1.1 From (*R*)-phenylglycinol

A straightforward synthesis of enantiopure α-trifluoromethylated azetidine-2-carboxylic acid derivatives **181** and **182** was recently reported, starting from (*R*)-phenylglycinol **175** and ethyl 4,4,4-trifluoroacetoacetate **174** (Scheme 27).[112] The starting fluorinated oxazolidine **176** was prepared *via* condensation of phenylglycinol **175** and acetate **174**. Subsequent reduction with $NaBH_4$ afforded alcohol **177** without any degradation of the oxazolidine moiety. The synthesis of the bicyclic compound **179** was realized *via* cyclization of the iodo derivative **178** using sodium hydride in THF under reflux. The introduction of the nitrile group was accomplished *via* Strecker-type reaction across iminium ion **180**. A diastereomeric mixture of 2,2-disubstituted azetidines **181** and **182** was formed and the two diastereomers were conveniently separated by silica gel chromatography to give (*R*,*R*)-**182** and (*R*,*S*)-**181** in 58% and 41% yield, respectively.



Scheme 27

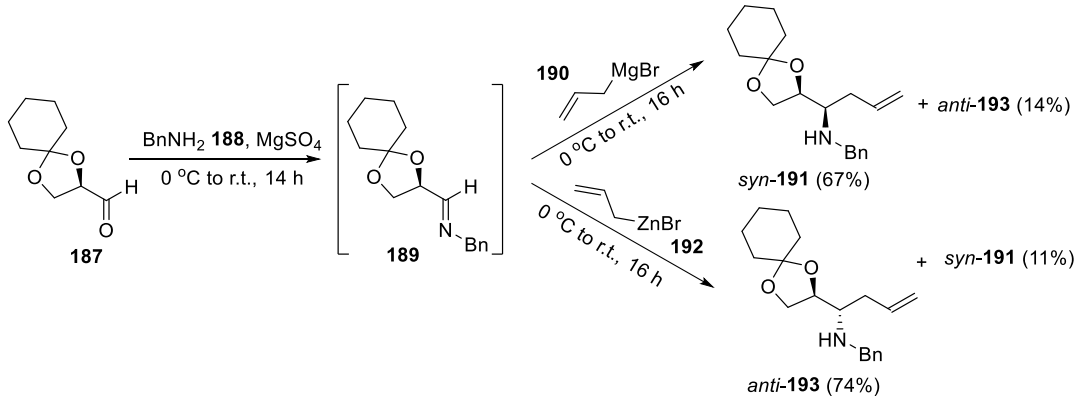
The hydrolysis of the nitrile group of major isomers (*R*,*R*)-**182** under basic conditions afforded the azetidine-2-carboxylic acid derivatives **183** (Scheme 28). The direct hydrogenolysis of compound **183** in order to remove the *N*-protection failed, leading to the degradation of starting material. Therefore, substrate **183** was subjected toward esterification reaction giving ester **185**. Finally, the reaction of azetidine **185** with CAN gave the corresponding amino ester **186** in a modest yield of 22%.



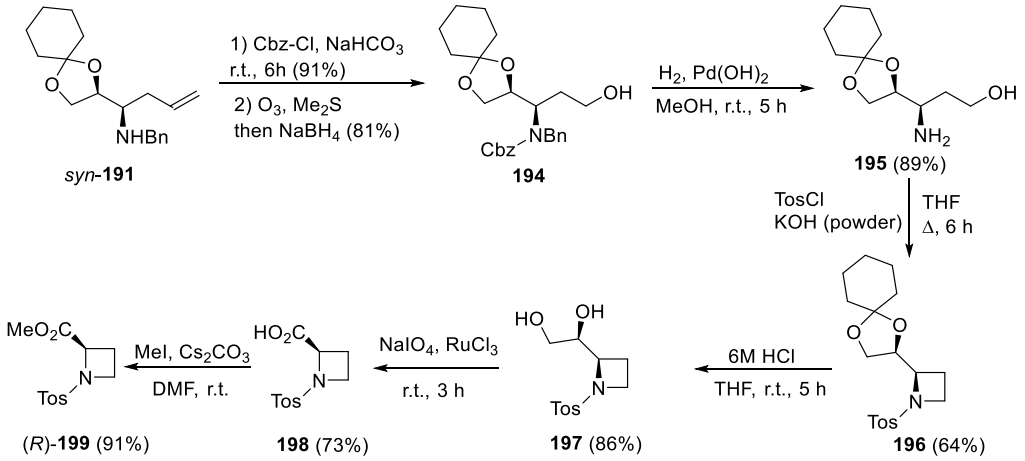
Scheme 28

2.4.1.2 From chiral glyceraldehyde derivatives

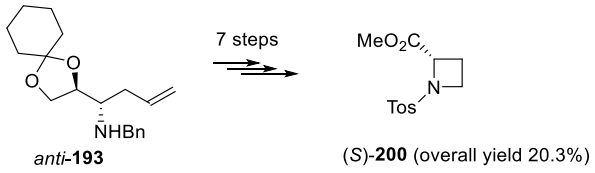
As a continuation of previous research, the Chattopadhyay group envisioned the homoallylic amines **191** and **193** as precursors for the synthesis of *N*-protected azetidine-2-carboxylic acid derivatives **199** and **200** (Schemes 30 and 31).[113] The starting amines **191** and **193** were prepared *via* allylation of imine **189** derived from (*R*)-2,3-cyclohexylideneglyceraldehyde **187** (Scheme 29). When imine **189** was treated with allylmagnesium bromide **190**, *syn*-adduct **191** was obtained. The reversal of stereoselectivity was observed when allylation was performed with allylzinc bromide **192**, affording amine *anti*-**193**. The Cbz-protected amine derived from amine **191** was subjected to ozonolysis and *in situ* reduction of the resulting aldehyde delivered primary alcohol **194** (Scheme 30). The removal of Cbz and benzyl groups from **194** produced amine **195**. *N*-Heterocyclization of substrate **195** using TosCl-KOH led to the formation of the azetidine derivative **196**. Acid-mediated deprotection of the cyclohexylidene acetal in azetidine **196** and subsequent transformation of the diol functionality into a carboxylic acid function using $NaIO_4$ and a catalytic amount of $RuCl_3$, followed by esterification, afforded (*R*)-azetidine-2-carboxylic acid derivative (*R*)-**199**. In the same manner, the *anti*-homoallylic amine **193** was transformed into (*S*)-enantiomer **200** in 20.3% overall yield (Scheme 31).



Scheme 29



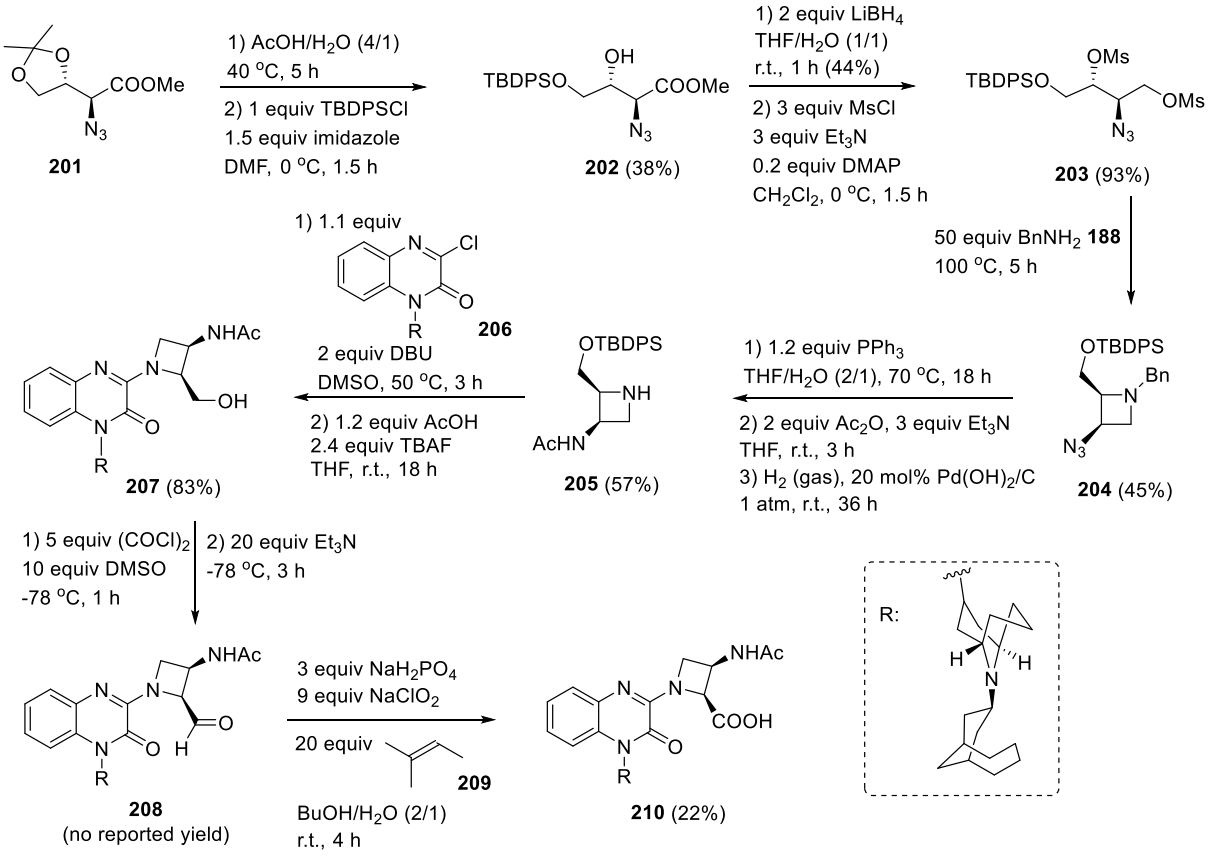
Scheme 30



Scheme 31

Recently, the synthesis of 3-aminoazetidine-2-carboxylic acid derivative **210** was described in a patent, starting from azido dioxolan-4-yl acetate **201** (Scheme 32).[114] Deprotection of the dimethyl acetal **201** and subsequent selective protection of the primary hydroxyl group with TBDPSCl afforded monoprotected methyl α-azido-β-hydroxybutanoate **202**. The ester function of the latter was reduced towards a primary hydroxy group. Subsequently, *bis*-mesylation of the hydroxyl groups in the obtained azido alcohol gave the compound **203**. The addition of benzylamine to substrate **203** followed by intramolecular *4-exo-tet* cyclization led to the formation of 2,3-disubstituted azetidine **204**. A Staudinger reduction of the azido azetidine **204** and subsequent acylation of the amino functionality followed by removal of the benzyl group afforded azetidine **205**. The addition of azetidine **205** across 3-chloroquinoxalin-2(1*H*)-one derivative **206** gave the adduct **207** in good yield.

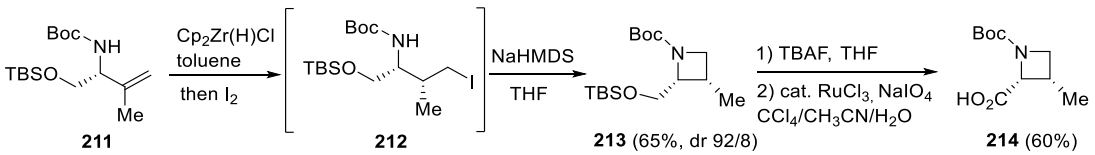
Two subsequent oxidation reactions, a Swern oxidation followed by a Pinnik oxidation, transformed the 2-hydroxymethyl functionality of azetidine **207** to a carboxylic acid to give functionalized 3-aminoazetidine-3-carboxylic acid **210** in moderate yield.



Scheme 32

2.4.1.3 From Boc-protected chiral allylic amines

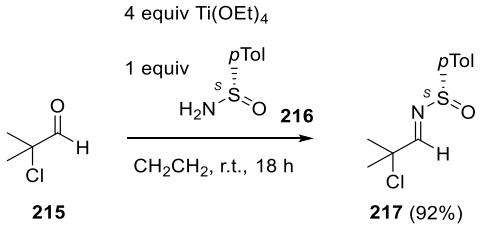
Pradhan *et al*. reported the synthesis of *cis*-2,3-disubstituted azetidines *via* diastereoselective hydrozirconation of the C=C bond of allylamine **211**.[115] First, chiral allylamine **211** was treated with Schwartz reagent, $Cp_2Zr(H)Cl$, followed by treatment of the hydrozirconated intermediate with iodine, affording the iodocarbamate **212** (Scheme 33). Subsequent treatment of intermediate **212** with NaHMDS in THF promoted the cyclization towards *cis*-2,3-disubstituted azetidine **213** in 65% yield and dr of 92/8. Further transformation of the obtained azetidine **213** *via* alcohol deprotection and ruthenium-based oxidation led to the formation of the *N*-Boc-protected 3-methylazetidine-2-carboxylic acid **214**.



Scheme 33

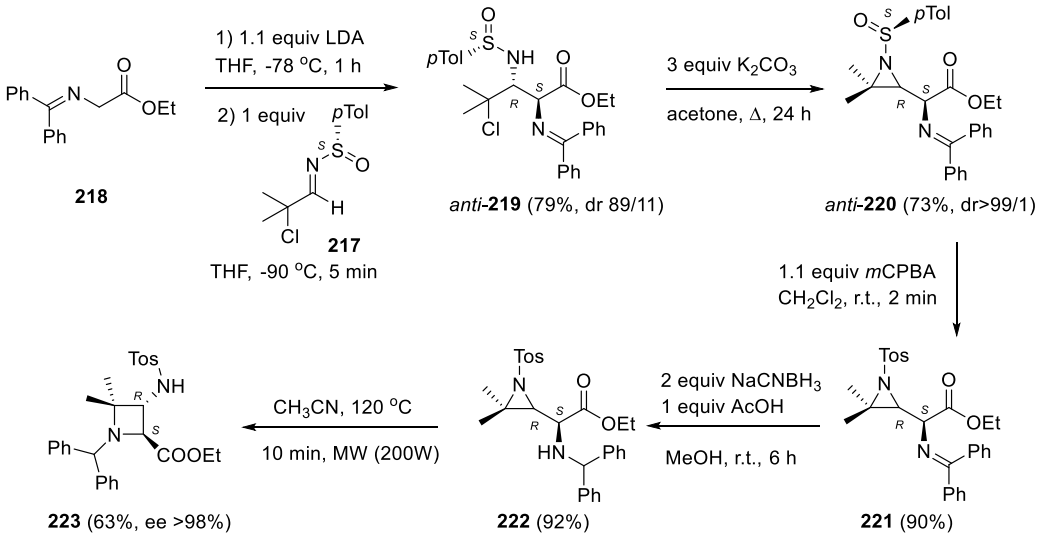
2.4.1.4 Synthesis based on chiral α-chloro-*N*-sulfinylimines

Another approach towards chiral 3-aminoazetidine-2-carboxylic acid derivatives was developed at the Department of Sustainable Organic Chemistry and Technology (UGent) based on enantiopure α-chloro-*N*-sulfinylimine **217**.[116] The latter was prepared by condensation of α-chloroisobutyraldehyde **215** with (*S*)-*p*-toluenesulfinamide **216** (Scheme 34).



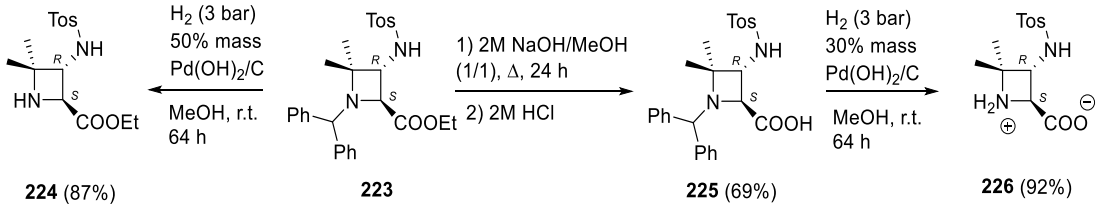
Scheme 34

The stereoselective Mannich-type addition of *N*-protected glycine ester **218** across chiral α-chloro-*N*-sulfinylimine **217** gave the *anti*-adduct **219** when LDA was used for the deprotonation of the glycine ester **218** (Scheme 35). The *anti*-addition product **219** was cyclized to the corresponding *N*-sulfinylaziridine **220** in good yield and diastereomeric ratio of 81/19. Furthermore, the *p*-toluenesulfinyl group of *N*-sulfinylaziridine *anti*-**220** was selectively oxidized with *m*CPBA, resulting in *N*-sulfonylaziridine **221**. The reduction of the *N*-diphenylmethylene moiety of the aziridine **221** gave the *N*-sulfonylaziridine **222**. The ring transformation of the latter towards *trans*-3-(*N*-tosylamino)azetidine-2-carboxylate **223** was performed *via* simple heating in CH_3CN under microwave conditions.



Scheme 35

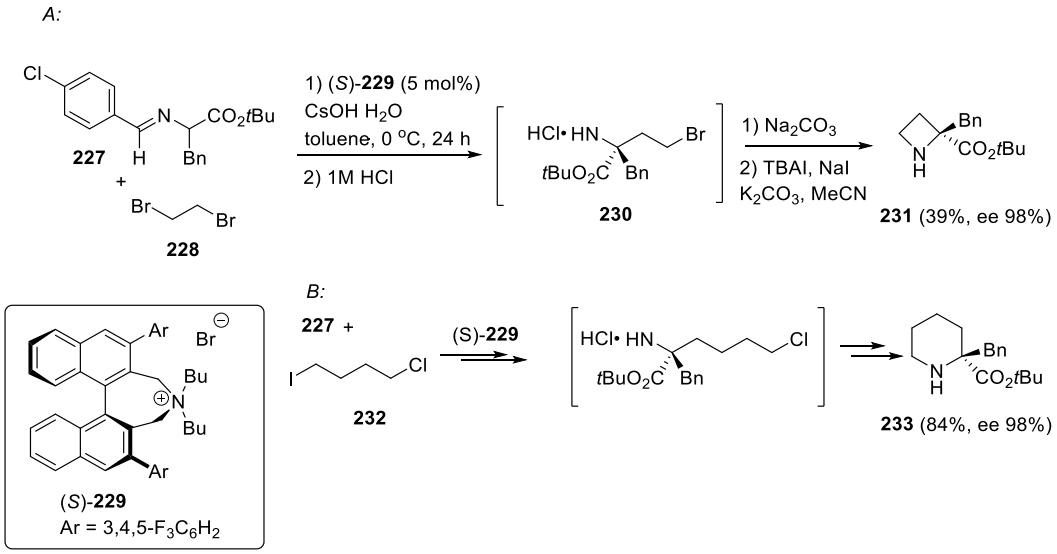
Moreover, the enantiomerically pure 3-aminoazetidine-2-carboxylic acid derivative **223** was subjected to deprotection reactions, including the removal of the diphenylmethyl moiety and hydrolysis of the ester group, to give the azetidine-2-carboxylic acid derivatives **224**, **225** and **226** (Scheme 36).



Scheme 36

2.4.2 Organocatalytic asymmetric synthesis

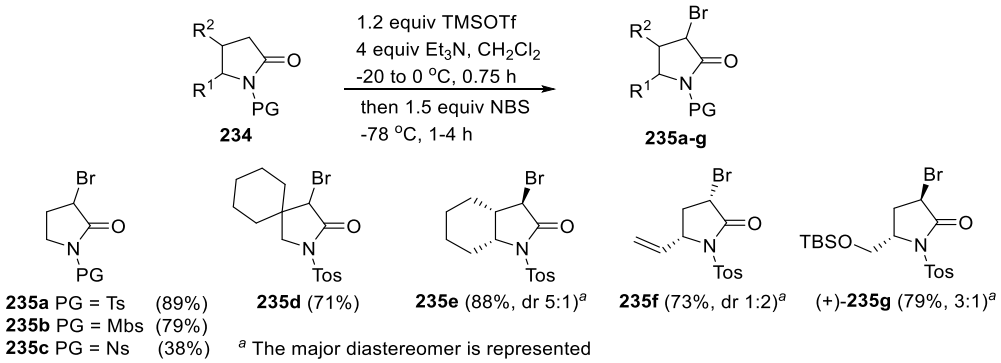
The catalytic asymmetric C-alkylation of glycine ester derivative **227** using dibromoethane **228** in the presence of a chiral phase transfer catalyst (*S*)-**229** and subsequent intramolecular *N*-alkylation afforded 2-substituted azetidine-2-carboxylic acid derivative **231** in 39% yield and enantiomeric excess of 98% (Scheme 37, A).[117] Noteworthy, this methodology was also applied for the synthesis of enantiomerically pure pipecolic acid derivative **233** by switching of the dihaloalkane to 1-chloro-4-iodobutane **232** (Scheme 37, B).



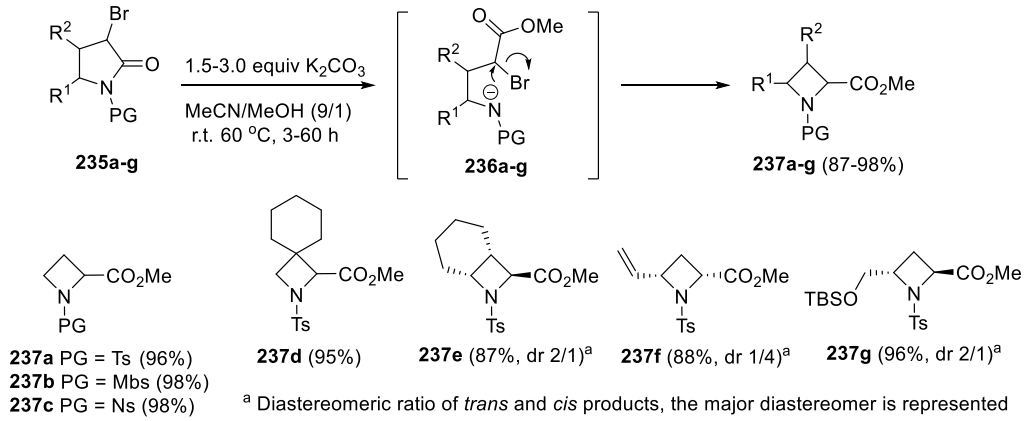
Scheme 37

2.4.3 Ring contraction of functionalized pyrrolidinones

A simple one-pot nucleophilic addition-ring contraction strategy was applied for the synthesis of a broad scope of highly functionalized azetidine-2-carboxylic acid derivatives **237** (Scheme 39).[118] The starting α-bromo *N*-sulfonylpyrrolidinones **235a-g** were obtained *via* the selective monobromination of *N*-sulfonylpyrrolidinones **234** (Scheme 38). Nucleophilic addition of methanol across substrates **235** in acetonitrile in the presence of potassium carbonate and subsequent *4-exo-tet* cyclization afforded functionalized azetidine-2-carboxylates **237** in good yields (87-98%) (Scheme 39).



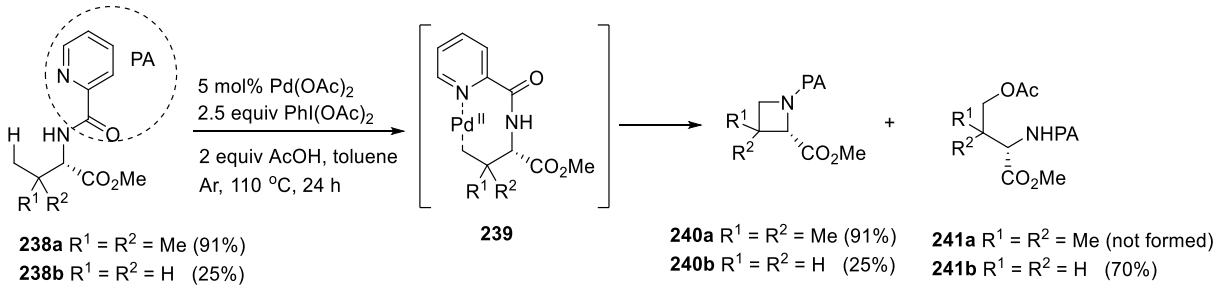
Scheme 38



Scheme 39

2.4.4 Pd-catalyzed intramolecular amination

The reaction of picolinamide protected amine substrates **238** and $PhI(OAc)_2$ as oxidant under palladium catalysis resulted in intramolecular amination of γ-C(sp^3)-H bond, affording azetidine-2-carboxylic acid derivatives **240** (Scheme 40).[119] Noteworthy, the absence of β-substituents in the substrate **238b** disfavored the cyclization towards azetidine **240b**, giving non-cyclic acetoxylated compound **241b** as major product.

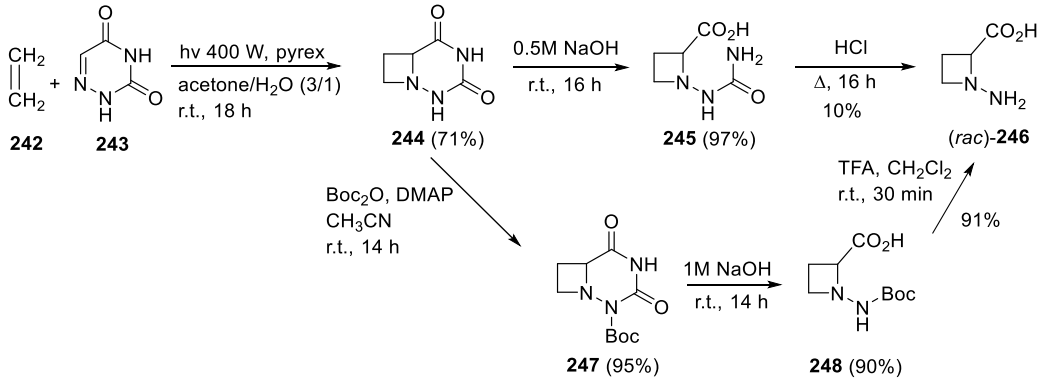


Scheme 40

2.4.5 [2+2]-cycloaddition strategy

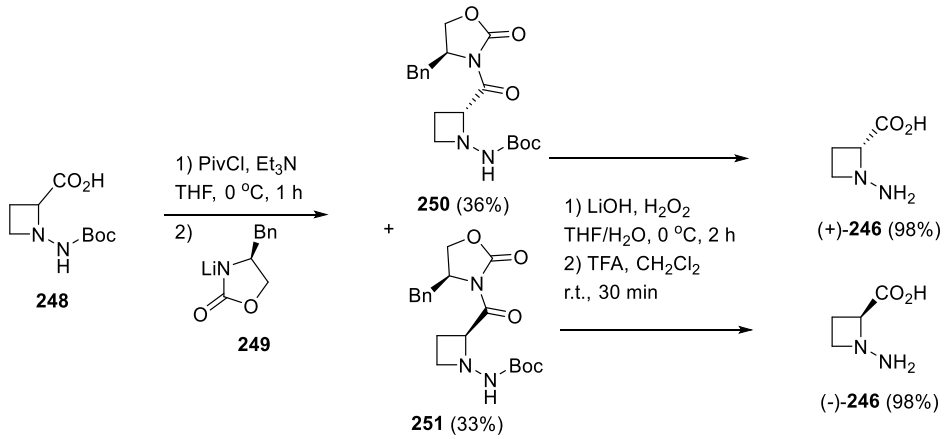
The synthesis azetidine-2-carboxylates *via* a [2+2]-cycloaddition strategy starting from commercially available 6-azauracil **243** was reported by the Aitken research group.[120] A solution of azauracil **243** was irradiated with a 400 W Hg lamp and ethylene **242** was bubbled through the mixture, affording [2+2] adduct **244** (Scheme 41). Treatment of adduct **244** with NaOH provided semicarbazide **245** which was hydrolyzed to the hydrazino acid **246**, however, in a low yield of 10%. Therefore, another route from adduct **244** was applied, which included selective *N1*-Boc protection, cleavage of the heterocyclic ring in **247** and Boc-deprotection of azetidine **248**, leading to the formation of racemic *N*-aminoazetidine-2-carboxylic acid **246** in good yield of 91%. Moreover, the

asymmetric synthesis of acid **246** was accomplished *via* chiral resolution of the intermediate **248** using (*S*)-benzyloxazolidin-2-one (Scheme 42). The activated carboxylic acid **248** as its *tert*-butyl anhydride reacted with the lithium salt of (*S*)-benzyloxazolidin-2-one **249** to provide the diastereomeric mixture which was separated *via* column chromatography, affording diastereomers **250** and **251** in 36% and 33% yield, respectively. The cleavage of the oxazolidinone auxiliary in derivatives **250** and **251** with LiOOH and subsequent TFA-mediated Boc removal afforded the two enantiomerically pure azetidines (+)-**246** and (-)-**246**.



242 **243** **244** (71%) **245** (97%) (*rac*)-**246** **247** (95%) **248** (90%)

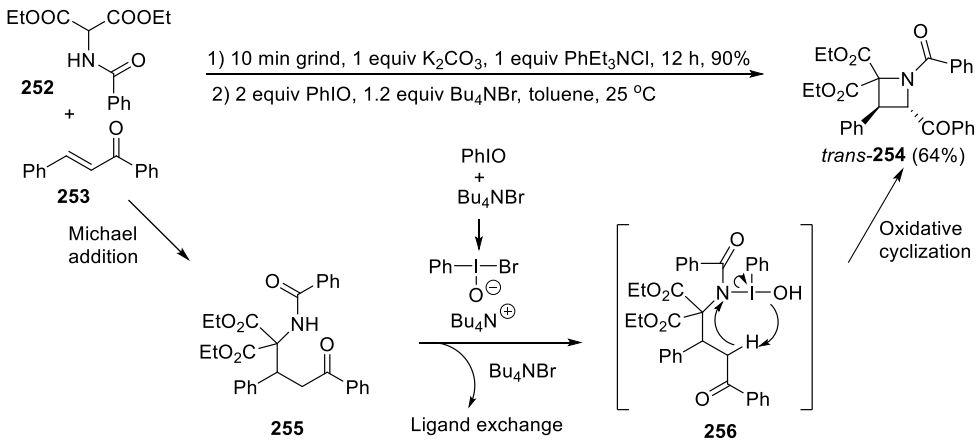
Scheme 41



248 **249** **250** (36%) **251** (33%) (+)-**246** (98%) (-)-**246** (98%)

Scheme 42

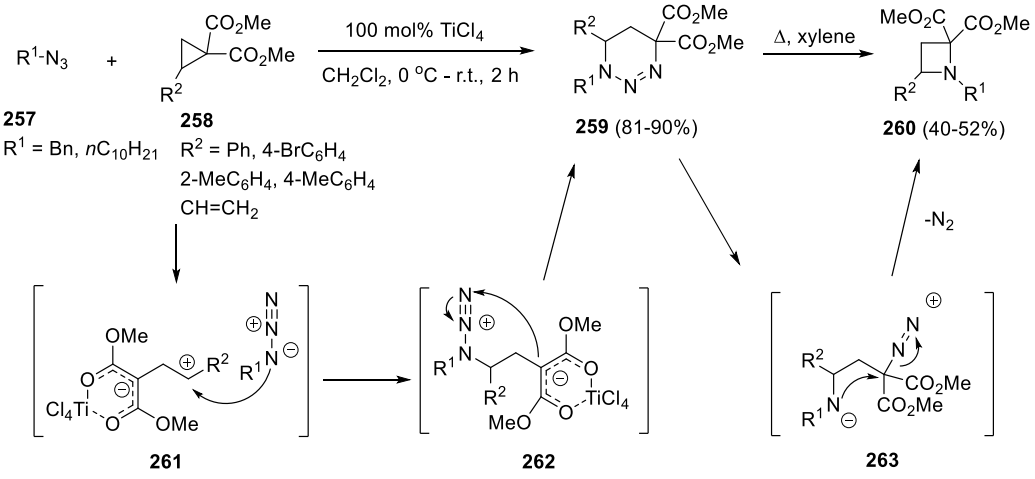
In another report, selective [2+2]-cycloaddition of 2-(*N*-benzoylamino)malonate **252** with chalcone **253** *via* phase transfer catalyzed solvent free Michael addition and a PhIO/Bu_4NBr-mediated oxidative cyclization led to formation of highly substituted diethyl azetidine-2,2-dicarboxylate *trans*-**254** (Scheme 43).[121] A library of 24 derivatives of azetidine **254** was created using the aforementioned method (structures are not presented). The presumed pathway includes the formation of adduct **255**. The latter reacts with an iodine species, generated in situ from iodosobenzene and tetrabutylammonium bromide, *via* a ligand exchange to form intermediate **256**, which readily undergoes an intramolecular reductive elimination to afford azetidine **254**.



Scheme 43

2.4.6 $TiCl_4$-promoted formal [3+3]-cycloaddition

The Lewis acid-promoted transformation of cyclopropane-1,1-diesters **258** with azides **257** afforded the functionalized triazines **259**, which were easily transformed towards azetidine-2,2-dicarboxylic acid derivatives **260** by means of simple thermolysis (Scheme 44).[122] A plausible pathway of the formation of triazines **259** includes the $TiCl_4$-mediated ring opening of the cyclopropane ring **258**, affording 1,3-zwitterionic intermediates **261**. Then, a nucleophilic attack of an azide occurs to form a zwitterion **262**, which undergoes an intramolecular nucleophilic attack to afford the triazines **259**. The elimination of N_2 from **259** under reflux gave azetidines **260**.

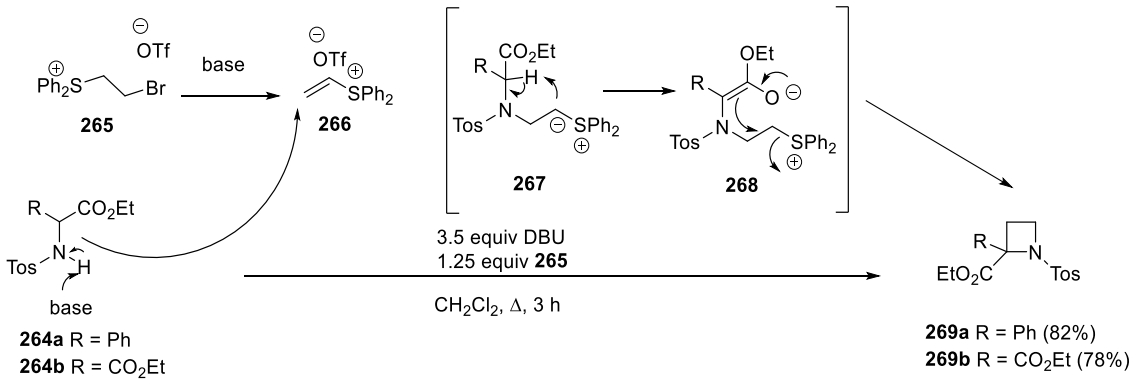


Scheme 44

2.4.7 Cyclization of glycine derivatives

As extension of the application of sulfonium triflate,[123] the cyclization of derivatives **264** to functionalized azetidine-2-carboxylic acid derivatives **269** using (2-bromoethyl)sulfonium triflate **265** under basic conditions was reported (Scheme 45).[124] The proposed mechanism includes the

following steps: nucleophilic addition of ester **264** across the vinylsulfonium salt **266**, generated *in situ* from sulfonium triflate **265** and base, gave the ylide intermediate **267** and, after proton transfer, formed enolate **268**, which underwent intramolecular attack to furnish the azetidine ring. Noteworthy, the use of derivative **264b** as starting material furnished the azetidine-2,2-dicarboxylic acid derivative **269b** in good yield of 78%.

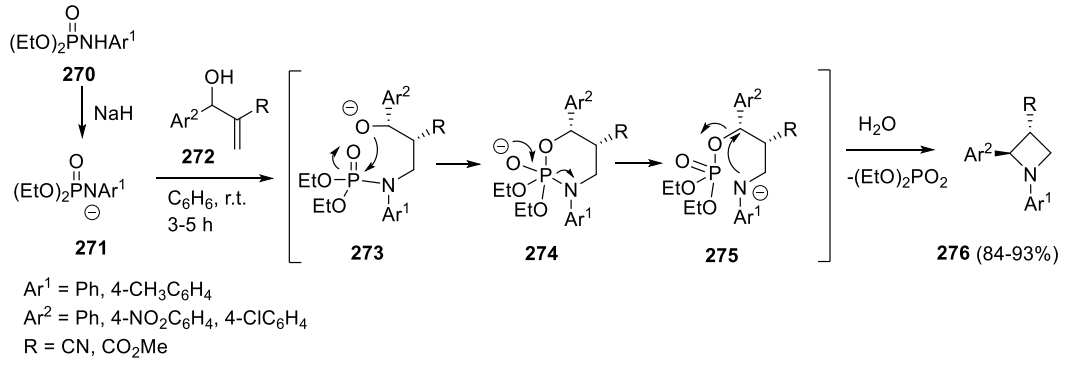


Scheme 45

2.5 Synthesis of azetidine-3-carboxylic acid derivatives

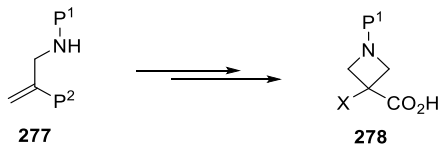
The synthetic approaches towards azetidine-3-carboxylic acid and its derivatives are not so diverse as for azetidine-2-carboxylic acid.

In a first example, one-pot diastereoselective annulation of Baylis-Hillman adducts **272** with *N*-arylphosphoramidates **270** afforded *trans*-1,2-disubstituted azetidine-3-carbonitriles/carboxylates **276**, which are the precursors of azetidine-3-carboxylic acids (Scheme 46).[125] Diethyl *N*-arylphosphoramidates **270** were treated with sodium hydride to generate anions **271** *in situ*, which underwent aza-Michael addition across Baylis-Hillman adducts **272** followed by cyclization of adduct **273** to afford the azetidine-3-carbonitriles/carboxylates **276** in 84–93% yield. The formation of azetidines **276** might be explained through intramolecular attack of the alkoxide ion **273** on the phosphorus atom.



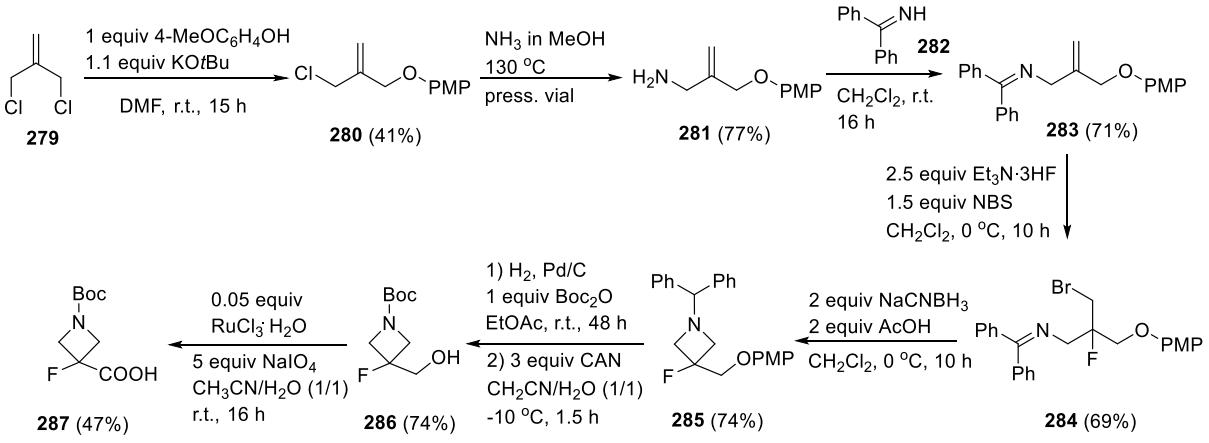
Scheme 46

Several other methods for the synthesis of azetidine-3-carboxylic acids **278** included the functionalization of the double bond of allylamine derivatives **277** as a key step (Scheme 47).



Scheme 47

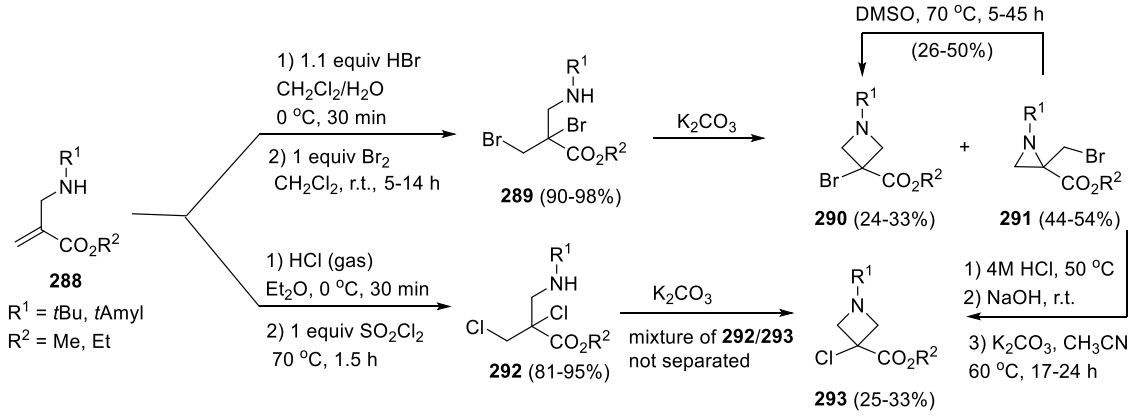
The synthesis of 3-fluoroazetidine-3-carboxylic acid **287** was reported by the research group at the Department of Sustainable Organic Chemistry and Technology (UGent) (Scheme 48).[126] Preparation of the starting allylamine **281** was performed *via* reaction of 3-chloro-2-chloromethylpropene **279** with 4-methoxyphenol in the presence of KO*t*Bu, and subsequent reaction of the obtained 3-chloro-2-(4-methoxyphenoxymethyl)propene **280** with ammonia in methanol in a pressure vessel. Transimination of imine **282** with allylamine **281** gave imine **283**, which was regioselectively bromofluorinated using triethylamine trihydrofluoride and NBS in dichloromethane. Furthermore, imine **284** was subjected to reductive cyclization using sodium cyanoborohydride in the presence of acetic acid to form fluorinated azetidine **285**. After hydrogenolysis of the *N*-protecting group of azetidine **285**, reaction with Boc_2O and cleavage of the *O*-protecting group, the efficient oxidation of 3-fluoro-3-hydroxymethylazetidine **286** using $NaIO_4/RuCl_3{\cdot}3H_2O$ towards 3-fluoroazetidine- 3-carboxylic acid **287** was accomplished.



Scheme 48

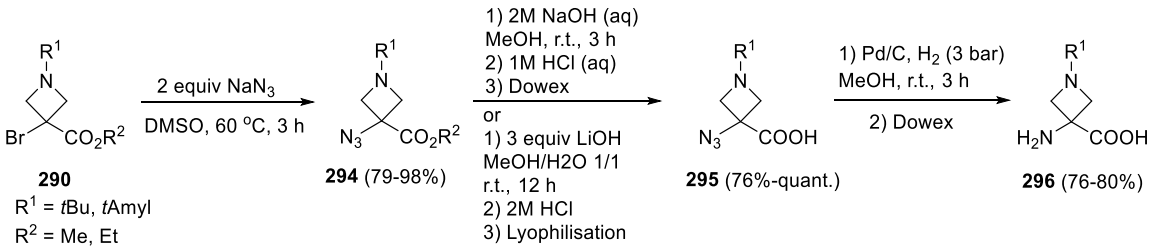
The same research group developed the synthesis of azetidine-3-carboxylates **290** and **293** from allylamines **288** (Scheme 49).[127] The dihalogenation of the double bond in **288** afforded substrates **289** and **292** which were cyclized towards azetidines **290** and **293**, respectively, under basic conditions. When dibromo derivatives **289** were used as starting material, formation of aziridines **291** was observed together with azetidines **290**.[127a, 127b] The isomerization of aziridines **291** to

azetidines **290** occurred under heating in DMSO in a highest yield of 50%. The base-promoted ring closure of dichlorinated ester **292** was less efficient, giving a mixture of starting material **292** and product **293**.[127c] However, the aziridines **291** were transformed to the desired 3-chloroazetidines **293** *via* ring opening of the aziridine ring at the sterically hindered C-2 carbon using HCl and subsequent base-promoted cyclization.



Scheme 49

The 3-bromoazetidine-3-carboxylates **290** have proven to be suitable precursors for the synthesis of C^{α}-tetrasubstituted α-amino acid derivatives which appeared to be a β-turn inducer in peptides.[51a] Transformation of substituted azetidines **290** *via* nucleophilic substitution of bromide with azide gave 3-azidoazetidines **294**. Subsequent elaboration of the carboxylic group and amino group afforded 3-aminoazetidine-3-carboxylic acid derivatives **295** and **296** which are of intrest for an application in the field of foldamers (Scheme 50).[51a, 127b]



Scheme 50

2.6 Conclusion

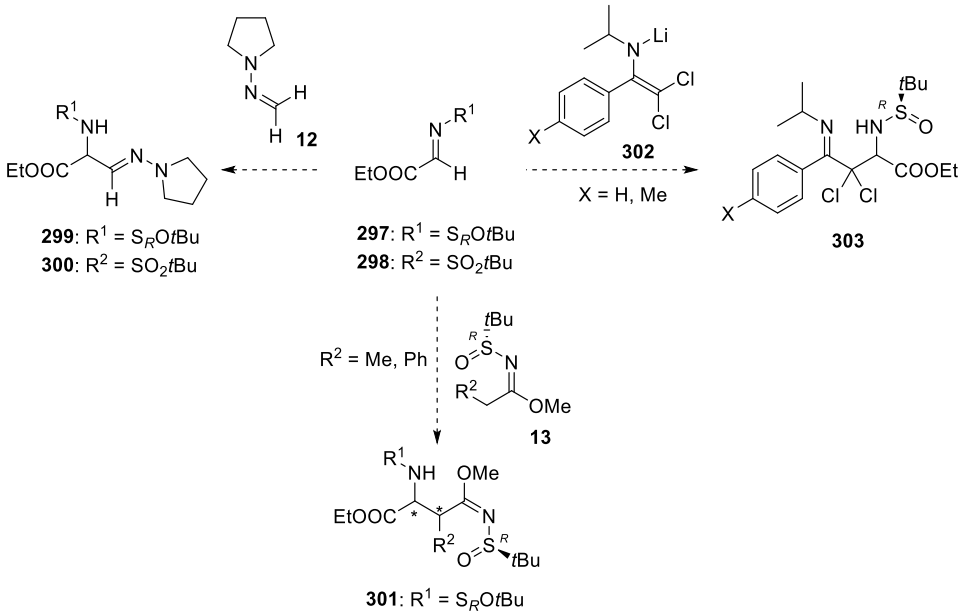
In conclusion, the discussed *N*-heterocycles, *i.e.* azetidine- and piperidinecarboxylic acid derivatives, are some of the most important building blocks. Due to their role as potential pharmaceuticals, continuous attempts towards developing new efficient synthetic methods constantly appear in the literature. Asymmetric synthesis of enantiomerically pure derivatives of these azacyclic amino acids are mainly based on chiral pool approaches, which often requires inefficient multi-step

transformations. Some other methods that were accomplished use expensive/exclusive reagents/catalysts. Therefore, the development of new efficient synthetic methods for the polysubstituted azacyclic α- and β-amino acids remains an important challenge.

3 Results and discussion

3.1 Synthesis and elaborations of *N*-(sulfinyl)iminoacetates 297 and *N*-(sulfonyl)iminoacetates 298 towards diamino acid derivatives

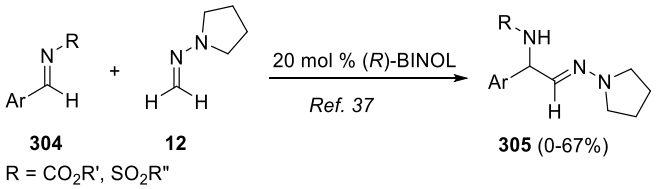
In the first chapter, *N*-(sulfinyl)- and *N*-(sulfonyl)iminoacetates **297** and **298** were explored as key substrates for the synthesis of diamino acid derivatives which possess interesting biological activity (see *Introduction and Goals*). Previously reported synthesis of β-ODAP **3** were mainly based on chiral pool synthesis. For instance, synthesis from aspartic acid involved a step with *in situ* formed highly explosive hydrazoic acid from sodium azide and sulfuric acid.[128] Another synthesis starting from tosyl-L-asparagine displayed a lack of reproducibility as well as a low yields of the desired acid **3**.[44] Additionally, the preparation of β-ODAP **3** from the copper chelate of L-2,3-diaminopropionic acid and various oxalate esters is not economically viable due to poor yields.[22a, 129] Several formal syntheses of BMAA **2** were reported. For example, an inefficient synthesis of BMAA hydrochloride from methylamine and acetamidoacrylic acid followed by enzymatic enantioselective hydrolysis of the acetamide group was reported.[130] Other approaches were based on transformations of protected L-serine.[131] [132] Among synthetic methods towards diaminobutyric acid **4** (DABA), Curtius,[133] Schmidt[134] or Hofmann[135] degradations from (*S*)-glutamic acid and the ring opening of γ-butyrolactone derivatives with potassium phthalimide[136] could be highlighted. Moreover, asymmetric synthesis of both enantiomers of DABA was performed using 2-hydroxypinan-3-one as inducer of chirality, however, with lack of diastereoselectivity.[137] Therefore, the development of new synthetic routes towards aforementioned amino acids remains challenging. Thus, it was envisioned that the condensation of α-iminoacetates **297** and **298** with different nucleophiles, such as 1- (methylenamino)pyrrolidine **12**, *N*-sulfinyl imidates **13** or 3,3-dichloro-1-azaallylic anions **302** could result in a short synthetic pathway towards new derivatives of diamino acids (Scheme 51).



Scheme 51

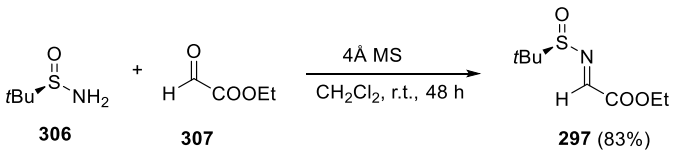
3.1.1 Addition reactions of 1-(methylenamino)pyrrolidine 12 across *N*-(sulfinyl)- and *N*-(sulfonyl)iminoacetates 297 and 298

Enantioselective addition reactions of 1-(methylenamino)pyrrolidine **12** across *N*-substituted aromatic aldimines **304** have been reported (Scheme 52).[39, 138] However, to the best of my knowledge, the addition of pyrrolidine **12** across α-iminoacetates has not been described.



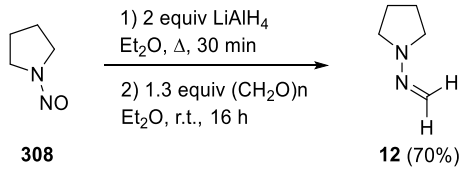
Scheme 52

The synthesis of starting (*R*)-ethyl 2-(*tert*-butylsulfinyl)iminoacetate **297** and 1-(methylenamino)pyrrolidine **12** was performed following literature procedures. The condensation of (R_S)-*tert*-butanesulfinamide **306** and ethyl glyoxalate **307** in dichloromethane in the presence of molecular sieves for 48 hours at room temperature afforded iminoacetate **297** in 83% yield (Scheme 53).[40] (*tert*-Butylsulfinyl)iminoacetate **297** was observed exclusively as *E*-isomer.[139]



Scheme 53

1-(Methylenamino)pyrrolidine **12** was prepared from commercially available *N*-nitrosopyrrolidine **308** *via* reduction with $LiAlH_4$ followed by addition of paraformaldehyde to the prepared 1-aminopyrrolidine (Scheme 54).[140]

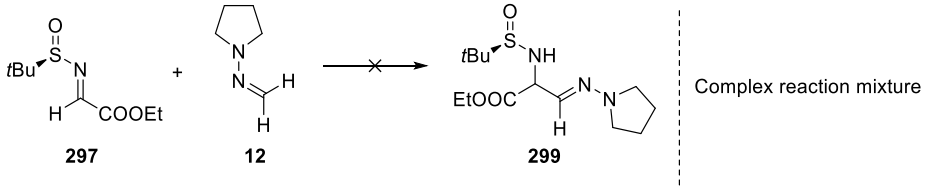


308 **12** (70%)

Scheme 54

Next, the addition reaction of hydrazone **12** across imine **297** was attempted (Table 1). In a first attempt, the reaction was performed without catalyst in chloroform for 8 hours at room temperature, giving no reaction (Table 1, entry 1). The gradual increase of the reaction temperature and elongation of the reaction time resulted in the degradation of starting materials to unidentified side products (Table 1, entry 1). The use of Brønsted acid (BINOL)[138] (Table 1, entry 2) as well as different Lewis acids, such as $BF_3{\cdot}OEt_2$, $ZnCl_2$, $Cu(OTf)_2$ (Table 1, entries 3-11),[141] did not lead to the formation of the desired ethyl 2-((*tert*-butylsulfinyl)amino)-3-(pyrrolidin-1-ylimino)propanoate **299**. The variation of the solvents ($CDCl_3$, CH_2Cl_2 or THF), temperatures and reaction times, unfortunately, did not positively influence the reaction outcome and only very complex mixtures were obtained which were not further analyzed (Table 1, entry 3-10).

Table 1. The addition reaction of hydrazone **12** across imine **297**.



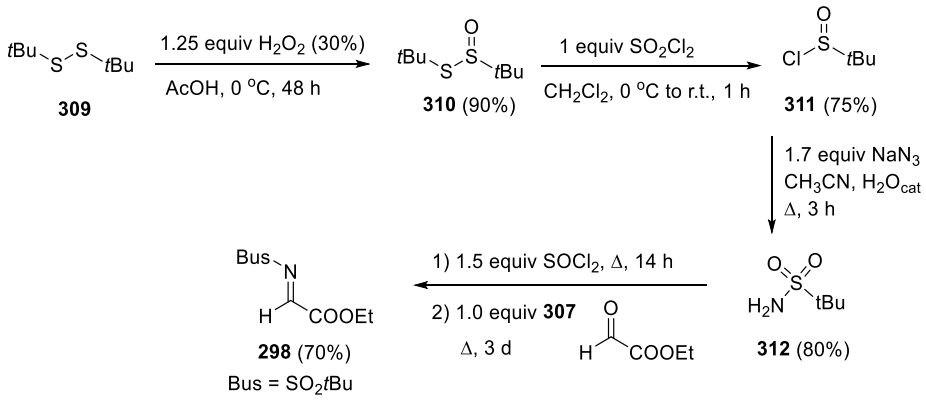
297 **12** **299**

Entry	Equiv **12**	Catalyst/equiv	Temp (°C)/ Time (h)	Solvent	Results [a]
1	1.5	No cat.	r.t./8	$CDCl_3$	No reaction
			+40/2.5-4		No reaction
			+50/12		No reaction
			Δ/6-48		-[c]
2	0.5	BINOL/20%mol	r.t./0.75	$CDCl_3$	No reaction

			+r.t./5		No reaction
			+50/2-24		-[c]
3	1.5	$BF_3 \cdot OEt_2$/2	r.t./0.75	CH_2Cl_2	No reaction [b]
4	1.5	$BF_3 \cdot OEt_2$/2	0/75	CH_2Cl_2	No reaction
			+r.t./48		-[c,d]
5	1.5	$BF_3 \cdot OEt_2$/2	0/7	THF	No reaction
			+r.t./48		-[c,d]
6	1	$BF_3 \cdot OEt_2$/1	0/3.5	CH_2Cl_2	No reaction
			+r.t./21		-[c,d]
			+r.t./21		-[c,e]
7	1.5	$BF_3 \cdot OEt_2$/1	0/3.5	CH_2Cl_2	No reaction
			+r.t./21		-[c]
8	2	$BF_3 \cdot OEt_2$/2	0/3.5	CH_2Cl_2	No reaction
			+r.t./21		-[c]
9	1	$ZnCl_2$/1	r.t./24	CH_2Cl_2	-[c]
10	1.5	$Cu(OTf)_2$/1.1	r.t./30-48		-[c,e]

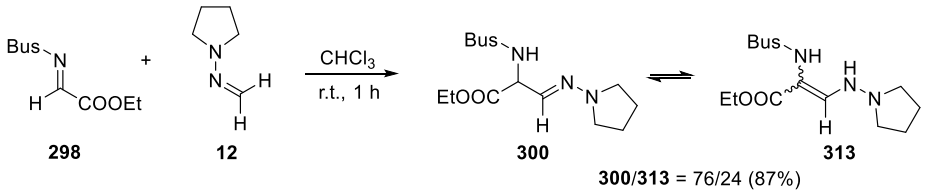
[a] Based on ^{1}H NMR and TLC analysis of the crude reaction mixture. [b] Starting product **297** is present. Degradation of **12** which is thought to form complex with $BF_3 \cdot OEt_2$. [c] Complex reaction mixture. [d] Small amount of starting product **297** is still present. [e] After flash chromatography no products could be identified by ^{1}H NMR and LC-MS analysis.

In the next part, the addition of hydrazone **12** across the more electrophilic sulfonyl iminoacetate **298** was attempted. The starting imine **298** was synthesized from 1,2-di-*tert*-butyldisulfane **309** in five steps following a literature procedure (Scheme 55).[142]



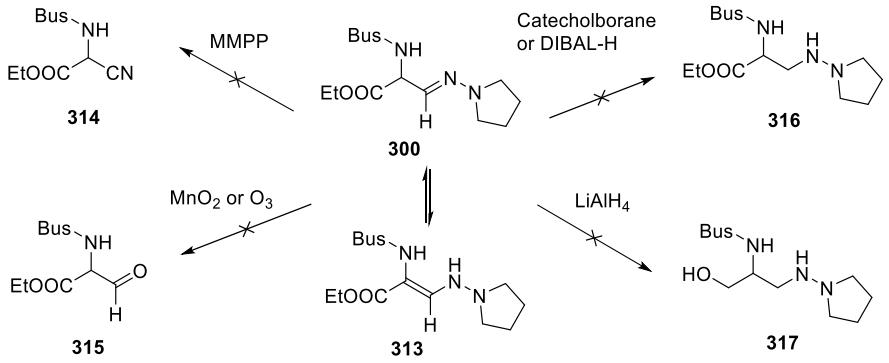
Scheme 55

The addition of hydrazone **12** across imine **298** was performed at room temperature in chloroform, affording an equilibrium mixture of adducts **300** and **313** in a ratio 76/24 determined *via* ^{1}H NMR analysis of the crude reaction mixture. Purification of the crude mixture by column chromatography afforded the mixture **300**/**313** in the same ratio of 76/24 in 87% yield (Scheme 56).



Scheme 56

With the mixture of ethyl (*E*)-2-((1,1-dimethylethyl)sulfonamido)-3-(pyrrolidin-1-ylimino)propanoate **300** and ethyl 2-((1,1-dimethylethyl)sulfonamido)-3-(pyrrolidin-1-ylamino)acrylate **313** in hand, the reactivity of the addition products was investigated (Scheme 57). The attempts are listed in Table 2. Oxidation of the pyrrolidin-1-ylimino moiety of substrate **300** with magnesium monoperoxyphthalate hexahydrate (MMPP·6H_2O) towards the corresponding nitrile adduct **314** failed, giving a complex mixture (Table 2, entries 1-2). Furthermore, compounds **300/313** were explored in an oxidative cleavage with ozone or manganese(IV) oxide in order to obtain the oxopropanoate **315** which could serve as a versatile building block for further elaborations (Table 2, entries 3-5). Unfortunately, only formation of unidentified side products was detected. The attempts to establish the structure of those side products by means of purification *via* column chromatography or preparative thin layer chromatography were not successful. Unsatisfactory results were obtained when substrates **300**/**313** were treated with catecholborane,[143] *di*-isobutylaluminium hydride or lithium aluminium hydride towards the synthesis of diamino acid derivative **316** or amino alcohol **317** (Table 2, entries 6-10).



Scheme 57

Table 2. Investigation of reactivity of the tautomeric mixture **300**/**313**.

Entry	Reagent/ equiv	T(ºC) /t(h)	Solvent	Results
1	$MMPP{\cdot}6H_2O$[a]/ 2.5	0/ 1	MeOH	-[b]
2	$MMPP{\cdot}6H_2O$[a]/ 5	0/ 0.08	MeOH	-[b]
3	O_3 (gas)	-78/ 0.5	THF	-[b]
4	MnO_2/ 2.5	Δ/ 3	CH_2Cl_2	-[b]
5	MnO_2/ 5.0	rt/ 1	CH_2Cl_2	-[b]
6	DIBAL-H[b]/ 1.0	0/ 0.5 to r.t./15	EtO_2	-[b]
7	Catecholborane/ 2.0	0/ 0.5 to r.t./16	EtO_2	-[b]
8	Catecholborane/ 2.5	0/ 0.5 to r.t./16	EtO_2	-[b]
9	Catecholborane[c]/ 2.0	0/ 0.5 to r.t./24	THF	-[b]
10	$LiAlH_4$/ 1.05	0/ 2	THF	-[b]

[a] Magnesium bis(monoperoxyphthalate) hexahydrate. [b] 1M solution in heptane. [c] 1M solution in THF. [b] Complex reaction mixture.

Despite the multiple attempts to reduce the double bond in compounds **300**/**313**, some additional variations of the reaction conditions could be foreseen for future research. For instance, use of sodium cyanoborohydride as reducing agent which was efficient towards reduction of the C=N bond in hydrazone-containing derivative of ethyl 3-hydroxyacrylate.[144] Moreover, reduction under milder conditions, involving the use of sodium borohydride, could be promising. Additionally,

hydrogenation of both tautomers could be performed with catalytic hydrogenation under phase transfer conditions.

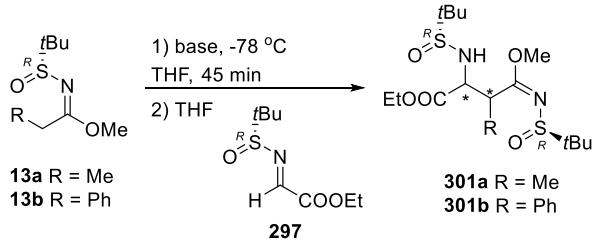
Further investigation of the reactivity of the obtained compounds **300**/**313** was not conducted due to their instability and the goal of developing new pathways towards diamino acid derivatives could not be realized *via* these unstable compounds. Nevertheless, the application of *N*,*N*-dialkylhydrazones has proven to be an useful synthetic tool.[39, 138, 145] Therefore, the addition reactions of methylenaminopyrrolidine **12** across iminoacetates **297** and **298** is still potentially of interest. Further optimizations could involve the modification of the electrophile[146] and/or the potential use of different catalysts.[147]

3.1.2 Addition of the (R_S)-imidates 13 across *N*-(*tert*-butylsulfinyl)iminoacetate 297

In the next part of this research, the reactivity of (*R*)-ethyl 2-(*tert*-butylsulfinyl)iminoacetate **297** towards Mannich-type reaction with chiral (R_S)-imidates **13** was studied (Scheme 58).

The addition reaction of imidate (R_S)-**13a** across iminoacetate (R_S)-**297** was optimized by systematically changing the reaction conditions in the synthesis of ethyl 2-(sulfinylamino)-4-(sulfinylimino)-4-methoxy-3-methylbutanoate **301a** (Table 3). In a first attempt, the use of one equivalent of LiHMDS at -78 °C to deprotonate imidate **13a** resulted after addition of iminoacetate **297** in the formation of imidate **301a** with good diastereoselectivity, but with incomplete conversion of the starting imidate **13a** after one hour (Table 3, entry 1). Next, similar conditions were applied, however, the reaction time after addition of iminoacetate **297** was extended to two hours, affording adduct **301a** with a slight decrease of the diastereoselectivity (Table 3, entry 2). Full conversion of imidate **13a** and moderate diastereoselectivity (major/minor 67/33) of imidate **301a** was achieved when 1.2 equivalents of LiHMDS were used and the reaction was performed at -78 °C for one hour. Column chromatography allowed to separate two diastereomers although in low yields of 18% (dr >99/1) and 9% (dr >99/1), probably caused by instability of compound **301a**. Further modification of the reaction conditions by means of variation of the base (KHMDS, NaHMDS, LDA) (Table 3, entries 4-6), addition of $ZnCl_2$ as Lewis acid (Table 3, entry 7), change of solvent (Table 3, entry 8), or performing the reaction at -97 °C (Table 3, entry 9) did not result in improved diastereomeric ratios and/or conversion. An additional experiment was performed starting from imidate **13b**. The addition reaction was performed under optimized conditions, namely: deprotonation of imidate **13b** with 1.2 equiv LiHMDS in THF at -78 °C for 45 minutes followed by addition of 1.2 equivalents iminoacetate **297** at -78 °C and stirring the reaction mixture at the same temperature for one hour. Two diastereomers were formed in a ratio of major/minor 71/29 and isolation of single diastereomers by column chromatography afforded two isomers of adduct **301b** in 8% and 6% yield.

However, due to insufficient selectivity and low yield of adducts **301**, further transformations were not performed. The absolute and relative stereochemistry of compounds **301a** and **301b** was not established.



Scheme 58

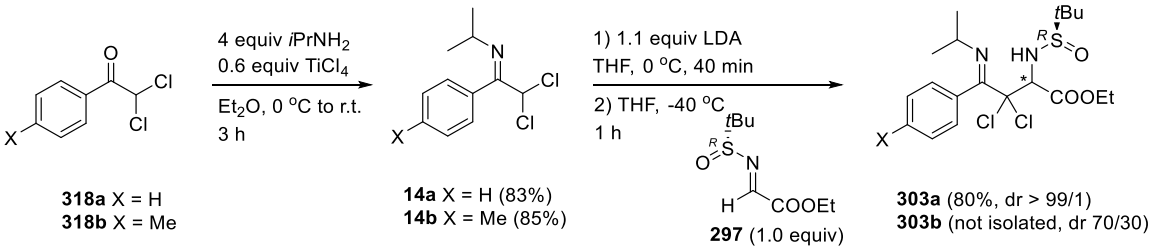
Table 3. Addition reaction of imidates (*Rs*)-**13** across iminoacetate (*Rs*)-**297.**

Entry	Base/equiv	*N*-sulfinyl imidate **13**	Equiv of **297**	Time (h)/ Temp (°C)	Conversion of **13** (%) [a]	Result	dr of **301** [a]
1	LiHMDS/ 1	**13a**	1	-78/1	94	**301a**	71/29
2	LiHMDS/ 1	**13a**	1	-78/2	99	**301a**	67/33
3	LiHMDS/1.2	**13a**	1.2	-78/1	100	**301a**	67/33 [b]
4	KHDMS/ 1	**13a**	1	-78/1	87	**301a**	53/45
5	NaHMDS/ 1	**13a**	1	-78/1	82	**301a**	63/32
6	LDA/ 1.1	**13a**	1	-78/1	100	**301a**	60/30
7	LDA/ 1.1 [c]	**13a**	1	-78/1	60	**301a**	63/37
8	LDA/ 1.1	**13a**	1	-78/1 [d]	97	**301a**	55/44
9	LDA/ 1.3	**13a**	1	-97/1	0	-	-
10	LiHMDS/1.2	**13b**	1.2	-78/1	100	**301b**	71/29 [e]

[a] Determined *via* ^{1}H NMR analysis of the crude reaction mixture. [b] After column chromatography two diastereomers **301a** were isolated in 18% and 9% yield. [c] 1.05 equiv of $ZnCl_2$ was added after deprotonation at -78 °C for 15 min. [d] Reaction was performed in dry Et_2O instead of dry THF. [e] After flash chromatography two diastereomers **301b** were isolated in 8% and 6% yield.

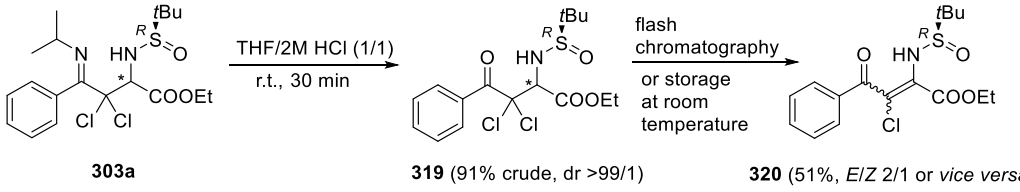
3.1.3 Reaction of α-iminoacete 297 with 3,3-dichloro-1-azaallylic anions

In a last part, α-iminoacetate **297** was subjected to reaction with 3,3-dichloro-1-azaallylic anions **302**, generated by deprotonation of α,α-dichloroketimines **14** with lithium diisopropylamide,[148] to produce the Mannich-type products ethyl 2-(*tert*-butylsulfinylamino)-3,3-dichloro-4-(isopropylimino)-4-arylbutanoates **303** (Scheme 59). The condensation reaction of α,α-dichlorinated imines **14** with *N*-sulfonylaldimines has been reported in literature.[149] The resulting adducts proved to be useful substrates towards hydrolysis of the imino functionality and diastereoselective ring closure to the corresponding functionalized aziridines. Therefore, it was of interest to explore this methodology on chiral substrates. α,α-Dichloroketimines **14a,b** were prepared by condensation of the corresponding α,α-dichloroketones **318** with primary amine in the presence of titanium(IV) chloride in diethyl ether (Scheme 59).[150] Deprotonation of α,α-dichloroketimines **14** with 1.1 equivalents of lithium diisopropylamide in THF at 0 °C for 40 minutes afforded 3,3-dichloro-1-azaallylic anions **302**, which reacted as nucleophiles with (R_S)-iminoacetate **297** at -40 °C for one hour. Notheworthy, the diastereoselectivity of the reaction was divergent for different substrates **303**. Thus, a diastereomeric ratio of >99/1 for adduct **303a** was determined *via* ^{1}H NMR analysis of the crude reaction mixture, while a ratio of 70/30 for adduct **303b** was obtained. Further elaborations were performed with substrate **303a**, which was isolated by column chromatography in 80% yield.



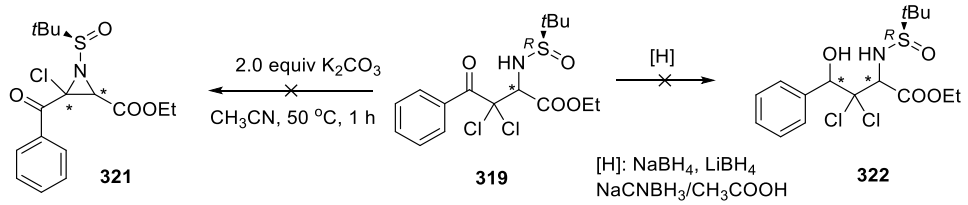
Scheme 59

The imino functionality of adduct **303a** was hydrolyzed in aqueous hydrochloric acid, resulting in the ketone **319** in 91% crude yield (Scheme 60). The elimination of hydrogen chloride occurred during purification *via* flash chromatography and compound **320** was isolated as a mixture of *E*/*Z*-isomers in a ratio of 2/1 (or *vice versa*) in 51% yield. Noteworthy, ketone **319** underwent also elimination of hydrogen chloride when stored at room temperature.



Scheme 60

Finally, the base-induced ring closure of compound **319** was attempted towards aziridine **321**, unfortunately, with no success (Scheme 61). The selective reduction of ketone **319** to the amino alcohol **322** was tried with different reducing agents ($NaBH_4$, $LiBH_4$, $NaCNBH_3/CH_3COOH$). However, only complex mixtures were formed which contained no desired product **322** (Scheme 61).



Scheme 61

In conclusion, the reactivity of iminoacetates **297** and **298** towards nucleophilic addition of 1- (methylenamino)pyrrolidine **12**, *N*-sulfinyl imidates **13** and anions of α,α-dichloroketimines **302** was investigated. Adducts obtained from aforementioned additions in sufficient yields were subjected to different transformations, including reduction, hydrolysis and oxidation, showing a lack of selective reactivity, however.

3.2 Synthesis of *N*-sulfinyl imidates and their transformation towards four- and six-membered azaheterocycles

In this part, the synthesis of chiral azetidine-2-carboxylic acid derivatives from 2-aryl-3-chloroazetidines **22** *via* oxidation of the aryl substituent was attempted. Asymmetric synthesis of precursors **22** was previously developed at the Department of Sustainable Organic Chemistry and Technology, UGent (Scheme 62).[47] This method includes the synthesis of *N*-*tert*-butanesulfinyl α-chloro-β-sulfonylaminoimidates **325** *via* the highly *anti*-diastereoselective Mannich-type addition of *N*-*tert*-butanesulfinyl α-chloro acetimidate **324** across aromatic aldimines **27** as a key step.[47] Secondly, the synthesis of new *N*-*tert*-butanesulfinyl δ-chloro-β-sulfonylaminoimidates **339**-**340** was investigated. The latter were studied for the synthesis of enantiomerically pure *N*-(de)protected 2,3-functionalized piperidines.

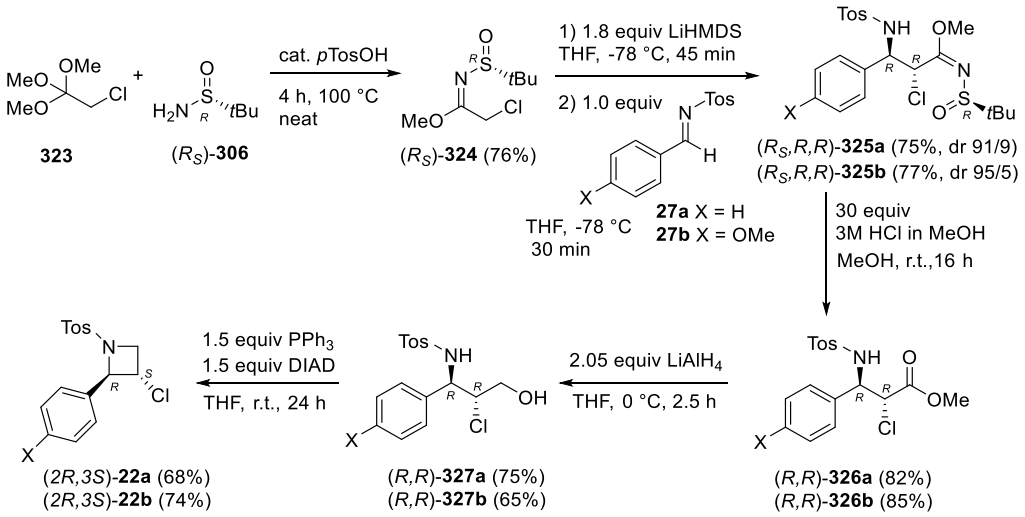
The asymmetric Mannich reaction is a very important method for the preparation of β-amino carbonyl compounds.[151] The Kobayashi group developed a (super)base-catalyzed addition reaction of *N*-sulfonylimidates with activated aromatic or aliphatic aldimines leading to racemic adducts with high *anti*-diastereoselectivity.[152]

Over the last decade, chiral *N*-sulfinamides have proven to be among the most efficient classes of auxiliaries in asymmetric synthesis.[47, 123a, 153] In particular, *N*-(*tert*-butanesulfinyl)imidates are very useful chiral enolate precursors for Michael addition,[154] α-alkylation[155] and aldol addition.[156] Recently, our group elaborated the asymmetric, highly *anti*-selective Mannich-type reactions of α-methyl- and α-chloro-*N*-sulfinyl imidates across *N*-tosyl aldimines.[47, 153e] These imidates were used in the synthesis of enantiopure β-sulfonylamino amides and esters as new chiral β-amino acid derivatives.

3.2.1 Synthesis of 2-aryl-3-chloroazetidines 22 and their attempted transformation towards azetidine-2-carboxylic acid derivatives

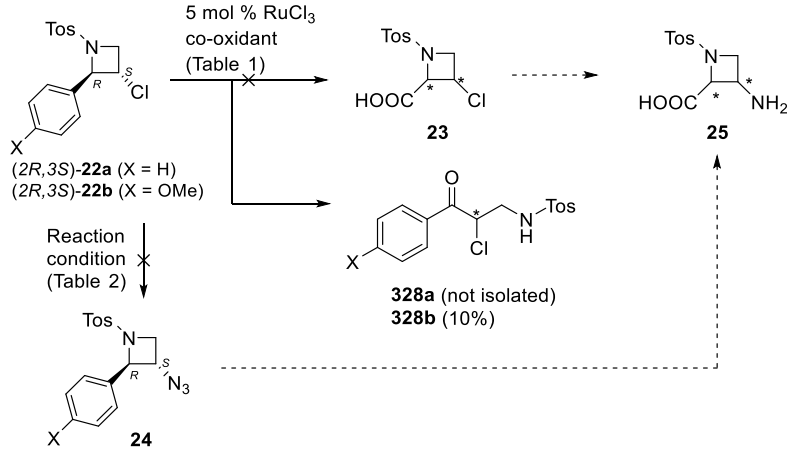
The synthesis of 2-aryl-3-chloroazetidines **22** was performed *via* a method developed at the Department of Sustainable Organic Chemistry and Technology, UGent. Starting α-chloro *N*-sulfinyl imidate **324** was synthesized *via* condensation of (R_S)-*tert*-butanesulfinamide **306** and orthoester **323** without solvent at 100 °C for 4 hours. Subsequently, *anti*-selective Mannich-type reaction of *N*-sulfinyl imidate **324** and aromatic aldimines **27** afforded *N*-*tert*-butanesulfinyl α-chloro-β-sulfonylaminoimidates **325a** and **325b**. The reaction was performed under optimized reaction conditions, namely, deprotonation of *N*-sulfinyl imidate (R_S)-**324** by means of LiHMDS in THF at -78 °C for 45 minutes, followed by addition of aldimines **27a** and **27b** with reaction at -78 °C for 30 minutes. The formation of four diastereomers **325** was detected by ^{1}H NMR analysis of the crude reaction mixture, namely, *major*-(R_S,*R*,*R*)-**325**/*minor*-**325**=(R_S,*S*,*S*)-**325**+(R_S,*S*,*R*)-**325**+(R_S,*R*,*S*)-**325**

in 91/9 (for **325a**) and 95/5 (for **325b**) ratio. Major isomers (R_S,*R*,*R*)-**325a,b** were separated by column chromatography and were subjected to the next steps. *N*-Deprotection of the *N*-sulfinyl group towards esters **326**, reduction of ester **326** to the primary alcohols **327**, and subsequent cyclization under Mitsunobu conditions afforded functionalized azetidines **22a** and **22b** in good yields (Scheme 62).



Scheme 62

With enantiomerically pure azetidines **22** in hand, further transformation towards azetidine-2-carboxylic acid derivatives **23** and **25** was attempted (Scheme 63).



Scheme 63

Oxidation was attempted by catalytic oxidation of the aromatic substituent with ruthenium(VIII) oxide in a biphasic solvent system consisting of water, acetonitrile and tetrachloromethane or in anhydrous conditions.[157] Periodic acid was used as co-oxidant based on several literature procedures.[158] Initially, the 3-chloro-2-phenylazetidine **22a** was treated with ruthenium(III) chloride and H_5IO_6 in tetrachloromethane and acetonitrile at room temperature for 2.5 hours. However, only

a complex mixture was observed and attempts to determine the composition of the mixture failed (Table 4, entry 1). Next, two times less equivalents of oxidizing agent under anhydrous conditions at 0 °C for 15 minutes were applied, leading to the formation of a mixture of unidentified products (Table 4, entry 2). Unsatisfying results were obtained upon applying $CH_3CN/CCl_4/H_2O$ 1/1/1 as solvent system at 0 °C or at room temperature, following literature procedure (Table 4, entries 3 and 4).[158b] When 3-chloro-2-(4-methoxyphenyl)-1-tosylazetidine **22b** was subjected to the oxidation with $RuCl_3/H_5IO_6$ in a solvent system of $CH_3CN/CCl_4/H_2O$ at room temperature for 2.5 hours, only side product **328b** resulting from a ring opening/oxidation sequence was isolated in a poor yield of 10% (Table 4, entry 5).

Table 4. Attempted oxidation of the 2-aryl substituent of azetidines **22** towards a carboxylic group.

Entry	X	Equiv of H_5IO_6	Solvent system	time, h/Temp	Result
1	H	10.0	CH_3CN/CCl_4 (1/1)	0.5/0 °C +2.5/r.t.	-[a]
2	H	5.0	CH_3CN/CCl_4 (1/1)	0.25/ 0 °C	-[a]
3	H	10.0	$CH_3CN/CCl_4/H_2O$ (1/1/1)	0.75/ 0 °C	-[a]
4	H	15.0	$CH_3CN/CCl_4/H_2O$ (1/1/1)	24/r.t.	-[a]
5	OMe	10.0	$CH_3CN/CCl_4/H_2O$ (1/1/1)	2.5/r.t.	**328b** (10%) [b]

[a] Complex reaction mixture. [b] Yield after column chromatography.

Based on the attempted conditions it may be concluded that the use of $RuCl_3/H_5IO_6$ has a lack of reactivity and selectivity towards the desired oxidation. In future research, the oxidation of the aromatic ring could be performed prior to cyclization in ester **326** in order to avoid side reactions such as the formation of ring opened products **328**.

Additionally, nucleophilic substitution of chloride from azetidine **22a** with azide was tested (Scheme 63). Unfortunately, attempted substitution with 1.1-2.0 equivalents of sodium azide in acetone at 50-60 °C for 17-24 hours failed (Table 5, entries 1 and 2). The performance of the reaction in DMF or DMSO at 60 °C for 5 hours (Table 5, entries 3 and 4) gave no reaction while use of harsher conditions resulted in complex reaction mixtures which were not further analyzed (Table 5, entries 5 and 6).

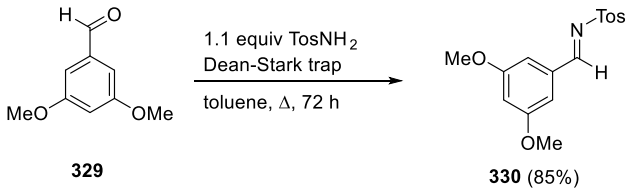
Table 5. Attempted substitution reaction of 3-chloroazetidine **22a** with NaN_3.

Entry	Reaction conditions	Result
1	1.1 equiv NaN_3, acetone, 50 °C, 17 h	No reaction
2	2.0 equiv NaN_3, acetone, 60 °C, 24 h	No reaction
3	1.5 equiv NaN_3, DMF, 60 °C, 5 h	No reaction
4	2.0 equiv NaN_3, DMSO, 60 °C, 5 h	No reaction
5	4.0 equiv NaN_3, DMSO, 110 °C, 15 h	Complex reaction mixture
6	3.0 equiv NaN_3, 3.0 equiv NaI, DMSO, 80 °C, 16 h	Complex reaction mixture

3.2.2 Attempted synthesis of 3-chloro-2-(3,5-dimethoxyphenyl)-1-tosylazetidine

Due to the reactivity of 2-aryl-3-chloroazetidine **22b** towards the ring opening process, a modification of the aromatic unit to a 3,5-dimethoxyphenyl moiety was suggested to facilitate the oxidation process prior of ring opening.[159]

Starting aldimine **330** was synthesized *via* condensation of 3,5-dimethoxybenzaldehyde **329** and *p*-toluenesulfonamide in toluene at reflux for 72 hours (Scheme 64).[160] After filtration of the reaction mixture over Celite®, evaporation of the solvent *in vacuo* and recrystallization from ethyl acetate, *N*-(3,5-dimethoxybenzylidene)-4-methylbenzenesulfonamide **330** was obtained in 85% yield.



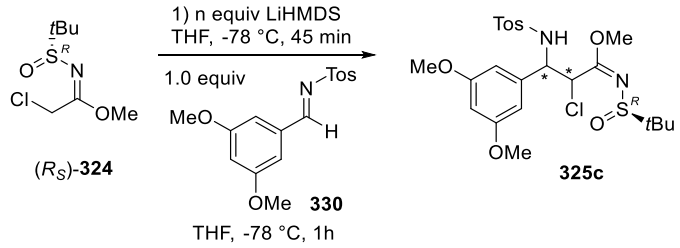
329 **330** (85%)

Scheme 64

Next, the addition reaction of α-chloro *N*-sulfinyl imidate **324** across imine **300** was initially performed under optimized reaction conditions (Table 6, entry 1). However, the selectivity of the reaction dropped dramatically. Additionally, conversion of starting substrate **324** was only 37%. Then, 1.5 equivalents of imidate **324** was deprotonated with 1.5 equivalents of LiHMDS in THF at -78 ºC for 45 minutes, followed by addition of one equivalent of aldimine **330** (Table 6, entry 2). Again, only moderate selectivity could be achieved (*major*-(R_S,*R*,*R*)-**325c**/*minor*-**325c**=(R_S,*S*,*S*)-**325c**+(R_S,*S*,*R*)-**325c**+(R_S,*R*,*S*)-**325c** = 73/27). The relative and absolute stereochemistry was assumed in analogy with previous results.[47] The crude mixture was purified by column chromatography,

affording the single diastereomer methyl (R_S)-*N*-(*tert*-butylsulfinyl)-*2R*-chloro-*3R*-(3,5-dimethoxyphenyl)-3-(*p*-toluenesulfonylamino)propanimidate (R_S,*R*,*R*)-**325c** in a moderate yield of 33%.

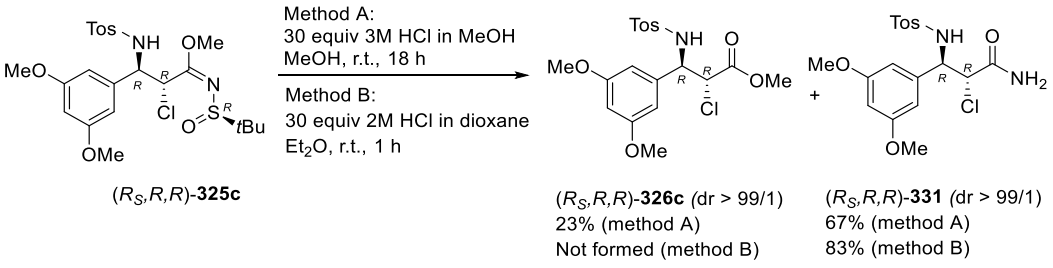
Table 6. Addition reaction of imidate (R_S)-**334** across imine **27d**.



Entry	n	Conversion of **324**	*dr* of **325c**[a]	Yield of (R_S,*R*,*R*)-**325c** (%)
1	1.8	37	**325c** (68/10/13/9)	-
2	1.5	92	**325c** (73/11/6/10)	33 (*dr* > 99/1)[b]

[a] Determined *via* ^{1}H NMR analysis of the crude reaction mixture. [b] After purification *via* flash chromatography.

Deprotection of *N*-sulfinyl β-amino-α-chloro imidate (R_S,*R*,*R*)-**325c** with HCl in methanol led to formation of a mixture of ester **326c** and amide **331** in a ratio of 30/70 (Scheme 65). The individual compounds **326c** and **331** were isolated by column chromatography in 23% and 67% yield, respectively. A second attempted deprotection of imidate **325c** was carried out by means of HCl (3M solution in dioxane) in diethyl ether at room temperature for one hour. Evaporation of the solvents *in vacuo* and recrystallization from diethyl ether afforded exclusively amide **331** in 83% yield (Scheme 65).



Scheme 65

Due to the low efficiency of the key step of the formation of the imidate **325c**, as well as the lack of selectivity towards the formation of desired ester **326c**, further synthesis of the corresponding functionalized enantiomerically pure azetidine was abandoned at this stage.

3.2.3 Synthesis of δ-chloro *N*-sulfinyl imidates 26 and their elaboration towards the synthesis of substituted piperidines

The present chapter presents the results towards the synthesis of new methyl *N*-sulfinyl-5-chloropentanimidates **26** and their elaboration towards the synthesis of new δ-chloro *N*-sulfinyl imidates **339** and **340** *via anti*-diastereoselective Mannich-type addition. The latter were investigated as versatile building blocks for the preparation of enantiomerically pure 2,3-disubstituted piperidines.

3.2.3.1 Introduction.

Functionalized piperidines and their derivatives form a well-known class of organic compounds due to their natural occurrence in various bioactive alkaloids.[161] Piperidine motifs are also found in pharmaceuticals and synthetic intermediates.[162] Particular attention has been given to 2,3-disubstituted piperidines as the basic skeleton of many pharmacologically active compounds.[52d, 163] For example, piperidines **332** and **333** (Figure 11) and their analogues are nonpeptide antagonists of substance P which has been implicated in the pathophysiology of a wide range of diseases including neurogenic inflammation, transmission of pain and depression.[164] *Cis*- and *trans*-piperidine-2,3-dicarboxylic acids **334** and **335** are cyclic analogues of *N*-methyl-D-aspartic acid **336** (NMDA) which are intensively studied in view of their interactions with amino acid neuromediated receptors (Figure 11).[52d, 165]

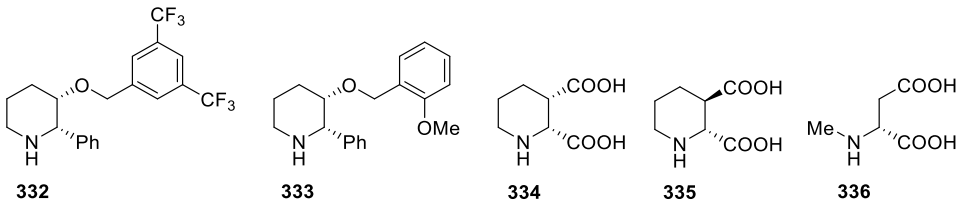


Figure 11. 2,3-Disubstituted piperidines **1**, **2** as antagonists of substance P and **3**, **4** as analogues of NMDA **5**.

Both the relative configuration and the absolute configuration of the chiral centres of the piperidine ring have an influence on the biological activity.[165d, 166] Moreover, chiral functionalized piperidine-3-carboxylic acids are conformationally restricted azacyclic analogues of alicyclic β-amino acids, which are known to be useful building blocks for the synthesis of peptides with modified and improved pharmacological activities.[32c, 32d, 33e, 58a, 67, 167] It has also been established that piperidine-3-carboxylic acid (nipecotic acid) **9** can be incorporated into short homochiral peptides that appear to adopt well-defined conformations. Nipecotic acid-containing heterochiral dipeptides also strongly stabilize reverse-turn formation.[32e, 34, 37]

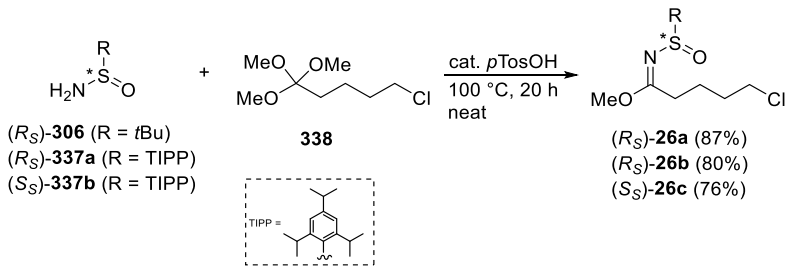
A number of asymmetric approaches for the synthesis of 2,3-disubstituted piperidines are based on chiral pool syntheses starting with readily available amino acids[165e, 168] and diols[169] through a multistep synthesis. Among other methods, ring expansion[164d, 170] and domino reactions starting

from Baylis-Hillman adducts using lithium amide[106, 166a, 171] have been reported recently. The development of new simple and efficient methods towards the synthesis of functionalized piperidines with controlled diastereo- and enantioselectivity keeps to attract the continuous attention of organic chemists.

Therefore, it was envisioned that the use of δ-chloro *N*-sulfinyl imidates in the addition reaction across aromatic aldimines could lead to the synthesis of new chiral β-aryl-δ-chloro-substituted β-amino acid derivatives as potential building blocks of enantiopure functionalized piperidines.

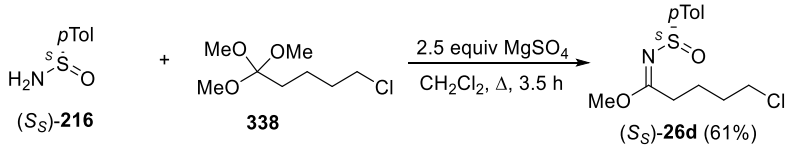
3.2.3.2 Synthesis of *N*-sulfinyl δ-chloro-β-sulfonylamino imidates 339 and 340

The synthesis of δ-chloro *N*-sulfinyl imidates **26** was achieved *via* a modified literature procedure.[155a, 155b] Condensation of sulfinamides **306**, **337a,b** and orthoester **338** with a catalytic amount of *p*TosOH without solvent afforded imidates **26a-c** in high yields of 76-87% (Scheme 66). A single isomer was observed which is supposed to have *E*-configuration based on recent literature data.[156] Additionally, several NOESY experiments were performed for imidate (R_S)-**26a**, however, giving no conclusive results due to the lack of strong NOE's.



Scheme 66

The imidate **26d** was synthesized *via* condensation of (S_S)-*p*-toluenesulfinamide (S_S)-**216** with orthoester **338** in the presence of $MgSO_4$ in CH_2Cl_2 at reflux for 3.5 hours. Purification *via* flash chromatography afforded chiral *N*-*p*-toluenesulfinyl imidate (S_S)-**26d** in 61% yield (Scheme 67).[155a]

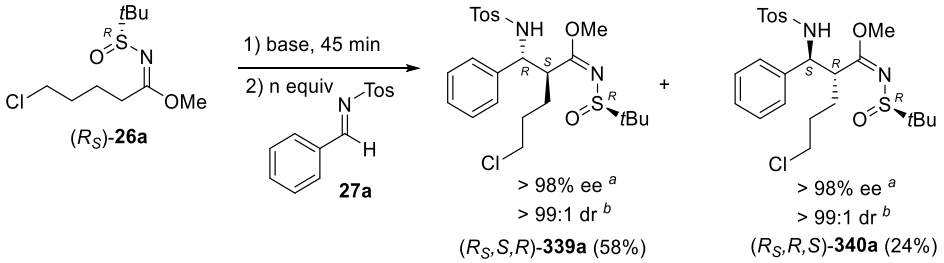


Scheme 67

Examination of the addition reaction of imidate (R_S)-**26a** across *N*-tosyl aldimine **27a** was carried out by systematic variation of the reaction conditions (Table 7). Screening of the reaction conditions showed that deprotonation of imidate (R_S)-**26** with 1.8 equivalents LiHMDS in THF at -78 ºC followed by addition of *N*-tosyl aldimine **27a** at -78 °C provided the desired adduct **339a** and **340a**

in good yield with a high relative stereocontrol (dr > 99/1) and moderate absolute stereocontrol ((*R*S,*S*,*R*)-*anti*-**339a**/(*R*S,*R*,*S*)-*anti*-**340a** = 72/28) (Table 7, entry 1). Separation of the two diastereoisomers *via* flash chromatography afforded the optically pure δ-chloro-β-amino-*N*-sulfinyl imidates (*R*S,*S*,*R*)-*anti*-**339a** and (*R*S,*R*,*S*)-*anti*-**340a** in 58% and 24% yield, respectively. The selectivity could not be improved by means of changing the ratio reagent/base (Table 7, entries 2-6). The use of KHMDS, NaHMDS or LDA led to a decrease in absolute stereocontrol while relative stereocontrol was exclusively *anti* (Table 7, entries 7-10). Furthermore, the reaction was repeated with 1.2 equivalents LiHMDS at -78 °C for one hour, followed by 16 hours at room temperature leading to a decline of the stereoselectivity (Table 7, entry 11) indicating reversibility of the addition reaction. Reversed stereocontrol was observed ((*R*S,*S*,*R*)-*anti*-**339a**/(*R*S,*R*,*S*)-*anti*-**340a** = 24/76) when the reaction was repeated at -78 °C for one hour, followed by reflux for one hour with an overall crude yield of only 44% which indicated the possible degradation of (*R*S,*S*,*R*)-*anti*-**339a** under strong basic conditions (Table 7, entry 12) and only a trace of the cyclization product **344a** and **345a** was observed *via* LC-MS analysis. The changing of solvents to toluene or hexane did not lead to enhanced stereoselectivity (Table 7, entries 13 and 14). In a last attempt to improve the selectivity of the addition reaction, some Lewis acids were tested. The addition of $ZnCl_2$ led to a reversal of absolute *anti*-stereocontrol ((*R*S,*S*,*R*)-*anti*-**339a**/(*R*S,*R*,*S*)-*anti*-**340a** = 47/53) (Table 7, entry 15), whereas the addition of $MgBr_2$ gave no conversion of the starting imidate (*R*S)-**26a** (Table 7, entry 16).

Table 7. Optimization of the addition reaction of *N*-sulfinyl imidate **26a** across aldimine **27a**.



Entry	(*R*S)-**26a** (equiv)	Equiv. of aldimine **27a**	Base (equiv)	Solvent	Temp (°C)/ Time (h)	(*R*S,*S*,*R*)-**339a**/ (*R*S,*R*,*S*)-**340a**[c]	*anti*/*syn*[c]	Yield (%)[d]
1	1.8	1.0	LiHMDS (1.8)[e]	THF	-78/1	72/28	> 99/1 > 99/1	(*R*S,*S*,*R*)-**339a** (58) (*R*S,*R*,*S*)-**340a** (24)
2	1.2	1.0	LiHMDS (1.2)[e]	THF	-78/1	64/36	> 99/1	-
3	1.5	1.0	LiHMDS (1.5)[e]	THF	-78/1	67/33	> 99/1	-

4	1.0	2.0	LiHMDS (1.2) [e]	THF	-78/1	58/42	> 99/1	-
5	1.5	1.0	LiHMDS (2.0) [e]	THF	-78/1	52/48	> 99/1	-
6	1.0	1.5	LiHMDS (1.5) [e]	THF	-78/1	65/35	> 99/1	-
7	1.2	1.0	KHMDS (1.2) [e]	THF	-78/1	58/42	> 99/1	-
					+r.t./16	41/59	> 99/1	-
8	1.2	1.0	NaHMDS (1.2) [e]	THF	-78/1	57/43	> 99/1	-
					+r.t./16	38/62	> 99/1	-
9	1.2	1.0	LDA (2.0) [e]	THF	-78/1	67/33	> 99/1	-
					+r.t./16	64/36	> 99/1	-
10	1.2	1.0	LDA (1.3) [e]	THF	-78/1	-	-	-
11	1.0	1.0	LiHMDS (1.2) [e]	THF	-78/1	70/30	> 99/1	-
					+r.t./16	65/35	> 99/1	-
12	1.6	1.0	LiHMDS (1.2) [e]	THF	-78/1	-	-	-
					+Δ/1	24/76	> 99/1	-
13	1.2	1.0	LiHMDS (1.2) [f]	Toluene	-78/1	69/31	> 99/1	-
14	1.2	1.0	LiHMDS (1.2) [g]	Hexane	-78/1	65/35	> 99/1	-
15	1.8	1.0	LiHMDS (1.8) [e,h]	THF	-78/1	47/53	> 99/1	-
16	1.8	1.0	LiHMDS (1.8) [e i]	THF	-78/1	-	-	-

[a] Determined by ^{1}H NMR analysis with Pirkle's alcohol. [b] Determined *via* ^{1}H NMR analysis of the purified compound. [c] Determined *via* ^{1}H NMR analysis of the crude reaction mixture. [d] Yield of a single diastereomers after flash chromatography. [e] Deprotonation was performed at -78 ºC for 45 min in THF ([f] in toluene, [g] in hexane). [h] 1.2 equiv of $ZnCl_2$ or [i] $MgBr_2$ was added after deprotonation at -78 ºC.

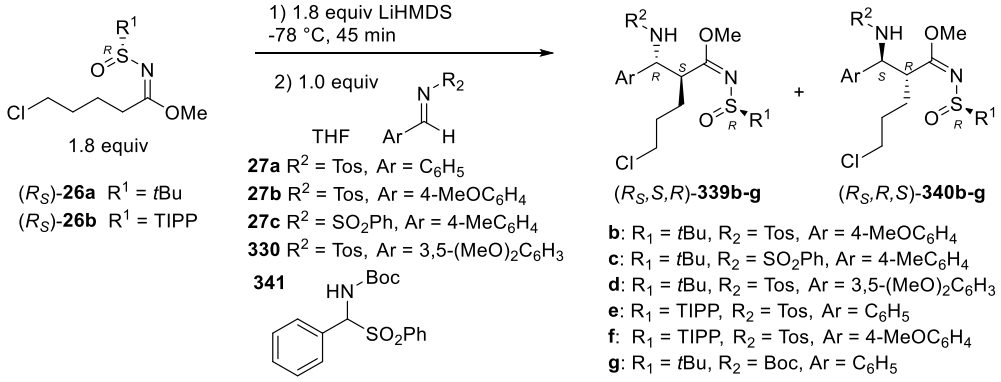
Analogously, several other new chiral imidates **339** and **340** were prepared *via* the optimized reaction conditions with excellent *anti*-diastereoselectivity (*anti/syn* > 99/1) and good overall yield (69-83%) (Table 8, entries 1 and 2). Noteworthy, the reaction of imidate (R_S)-**26a** with aldimine **27b** (Ar = 4-MeOC$_6$H$_4$) resulted in the formation of *N*-sulfinyl imidates (R_S,*R*,*S*)-*anti*-**340b** as major diastereomer obtained in enantiomerically pure form by recrystallization in 69% yield. Unfortunately, the minor diastereomer (R_S,*S*,*R*)-*anti*-**339b** could not be isolated in diastereomerically pure form and only a mixture of *(R_S,S,R)-anti*-**339b**/*(R_S,R,S)-anti*-**340b** = 74/26 in 10% yield was obtained which was not applied in further transformations. In case of the addition of imidate **26a**

across aldimine **27c**, optically pure imidates (R_S,*S*,*R*)-*anti*-**339c** and *(*R_S,*R*,*S)-anti*-**340c** were isolated after flash chromatography in 45% and 38% yield, respectively.

In order to improve the facial selectivity, more sterically hindered substrates **26b-d** and **330** or **341** were tested. When addition of imidate **26a** across *N*-(3,5-dimethoxybenzylidene)-4-methylbenzenesulfonamide **330** was performed under optimized reaction conditions, the diastereomeric ratio **339d**/**340d** was of 57/43 (Table 8, entry 3). The addition of methyl 5-chloro-*N*-((2,4,6-triisopropylphenyl)sulfinyl)pentanimidate (R_S)-**26b** across aldimines **26a** and **26b** resulted in the formation of adducts (R_S,*S*,*R*)-*anti*-**339e**/(R_S,*R*,*S*)-*anti*-**340e** in a ratio of 35/65 (Table 8, entry 4) and (R_S,*S*,*R*)-*anti*-**339f**/(R_S,*R*,*S*)-*anti*-**340f** in a ratio of 15/85 (Table 8, entry 5), respectively. The only negligible improvement of the diastereomeric ratio was observed when imidate **26b** was reacted with aldimine **27b**. Due to the reduced commercial availability and the low impact on the reaction outcome upon use of substrate **26b**, further research was based on the use of imidate **26a**.

In a next attempt, imidate **26a** and *N*-*tert*-butyl[phenyl(phenylsulfonyl)methyl]carbamate **341** were reacted under optimized reaction conditions (Table 8, entry 6). Formation of four diastereomers was observed *via* ^{1}H NMR analysis of the crude reaction mixture, which could not be isolated in pure form by column chromatography. Further analysis of this reaction mixture was not conducted.

Table 8. Extension of the addition reaction *N*-sulfinyl imidates **26a,b** across aldimines **27, 330** and **341**.

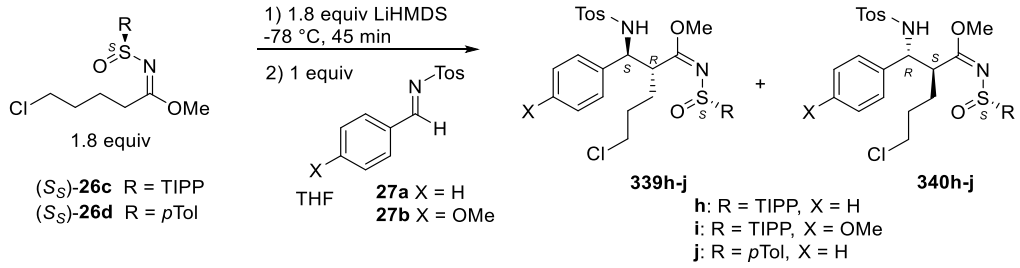


Entry	Imidate **26**	Aldimine **27**	(*R*S,*S*,*R*)-**339**/ (*R*S,*R*,*S*)-**340** [a]	*anti*/*syn* [a]	Yield (%) [b]
1	(*R*S)-**26a**	**27b**	17/83	> 99/1	(*R*S,*S*,*R*)-**339b** (-) (*R*S,*R*,*S*)-**340b** (69)
2	(*R*S)-**26a**	**27c**	60/40	> 99/1	(*R*S,*S*,*R*)-**339c** (45) (*R*S,*R*,*S*)-**340c** (38)
3	(*R*S)-**26a**	**330**	57/43	> 99/1	-
4	(*R*S)-**26b**	**27a**	35/65	> 99/1	-
5	(*R*S)-**26b**	**27b**	15/85	> 99/1	-
6	(*R*S)-**26a**	**341**	5/7/84/4[c]	-	-

[a] Determined *via* ^{1}H NMR analysis of the crude reaction mixture. [b] Yield of a single diastereomers after flash chromatography. [c] A mixture of four unidentified diastereomers was observed *via* ^{1}H NMR analysis of the crude reaction mixture

In a last attempt, the imidates (*S*S)-**26c** and (*S*S)-**26d**, with *S*-configuration of the sulfur atom, were applied towards Mannich-type reaction under optimized reaction conditions and results are listed in Table 9. Unfortunately, no significant improvements in the reaction outcome were observed with these substrates (Table 9, entries 1-3).

Table 9. Extension of the addition reaction *N*-sulfinyl imidates **26c,d** across aldimines **27a,b**.



Entry	Imidate **26**	Aldimine **27**	(S_S,*R*,*S*)-**339**/ (S_S,*S*,*R*)-**340** [a]	*anti*/*syn* [a]	Yield (%) [b]
1	(S_S)-**26c**	**27a**	40/60	> 99/1	- [c]
2	(S_S)-**26c**	**27b**	14/86	> 99/1	(S_S,*R*,*S*)-**339i** (10) (S_S,*S*,*R*)-**340i** (70)
3	(S_S)-**26d**	**27a**	45/55	> 99/1	- [c]

[a] Determined *via* ^{1}H NMR analysis of the crude reaction mixture. [b] Yield of a single diastereomers after flash chromatography. [c] Single diastereomers were not isolated.

3.2.3.3 Proposed transition state of formation of adducts 339 and 340

The relative diastereoselectivity of the addition reaction of *N*-sulfinyl imidate **26a** across *N*-sulfonyl aldimines **27** can be rationalized with a model in which the reaction proceeds *via* transition states **TS-1** and **TS-2** (Figure 12) with poor facial selectivity. Upon deprotonation of imidate **26**,[152c, 153e] the *E*-enolate will be preferably formed with the chloropropyl group and the *N*-*tert*-butylsulfinyl group at opposite sides of the C–C double bond, while the *N*-sulfonyl aldimines **27** adopt an *E*-configuration. Due to the steric repulsion between the sulfinyl group of imidate **26a** and the aryl group of aldimines **27** and between the chloropropyl substituent and the arylsulfonyl group in transition state **TS-3** it is concluded that transition states **TS-1** and **TS-2** are favored to give (R_S,*S*,*R*)-*anti*- and (R_S,*R*,*S*)-*anti* products, respectively (Figure 12). It is worth noting that currently the halogen does not play a role in this stereochemical outcome, contrary to a halogen at the β-position of the enolate which influences the *E*/*Z* ratio of the metal enolates.[47, 172]

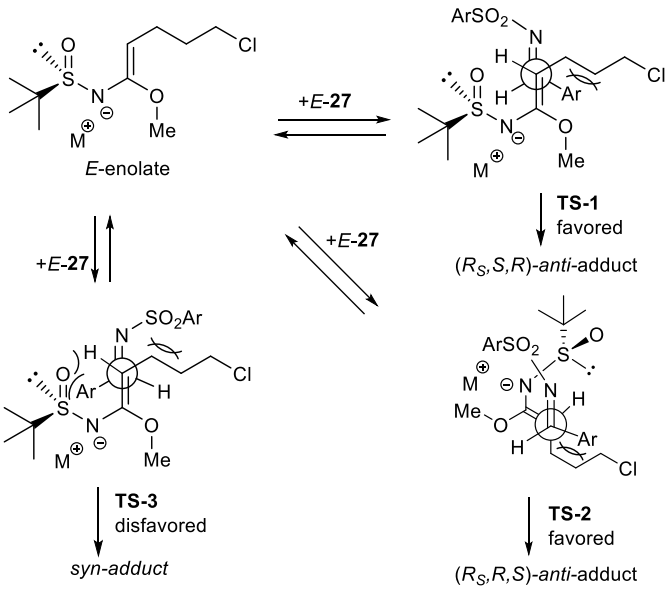


Figure 12. Proposed transition state model.

To confirm the *anti*-stereochemistry of adducts **339** and **340**, additional investigation was carried out. The structure and stereochemistry of (R_S,*R*,*S*)-*anti*-**339c** was confirmed by X-ray diffraction analysis (Figure 13). Noteworthy, the crystal data of adduct (R_S,*R*,*S*)-*anti*-**340c** also supports the suggestion about *E*-configuration of the imidates **26**. Furthermore, the oxidation of the sulfinyl group of imidates **339a** and **340a** to a sulfonyl group with *m*CPBA led to the formation of *N*-sulfonyl imidates (*S*,*R*)-**342** and (*R*,*S*)-**343** which demonstrate identical sets of chemical shifts in ^{1}H and ^{13}C NMR (Scheme 68). This result allowed to conclude that the two starting *N*-sulfinyl imidates **339a** and **340a** have *anti*-stereochemistry.

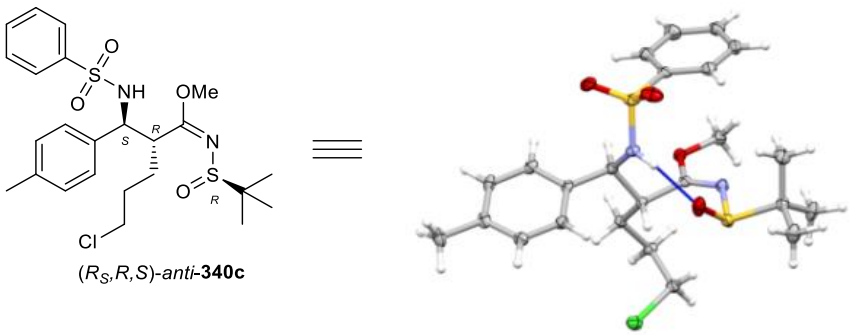
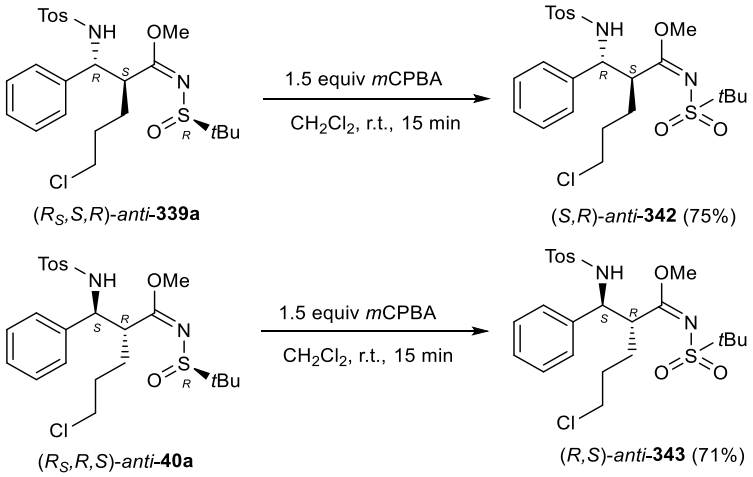


Figure 13. Asymmetric unit of the crystal structure of (R_S,*R*,*S*)-*anti*-**340c**, showing thermal displacement ellipsoids at the 50% probability level. The intramolecular H-bond between NH and S=O is indicated.



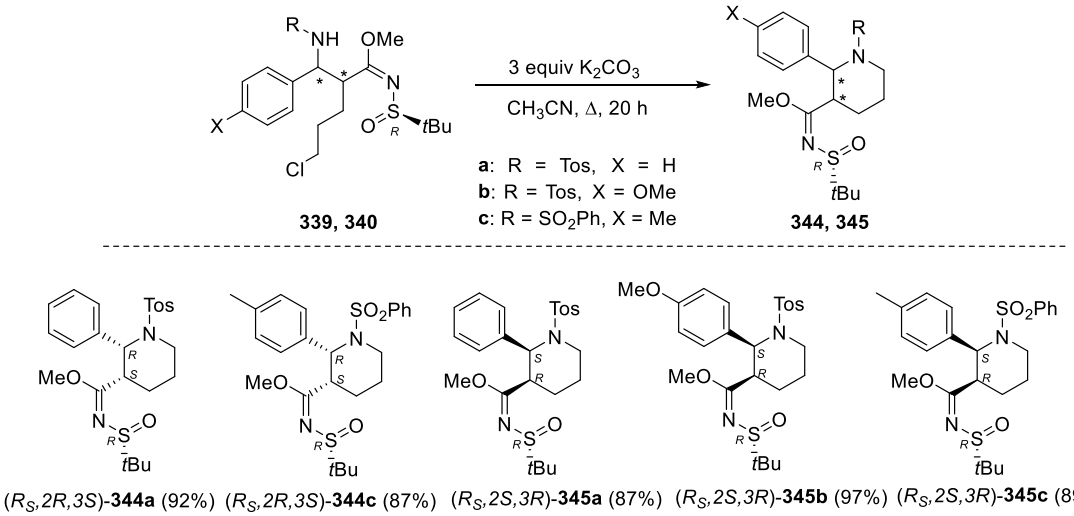
Scheme 68

3.2.3.4 Synthesis of 2,3-disubstituted piperidines 344-359

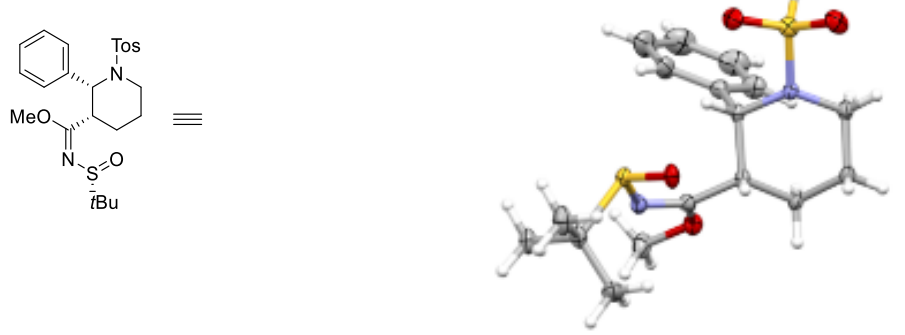
For the further transformations towards substituted piperidines, compounds **339a-c** and **340a-c** were chosen in order to demonstrate the applicability of the new imidates.

First, the chiral imidates **339** and **340** were evaluated for intramolecular cyclization to the corresponding piperidines **344** and **345** (Scheme 69).[173] Initial attempts to carry out a base-induced cyclization at room temperature resulted in poor conversion of *N*-sulfinyl imidate **339a**. Treatment of imidate (*R*$_S$,*S*,*R*)-*anti*-**339a** with three equivalents of potassium carbonate in acetonitrile under reflux for 20 hours resulted in full conversion of δ-chloro imidate **339a** into piperidine (*R*$_S$,*2R*,*3S*)-*cis*-**344a**, which was isolated in an excellent yield of 92%.

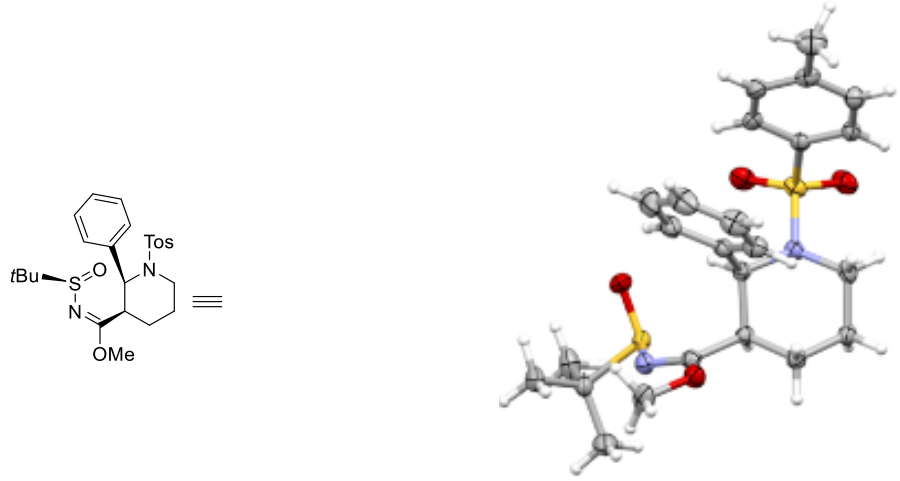
Other piperidines **344** and **345** were prepared in the same manner in good to excellent yields (87-97%) without any isomerization reactions being observed. The relative configuration of the synthesized methyl 2-aryl-1-sulfonylpiperidine-3-*N*-(*tert*-butylsulfinyl)carbimidates **344** and **345** was established as *cis* based on observed coupling constants of 6.1-6.2 Hz (^{1}H NMR, $CDCl_3$) between the protons at C-2 and C-3, whereas the corresponding *trans*-2,3-disubstituted piperidines have larger coupling constants (average 9.0-10.0 Hz).[174] The relative and absolute configurations were determined by means of X-ray diffraction analysis of the corresponding piperidines **344** and **345**, namely, (*R*$_S$,*2R*,*3S*)-*cis*-**344a**, (*R*$_S$,*2S*,*3R*)-*cis*-**345a**, and (*R*$_S$,*2S*,*3R*)-*cis*-**345b** (Figure 14). Noteworthy, the aryl substituent in the 2-position of *N*-protected piperidines **344** and **345** occupies an axial position, presumably, to minimize $A^{1,3}$ interactions of the 2-substituent with the substituent at nitrogen which is sp^2 hybridized.[175]


3 equiv K2CO3
CH3CN, Δ, 20 h
a: R = Tos, X = H
b: R = Tos, X = OMe
c: R = SO2Ph, X = Me
339, 340
344, 345
(RS,2R,3S)-344a (92%)
(RS,2R,3S)-344c (87%)
(RS,2S,3R)-345a (87%)
(RS,2S,3R)-345b (97%)
(RS,2S,3R)-345c (89%)

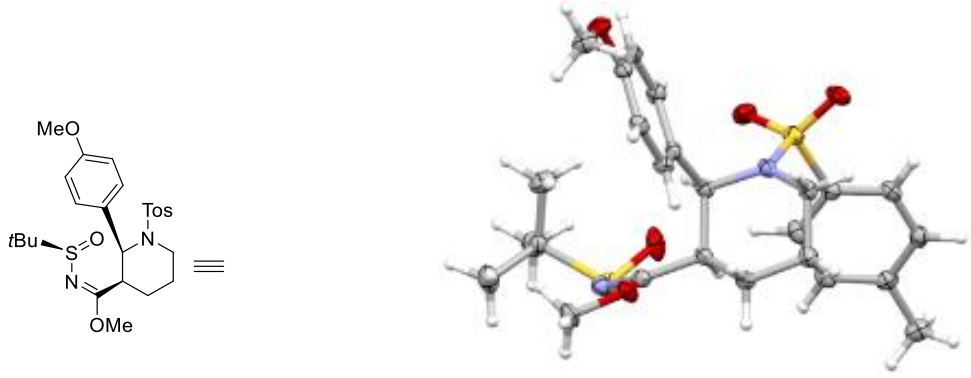
Scheme 69



(*R*S,2*R*,3*S*)-*cis*-**344a**



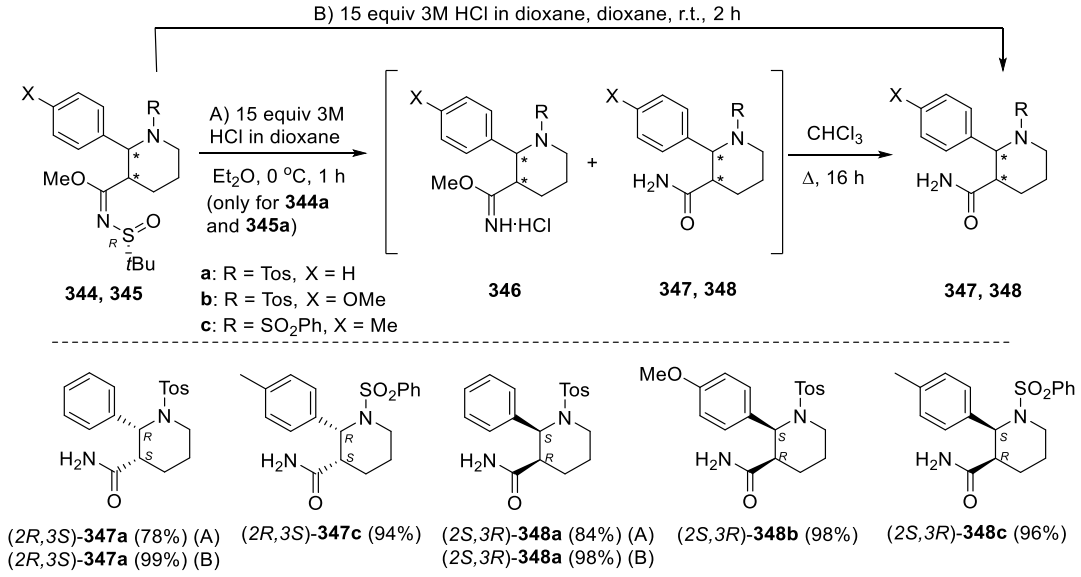
(*R*S,2*S*,3*R*)-*cis*-**345a**



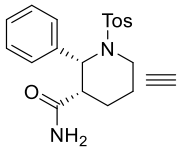
(*R*S,2*S*,3*R*)-*cis*-**345b**

Figure 14. Asymmetric units of the crystal structures of piperidines (*R*S,2*R*,3*S*)-*cis*-**344a**, (*R*S,2*S*,3*R*)-*cis*-**345a** and (*R*S,2*S*,3*R*)-*cis*-**345b**, showing thermal displacement ellipsoids at the 50% probability level.

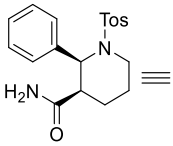
Furthermore, simple *N*-deprotection of the chiral piperidine-3-*N*-(*tert*-butylsulfinyl)carbimidates **344** and **345** with 3M HCl in dioxane afforded the corresponding new optically pure *N*-sulfonylpiperidine-3-carboxamides *cis*-**347** and *cis*-**348** in excellent yields (94-99%) (Scheme 70). Noteworthy, the use of diethyl ether as solvent led to formation of a mixture of *N*-sulfonylpiperidines *cis*-**347a** or **348a** and piperidinecarbimidate hydrochlorides **346** in 1/1 ratio. The latter can be easily transformed to piperidine-3-carboxamides *cis*-**347a** and *cis*-**348a** in chloroform under reflux for 16 hours, albeit, with lower yields of 78-84% (Scheme 70, A). The absolute and relative stereochemistry of the obtained amides **347** and **348** was determined by X-ray diffraction analysis (Figure 15), and the enantiomeric excess of >98% ee was measured *via* chiral HPLC analysis and based on NMR spectroscopic measurements with *(R)*-Pirkle's alcohol.

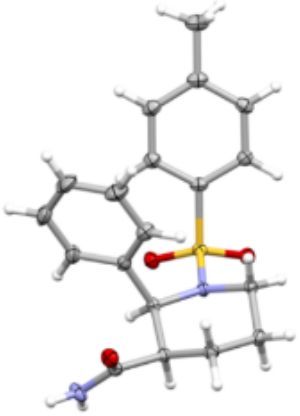


Scheme 70

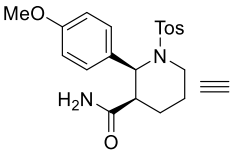


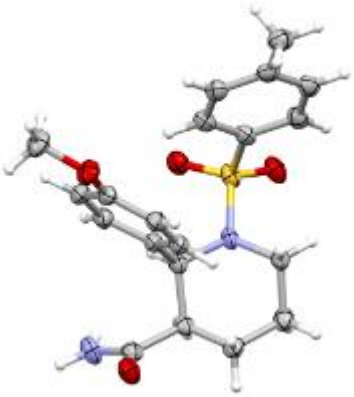
(*2R*,*3S*)-*cis*-**347a**





(*2S*,*3R*)-*cis*-**348a**

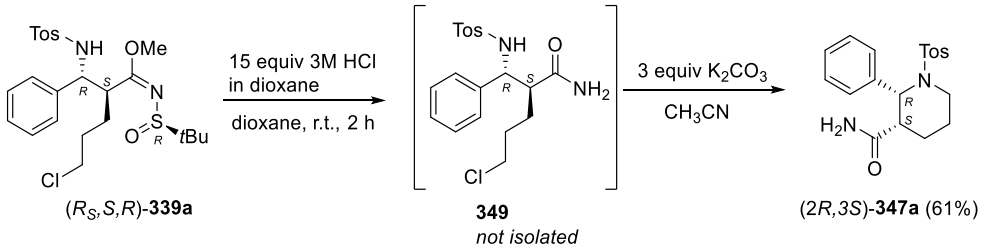




(*2S*,*3R*)-*cis*-**348b**

Figure 15. Asymmetric units of the crystal structures of piperidine-3-carboxamides (*2R*,*3S*)-*cis*-**347a**, (*2S*,*3R*)-*cis*-**348a** and (*2S*,*3R*)-*cis*-**348b**, showing thermal displacement ellipsoids at the 50% probability level. Solvent water molecules are omitted for clarity. For (*2S*,*3R*)-*cis*-**348b**, only one molecule of the asymmetric unit is shown.

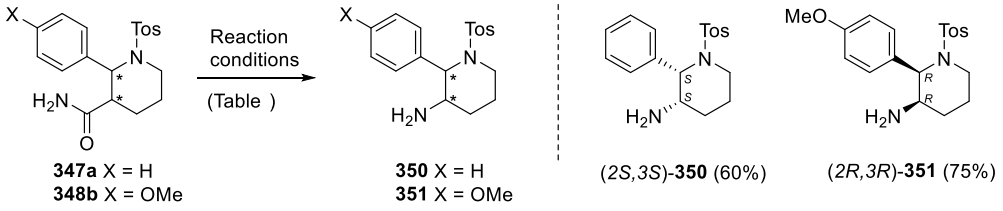
Noteworthy, when deprotection of the *N*-sulfinyl group was performed prior to cyclization, the yield of piperidine-3-carboxamide **347a** dropped dramatically (Scheme 71).



Scheme 71

Next, the successfully synthesized chiral piperidine-3-carboxamides *cis*-**347a** and *cis*-**348b** were converted by Hofmann rearrangement into the corresponding amines [*i.e.*, (*2S,3S*)-*cis*-**350** and (*2R,3R*)-*cis*-**351**] in good yields (60-75%) and with a diastereomeric ratio of >99/1 (Table 10, entries 1 and 2).[176] The use of a prolonged reaction time and excess of NaOH (6.0 equivalents) caused the isomerization of *cis*-3-aminopiperidine **350** to *trans*-**350** in a ratio *cis*/*trans* of 92/8 (Table 10, entry 3), whereas the formed piperidine **351** was not prone to isomerization when excess of base was increased to 6.0 equivalents (Table 10, entry 4).

Table 10. Optimization of the reaction conditions for the Hofmann rearrangement.

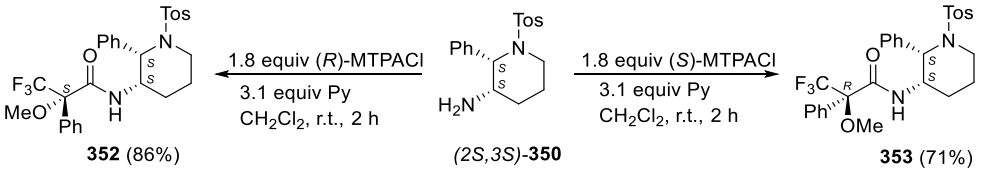


Entry	X	Reaction conditions	Result, dr [a]
1	H	1.1 equiv Br_2, 2.5 equiv NaOH, CH_3CN/H_2O = 2/1, 55 °C, 1 h	**350**, dr > 99/1 (60%)[b]
2	OMe	1.1 equiv Br_2, 2.5 equiv NaOH, CH_3CN/H_2O = 2/1, 55 °C, 1 h	**351**, dr > 99/1 (75%)[b]
3	H	1.1 equiv Br_2, 6 equiv NaOH, CH_3CN/H_2O = 2/1, 55 °C, 4 h	**350**, dr 92/8
4	OMe	1.1 equiv Br_2, 6 equiv NaOH, CH_3CN/H_2O = 2/1, 55 °C, 4 h	**351**, dr > 99/1

[a] Determined *via* ^{1}H NMR analysis of the crude reaction mixture. [b] Yield after preparative thin layer chromatography.

The enantiomer of compound *cis*-**350**, namely (*2R,3R*)-*cis*-3-amino-2-phenyl-1-tosylpiperidine **350**, is a reported compound in the literature.[170b] A comparison of optical rotations, however, did not give a results consistent with literature data [$[\alpha]_D$ (*2S,3S*)-**350** -17.0 (*c* 0.33, CH_2Cl_2) vs lit. (*2R,3R*)-**350** -71 (*c* 0.16, CH_2Cl_2, 89% ee)], and this prompted us to carry out additional experiments in order to confirm the structure of piperidine **350**.

Thus, (*S*)- and (*R*)-Mosher amides **352** and **353** were synthesized from 3-aminopiperidine **350** and (*R*)- and (*S*)-α-methoxy-α-(trifluoromethyl)phenylacetyl chlorides (MTPA-Cl), respectively, following a reported protocol (Scheme 72).[177] The analysis of (*S*)- and (*R*)-Mosher amide **352** and **353** confirmed the *S*-configuration of the stereogenic center at C-3 (Figure 16). The relative stereochemistry of **350** was assigned as *cis* based on the coupling constant of 6.2 Hz (^{1}H NMR, $CDCl_3$) between the protons at C-2 and C-3.[170] Additionally, ^{19}F and ^{1}H NMR analysis of (*S*)- and (*R*)-Mosher amides **352** and **353** allowed to conclude an enantiomeric excess of >98% (Figure 17).



352 (86%) (*2S,3S*)-**350** **353** (71%)

Scheme 72

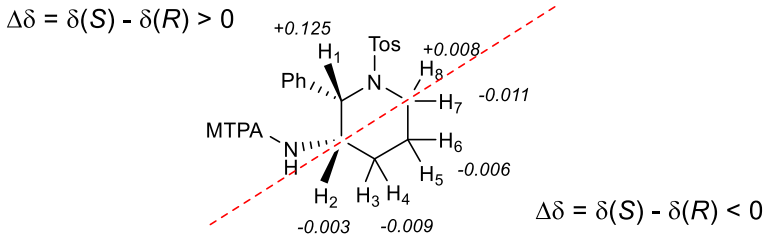


Figure 16. Schematic outcome of the Mosher analysis of (*S*)- and (*R*)-amides **352** and **353**.

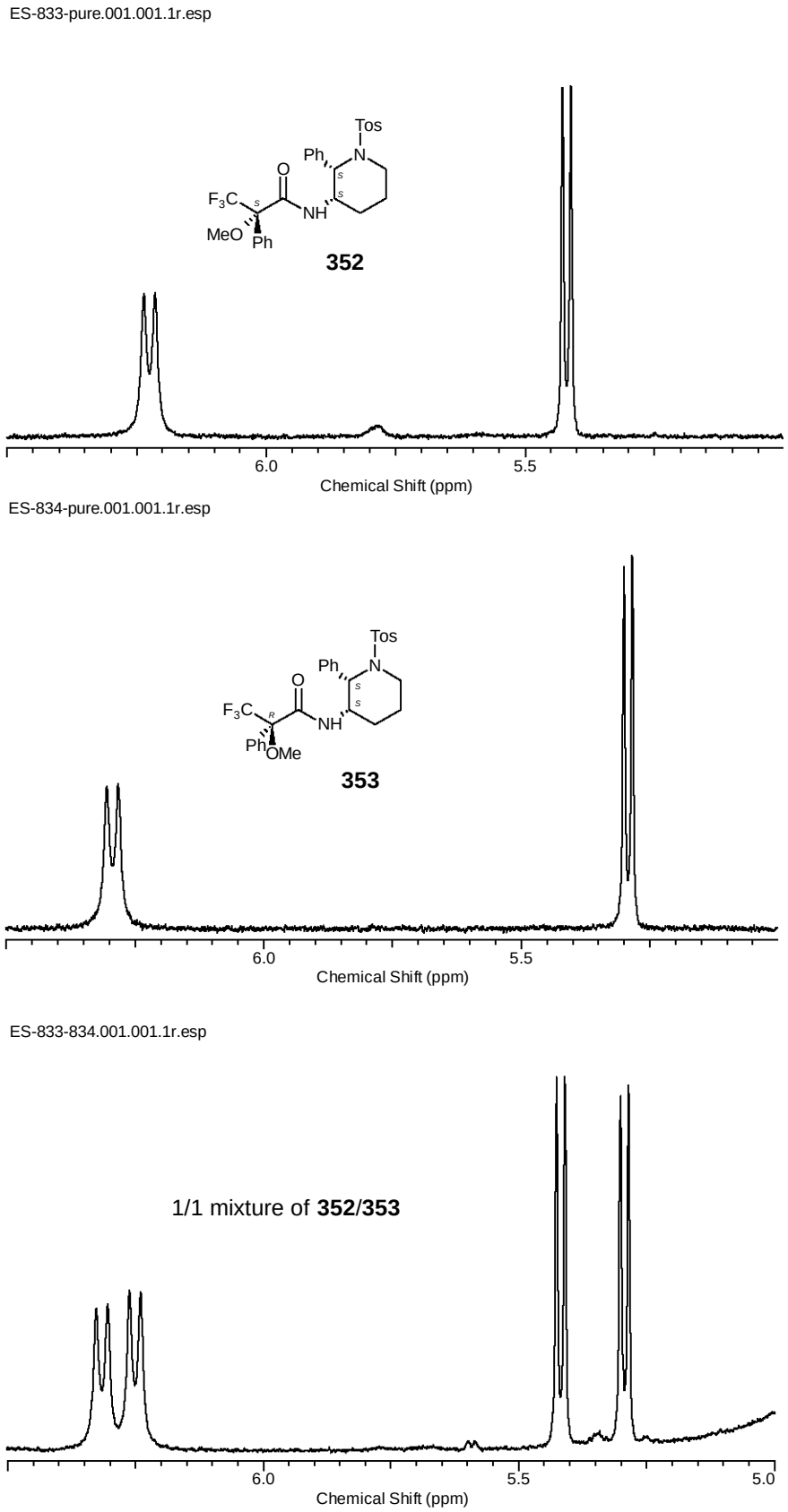
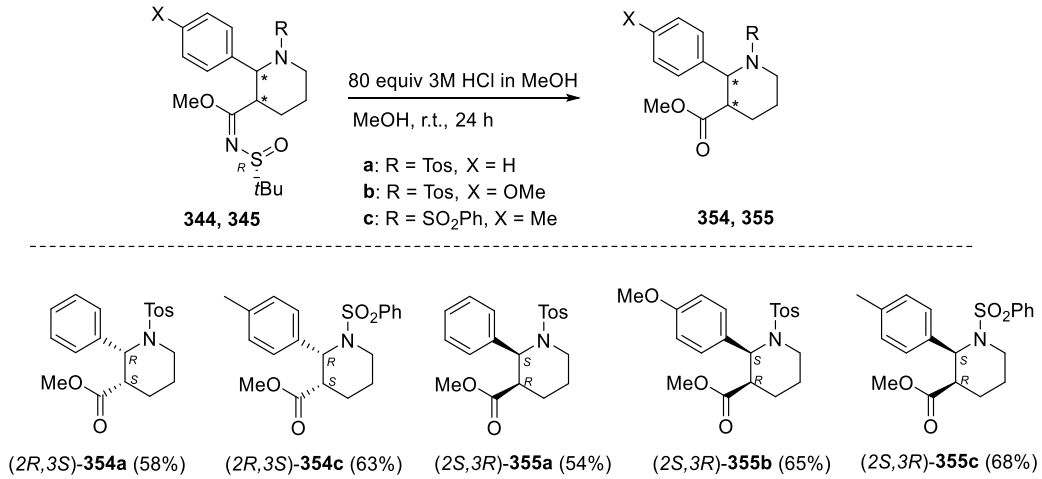


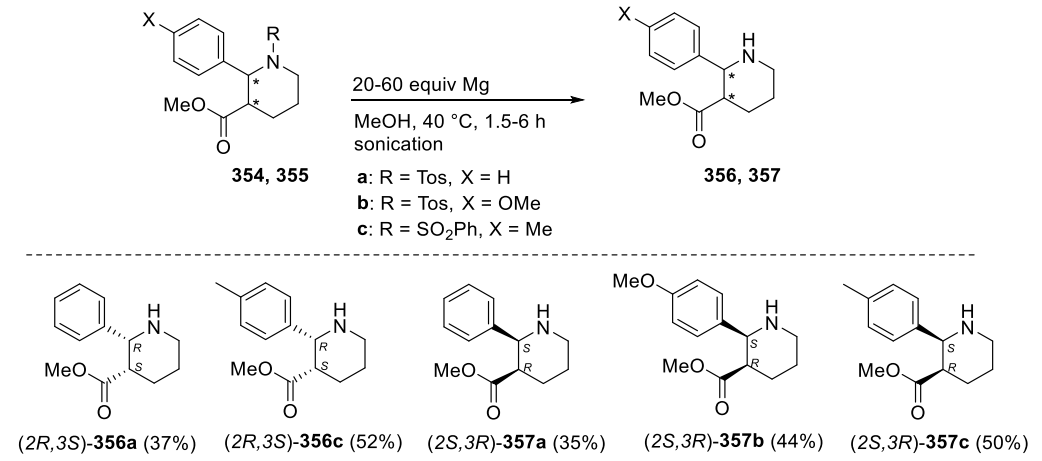
Figure 17. 1H NMR of **352** and **353**. Chemical shifts of the protons at C-2 and the protons of NH-group are presented.

When the deprotection reaction of *N*-sulfonylpiperidine-3-*N*-(*tert*-butylsulfinyl)carbimidates **344** and **345** was carried out with 3M solution of HCl in methanol, esters **354** and **355** were obtained in moderate yields (54-68%) (Scheme 73).



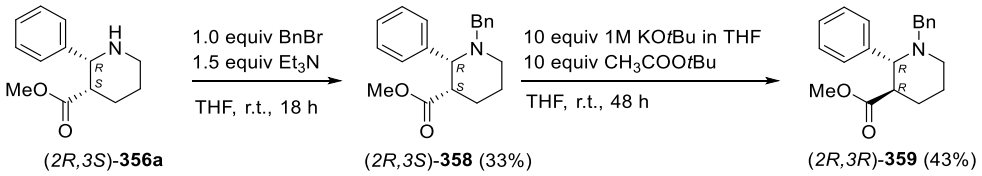
Scheme 73

In the next step, *N*-deprotection of *N*-sulfonylpiperidine-3-carboxylates *cis*-**354** and *cis*-**355** by sonication with Mg in MeOH at 40 °C afforded the chiral piperidines **356** and **357** in 35-52% yield (Scheme 74). Noteworthy, the deprotection of *N*-phenylsulfonylpiperidines (*2R,3S*)-**354c** and (*2S,3R*)-**355c** was complete within 1.5 hours after sonication with 20 equivalents of Mg, whereas for *N*-tosylpiperidines **354a** and **355a**,**b** a prolonged reaction time and 60 equivalents of Mg had to be used for full conversion of the starting esters into the desired chiral piperidines **356a** and **357a**,**b** to be achieved. Additionally, 2-arylpiperidine-3-carboxylates **356** and **357** are not only useful building blocks for peptide synthesis but could also serve as precursor for the synthesis of biologically relevant piperidine-2,3-dicarboxylic acids *via* possible oxidation of the phenyl group at C-2.



Scheme 74

Finally, piperidine (*2R,3S*)-*cis*-**356a** was treated with benzyl bromide and triethylamine in THF for 18 hours at room temperature, giving *N*-protected piperidine **358** (Scheme 10). The relative stereochemistry of piperidine **358** was assigned as *cis* based on the coupling constant of 5.6 Hz between the protons at C-2 and C-3. When methyl *N*-benzyl piperidine-3-carboxylate **358** was treated with 1M solution of KO*t*Bu in THF and *t*-butyl acetate at room temperature for 48 hours, the *trans*-2,3-disubstituted piperidine **359** was obtained in 43% yield (Scheme 75). The assignment of the relative stereochemistry as *trans* was based on the coupling constant of 10.1 Hz between the protons at C-2 and C-3.[106]



Scheme 75

The aforementioned transformations of piperidine **356a** towards *cis*- and *trans*-piperidines **358** and **359** were performed in order to demonstrate the potential use of piperidines **356** for further elaborations. However, the optimization of the reaction conditions is the object of following research.

Noteworthy, the aryl substituent in the 2-position of *N*-(de)protected piperidines **356**-**359** occupies an equatorial position to avoid unfavorable 1,3-diaxal interactions between the aryl group at C-2 and the hydrogens at C-4 and C-6, in contrast to piperidines bearing a tosyl group on nitrogen (*i.e.* **344**-**355**) where the strong $A^{1,3}$ strain results in the aryl substituent at C-2 to occupy the axial position.[175]

In conclusion, the reactivity of the enantiomerically pure 2-aryl-3-chloroazetidines **22** towards the synthesis of azetidine-2-carboxylic acid derivatives **25** was studied. Unfortunately, all transformations of 2-arylazetidines **22** to the desired azetidine-2-carboxylic acids **23**, **25** failed. In the second part, it was demonstrated that δ-chloro-β-amino-*N*-sulfinyl imidates **339** and **340** were readily prepared *via* highly *anti*-selective Mannich-type reactions of δ-chloro-*N*-sulfinyl imidates **26** across aromatic *N*-sulfonyl aldimines **27**. The absolute *anti*-diastereoselectivity obtained in the newly synthesized δ-chloro-β-amino-*N*-sulfinyl imidates **339**, **340** is in agreement with the stereochemical outcome observed for α-methyl-substituted imidates.[153e] Subsequent cyclization and deprotection reactions led to the formation of various chiral 2,3-disubstituted piperidines such as 3-amino-2-arylpiperidines **350**-**351** and 2-arylpiperidine-3-carboxylic acid derivatives **354**-**357** which belong to a class of compounds with potent biological activity or are of interest as valuable building blocks for the preparation of β-peptides with well-defined conformations.

3.3 Synthesis of fluorinated azetidines and study of their transformations

3.3.1 Introduction

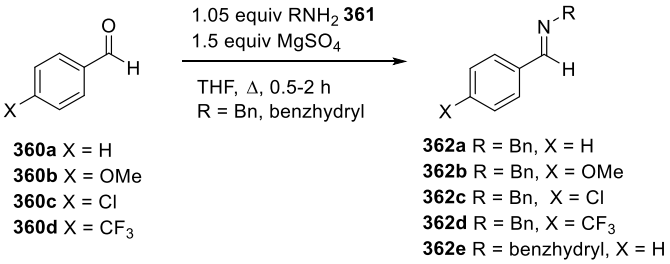
Fluorine chemistry interfaces with different fields of research including agrochemical industry, medicinal chemistry, synthetic organic chemistry, organometallic chemistry and catalysis, peptide chemistry, and chemical biology, due to the extraordinary potential of fluorine-containing biologically relevant compounds.[178] Incorporation of fluorine atoms into heterocycles can lead to spectacular changes in the molecular properties, including their stability, hydrogen bonding ability, their conformational behaviour and basicity.[179] For instance, enhancement of thermal stability of collagen was observed by replacement of (*4R*)-hydroxyproline or proline residues in the polypeptide chain of collagen with (*4R*)-fluoroproline.[180] All of this is associated with specificity of the C-F bond which can be briefly characterized as short, strong, polarized and unreactive. A large amount of research has been devoted to study the nature and influence of the C-F bond, involving experimental and computational methods.[181]

Particular interest in (3,)3-(di)fluorinated azetidines grows because of their ability to inhibit specific enzymes such as dipeptidyl peptidase IV what can be applied in the treatment of type 2 diabetes.[182] Another class of fluorinated small-membered rings are 2-fluoroaziridines which are even more rarely reported in literature although their non-fluorinated analogues gain great attention due to their utility as building blocks for diverse functionalized nitrogen-containing target compounds.[183] Noteworthy, synthetic methods towards 2-fluoroaziridine-2-carboxylates, with fluorine directly attached to the aziridine ring, are scantily described in literature.[184]

In this chapter, results are described on the synthesis and study of the reactivity of 3-bromo-3-fluoroazetidines as well as on the synthesis of 3-alkyl- and 3-aryl-2-fluoroaziridine-2-carboxylates with an electron-withdrawing/donating group at nitrogen.

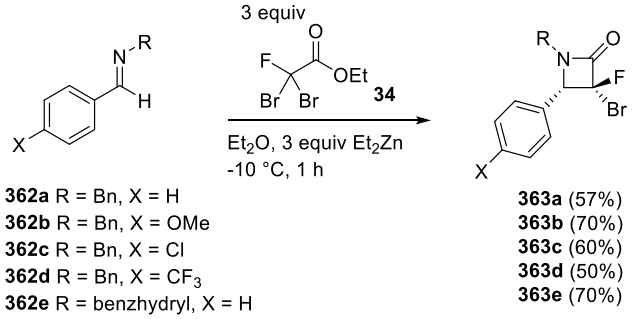
3.3.2 Reformatsky-type reaction of ethyl dibromofluoroacetate 34 across imines 362

Starting aldimines **362** were synthesized *via* condensation of aldehydes **360** with the corresponding amines **361** in tetrahydrofuran in the presence of magnesium sulfate as drying agent at reflux for 0.5-2 hours (Scheme 76).[185]



Scheme 76

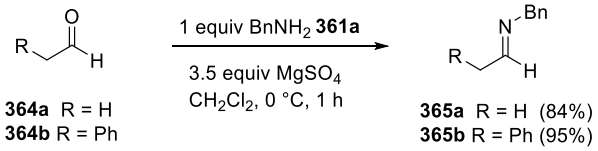
Next, aldimines **362** were subjected to the diastereoselective synthesis of α-bromo-α-fluoro-β-lactams **363** following a literature procedure.[49] The diethylzinc-mediated Reformatsky-type reaction of ethyl dibromofluoroacetate **34** across imines **362** in diethyl ether at -10 °C for one hour afforded diastereomerically pure *cis*-β-lactams **363** in good yields (Scheme 77).



Scheme 77

Furthermore, an attempt was made to extend the application of this Reformatsky-type reaction towards a broad range of aldimines, including aliphatic aldimines **365a** and **365b** and aldimine **27a**, which bears an electron-withdrawing group at nitrogen.[184]

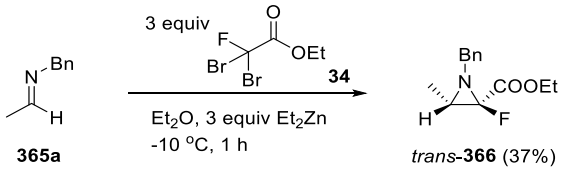
First, aliphatic aldimines **365a,b** were prepared *via* condensation of aldehydes **364a,b** and benzylamine **361a** in dichloromethane at 0 °C for one hour (Scheme 78).



Scheme 78

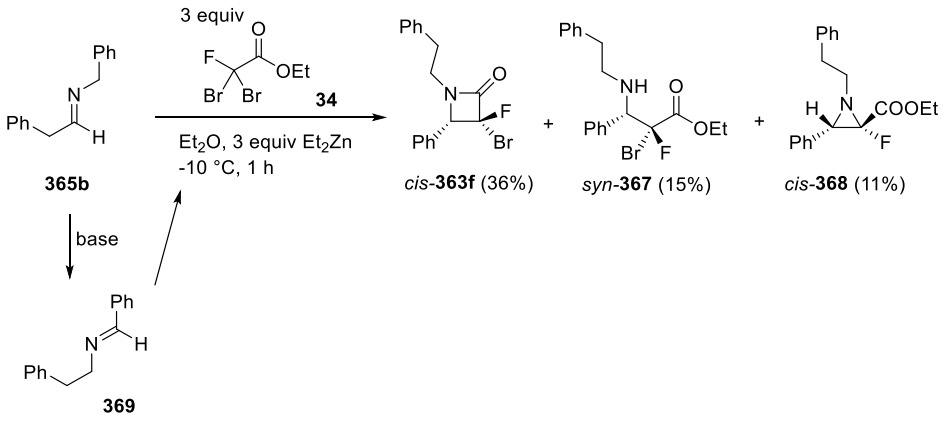
Imines **365a** and **365b** were immediately subjected to further reaction without purification due to their instability. When addition of ethyl dibromofluoroacetate **34** was carried out across *N*-(ethylidene)benzylamine **365a** under diethylzinc-mediated conditions, aziridine *trans*-**366** was obtained in a yield of 37% (Scheme 79). The relative *trans*-stereochemistry of aziridine **366** was assigned based on analysis of the coupling constants of the C-3 proton of the aziridine ring ($J^3_{H,F}$ =

11.1 Hz).[186] Partial degradation of aziridine **366** was observed after purification *via* column chromatography.



Scheme 79

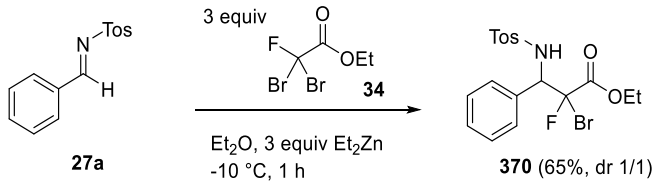
Reaction of *N*-(ethylidene)benzylamine **365b** and dibromofluoroacetate **34** led to the formation of a mixture of β-lactam **363f**, ethyl 2-bromo-2-fluoro-3-(phenethylamino)-3-phenylpropanoate **367** and aziridine **368**. The formation of compounds **363f**, **367** and **368** might be rationalized by the isomerization of starting *N*-benzylaldimine **365b** towards *N*-phenethylaldimine **369** *via* a base-catalyzed 1,3-proton shift in the imine **365b** (Scheme 80).[187]



Scheme 80

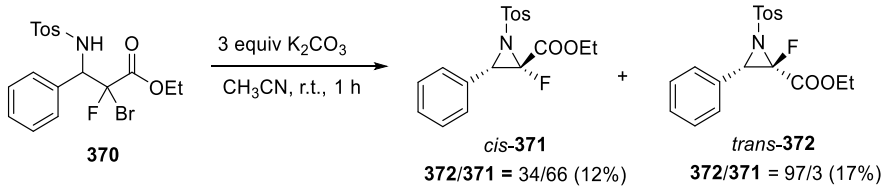
Compounds **363f**, **367** and **368** were separated *via* column chromatography and the relative stereochemistry of these molecules was assigned based on the coupling constants between proton and fluorine (for *cis*-**363f** $J^3_{H,F}$ = 10.3 Hz, for *syn*-**367** $J^3_{H,F}$ = 23.1 Hz, for *cis*-**368** $J^3_{H,F}$ = 4.4 Hz).[186] Noteworthy, the reaction proceeds regioselectively albeit with poor chemoselectivity.

In the next attempt, aldimine **27a**, bearing an electron-withdrawing group on nitrogen, was subjected to the Reformatsky-type reaction (Scheme 81). Only the open form adduct **370** was detected. Noteworthy, the stereoselectivity of this reaction was completely lost, giving a non-separable mixture of *syn*/*anti* isomers **370** in a ratio of 1/1.



Scheme 81

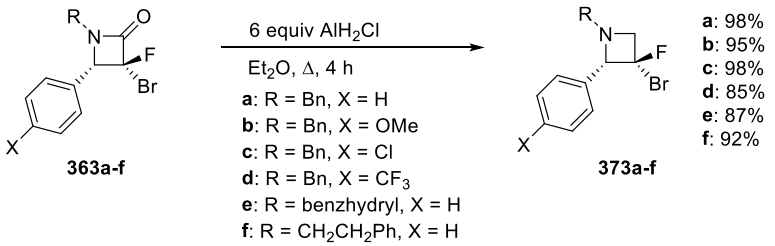
Subsequent treatment of ester **370** with potassium carbonate in CH_3CN at room temperature for one hour gave a mixture of substituted ethyl 2-fluoroaziridine-2-carboxylates *cis*-**371** and *trans*-**372** in a ratio of 20/80 (Scheme 82). However, isolation of the pure diastereomers could not be achieved and two mixtures of isomers were isolated in 12% (**372**/**371** 34/66) and 17% (**372**/**371** 97/3) yield. The relative stereochemistry of the diastereomers was assigned based on analysis of the coupling constants of the C- 3 proton of the aziridine ring (*trans*: $J^3_{H,F}$ = 8.1 Hz; *cis*: $J^3_{H,F}$ = 2.5 Hz).



Scheme 82

3.3.3 Synthesis of 2-aryl-3-bromo-3-fluoroazetidines 373 and investigation of their reactivity

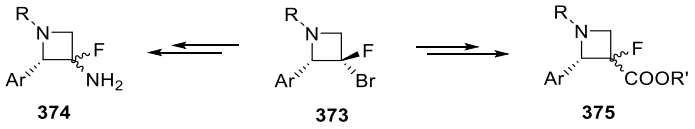
With β-lactams **363** in hands, synthesis of 3-bromo-3-fluoroazetidines **373** was achieved *via* reduction of the carbonyl group with chloroalane (AlH_2Cl) in diethyl ether at reflux for four hours in good yields (85-98%) (Scheme 83). The choice of chloroalane as a reducing agent relied on previously reported research on reduction of 3,3-dichloro-2-azetidinones.[45b] The relative configuration of the synthesized azetidines **373** was established as *cis* based on the observed coupling constants of 21-22 Hz between the proton at C-2 and fluorine at C-3.[188]



Scheme 83

3.3.3.1 Investigation of nucleophilic substitutions in 2-aryl-3-bromo-3-fluoroazetidines 373

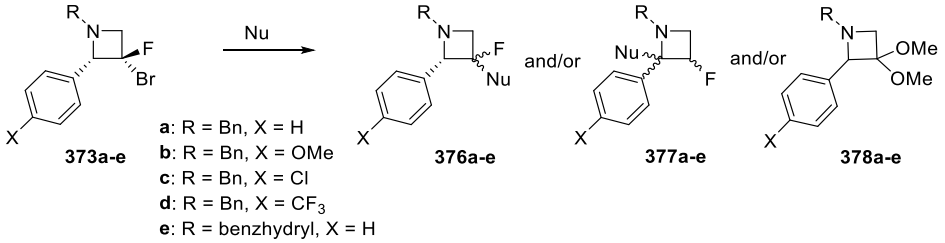
In this part, the reactivity of 3-bromo-3-fluoroazetidines **373** towards nucleophilic substitution was investigated. The main interest was to investigate a direct approach to the synthesis of fluorinated 3-aminoazetidines **374** or azetidine-3-carboxylic acid derivatives **375** (Scheme 84).



Scheme 84

In Table 11, the evaluated reaction conditions are enlisted. Initially, the introduction of an azido group on the azetidine ring *via* treatment of starting substrate **373a** and **373b** with sodium azide (1.5-10 equiv) in different solvents (DMSO, DMF, acetone, MeOH) failed and only starting material was recovered *via* column chromatography (Table 11, entries 1, 3-8). Variations of temperature and reaction time, as well as substrates **373**, did not lead to conversion of the starting material. Only degradation product was observed when 10 equivalents of sodium azide and prolonged reaction time was applied (Table 11, entry 2). In the next attempts, azetidines **373c,d,e** were treated with three equivalents sodium iodide and three equivalents sodium azide in DMSO in order to substitute bromide with iodide, which might promote reactivity towards nucleophilic substitution (Table 11, entries 9-11). However, the addition of sodium iodide did not result in conversion of the starting material. Analogously, attempts at the substitution of bromide with iodide by reaction of **373b** with sodium iodide also failed (Table 11, entries 13 and 14).

Table 11.. Attempted nucleophilic substitution of azetidines **373**.



Entry	R	X	Nu/ equiv	Solvent	T, °C/ t	Result (yield, %) [a]	*dr* of **377** [b]
1	Bn	H	NaN_3/3	DMSO	100/4.5 h	(-) [c,d]	
2	Bn	H	NaN_3/10	DMSO	100/24 h	(-) [e]	
3	Bn	H	NaN_3/1.5-3	DMF	60-100/3-24 h	(-) [c,d]	

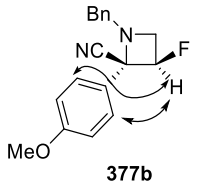
4	Bn	H	NaN_3/3	acetone	Δ/24 h	(-) [c,d]	
5	Bn	H	NaN_3/3	MeOH	Δ/24 h	(-) [c,d]	
6	Bn	OMe	NaN_3/3	DMF	Δ/24 h	(-) [c,d]	
7	Bn	OMe	NaN_3/3	acetone	Δ/24 h	(-) [c,d]	
8	Bn	OMe	NaN_3/3	MeOH	Δ/24 h	(-) [c,d]	
9	Bn	Cl	NaN_3-NaI/3-3	DMSO	100/24 h	(-) [c,d]	
10	Bn	CF_3	NaN_3-NaI/3-3	DMSO	100/24 h	(-) [c,d]	
11	$CHPh_2$	H	NaN_3-NaI/3-3	DMSO	100/24 h	(-) [c,d]	
13	Bn	OMe	NaI/3	DMSO	60-90/3-20 h	(-) [c,d]	
14	Bn	OMe	NaI/3	DMF	60-90/3-20 h	(-) [c,d]	
15	Bn	H	KCN/3	DMF	Δ/20 h	(-) [c,d]	
16	Bn	H	NaCN/3	EtOH	Δ/6 h	**377a**/**373a** = 55/45 [b]	53/47
17	Bn	H	NaCN/3	DMSO	100/6 h	**377a**	34/66
18	Bn	H	KCN/2+2	DMSO	100/20 h	**377a** (34%)	74/26
19	Bn	H	KSCN/4	DMSO	100/24 h	(-) [c,d]	
20	Bn	H	KCN/1	DMSO	125/10 min [f]	**377a**/**373a** = 70/30 [b]	79/21
21	Bn	H	KCN/1	DMSO	135/10 min [f]	(-) [e]	
22	Bn	H	KCN/2	DMSO	125/10 min [f]	**377a** (24%)	84/16
23	Bn	H	KCN/4.3	MeOH	100/30 min [f]	**377a** (46%) **378a** (37%)	84/16
24	Bn	OMe	KCN/4.3	MeOH	125/45 min [f]	**377b**(36%) **378b**(41%)	85/15
25	Bn	H	KCN/4.3	*t*BuOH	125/30 min [f] 125/10 min[f]	(-) [c] (-) [f]	

				+3 equiv MeOH		
26	Bn	H	KCN/4	EtOH	125/30 min [f]	(-) [c,d]
27	Bn	H	KCN/4	DMF	125/30 min [f]	(-) [e]
28	Bn	H	KCN/2-5	Toluene	125/30 min [f]	(-) [e]
29	Bn	H	Acetone cyanohydrine/2	MeOH	100/1-8 h (press.vial)	(-) [e]
30	Bn	H	Acetone cyanohydrine/1	CH_2Cl_2	100/30 min [f]	(-) [c]
31	Bn	H	Acetone cyanohydrine/3	CH_2Cl_2	100/30 min [f]	(-) [e]

[a] Isolated yield after column chromatography or preparative TLC. [b] Determined based on ^{1}H NMR analysis of crude reaction mixture. [c] No reaction. [d] Starting material was recovered. [e] Complex reaction mixture. [f] Microwave assisted synthesis.

Furthermore, the introduction of a cyano group into 3-bromo-3-fluoroazetidines **373** was evaluated by use of different nucleophilic reagents, such as sodium cyanide, potassium cyanide and acetone cyanohydrine. At first, the reaction of azetidine **373a** with potassium cyanide in DMF at reflux for 20 hours did not result in any conversion of starting material (Table 11, entry 15). Next, treatment of azetidine **373a** with three equivalents of sodium cyanide in EtOH at reflux for six hours afforded a mixture of 2-cyano-3-fluoroazetidine **377a** and starting material **373a** in a ratio of 55/45 (Table 11, entry 16). Noteworthy, formation of 3-cyano-3-fluoroazetidine **376a** was not detected. After analysis of ^{1}H and ^{19}F NMR spectroscopic data, it was concluded that two diastereomers of 2-cyano-3-fluoroazetidine **377a** were formed in a ratio of 53/47. When the reaction was performed in DMSO at 100 °C for six hours, full conversion of starting material was achieved and the ratio of diastereomers of **377a** was 34/66 (Table 11, entry 17). When two equivalents of potassium cyanide in DMSO at 100 °C for six hours were used, the starting material was not fully converted. Subsequently, two more equivalents of potassium cyanide were added and the reaction time was extended to 20 hours, affording full conversion of azetidine **373a** based on TLC and LC-MS analyses (Table 11, entry 18). Purification *via* column chromatography gave *N*-benzyl 2-cyano-3-fluoro-2-phenylazetidine **377a** as a 74/26 mixture of major/minor isomers in 34% yield. On the other hand, substitution with potassium thiocyanate failed (Table 11, entry 19). Next, a series of microwave-assisted experiments towards nucleophilic substitution were performed. In a first attempt, the use of one equivalent of potassium cyanide in DMSO at 80 °C for 10 minutes did not lead to conversion of starting material **373a**, and

a gradual increase of the temperature to 125 ºC afforded a mixture of product **377a** (major/minor = 79/21) and starting material **373a** in a ratio of 70/30 (Table 11, entry 20). An increase of the temperature up to 135 ºC led to a very complex mixture which was not further analysed (Table 11, entry 21). Conversion of starting azetidine **373a** was complete when two equivalents of potassium cyanide were used in DMSO at 125 ºC for 10 minutes under microwave irradiation, affording 2-cyano-3-fluoroazetidine **377a** in 24% yield after chromatography in a ratio 84/16 of major/minor isomer (Table 11, entry 22). Furthermore, also MeOH was evaluated as a solvent. After several test reactions, the use of 4.3 equivalents of KCN in MeOH at 100 ºC for 30 minutes under microwave irradiation afforded azetidine **377a** in 46% yield and the side product 3,3-dimethoxyazetidine **378a** in 37% yield (Table 11, entry 23). Noteworthy, azetidine **377a** was isolated as a mixture of major and minor isomer in a ratio of 84/16 similar to the ratio that was observed for other experiments with potassium cyanide. These optimized conditions were applied on substrate **373b**, giving similar results, although, the reaction time was prolonged to 45 minutes in order to get full conversion of starting azetidine **373b** (Table 11, entry 24). Analysis of the relative configuration of major and minor diastereomers **377** was performed *via* a NOESY experiment of azetidine **377b** based on the assumption that the proton at the C-3 atom of the azetidine ring and the protons at C-2/C-6 atoms of the 2-(4-methoxyphenyl)-substituent must give a cross-peak when these protons are positioned on the same side of the azetidine ring. In a NOESY experiment on **377b**, the aforementioned cross-peak was observed only for the major isomer which led to the conclusion that the aromatic substituent at C-2 and the proton at C-3 are on the same side what corresponds with *cis*-2-cyano-3-fluoro-2-(4-methoxyphenyl)azetidine **377b** (Figure 18). Thus, in the minor isomer, the fluoro atom is *trans*-oriented with respect to the cyano group. Due to the similarity of azetidines **377a** and **377b**, it was assumed that the major isomer of **377a** had *cis*-configuration and the minor **377a** is *trans*.

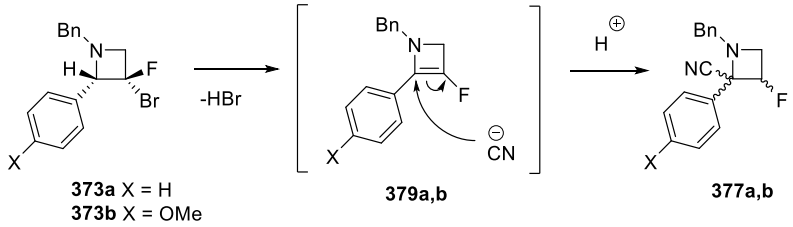


377b

Figure 18. Arrow lines show NOE's in NOESY spectrum ($CDCl_3$) of **377b**.

Several additional microwave-assisted experiments were performed in search of a better control of the nucleophilic substitution of azetidine **373a** with cyanide. However, the use of different solvents (*t*BuOH, EtOH, DMF, toluene) (Table 11, entries 25-28) as well as changing the source of cyanide to acetone cyanohydrine in MeOH or CH_2Cl_2 (Table 11, entries 29-31) did not give any improvements, and mainly complex reaction mixtures were formed which were not further analysed in detail.

A tentative pathway for the formation 3-fluoroazetidines **377** is shown in Scheme 85. Elimination of hydrogen bromide generates an unstable 2-azetine **379** which subsequently undergoes attack by the cyanide-anion. A related conversion of 3,3-dichloroazetidines into aziridines proceeding *via* elimination of hydrogen chloride, generating the corresponding 2-azetines, followed by addition of methanol has been described.[45b]



Scheme 85

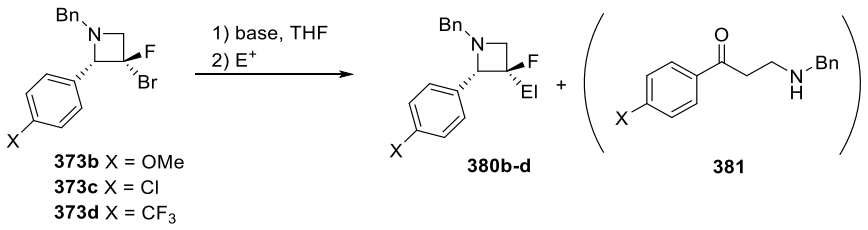
3.3.3.2 Elaboration of 2-aryl-3-bromo-3-fluoroazetidines 373 *via* halogen-lithium exchange

In this part of the research, 2-aryl-3-bromo-3-fluoroazetidines **373** were used as substrates in a halogen-lithium exchange strategy and the results are presented in Table 12. Optimization of the reaction conditions was performed for azetidine **373b**. In a first attempt, 2-aryl-3-bromo-3-fluoroazetidine **373b** was treated with *n*-butyllithium in THF at -78 °C for 45 minutes and was subsequently quenched by the addition of water as an electrophile (Table 12, entry 1). Analysis of the crude reaction mixture by means of ^{1}H and ^{19}F NMR revealed the formation of 3-fluoroazetidine **380b** along with several unidentified nonfluorinated side products. Attempts to isolate and characterize the side products failed. Further optimization of reaction conditions by variations of the Li-source, temperature and time was carried out and the results are summarized in Table 12, entries 2-13. The optimum reaction conditions were determined to be as follows: addition of 1.4 equivalents of *sec*-BuLi at -90 °C in THF and stirring for 30 minutes, followed by the addition of 5 equivalents of water and subsequent stirring at room temperature for two hours gave a mixture of azetidine **380b**, which was isolated in 27% yield, and a tentative identified product (**381b**) in a ratio of 40/60 (Table 2, entry 12). Though the ratio of desired product **380b** to side product (**381b**) was higher when using the conditions described in Table 12, entry 5 (**380b**/(**381b**) = 66/34), the crude reaction mixture appeared to be more complex and azetidine **380b** was isolated in only 12% yield. Isolation of side products failed. The optimized reaction conditions were applied for substrates **373c** and **373d** (Table 12, entries 14 and 15). A mixture of **380c** and (**381c**) was obtained from azetidine **373c**, and 3-fluoroazetidine **380c** was isolated in 30% yield. When azetidine **373d** was used as starting substrate, the desired 3-fluoroazetidine **380d** was isolated in 35% yield. Formation of side product (**381d**) was not observed in the crude reaction mixture. The unknown compounds (**381c**) and (**381b**) have a similar structure based on ^{1}H NMR analysis of the crude reaction mixture. For both compounds, two triplets at 3.04 ppm and 3.18 ppm (J = 6 Hz) were observed as well as LC-MS data supported the

tentative structures of **381b,c**. Additionally, it was established by ^{19}F NMR analysis that these side products do not contain fluorine in their structure. A possible structure for these unknown compounds is that of β-aminoketone **381**. The problems with the isolation of putative compound **381** are believed to be caused by the lack of their stability. Remarkably, the reaction of halogen-lithium excenge proceeds stereoselectively and is assumed to furnish the *trans*-3-fluoroazetidines **380**, based on analysis of coupling constants between the proton at C-2 and fluorine at C-3 atom ($J^3_{H,F}$ = 22 Hz).[188]

Further attempts to extend this reaction to the use of other electrophiles, unfortunately, failed. Introduction of ethoxycarbonyl or alkyl groups was problematic and led to formation of very complex mixtures (Table 12, entries 16-20). ^{19}F NMR data clearly indicated that the crude reaction mixtures did not contain fluorinated compounds.

Table 12. Optimization of halogen-lithium exchange reaction of 3-bromo-3-fluoroazetidines **373**.



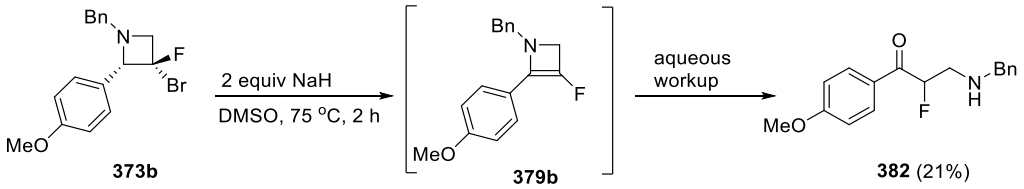
Entry	X	Base/ equiv	Electrophile/equiv	T/t	Results [a]
1	OMe	*n*BuLi/ 1.5	H_2O/5	1) -78 ºC/ 45 min 2) -78 ºC to rt, 2h	**380b** [b]
2	OMe	*n*BuLi/ 3.0	H_2O/5	1) -90 ºC/ 30 min 2) -90 ºC to rt, 2h	**380b**/**381b** = 40/60
3	OMe	*sec*BuLi/ 1.0	H_2O/5	1) -78 ºC/ 10 min 2) -78 ºC to rt, 2h	**381b**/**373b** = 66/34
4	OMe	*sec*BuLi/ 1.5	H_2O/5	1) -78 ºC/ 15 min 2) -78 ºC to rt, 2h	**380b**/**373b** = 40/60
5	OMe	*sec*BuLi/ 1.7	H_2O/5	1) -78 ºC/ 15 min 2) -78 ºC to rt, 2h	**380b**/**381b** = 66/34 **380b** (12%) [c]
6	OMe	*sec*BuLi/ 2.0	H_2O/5	1) -78 ºC/ 20 min	**380b**/**381b** [e]

				2) -78 ºC to rt, 2h	
7	OMe	*sec*BuLi/ 4.0	H_2O/5	1) -90 ºC/ 30 min 2) -90 ºC to rt, 2h	(-) [f]
8	OMe	*sec*BuLi/ 2.0	H_2O/5	1) -95 ºC/ 60 min 2) -95 ºC to rt, 2h	**373b**/**380b**/**381b** = 20/29/51
9	OMe	*sec*BuLi/ 3.0	H_2O/5	1) -90 ºC/ 45 min 2) -90 ºC to rt, 2h	**380b**/**381b** = 20/80
10	OMe	*sec*BuLi/ 2.0	H_2O/5	1) -90 ºC/ 80 min 2) -90 ºC to rt, 2h	**380b**/**381b** = 30/70
11	OMe	*sec*BuLi/ 1.0	H_2O/5	1) -90 ºC/ 30 min 2) -90 ºC to rt, 2h	**380b**/**381b** = 35/65
12	OMe	*sec*BuLi/ 1.4	H_2O/5	1) -90 ºC/ 30 min 2) -90 ºC to rt, 2h	**380b**/**381b** = 40/60 **380b** (27%) [c]
13	OMe	*sec*BuLi/ 1.5 [g]	H_2O/5	1) -90 ºC/ 30 min 2) -90 ºC to rt, 2h	**380b**/**373b** = 65/35
14	Cl	*sec*BuLi/ 1.4	H_2O/5	1) -90 ºC/ 30 min 2) -90 ºC to rt, 2h	**380c**/**381c** = 50/50 **380c** (30%) [c]
15	CF_3	*sec*BuLi/ 1.4	H_2O/5	1) -90 ºC/ 30 min 2) -90 ºC to rt, 2h	**380d** (35%) [c,d]
16	OMe	*sec*BuLi/ 1.4	ClCOOEt/1	1) -90 ºC/ 30 min 2) -90 ºC/ 20 min	(-) [f,h]
17	OMe	*sec*BuLi/ 1.0	ClCOOEt/1	1) -78 ºC/ 40 min 2) -78 ºC/ 20 min	(-) [f,h]
18	OMe	*sec*BuLi/ 1.5	ClCOOEt/1	1) -90 ºC/ 5 min 2) -90 ºC/ 20 min	(-) [f,h]

19	OMe	*sec*BuLi/ 1.5	CH_3I/2 eq	1) -90 ºC/ 5 min 2) -90 ºC/ 20 min	(-) [f,h]
20	OMe	*n*BuLi/ 1.0	CO_2 (dry)	1) -78 ºC/ 15 min 2) -78 ºC/ 60 min	(-) [f,h]

[a] Based on ^{1}H and ^{19}F NMR analysis of the crude reaction mixture. [b] Several unidentified side products were observed in the crude reaction mixture. [c] Yield after column chromatography. [d] Formation of **381d** was not observed. [e] Ratio was not determined due to the complexity of the crude reaction mixture. [f] Complex reaction reaction mixture. [g] Dioxane was used as solvent. [h] No fluorinated products were detected *via* ^{19}F NMR analysis.

Additionally, reaction of 1,2,3,3-tetrasubstituted azetidine **373b** with sodium hydride in dimethyl sulfoxide for two hours at 75 ºC afforded ring opened product **382** in a poor yield of 21% (Scheme 86). The reaction outcome could be rationalized *via* formation of the strained 2-azetine **379b** by means of elimination of hydrogen bromide, followed by hydrolysis of the reactive intermediate during the aqueous work-up procedure.[45b] An attempt to characterize the intermediate **379b** by direct NMR-monitoring of the reaction, which was carried out in an NMR tube in DMSO-D_6, was not successful due to the complexity of the reaction mixture.



Scheme 86

3.3.4 Synthesis of *trans*-*N*-benzyl-3-fluoro-3-iodo-2-phenylazetidine 383

In this part, the influence of substrate structure on the reactivity 3-fluorinated azetidines was investigated. It has been reported that the preferred conformation for both *cis*- and *trans*-2,3-disubstituted azetidines is that conformer in which the *N*-alkyl and 2-aryl substituents occupy pseudoequatorial positions in order to decrease steric interactions.[188-189] Analogously, *N*-benzyl *cis*-2-aryl-3-bromo-3-fluoroazetidine *cis*-**373** occurs as conformer **A** rather than as conformer **B** (Figure 19). However, in conformer **A** bromide occupies a pseudoaxial position, which might encumber the nucleophilic substitution assisted by the azetidine nitrogen. It was envisioned that the use of *trans*-2-aryl-3-fluoro-3-iodoazetidine **383** (occurs as conformer **C**, Figure 19) as starting substrate could solve that problem. In order to have a better leaving group to promote the nucleophilic substitution, *trans*-3-iodinated azetidine **383** was synthesized instead of the 3-brominated substrate.

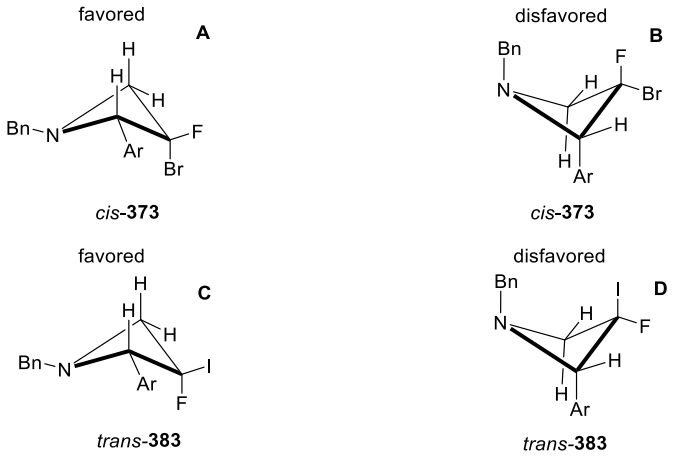
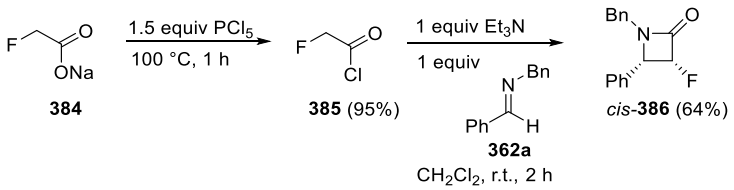


Figure 19

First, the synthesis of *cis*-4-aryl-3-fluoroazetidinone **386** was conducted *via* a modified literature procedure.[190] Sodium 2-fluoroacetate **384** reacted with phosphorus(VI) chloride at 100 °C for one hour, affording fluoroacetyl chloride **385** in excellent yield of 95% (Scheme 87).[191] Subsequently, 2-fluoroacetyl chloride **385** was subjected to condensation across imine **362a** in dichloromethane at room temperature for two hours, resulting in the selective formation of *cis*-3-fluoro-4-phenylazetidinone **386** in good yield of 64%. The selectivity of this condensation was previously described as the selective reaction of imine **362a** with fluoroketene, which is formed after treatment of acid chloride **385** with triethylamine.[190, 192]

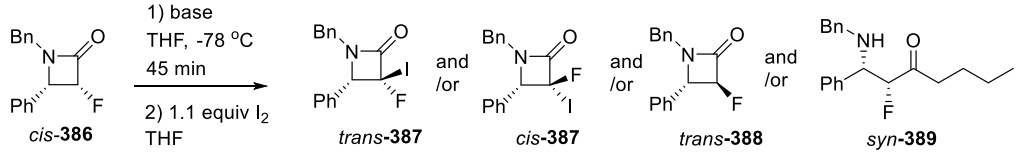


Scheme 87

Next, the synthesis of 3-fluoro-3-iodo-2-azetidinone **387** was attempted *via* iodination of the enolate of 3-fluoro-β-lactam **386**. In a first attempt, β-lactam **386** was treated with *n*-butyllithium in THF at -78 °C for 45 minutes and the resulting enolate was subsequently added to a solution of iodine in THF at -78 °C following a literature procedure (Table 13, entry 1).[193] The reaction was stirred for one hour affording aminoketone **389**, which was a result of the nucleophilic attack of the *n*-butyllithium across carbonyl group of β-lactam **386**. Remarkably, only the difluorinated analogue of the obtained β-amino-α-fluoroketone **389** was reported in literature.[194] When one equivalent of LiHMDS was used as a base, the desired 3-fluoro-3-iodo-2-azetidinone **387** was obtained. However, this compound occurred as a mixture of *trans*/*cis* isomers in a ratio of 85/15 (Table 13, entry 2). Moreover, conversion of starting material *cis*-**386** was limited to 33% and formation of the *trans*-isomer *trans*-**388** of starting material **386** was observed in the crude reaction mixture. Interestingly,

stirring the reaction mixture for an additional 18 hours at room temperature gave no changes in the ratio of the formed products. In order to obtain a better conversion of starting azetidinone **386**, the amount of base was increased to 1.5 and 2.0 equivalents (Table 13, entries 3 and 4). Both attempts gave very similar results, namely, conversion of starting material was around 80% and formation of *trans*-isomer **388** of starting material increased up to 20% versus 5% in case of using of one equivalent of LiHMDS. The desired 3-iodo-2-azetidinone **387** was isolated as a mixture of its *trans*/*cis* isomers in a ratio of 85/15 in low yields (20-31%). The distinction between both stereoisomeric compounds was easily made by means of the coupling constants between C-4 proton and C-3 fluorine (*trans*: $J^3_{H,F}$ = 2.8 Hz; *cis*: $J^3_{H,F}$ = 11.3 Hz). Finally, lithium diisopropylamide was applied as a base. Using one equivalent of LDA in THF at -78 °C for 45 minutes, followed by the addition of a solution of 1.1 equivalents of iodine in THF at -78 °C and stirring the reaction mixture for one hour, led to formation of a mixture of azetidinones **387**, starting material *cis*-**386** and unidentified side product (**390**), which could not be separated from the azetidinone **387** (Table 13, entry 5). Continuation of the reaction at room temperature for 18 hours did not shift the ratio of the constituents of the crude reaction mixture. Applying 2.5 equivalents of LDA and performing the reaction at -78 °C for 1.5 hours gave a mixture of desired iodo compound **387** and unidentified side product (**390**) in a ratio of 50/50 (Table 13, entry 6). Noteworthy, the stereoselectivity of the iodination reaction under the described conditions dropped, giving a mixture of *trans*- and *cis*-isomers **373** in a ratio of 72/28.

Table 13. Optimization of the reaction conditions towards synthesis of the 3-iodo-3-fluoroazetidinone **387**.



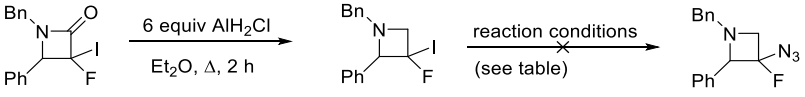
Entry	Base/ equiv	T, °C/ t, h	Results	Ratio of *trans*/*cis* **387** [a] (yield, %) [b]
1	*n*BuLi/ 2.0	-78/ 1 [c]	*syn*-**389** (85%)	
2	LiHMDS/ 1.0	-78/ 1	**387**/**386**/**388** = 28/67/5	85/15
		+rt/ 18	**387**/**386**/**388** = 28/67/5	85/15
3	LiHMDS/ 1.5	-78/ 1 [c]	**387**/**386**/**388** = 60/20/20	85/15 (20%)
4	LiHMDS/ 2.0	-78/ 1	**387**/**386**/**388** = 62/23/15	85/15 (31%)
5	LDA/ 1.0	-78/ 1	**387**/**386**/(**390**) [d] = 50/25/25	- [e]

		+rt/ 18	**387**/**386**/(**390**) [d] = 50/25/25	- [e]
6	LDA/ 2.5	-78/ 1.5	**387**/(**390**) [d] = 50/50	72/28 [f]

[a] Determined based on ^{1}H NMR analysis of crude reaction mixture. [b] Yield after purification *via* column chromatography. [c] Iodination of enolate using inverse addition technique. [d] **390** is unidentified product [e] Determination is complicated due to overlap of signals in crude reaction mixture. [f] Unidentified product **390** could not be separated from product **387** and a mixture of **387**/**390** (1/1) was obtained after purification *via* column chromatography.

The isolated mixture of *trans*/*cis*-β-lactams **387** was further subjected to reduction with chloroalane in diethyl ether at reflux for two hours, affording the desired azetidine **383** in good yield of 78% and ratio *trans*/*cis* isomers of 96/4. This mixture was treated with sodium azide in DMSO or acetone. However, the substitution failed, giving no reaction or a complex reaction mixture when harsh conditions were applied (Table 14, entries 1-3).

Table 14. Attempted transformation of β-lactam **387** towards azetidine **391**.



387
trans/*cis* 85/15

383 (78%)
trans/*cis* 96/4

391

Entry	Reaction conditions	Result
1	3 equiv NaN_3, DMSO, 70 °C, 10 min	(-) [a,b,c]
	+ 80 °C, 30 min	(-) [a,b,c]
	+1 equiv NaN_3, 90 °C, 10 min	(-) [a,d]
2	4 equiv NaN_3, DMSO, 100 °C, 5 h	(-) [d]
3	3 equiv NaN_3, acetone, Δ, 24 h	(-) [b,c]

[a] Microwave assisted synthesis. [b] No reaction.[c] Starting material was recuperated. [d] Partial or full degradation of starting material.

Based on the performed experiments with the different 3-halo-3-fluoroazetidines, it can be concluded that the presence of fluorine dramatically decreases the reactivity of the attached halocarbon towards nucleophiles.

In conclusion, the synthesis of new *N*-benzyl 3-bromo-3-fluoroazetidines *cis*-**373** was performed *via* direct reduction of the corresponding β-lactams *cis*-**363** without loss of stereochemistry. The reactivity of 3-bromo-3-fluoroazetidines **373** with nucleophiles and electrophiles was studied. The

obtained *N*-benzyl-3-fluoro-2-phenylazetidine-2-carbonitriles **377** and *N*-benzyl-2-aryl-3-fluoroazetidines **380** can serve as versatile building blocks for further elaboration (e.g. synthesis of azetidine-2-carboxylic acids, ring opening, …). Additionally, the synthesis of new *N*-benzyl 4-aryl-3-fluoro-3-iodo-2-azetidinones **387** and 3-fluoro-3-iodoazetidines **383** was achieved. Moreover, the diethylzinc-mediated Reformatsky-type reaction of ethyl dibromofluoroacetate **34** across aldimines was extended to diverse substrates, including aliphatic aldimines and aldimines bearing an electron-withdrawing group at nitrogen, giving new ethyl 2-fluoroaziridine-2-carboxylates **366**, **368** and ethyl 3-amino-2-bromo-2-fluoro-3-phenylpropanoates **367** and **370**. The importance of aziridine-2-carboxylate units is worth to note, as they present one of the classes of natural aziridine-containing alkaloids which are an important source of drug prototypes.[195]

3.4 Synthesis of 3-amino-1,2-diols and their elaboration towards small membered amino acid derivatives bearing an aziridine, azetidine or epoxide scaffold

In the following chapter, results are disclosed on the elaboration of *N*-substituted alkyl 2-(aminomethyl)acrylates **42** towards the synthesis of the corresponding 2-(aminomethyl)oxirane-2-carboxylates **44**, aziridine-2-carboxylates **45** or azetidine-3-carboxylates **46** (Figure 20). The present research is an extension of results preliminary reported by our research group.[50]

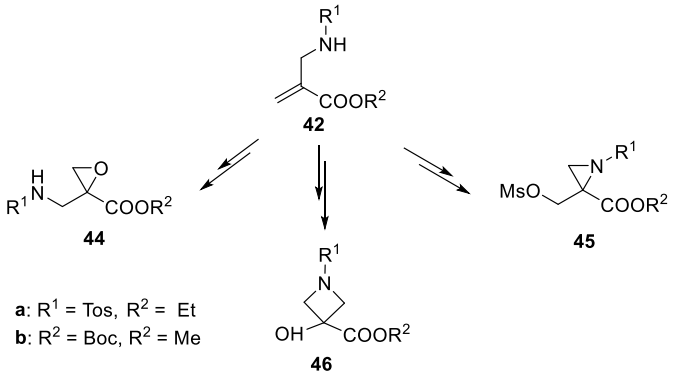


Figure 20. Overview of the targeted amino acids derivatives.

3.4.1 Introduction

N-Substituted allylamines **392** (Figure 21) are attractive substrates for diverse organic syntheses due to the reactivity of the double bond towards diverse transformations such as dihalogenation,[127, 196] epoxidation,[197] direct aziridination,[198] halohydroxylation,[199] aminohalogenation,[200] haloazidation,[201] aminohydroxylation,[202] and asymmetric dihydroxylation[203]. Moreover, *N*-substituted allylamines **392** and **393** are valuable building blocks for numerous elaborations towards the synthesis of bioactive compounds.[45a, 204]

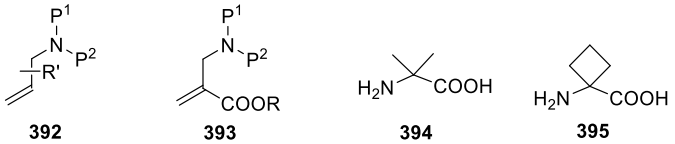
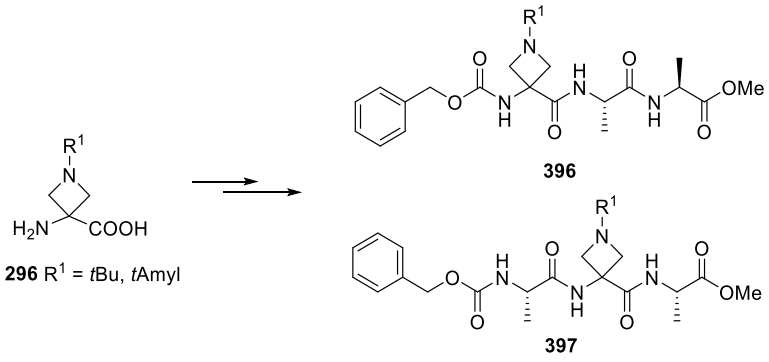


Figure 21

C^{α}-Tetrasubstituted α-amino acids, for example, α-aminoisobutyric acid **394** and 3-aminocyclobutane-1-carboxylic acid **395** (Figure 21), play an important role in the design of peptides and peptidomimetics with enhanced properties, as they possess a stereochemically stable quaternary carbon center which results, after incorporation into peptides, in a significant conformational bias.[51b, 51c, 205]

Recently, our research group reported on the synthesis of heterocyclic analogues **296** of amino acid **395** bearing an electron donating group at nitrogen (Scheme 88).[127b] Subsequently, investigation of the conformational features of these amino acids in model peptides **396** and **397** allowed to conclude that such a 3-aminoazetidine-3-carboxylic acid moiety **296** is a β-turn inducer.[51a] Moreover, the 3-aminoazetidine-3-carboxylates may be important building blocks for the synthesis of diverse bioactive compounds.[206]



Scheme 88

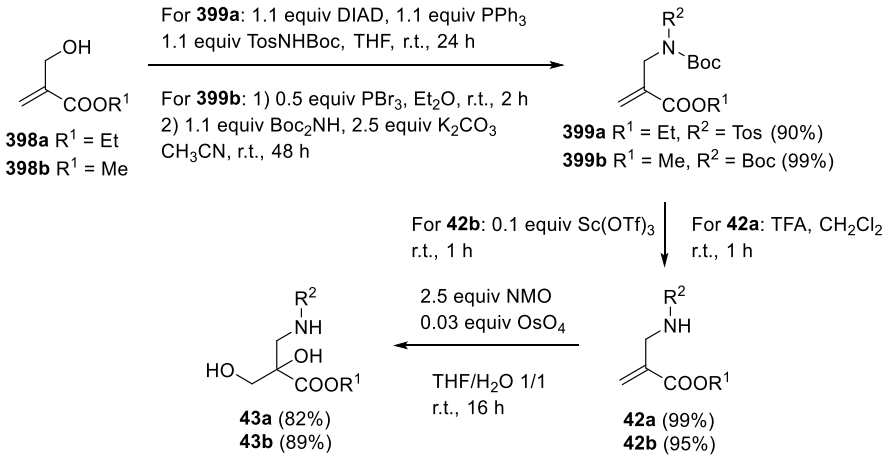
Aziridine-2-carboxylic acid derivatives are known building blocks for the synthesis of proteinogenic and non-proteinogenic amino acids and biologically active compounds.[207]

On the other hand, the use of β-amino acids in the development of β-peptide foldamers, pioneered by Seebach,[31b] has received much interest due to the stability of β-peptides compared to peptides constituted from α-amino acids. Alicyclic β-amino acids are a well known class of non-proteinogenic amino acids which are found in nature both in free form and in peptides.[208] Their synthetic analogues are useful units for the synthesis of peptides with modified and improved pharmacological properties.[32c, 32d, 167a, 207c, 209] The synthesis and study of α-epoxy-β-amino acids is rarely described in the literature.[210] However, the oxirane ring has proven to be a versatile building block and synthetic intermediate.[211]

3.4.2 Synthesis of 3-amino-1,2-diols 43 and study of their transformations

N-substituted alkyl 2-(aminomethyl)acrylates **42a** and **42b** were prepared *via* literature procedures starting from the corresponding ethyl **398a** and methyl 2-(hydroxymethyl)acrylate **398b**, respectively.[196b, 204g, 212] Next, Upjohn dihydroxylation was performed under the conditions previously optimized by our research group.[50] Using a catalytic amount of OsO_4 and 2.5 equivalents of *N*-methylmorpholine-*N*-oxide (NMO) as co-oxidant, full dihydroxylation of acrylates **42a,b** was achieved at room temperature. After flash chromatography, aminodiols **43a,b** were isolated in 82% and 89% yield, respectively (Scheme 89). Noteworthy, for the formation of methyl 2,3-

dihydroxypropanoate **43b** a prolonged reaction time up to 18 hours was required to archieve full conversion.

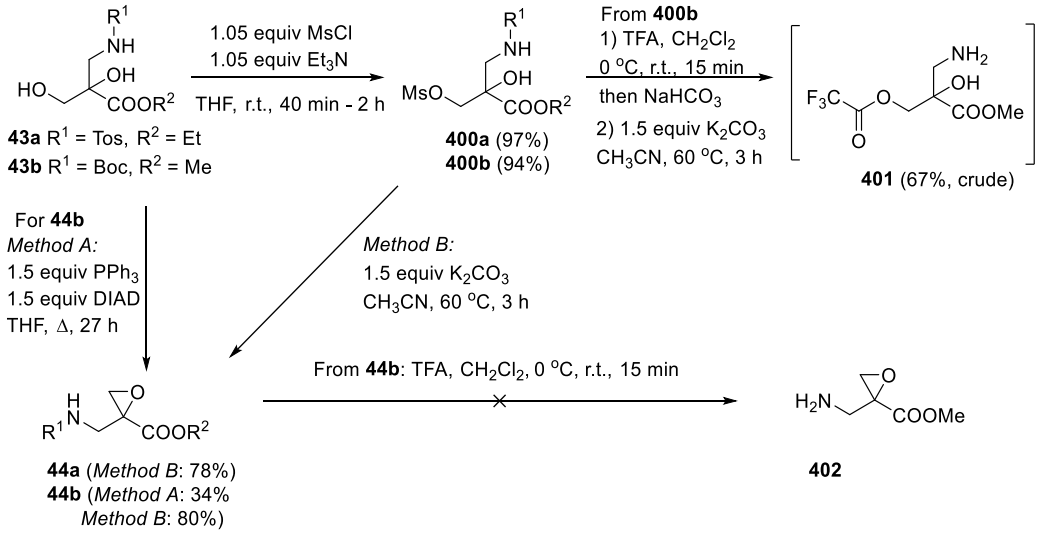


Scheme 89

Subsequently, the reactivity of versatile building blocks **43a,b** and their cyclization towards aziridines, azetidines and epoxides was studied.

First, cyclization of 3-amino-1,2-diol **43b** under Mitsunobu conditions was carried out in analogy with the reported cyclization of **43a** (Scheme 3).[50] The use of 1.5 equivalents of PPh_3 and 1.5 equivalents of diisopropyl azodicarboxylate (DIAD) in dry THF at reflux for 27 hours afforded oxirane **44b** in 34% yield. Furthermore, a more efficient method for cyclization towards epoxides **44**, which involves the activation of the primary alcohol into a good leaving group by means of mesylation, was applied (Scheme 90).[50]

Treatment of 3-amino-1,2-diol **43a** with 1.05 equivalents of triethylamine and 1.05 equivalents of methanesulfonyl chloride in dry THF at 0 °C followed by warming up to room temperature for two hours afforded monomesylated aminoalchohol **400a** (Scheme 90). For the synthesis of *N*-Boc-protected derivative **400b** similar reaction conditions were applied, though the reaction time could be shortened to 40 minutes.



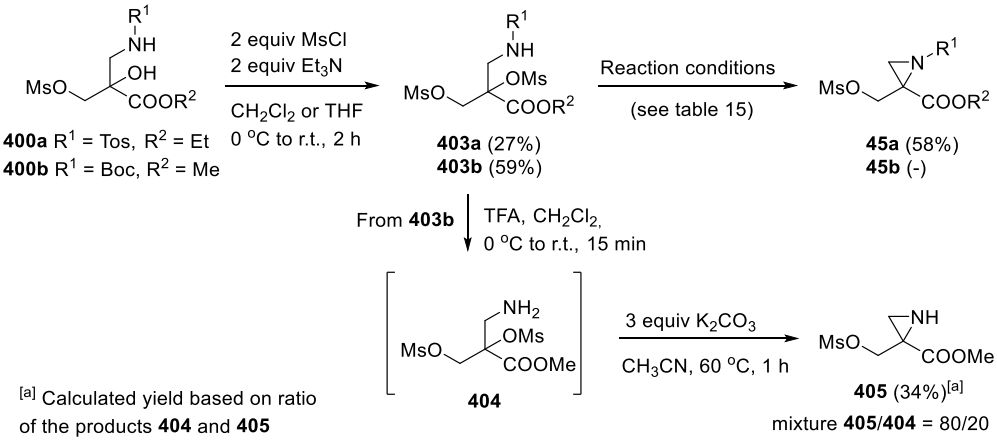
Scheme 90

Next, monomesylated aminodiols **400a** and **400b** were treated with 1.5 equivalents of K_2CO_3 in acetonitrile at 60 °C for three hours, exclusively affording epoxides **44a** and **44b** in 78% and 80% yield, respectively (Scheme 90). In order to demonstrate the potential applicability of the synthesized β-amino acid derivatives, *N*-deprotection of epoxide **44b** was attempted by treatment with TFA in CH_2Cl_2, unfortunately with no success and only complex mixture of unidentified products was formed (Scheme 90). When initial *N*-Boc deprotection of mesylate **400b** was performed with TFA followed by base mediated cyclization, the desired oxirane **402** was not observed and only plausible side product **401** could be detected as tentatively assigned *via* ^{1}H and ^{13}C NMR. However, further efforts to isolate an analytically pure product **401** *via* column chromatography or preparative thin layer chromatography failed. The formation of *O*-protected amino-1,2-diol **401** might be explained by instability of epoxides in acidic conditions.[213]

Based on a preliminary study by our research group, the selective synthesis of aziridines and azetidines from aminodiols **400**, avoiding ring closure towards epoxides, could be achieved by simple manipulations.[50]

Thus, monomesylated aminodiols **400** were subjected to further mesylation, since bismesylated aminodiol **400a** proved to be a good substrate for the synthesis of the corresponding aziridine **45a** (Scheme 91). The use of two equivalents of triethylamine and two equivalents of methanesulfonyl chloride in CH_2Cl_2 (for **400a**) or THF (for **400b**) at room temperature for two hours afforded derivatives **403a** and **403b** in 27% and 59% yield, respectively (Scheme 91). Noteworthy, when THF was used as solvent for mesylation of substrate **400a**, the yield of product **403a** dropped to less than 10%.

Next, 2-(methanesulfonyloxymethyl)-1-(toluene-4-sulfonyl)aziridine-2-carboxylate **45a**, resulting from *3-exo-tet* ring closure, was prepared in 58% yield upon treatment of mesylate **403a** with three equivalents of K_2CO_3 in CH_3CN at 60 °C for 1.5 hours (Table 15, entry 1).[50] Noteworthy, formation of the alternative azetidine, the *4-endo-tet* product, did not occur. Treatment of *N*-Boc derivative **403b** under similar reaction conditions gave no reaction, while subsequent prolongation of the reaction time and increase of the temperature gave only complex reaction mixtures (Table 15, entry 2). This might be explained by the strong deactivating character of the *tert*-butoxycarbonyl group on nitrogen, which can prevent cyclization. It was foreseen that the aforementioned problem could be eliminated by *N*-deprotection of substrate **403b** followed by intramolecular cyclization (Scheme 91). Thus, bismesylate **403b** was treated with TFA in CH_2Cl_2 and intermediate **404** was subjected to the cyclisation reaction with potassium carbonate in CH_3CN affording methyl 2-[(methanesulfonyloxy)methyl]aziridine-2-carboxylate **405** although the full conversion of mesylate **404** was not achieved. The purification of the resulting crude mixture *via* preparative HPLC did not lead to separation of the individual compounds **404** and **405** which were obtained as a mixture of **404**/**405** in a ratio of 20/80 (Scheme 91).



Scheme 91

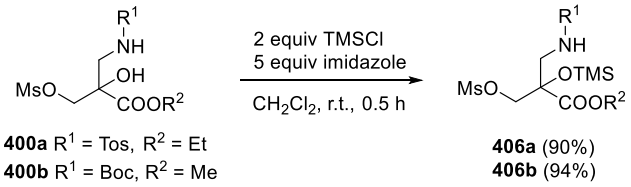
Table 15. Investigation of the ring closure of bismesylates **403**.

Entry	R^1	R^2	Reaction conditions	Result[a]
1	Tos	Et	3 equiv K_2CO_3, CH_3CN, 60 °C, 1.5 h	**45a** (58%)
2	Boc	Me	1.5-3 equiv K_2CO_3, CH_3CN, 60-90°C, 2-24 h	-[b]

[a] Yield after purification by flash chromatography. [b] Degradation of starting material.

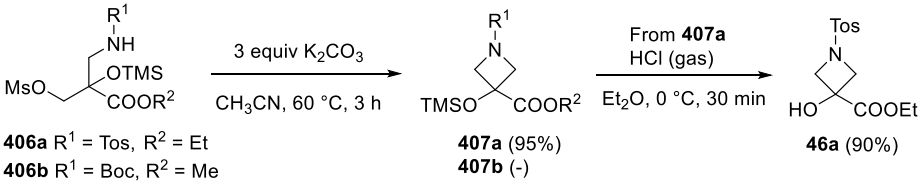
In order to prepare substrates for the direct cyclization of monomesylated aminodiols **400** towards azetidines, protection of the tertiary hydroxyl group was performed by using preliminary optimized

reaction conditions.[50] Substrates **400a** and **400b** were treated with two equivalents of TMSCl and five equivalents of imidazole in CH_2Cl_2 at room temperature for 30 minutes, affording disubstituted aminoalcohols **406a** and **406b** in 90% and 94% yield, respectively (Scheme 92). Noteworthy, when THF was used instead of CH_2Cl_2, no conversion of starting material **400a** was observed even when the reaction time was extended to 28 hours.



Scheme 92

In the next step, mesylate **406a** was easily cyclized to azetidine **407a** (95% yield) *via* addition of three equivalents of K_2CO_3 in acetonitrile (Scheme 92).[50] Contrary, cyclization of *N*-Boc substituted derivative **406b** did not proceed towards the desired compound **407b**, while increasing the temperature and the reaction time up to 18 hours led to the formation of epoxide **44b**. The latter could be explained *via* the degradation of starting material **407b** to its precursor **406b**, and subsequent cyclization. Due to the problematic synthesis of *N*-Boc protected azetidine **407b**, further transformations were performed on *N*-Tos protected azetidine **407a** exclusively. 3-Hydroxyazetidine **46a** was easily accessed (90% yield) after deprotection of the TMS-group with an excess of gaseous HCl in diethyl ether (Scheme 93).[50]

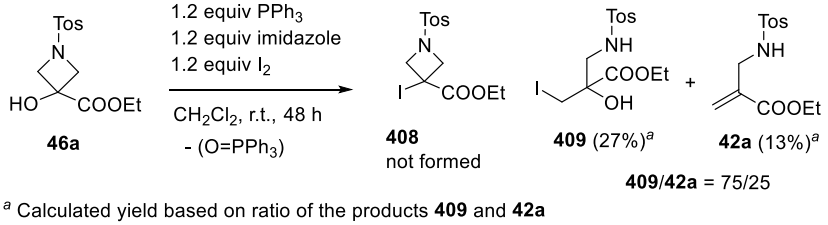


Scheme 93

Azetidine **46a** was envisioned as a suitable substrate for the preparation of derivatives of C^{α}-tetrasubstituted amino acids *via* nucleophilic substitution of the hydroxyl group and further transformations. In a first attempt, substitution of the tertiary hydroxyl group of **46a** with iodide was tested. Following a literature procedure,[214] substitution of the hydroxyl group with iodide was performed by treatment of azetidine **46a** with 1.2 equivalents of triphenylphosphine, 1.2 equivalents of imidazole and 1.2 equivalents of iodine in CH_2Cl_2 at room temperature. After full consumption of starting material (LC-MS and TLC control), no formation of 3-iodoazetidine **408** was detected by LC-MS and ^{1}H NMR analysis of the crude reaction mixture. Instead, a non-separable mixture of two ring-opened products was isolated after column chromatography. The composition of the mixture

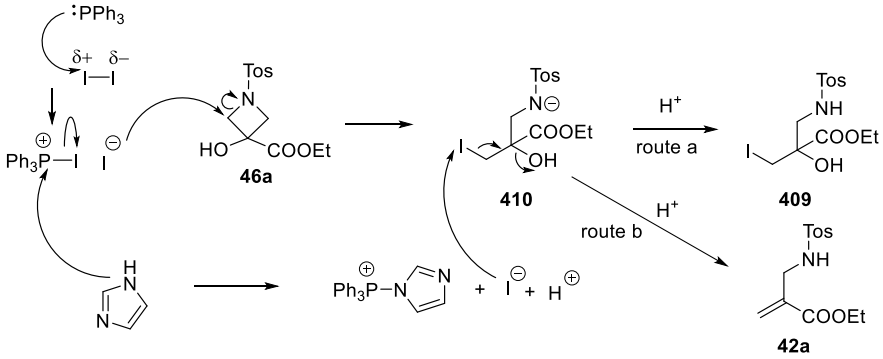
was determined as ethyl 2-hydroxy-3-iodo-2-[(tosylamino)methyl]propanoate **409** and ethyl 2-[(tosylamino)methyl]acrylate **42a** in a ratio of 75/25 (Scheme 94).

Recently, the use of PPh_3/halogenating agents was reported as a highly efficient approach for the ring opening of activated and non-activated aziridines with halides.[215] However, this methodology was not applied for azetidine ring opening. Due to the poor reactivity of (non)activated azetidines, an additional activation step, leading to the formation of an azetidinium ion, is needed to promote the ring opening reaction.[216] Moreover, the ring opening of 3-substituted azetidines has only been reported in one recent publication, where the reaction proceeds *via* nitrogen activation as well.[217]



Scheme 94

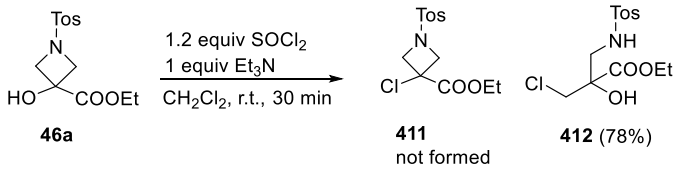
The obtained results could be explained by the high reactivity of the azetidine ring **46a** towards nucleophilic ring opening. Presumably, triphenylphosphine acts as a Lewis base and attacks iodine, giving iodotriphenylphosphonium iodide (Scheme 95).[218] Subsequently, the activated azetidine **46a** undergoes nucleophilic attack by iodide at C-2, leading to the ring opened product **409** after protonation (route *a*). Formation of acrylate **42a** could be rationalized by halophilic reaction of the intermediate **410** and *in situ* generated iodide (Scheme 95, route *b*), which, likely, was formed *via* reaction of the iodotriphenylphosphonium cation and imidazole.[219]



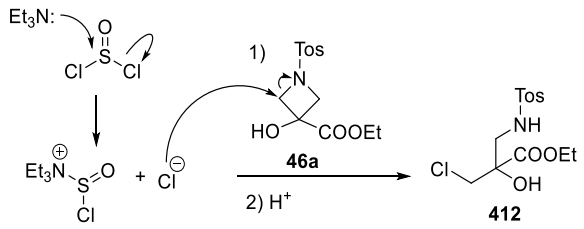
Scheme 95

In subsequent attempts, the reaction of 3-hydroxyazetidine **46a** and thionyl chloride was tested. When azetidine **46a** was treated with 1.2 equivalents of thionyl chloride at room temperature for up to four days, only starting material was detected. Addition of one equivalent of triethylamine to the reaction resulted in full consumption of starting material **46a** at room temperature within 30 minutes

(Scheme 96). Analysis of the crude reaction mixture by LC-MS and ^{1}H NMR led to conclude, that the expected 3-chloroazetidine **411** was not formed. The crude mixture was purified by column chromatography and the isolated product was identified as ethyl 3-chloro-2-hydroxy-2-[(tosylamino)methyl]propanoate **412** (78%), which is an analogue of the aforementioned 3-iodopropanoate **409** (Scheme 96). The proposed pathway of this reaction includes similar steps as described above: formation of the nucleophile by reaction of triethylamine with thionyl chloride and nucleophilic attack of chloride at the azetidine carbon C-2 of **46a**, followed by protonation of the sulfonamide upon work-up (Scheme 97).



Scheme 96

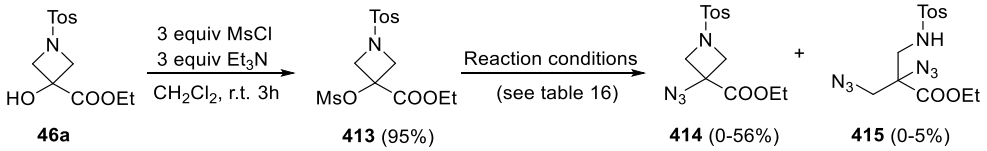


Scheme 97

The similar outcome points to the high propensity of this type of azetidine **46a** towards nucleophilic ring opening. The proposed reaction routes could be elaborated by a more detailed mechanistic study, which was not conducted in the context of the present PhD.

Furthermore, mesylation of the tertiary hydroxyl group of azetidine **46a** by treatment with three equivalents of Et_3N and three equivalents of MsCl in THF afforded mesylate **413** in 95% yield (Scheme 98).[50] Next, the activity of the latter compound towards nucleophilic substitution was examined. Treatment of azetidine **413** with NaN_3 in DMSO, DMF or acetone gave no conversion of starting material and only some decomposition was observed after prolonged heating (Table 16, entries 1-3). Subsequently, substitution was attempted by using four equivalents of NaI and four equivalents of NaN_3 in DMSO at 110 °C for 24 hours, which afforded the desired 3-azidoazetidine **414** in 25% isolated yield (Table 16, entry 4). Full conversion, however, was not achieved and the remaining starting material could be isolated in 8% yield. Besides, side product **415** was formed and isolated in 5% yield. Based on this analysis of the reaction mixture, it is clear that applying more harsh conditions (a larger excess of nucleophile, high temperatures and prolonged reaction times) would promote the formation of side product **415** and decomposition of the starting material **413**.

Reaction with three equivalents of NaI and three equivalents of NaN_3 in DMSO at 85 °C for 20 hours resulted in a mixture of starting **413** and product **414** in a ratio of 3/1. After work-up and purification *via* column chromatography, 3-azidoazetidine **414** was isolated in 21% yield and the recovered starting material was subsequently subjected to further substitution under the same reaction conditions. After repeating the sequence one more time, full conversion of starting material **413** was achieved, affording 3-azidoazetidine **414** in a combined yield of 56% (Table 16, entry 5). Changing the solvent to ethanol resulted in a low conversion of starting material **413** (Table 16, entry 6). Further, the enhancement using microwave heating was tested. In a first attempt, azetidine **413** was treated with two equivalents of NaI and two equivalents of NaN_3 in DMSO at 80 °C for 30 minutes. This gave no satisfying result, while subsequent increase of the temperature up to 120 °C afforded a reaction mixture of **414**/**415**/**413** in a ratio 69/12/19 based on ^{1}H NMR analysis of the crude reaction mixture (Table 16, entry 7). Finally, DMF was used as a solvent, resulting in a lower conversion of starting mesylate **413** (Table 16, entry 8). Despite the advantage of microwave assisted synthesis, *i.e.* a better conversion of the starting compound, it seems to be more difficult to control the ring opening as a side reaction. Importantly, the formation of α,β-diazido ester **415** makes the reaction potentially dangerous due to the explosive propensity of azido compounds.



46a **413** (95%) **414** (0-56%) **415** (0-5%)

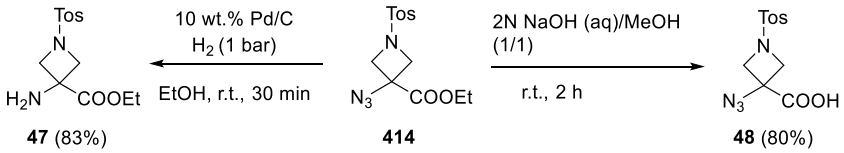
Scheme 98

Table 16. Optimization of the substitution reaction with NaN_3.

Entry	Reaction conditions	Result [a]
1	4 equiv NaN_3, DMSO, 65 °C, 20 h	-[b]
2	4 equiv NaN_3, acetone, Δ, 20 min	-[b]
3	2 equiv NaN_3, DMF, 70°C, 4 h	-[b]
4	4 equiv NaI, 4 equiv NaN_3, DMSO, 110 °C, 24 h	**414** (25%), **415** (5%), **413** (8%)
5	3 equiv NaI, 3.0 equiv NaN_3, DMSO, 85 °C, 20 h	**414** (56%)[c]
6	3 equiv NaI, 3.0 equiv NaN_3, EtOH, Δ, 1-48 h	**414**/**413** = 5/95[d]
7	2 equiv NaI, 2 equiv NaN_3, DMSO, 120 °C, 20 min[e]	**414**/**415**/**413** = 69/12/19[d]
8	2 equiv NaI, 2 equiv NaN_3, DMF, 80-120 °C/30-60 min[e]	**414**/**415**/**413** = 53/4/43[d]

[a] Yield after purification by flash chromatography. [b] No reaction. [c] Yield after 3 sequences of recuperation of unreacted starting material **413** followed by repeating the reaction conditions. [d] Determined *via* ^{1}H NMR of crude reaction mixture. [e] Microwave assisted reaction.

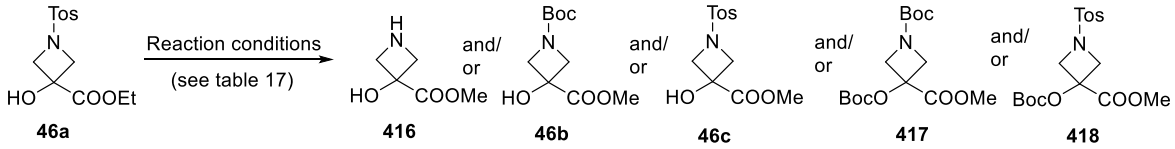
In order to demonstrate the usefulness of the synthesized constrained amino acid precursor **414** as possible building block for the synthesis of foldamers, it was subjected to hydrogenolysis and hydrolysis reaction conditions.[51a, 127b] Simple hydrogenolysis of 3-azidoazetidine **414** using 10 wt.% palladium on carbon in ethanol at room temperature for 30 minutes afforded 3-aminoazetidine **47** in 83% yield. Additionally, hydrolysis of ester **414** to the corresponding 3-azidoazetidine-3-carboxylic acid **48** was achieved in 80% yield upon reaction with 2M aqueous NaOH in methanol (1/1) at room temperature for two hours (Scheme 99).



Scheme 99

In a last part, the detosylation of azetidine **46a** was attempted in order to obtain a valuable building block **416** for potentially active pharmaceutical compounds as well as for the synthesis of β-peptides (Scheme 100).[190, 220] When the reaction of azetidine **46a** was performed with 10-20 equivalents of Mg turnings in dry methanol using sonication at 40 ºC for 1-24 hours, only complex reaction mixtures were obtained (Table 17, entry 1). Performing the reaction with Mg turnings upon sonication followed by treatment with Boc_2O and DMAP in acetonitrile gave a mixture of azetidines **417** and

418 in 8% and 5% yield, respectively (Table 17, entry 2). In the next attempt, 10 equivalents of Mg powder were used in dry methanol at room temperature for two hours and consequently 1.1 equivalents of Et_3N and 1.1 equivalents of Boc_2O were added to the reaction mixture and the reaction was stirred at room temperature for 3 hours, resulting in a mixture of **46b** and **46c** in a 68/32 ratio based on the ^1H NMR analysis of the crude reaction mixture (Table 17, entry 3). Noteworthy, under such reaction conditions the starting carboxylate **46a** underwent full transesterification to the corresponding methyl azetidine-3-carboxylate. Using 15 equivalents of Mg for three hours caused a slight increase in the conversion of the starting material (Table 17, entry 4). Finally, extension of the reaction time to 18 hours led to a full consumption of *N*-Tos protected azetidine **46a** and treatment of the reaction mixture with Boc_2O gave *N*-Boc protected azetidine **46b** in 54% yield (Table 17, entry 5).



Scheme 100

Table 17. Optimization of Tos-deprotection of 3-hydroxyazetidine-3-carboxylate **46a** and subsequent protection with a Boc-group.

Entry	Reaction conditions	Result [a]
1	10-20 equiv Mg (turnings), MeOH, 40 °C, sonication 1-24 h	-
2	1) 20 quiv Mg (turnings), MeOH, 40 °C, sonication, 5 h 2) 1.1 equiv Boc_2O, 0.1 mol DMAP, CH_3CN, r.t., 3 h	**417** (8%), **418** (5%)
3	1) 10 equiv Mg (powder), MeOH, r.t., 2 h 2) 1.1 equiv Boc_2O, 1.1 equiv Et_3N, MeOH, r.t., 3 h	**46b**/**46c** = 68/32[b]
4	1) 15 equiv Mg (powder), MeOH, r.t., 3 h 2) 1.1 equiv Boc_2O, 1.1 equiv Et_3N, MeOH, r.t., 3 h	**46b**/**46c** = 77/23[b]
5	1) 15 equiv Mg (powder), MeOH, r.t., 18 h 2) 1.1 equiv Boc_2O, 1.1 equiv Et_3N, MeOH, r.t., 3 h	**46b** (54%)

[a] Yield after purification by flash chromatography (or preparative TLC). [b] Determined *via* ^1H NMR analysis of the crude reaction mixture.

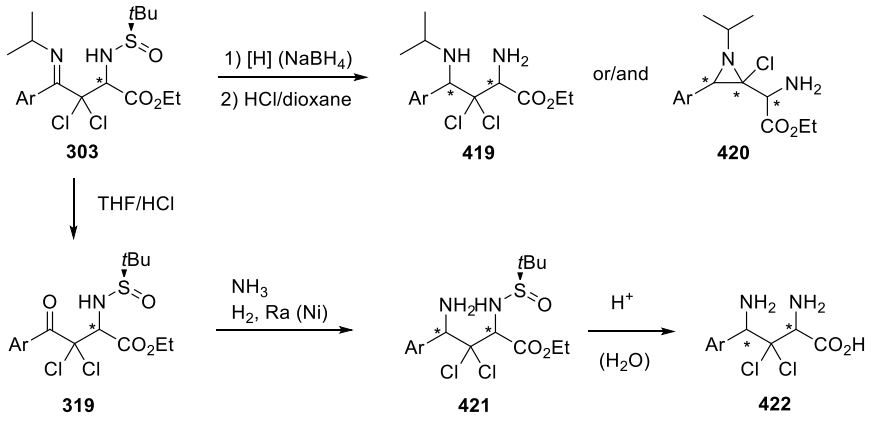
In conclusion, an efficient synthesis of alkyl 2-(aminomethyl)oxirane-2-carboxylates **44**, alkyl 2-[(methanesulfonyloxy)methyl]aziridine-2-carboxylates **45**, and 3-hydroxyazetidine-3-carboxylates **46** was developed starting from *N*-substituted allylamines **42**. The versatility of the *N*-tosyl-3-hydroxyazetidine-3-carboxylate **46a** was demonstrated by its transformation to the corresponding C^{α}-tetrasubstituted α-amino acid derivatives, namely, ethyl 3-aminoazetidine-3-carboxylate **47**, 3-azidoazetidine-3-carboxylic acid **48** and *N*-Boc protected methyl 3-hydroxyazetidine-3-carboxylate **46b**. The obtained small ring heterocyclic α- and β-amino acid derivatives can be considered as valuable building blocks for potential application in foldamer research and medicinal chemistry.

4 Perspectives

The development of new short efficient synthetic routes towards acyclic and cyclic biologically relevant α- and β-amino acid derivatives was a main issue of the present PhD research. Albeit some methods did not lead to the desired results, the optimization and modification of the reaction conditions and substrates seems an interesting and challenging field for further research.

A first proposal relates to the addition reaction of α-anions of α,α-dichloroketimines (1-azaenolates) across imines (Section 3.1.3).

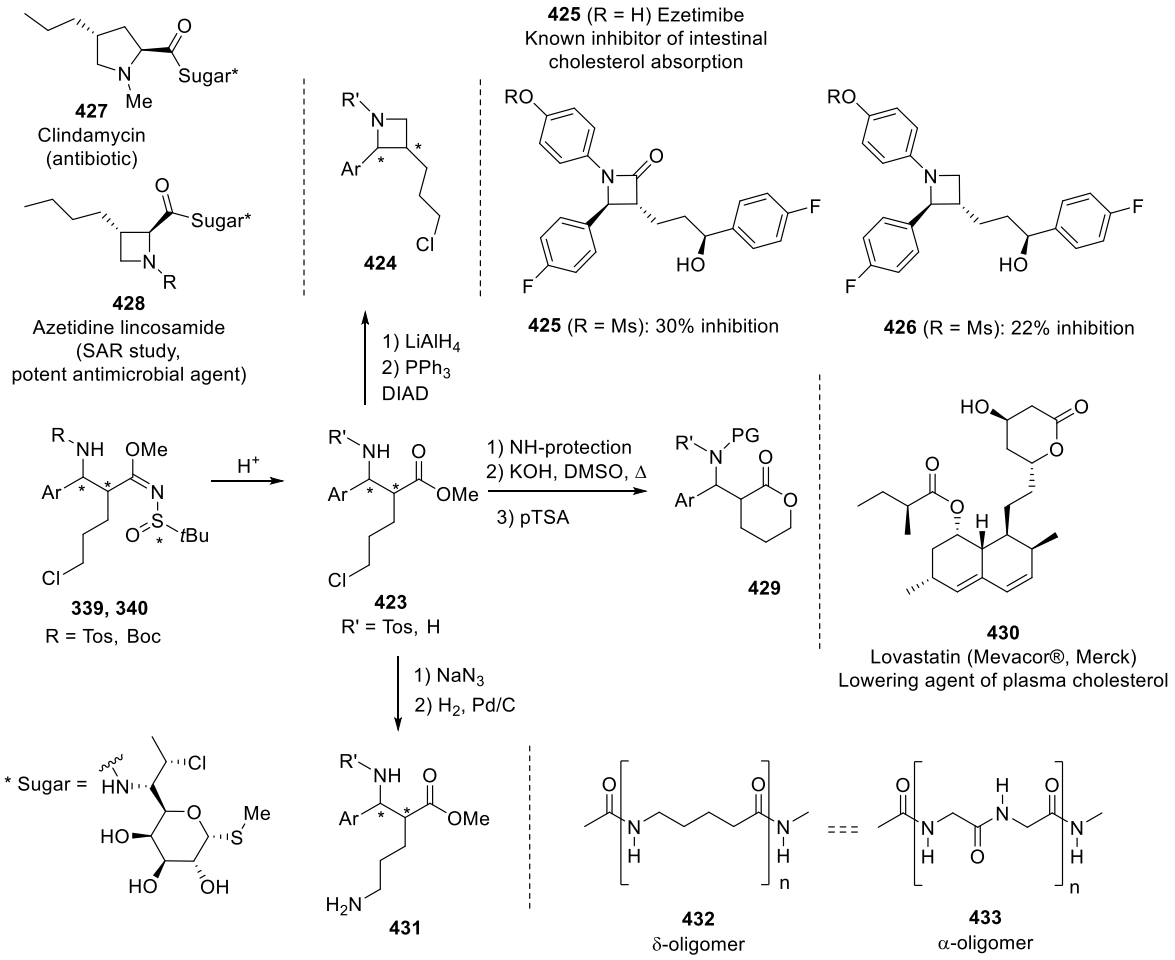
The adducts **303** might be subjected to transformations leading to the possible formation of dichlorinated diamino acid derivatives **419** or 2-aziridinyl amino ester **420** (Scheme 101). These transformations might include the selective reduction of the C=N bond and *N*-sulfinyl deprotection. From the other hand, reductive amination of the hydrolyzed product **319** could give compound **421** and subsequent NH-deprotection could provide free α,γ-diaminocarboxylic acid **422**. Important considerations to be taken into account concerns the necessity to carefully control the reaction conditions such as temperature and solvent as well as the work-up conditions to minimize side reactions, such as elimination of hydrogen chloride and degradation of the formed substrates **419**-**422**.



Scheme 101

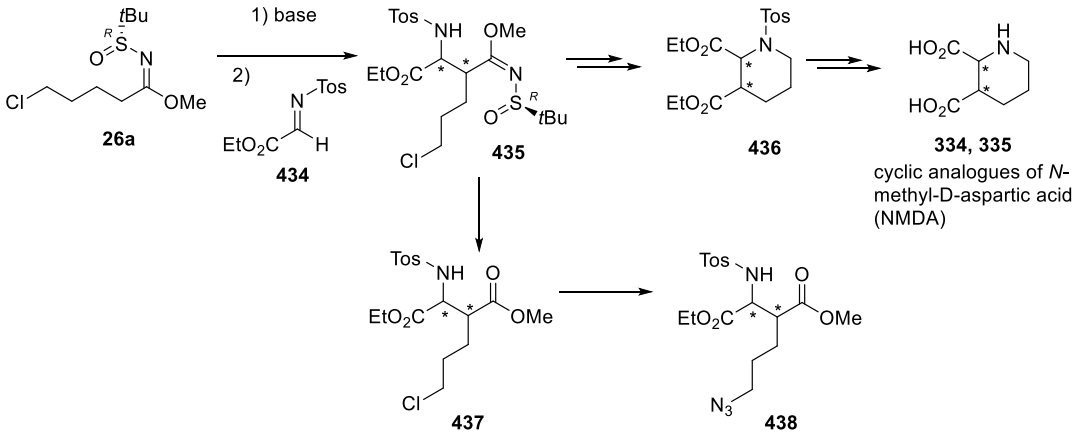
In the second part of this thesis (Section 3.2.2), it was demonstrated that the δ-chloro-β-amino-*N*-sulfinyl imidates **339**/**340** are efficient building blocks for the synthesis of various chiral 2,3-disubstituted piperidines such as 3-amino-2-arylpiperidines **350**/**351** and 2-arylpiperidine-3-carboxylic acid derivatives **354**-**357**. In order to extend the application of the imidates **339**/**340**, the *N*-sulfinyl deprotection leading to the formation of ester **423** can serve as a method for the synthesis of a new scaffold of β-amino acid derivatives (Scheme 102). Moreover, the functionalized β-amino esters **423** could be envisioned as synthons for further elaborations towards biologically relevant molecules. For example, following the developed procedure at the Department of Sustainable

Organic Chemistry and Technology (UGent) towards chiral 3-chloroazetidines,[47] substrates **423** could be transformed to 2,3-disubstituted azetidines **424** *via* reduction of the ester group of **423** towards primary alcohols and subsequent cyclization under Mitsunobu conditions. In previous research, it was shown that azetidine derivatives **426** are as potent as their β-lactam counterparts **425** (*e. g.* ezetimibe) in inhibiting cholesterol absorption *in vitro*.[221] Thus, the proposed azetidines **424** could be seen as precursors for the design of small-molecule cholesterol absorption inhibitors that can be useful in preventing cardiovascular disease by lowering blood cholesterol level. Moreover, the 2,3-substituted azetidines **424** might act as valuable building blocks for the synthesis of analogues of clindamycin **427**, such as azetidine lincosamides **428** with promising antimicrobial activities.[222] As it was reported in Section 3.2.1, a successful oxidation of the aryl substituent at C-2 of azetidines **424** might be a challenging step of the aforementioned transformation. Additionally, the δ-chloro-β-amino esters **423** could be elaborated towards substituted δ-lactones **429** [223] which can be found in the structure of some bioactive compounds. For example, the δ-lactone unit is present in the structure of the Lovastatin **430** (Mevacor®, Merck), the first marketed statin used as cholesterol lowering drug.[224] Also, compounds with a δ-lactone core were detected in the pheromone system of the giant white butterfly *Idea leuconoe*.[225] The substitution of chloride in **423** with azide followed by reduction could afford the δ-amino acid derivatives **431**. Along with β- and γ-amino acids which have proven to be valuable building blocks for peptidomimetics,[31d] less studied δ-amino acid derivatives have potential application in the synthesis of peptides[226] with well-defined secondary structure as it was suggested by Hofmann in a theoretical study of the possible helix types in oligomers of δ-amino acids.[227] The main interest for the δ-peptides arises from the close correspondence between δ-amino acid oligomers **432** and dipeptide units in α-peptides **433**.



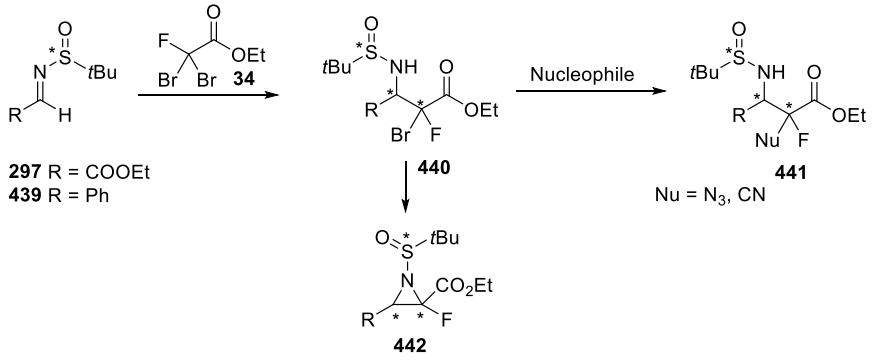
Scheme 102

In view of the successful Mannich-type addition of *N*-sulfinyl imidates **26a** across aromatic aldimines, the addition of *N*-sulfinyl imidates **26a** across ethyl (tosylimino)acetate **434** could lead to the synthesis of piperidine-2,3-dicarboxylic acid **334**/**335** *via* the established synthetic approach (Scheme 103). The latter piperidine **434**/**435** is a cyclic analogue of NMDA and could be used for the study of its interactions with amino acid neuromediated receptors. The adduct **435** could be also envisioned as a building block for the synthesis of amino dicarboxylic acid derivatives **437** and **438** (Scheme 103).



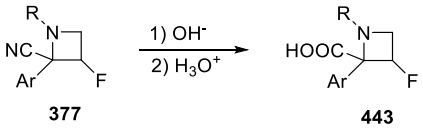
Scheme 103

Since the presence of fluorine atoms in molecular structures has a great impact on their physical, biological and chemical properties, it would be interesting to expand the described results in Section 3.3 with additional experiments. The asymmetric version of the Reformatsky-type reaction between ethyl dibromofluoroacetate **34** and aldimines **297**, **439** bearing an electron-withdrawing group at nitrogen could be performed in order to synthesize fluorinated β-amino acid derivatives **440** (Scheme 104).[228] Moreover, investigation of the nucleophilic substitution of the bromide in the acyclic adducts **440** could give additional information about the reactivity of the carbon atom attached to the fluorine. The suggested cyclization of adducts **440** to aziridines **442** constitutes a valuable transformation (Scheme 104). However, as it follows from the described results (Section 3.3), the isolation of cyclized products **442** could be difficult due to the instability of aziridines **442**.



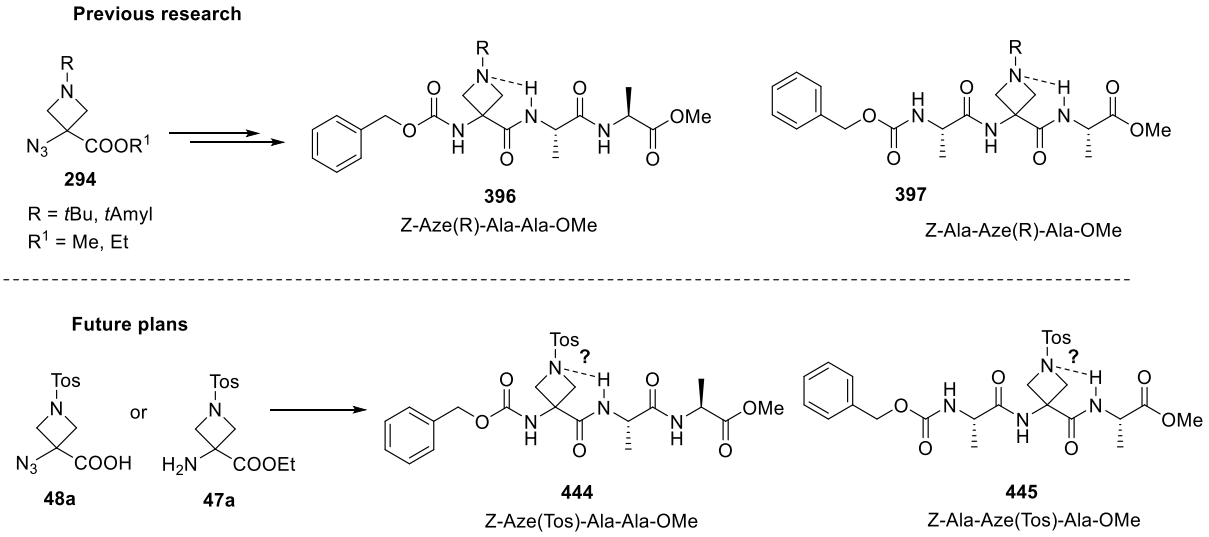
Scheme 104

Also, the 2-cyanoazetidine derivatives **377** (Section 3.3.3.1) form a direct precursor for the synthesis of fluorinated azetidine-2-carboxylic acid derivatives **443** (Scheme 105).



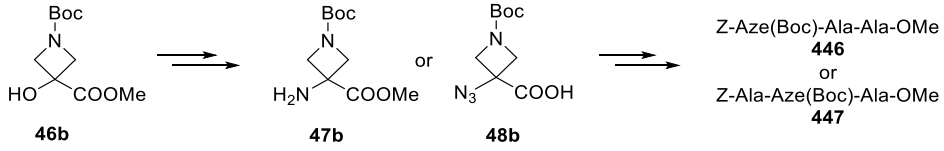
Scheme 105

Based on previous research, azetidine-3-carboxylic acid derivatives **294** with an electron-donating group on nitrogen act as β-turn inducers in model peptides **396** and **397**.[51a] Noteworthy, an interesting main-chain-to-side-chain hydrogen bond has been detected between the trisubstituted nitrogen of the azetidine ring and amide NH of the immediately following residue, forming a six-membered pseudo-cycle. Therefore, the incorporation of the azetidine-3-carboxylic acid derivatives **47a** and **48a** (Scheme 106) into peptides (*e. g.* **444** and **445**) followed by study of their structures might be helpful in order to establish the influence of the electron-withdrawing *N*-substituents on the azetidine nitrogen on the peptide structure.



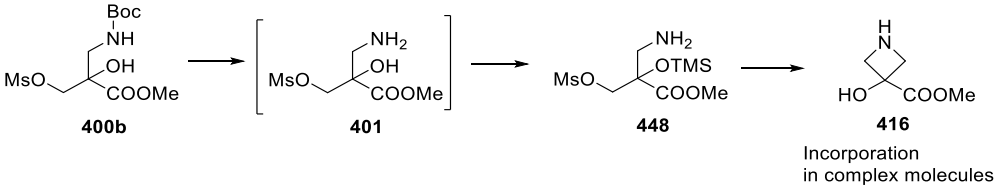
Scheme 106

In the same manner, substrate **46b** could be elaborated to C^{α}-tetrasubstituted amino acid derivatives **47b** and **48b** (Scheme 107) which are of interest in peptide modeling (e. g. **446** and **447**). Noteworthy, the *N*-Boc protected derivatives have an advantage in being more synthetically friendly towards *N*-deprotection compared to *N*-Tos derivatives what can be used advantageously in further elaborations.



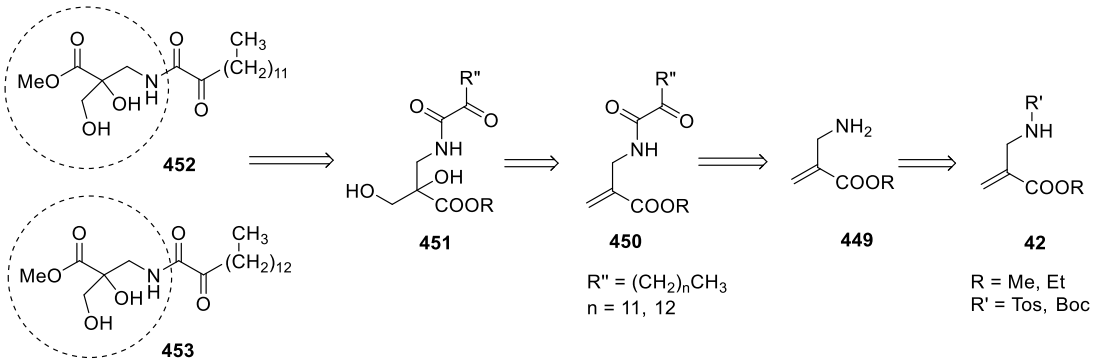
Scheme 107

Additional attempts could be performed towards the preparation of cyclic β-amino acid derivative **416** (Section 3.4.2) (Scheme 108) *via N*-Boc deprotection of mesylate **400b** as key step. Further *O*-TMS protection of intermediate **401** and cyclization of substrate **448** could afford the desired methyl 3-hydroxyazetidine-3-carboxylate **416**.



Scheme 108

Moreover, the structural moiety of the aminodiols **42** (Section 3.4.2) is present in the structure of α-oxoamides, salaramide A (**452**) and its homologue salaramide B (**453**), isolated from the Madagascar marine sponge *Hippospongia* sp.[229] Having a good dihydroxylation method for the allylamines **42** in hand, the latter could be foreseen as promising precursors for the synthesis of natural compounds **452** and **453** in order to investigate their potential biological activity (Scheme 109). It might be more practical to start the synthesis with the deprotection and subsequent derivatization (*i.e.* acylation with 2-oxotetradecanoyl chloride or 2-oxopentadecanoyl chloride) of the allylamines **42** [230] followed by dihydroxylation of the double bond in substrate **450**.



Scheme 109

5 Experimental part

5.1 General methods

Flame-dried glassware was used for all non-aqueous reactions. Commercially available solvents and reagents were purchased from common chemical suppliers and used without further purification , unless stated otherwise.

Solvents

Diethyl ether (Et_2O), tetrahydrofuran (THF) and toluene were dried by distillation over sodium/benzophenone ketyl, whereas hexane was distilled from calcium hydride. Methanol (MeOH) was reacted in the presence of magnesium and iodine, distilled and kept over molecular sieves. Dichloromethane (CH_2Cl_2) was distilled from calcium hydride prior to use. Petroleum ether refers to the 40-60 ^oC boiling fraction. Acetonitrile (CH_3CN) was kept over molecular sieves at least 24 hours prior to use.

Column chromatography

The purification of the reaction mixtures was performed by column chromatography with silica gel (Acros, particle size 0.035-0.070 mm, pore diameter ca. 6 nm). Solvent systems were determined via thin layer chromatography (TLC) on glass plates coated with silica gel (Merck, Kieselgel 60 F_{254}, precoated 0.25 mm) using standard visualization techniques or agents: UV fluorescence (254 nm and 366 nm) and coloring with iodine vapors or with potassium permanganate solution.

Liquid chromatography

Liquid chromatography analysis was performed by a reverse phase LC-column (Eclipse plus C18 column). The LC column has dimensions of 50 x 4.6 mm and has a particle size of 3.5 µm. Gradient elution was used (30% acetonitrile in water to 100% acetonitrile over 6 minutes).

Chiral HPLC analysis was performed using a Daicel Chiralcel IA column [amylose tris (3,5-dimethylphenylcarbamate) immobilised on 5 µm silica gel] or IB column [cellulose tris (3,5-dimethylphenylcarbamate) immobilised on 5 µm silica gel] and with a solvent mixture of hexane/ethanol as the mobile phase.

Mass spectrometry

Low-resolution mass spectra were recorded using a direct inlet system with an Agilent 1100 series LC/MSD type SL with a UV detector and mass spectrometer with electrospray ionisation geometry (ESI 70 eV) using a Mass Selective Detector (quadrupole).

High-resolution mass spectra were obtained using an Agilent 1100 series HPLC coupled to an Agilent 6210 TOF-Mass Spectrometer, equipped with ESI/APCI-multimode source.

NMR spectroscopy

^{1}H (300 or 400 MHz), ^{13}C (75 or 100.6 MHz) and ^{19}F-NMR (376.5 or 282 MHz) NMR spectra were recorded on a Jeol Eclipse FT 300 NMR spectrometer or a Bruker Avance III Nanobay 400 MHz spectrometer at room temperature. Peak assignments were obtained with the aid of DEPT, COSY, HSQC and/or HMBC spectra. The compounds were diluted in deuterated solvents, quoted in parts per million (ppm) with tetramethylsilane (TMS) and trichlorofluoromethane ($CFCl_3$) as internal standards.

Infrared spectroscopy

IR spectra were recorded with a Perkin–Elmer Spectrum One FTIR spectrometer with an ATR (Attenuated Total Reflectance) accessory in neat form.

Melting point

Melting points were measured using a Kofler bench, type WME Heizbank of Wagner & Munz.

Optical rotation

Optical rotations were measured with a Jasco P-2000 polarimeter.

Microwave irradiation

All microwave reactions were performed in a CEM *Focused Microwave™ Synthesis System*, Model Discover, with a continuous 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 ^{o}C by adjusting the power output (1 Watt increments). The pressure control *IntelliVent™ Pressure control system*, used an direct measurement of the pressure by sensing changes in the external deflection of the septa on the top of 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 ^{o}C to 40 ^{o}C in less than 120 seconds.

X-ray analysis

X-ray intensity data were collected on a Agilent Supernova Dual Source (Cu at zero) diffractometer equipped with an Atlas CCD detector using CuKα radiation (λ = 1.54178 Å) and ω scans. The images were interpreted and integrated with the program CrysAlisPro (Agilent Technologies).[231] Using Olex2,[232] 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.[233] 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 and the hydroxyl group).

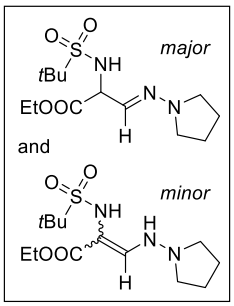
CCDC-1046634-1046639 and 1400317 contains the supplementary crystallographic data for the Section 3.2.3 and can be obtained free of charge *via* www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44-1223-336033; or deposit@ccdc.cam.ac.uk).

All X-ray diffraction analyzes were performed in collaboration with Prof. Dr. K. Van Hecke, XStruct, Department of inorganic and Physical Chemistry, Ghent University, Belgium.

5.2 Synthetic procedures

5.2.1 Synthesis of ethyl 2-((1,1-dimethylethyl)sulfonamido)-3-(pyrrolidin-1-ylimino)propanoate 300 and ethyl 2-((1,1-dimethylethyl)sulfonamido)-3-(pyrrolidin-1-ylamino)acrylate 313

To a solution of ethyl 2-((*tert*-butylsulfonyl)imino)acetate **298** (1.0 equiv, 4.52 mmol, 1.00 g) in $CHCl_3$ (15 mL) was slowly added *N*-(pyrrolidin-1-yl)methanimine **12** (1.0 equiv, 4.52 mmol, 0.44 g) at room temperature. The reaction mixture was stirred at ambient temperature for 1 hour. Subsequently, the solvent was removed *in vacuo* and the crude mixture was purified by column chromatography, affording an equilibrium mixture of 2-((1,1-dimethylethyl)sulfonamido)-3-(pyrrolidin-1-ylimino)propanoate **300** (major) and ethyl 2-((1,1-dimethylethyl)sulfonamido)-3-(pyrrolidin-1-ylamino)acrylate **313** (minor) in a ratio of 76/24 and in 87% yield.

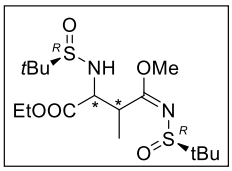


R_f = 0.60 (PE/EtOAc 1/3). Brown oil, yield 87%. **IR** (cm^{-1}): ν_{max} 1152, 1292, 1493, 1740, 3256. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 1.18-1.33 (6H, m, 2 x OCH_2CH_3), 1.45 (9H, s, tBu$_{major}$), 1.46 (9H, s, tBu$_{minor}$), 1.78-1.85 (4H, m, $CH_2CH_2CH_2CH_{2,minor}$), 1.86-1.94 (4H, m, $CH_2CH_2CH_2CH_{2,major}$), 2.82-2.93 (4H, m, $CH_2CH_2CH_2CH_{2,minor}$), 3.12-3.22 (4H, m, $CH_2CH_2CH_2CH_{2,major}$), 4.09-4.29 (4H, m, 2 x $OCH_2CH_{3,major\ and\ minor}$), 4.79 (1H, d, J = 3.9 Hz, CHNH$_{major}$), 6.38 (1H, d, J = 3.9 Hz, CH=N$_{major}$), 6.77 (1H, d, J = 11.0 Hz, CHNH$_{minor}$), 7.68 (1H, d, J = 11.0 Hz, CHNH_{minor}). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 14.2 ($OCH_2CH_{3,major}$), 14.6 ($OCH_2CH_{3,minor}$), 21.9 (2C, $CH_2CH_2CH_2CH_{2,minor}$), 23.5 (2C, $CH_2CH_2CH_2CH_{2,major}$), 24.2 (3C, tBu$_{major}$), 24.5 (3C, tBu$_{minor}$), 50.9 (2C, $CH_2CH_2CH_2CH_{2,major}$), 56.9 (2C, $CH_2CH_2CH_2CH_{2,minor}$), 57.1 (2 x C$_{quat}$, tBu$_{major\ and\ minor}$), 58.5 ($CHNH_{major}$), 61.9 ($OCH_2CH_{3,minor}$), 62.3 ($OCH_2CH_{3,major}$), 124.9 (CH=N$_{major}$), 129.5 (C=CH_{minor}), 146.1 (C=CH$_{minor}$), 170.4 (C=O$_{major\ and\ minor}$). **MS** (ES, pos mode) *m/z* (%): 320 (100) $[M + H]^+$.

5.2.2 Synthesis of ethyl 2-(sulfinylamino)-4-(sulfinylimino)-4-methoxybutanoates 301

The synthesis of **301a** is representative. A solution of imidate **13a** (1.0 equiv, 1.57 mmol, 0.30 g) in THF (6 mL) was cooled to -78 °C under nitrogen atmosphere. A 1M solution of LiHMDS (1.2 equiv, 1.88 mL, 1.88 mmol) in THF was slowly added and the resulting solution was stirred at the same temperature for 45 minutes. After deprotonation, a solution of (R_S)-iminoacetate **297** (1.2 equiv, 1.88 mmol, 0.39 g) in THF (6 mL) was added dropwise and the reaction mixture was stirred additionally for 1 hour. Subsequently, the reaction was quenched with a saturated solution of NH_4Cl (2 mL) and was brought to room temperature. To the reaction mixture 10 mL of saturated $NaHCO_3$ was added followed by extraction with EtOAc (3 x 8 mL). The combined organic phases were dried ($MgSO_4$), filtered and evaporated *in vacuo*. Purification by column chromatography afforded two diastereomers of **301a** in 18% and 9% yield. The stereochemistry was not established.

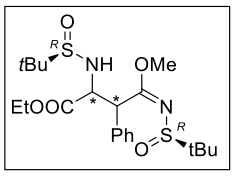
(R_S, R_S)-Ethyl 2-(*tert*-butylsulfinylamino)-4-(*tert*-butylsulfinylimino)-4-methoxy-3-methylbutanoate 301a



*Major isomer **301a***: R_f = 0.19 (PE/Et_2O 1/1). White amorphous solid, yield 18%. **[α]$_D$** -137.3 (*c* 0.6, $CHCl_3$). **IR** (cm^{-1}): ν_{max} 1057, 1257, 1603, 1734, 3228. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.19 (9H, s, tBu), 1.22 (9H, s, tBu), 1.23 (3H, d, J = 6.1 Hz, $CHCH_3$), 1.31 (3H, t, J = 7.2 Hz, OCH_2CH_3), 3.74 (3H, s, OCH_3), 3.71-3.83 (1H, m, $CHCH_3$), 4.01 (1H, dd, J = 9.9, 10.5 Hz, CHNH), 4.09 (1H, d, J = 10.5 Hz, CHNH), 4.25 (2H, q, J = 7.2 Hz, OCH_2CH_3). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ 14.2 (OCH_2CH_3), 15.1 ($CHCH_3$), 22.0 (3C, tBu), 22.6 (3C, tBu), 41.6 ($CHCH_3$), 54.3 (OCH_3), 56.1 (C$_{quat}$, tBu), 56.2 (C$_{quat}$, tBu), 61.5 ($CHNH$), 62.0 (OCH_2CH_3), 171.8 (C=N), 175.0 (C=O). **MS** (ES, pos mode) *m/z* (%): 397 (100) $[M + H]^+$.

*Minor isomer **301a***: R_f = 0.07 (PE/Et_2O 1/1). White amorphous solid, yield 9%. **[α]$_D$** -111.6 (*c* 0.7, $CHCl_3$). **IR** (cm^{-1}): ν_{max} 1041, 1090, 1181, 1292, 1607, 1736, 3164. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.21 (9H, s, *t*Bu), 1.24 (6H, m, OCH_2CH_3 and $CHCH_3$), 1.26 (9H, s, *t*Bu), 3.68 (1H, m, $CHCH_3$), 3.75 (3H, s, OCH_3), 4.18-4.29 (3H, m, OCH_2CH_3 and CHNH), 4.37 (1H, d, *J* = 7.7 Hz, CHNH). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ 14.1 and 15.1 (OCH_2CH_3 and $CHCH_3$), 22.0 (3C, *t*Bu), 22.8 (3C, *t*Bu), 41.6 ($CHCH_3$), 54.2 (OCH_3), 56.2 (C_{quat}, *t*Bu), 56.5 (C_{quat}, *t*Bu), 59.9 (CHNH), 62.3 (OCH_2CH_3), 171.3 (C=N), 174.4 (C=O). **MS** (ES, pos mode) *m/z* (%): 397 (100) $[M + H]^+$.

(*R*$_S$, *R*$_S$)-Ethyl 2-(*tert*-butylsulfinylamino)-4-(*tert*-butylsulfinylimino)-4-methoxy-3-phenylbutano-ate 301b



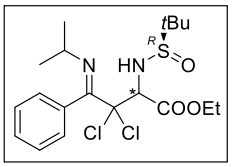
*Major isomer **301b***: R_f = 0.26 (PE/Et_2O 1/9). Pale yellow oil, yield 8%. **[α]$_D$** -247.2 (*c* 0.2, $CHCl_3$). **IR** (cm^{-1}): ν_{max} 1074, 1247, 1613, 1742, 3304. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.94 (3H, t, *J* = 7.1 Hz, OCH_2CH_3), 1.20 (9H, s, *t*Bu), 1.25 (9H, s, *t*Bu), 3.85 (3H, s, OCH_3), 3.88-3.94 (2H, m, OCH_2CH_3), 4.61 (1H, dxd, *J* = 11.2, 8.4 Hz, CHNH), 5.11 (1H, d, *J* = 11.2 Hz, CHPh), 5.26 (1H, d, *J* = 8.4 Hz, CHNH), 7.28-7.35 (3H, m, 3 x CH_{arom}), 7.41-7.45 (2H, m, 2 x CH_{arom}). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ 13.8 (OCH_2CH_3), 22.0 (3C, *t*Bu), 22.6 (3C, *t*Bu), 52.0 (CHPh), 55.3 (OCH_3), 56.5 (C_{quat}, *t*Bu), 56.7 (C_{quat}, *t*Bu), 61.0 (OCH_2CH_3), 61.5 (CHNH), 128.4 (CH_{arom}), 128.7 (2 x CH_{arom}), 128.8 (2 x CH_{arom}), 134.0 ($C_{arom,quat}$), 170.2 (C=N), 171.5 (C=O). **MS** (ES, pos mode) *m/z* (%): 459 (100) $[M + H]^+$.

*Minor isomer **301b***: R_f = 0.11 (PE/Et_2O 1/9). Pale yellow oil, yield 6%. **[α]$_D$** -129.6 (*c* 0.2, $CHCl_3$). **IR** (cm^{-1}): ν_{max} 1077, 1245, 1614, 1739, 3195. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.87 (9H, s, *t*Bu), 1.12 (9H, s, *t*Bu), 1.30 (3H, t, *J* = 7.1 Hz, OCH_2CH_3), 3.80 (3H, s, OCH_3), 3.98 (1H, d, *J* = 8.8 Hz, CHNH), 4.25 (2H, q, *J* = 7.1 Hz, OCH_2CH_3), 4.63 (1H, dxd, *J* = 10.2, 8.8 Hz, CHNH), 4.93 (1H, d, *J* = 10.2 Hz, CHPh), 7.23-7.39 (5H, m, 5 x CH_{arom}). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ 14.1 (OCH_2CH_3), 21.9 (3C, *t*Bu), 22.1 (3C, *t*Bu), 52.0 (CHPh), 55.4 (OCH_3), 56.1 (C_{quat}, *t*Bu), 56.4 (C_{quat}, *t*Bu), 60.2 (CHNH), 62.3 (OCH_2CH_3), 128.0 (CH_{arom}), 128.7 (2 x CH_{arom}), 129.7 (2 x CH_{arom}), 134.9 ($CH_{arom,quat}$), 170.6 (C=N), 171.1 (C=O). **MS** (ES, pos mode) *m/z* (%): 459 (100) $[M + H]^+$

5.2.3 Synthesis of (*R*$_S$)-ethyl 2-(*tert*-butylsulfinylamino)-3,3-dichloro-4-(isopropyl-imino)-4-phenylbutanoate 303a

To a flame dried round-bottomed flask with freshly distilled diisopropylamine (1.1 equiv, 14.4 mmol, 14 mL) in dry THF (5 mL) was added *n*BuLi (2.3M solution in hexane) (1.1 equiv, 14.4 mmol, 6.3 mL) under nitrogen atmosphere. The reaction mixture was stirred for 30 minutes at 0 °C. Subsequently, a solution of α,α-dichloroketimine **14a** (1.0 equiv, 13.10 mmol, 3.00 g) in dry THF (30 mL) was slowly added and the resulting solution was stirred at 0 °C for 40 minutes and was subsequently cooled to -40 °C. After 5 minutes, a solution of iminoacetate **297** (1.2 equiv, 15.67

mmol, 3.21 g) in dry THF (10 mL) was slowly added and the resulting solution was stirred at the same temperature for 1 hour. The reaction mixture was quenched with a saturated solution of NH_4Cl (6 mL) and was slowly warmed to room temperature followed by an extraction with EtOAc (3 x 30 mL). The combined organic phases were dried ($MgSO_4$), filtered and evaporated *in vacuo*. The crude product was purified by column chromatography to yield **303a** in 80% yield.

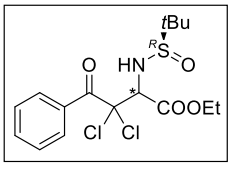


R_f = 0.19 (PE/Et_2O 1/1). Red oil, yield 80%. **[α]$_D$** -24.6 (*c* 0.9, $CHCl_3$). **IR** (cm^{-1}): ν_{max} 1085, 1186, 1740, 3240. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.04 (6H, 2 x d, *J* = 6.1 Hz, 2 x $CH(CH_3)_2$), 1.31 (9H, s, *t*Bu), 1.36 (3H, t, *J* = 7.2 Hz, OCH_2CH_3), 3.27 (1H, sep, *J* = 6.1 Hz, $CH(CH_3)_2$), 4.20-4.36 (2H, m, OCH_2CH_3), 4.88 (1H, d, *J* = 9.4 Hz, HN*H*), 5.19 (1H, d, *J* = 9.4 Hz, C*H*NH), 7.24-7.30 (2H, m, 2 x CH_{arom}), 7.39-7.46 (3H, m, 3 x CH_{arom}). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ 14.1 (2C, $CH(CH_3)_2$), 15.4 (OCH_2CH_3), 23.0 (3C, *t*Bu), 53.5 ($CH(CH_3)_2$), 57.3 (C_{quat}, *t*Bu), 62.2 (OCH_2CH_3), 66.7 (*C*HNH), 89.8 (CCl_2), 128.1 (2 x CH_{arom}), 128.4 (2 x CH_{arom}), 129.1 (CH_{arom}), 133.2 ($C_{arom,quat}$), 163.8 (C=N), 169.1 (C=O). **MS** (ES, pos mode) *m/z* (%): 435/437/439 (100) $[M + H]^+$.

5.2.4 Synthesis of (*R*$_S$)-ethyl 2-(*tert*-butylsulfinylamino)-3,3-dichloro-4-oxo-4-phenylbutanoate 319 and (*R*$_S$)-ethyl 2-(*tert*-butylsulfinylamino)-3-chloro-4-oxo-4-phenylbut-2-enoate 320

To a solution of (*R*$_S$)-ethyl 2-(*tert*-butylsulfinylamino)-3,3-dichloro-4-(isopropylimino)-4-phenylbutanoate **303a** (2.17 mmol, 0.94 g) in THF (25 mL) was added 2M HCl (25 mL) at room temperature. The reaction mixture was stirred at room temperature for 30 minutes and subsequently was cooled to 0 ºC. After 5 minutes, 2M NaOH was added until pH=8. The aqueous phase was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic phases were dried ($MgSO_4$), filtered and evaporated *in vacuo*, affording the α,α-dichloroketone **319**. The purification of the crude product by column chromatography (PE/Et_2O 1/1, R_f = 0.20, silica gel) triggered the dehydrochlorination reaction to give product **320** in yield of 51%.

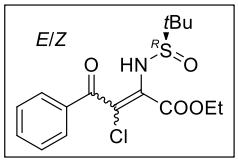
(*R*$_S$)-Ethyl 2-(*tert*-butylsulfinylamino)-3,3-dichloro-4-oxo-4-phenylbutanoate 319



R_f = 0.49 (PE/EtOAc 1/2). Brown oil, yield 91% (crude). **[α]$_D$** -28.1 (*c* 0.7, $CHCl_3$). IR (cm^{-1}): ν_{max} 690, 1079, 1185, 1241, 1695, 1741, 3145. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.28 (9H, s, *t*Bu), 1.29 (3H, t, *J* = 7.2 Hz, OCH_2CH_3), 4.18-4.36 (2H, m, OCH_2CH_3), 4.58 (1H, d, *J* = 8.3 Hz, CHN*H*), 5.13 (1H, d, *J* = 8.3 Hz, C*H*NH), 7.45-7.66 (5H, m, 5 x CH_{arom}). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ 13.9 (OCH_2CH_3), 22.7 (3C, *t*Bu), 57.2 (C_{quat}, *t*Bu), 63.0 (OCH_2CH_3), 65.6 (*C*HNH), 86.6 (CCl_2), 128.3 (2 x CH_{arom}), 130.3 (2 x CH_{arom}), 132.3 ($C_{arom,quat}$), 133.6 (CH_{arom}), 167.7 (C=O), 187.5 (C=O). **MS** (ES,

pos mode) *m/z* (%): 394/396/398 (100) $[M + H]^+$. **HRMS**: calcd. for $C_{16}H_{22}Cl_2NO_4S^+$ $[MH]^+$ 394.0641; found: 394.0657.

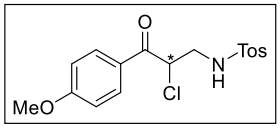
(R_S)-Ethyl 2-(*tert*-butylsulfinylamino)-3-chloro-4-oxo-4-phenylbut-2-enoate 320



R_f = 0.14 (PE/Et_2O 6/4). Yellow oil, yield 51%. **IR** (cm^{-1}): ν_{max} 696, 1089, 1259, 1545, 1735, 3061. <u>*Isomer 1 (major)*</u>: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.06 (3H, t, J = 7.2 Hz. OCH_2CH_3), 1.38 (9H, s, *t*Bu), 4.04-4.14 (2H, m, OCH_2CH_3), 6.10 (1H, s, N*H*), 7.34-7.52 (3H, m, 3 x CH_{arom}), 7.85-7.89 (2H, m, 2 x CH_{arom}). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ 13.4 (OCH_2CH_3), 22.3 (3C, *t*Bu), 58.2 (C_{quat}, *t*Bu), 63.1 (OCH_2CH_3), 118.7 (Cl*C*=C), 128.7 (2 x CH_{arom}), 129.5 (2 x CH_{arom}), 133.6 (CH_{arom}), 135.6 ($C_{arom,quat}$), 143.3 (ClC=*C*), 161.5 (C=O), 188.3 (C=O). **MS** (ES, pos mode) *m/z* (%): 358/360 (100) $[M + H]^+$. **HRMS**: calcd. for $C_{16}H_{21}ClNO_4S^+$ $[M + H]^+$ 358.0874; found: 358.0884. <u>*Isomer 2 (minor)*</u>: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.36 (9H, s, *t*Bu), 1.44 (3H, t, J = 7.2 Hz. OCH_2CH_3), 4.42-4.53 (2H, m, OCH_2CH_3), 7.56-7.62 (3H, m, 3 x CH_{arom}), 7.65-7.74 (2H, m, 2 x CH_{arom}), 11.31 (1H, s, N*H*). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ 14.1 (OCH_2CH_3), 22.3 (3C, *t*Bu), 58.5 (C_{quat}, *t*Bu), 63.3 (OCH_2CH_3), 126.9 (Cl*C*=C), 128.0 (2 x CH_{arom}), 128.5 (2 x CH_{arom}), 132.0 (CH_{arom}), 135.3 ($C_{arom,quat}$), 149.2 (ClC=*C*), 161.0 (C=O), 194.9 (C=O). **MS** (ES, pos mode) *m/z* (%): 358/360 (100) $[M + H]^+$. **HRMS**: calcd. for $C_{16}H_{21}ClNO_4S^+$ $[MH]^+$ 358.0874; found: 358.0884.

5.2.5 Synthesis of *N*-(2-chloro-3-(4-methoxyphenyl)-3-oxopropyl)-4-methylbenzene-sulfonamide 328b

To a solution of (*2R,3S*)-3-chloro-2-(4-methoxyphenyl)-1-tosylazetidine **22b** (92.6 mg, 0.26 mmol) in CCl_4 (1 mL), CH_3CN (1 mL) and deionized water (1 mL), periodic acid (H_5IO_6) (10 equiv, 593 mg, 2.6 mmol) was added and the flask contents were stirred until both phases became clear. To the mixture was slowly added ruthenium(III) chloride (0.05 equiv, 2.7 mg, 0.01 mmol) at 0 °C, and the reaction mixture was vigorously stirred for 2.5 hours at room temperature. After, the reaction mixture was cooled to 0 °C and diethyl ether was added with vigorous stirring for 20 minutes. The organic phase was separated and the aqueous phase extracted with EtOAc (2 x 3 mL). The combined organic phases were washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude mixture was purified by thin layer chromatography to yield the *N*-(2-chloro-3-(4-methoxyphenyl)-3-oxopropyl)-4-methylbenzenesulfonamide **328b**.

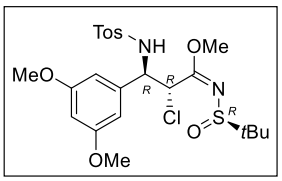


R_f = 0.19 (PE/Et_2O 8/2). Yellow oil, yield 10%. **IR** (cm^{-1}): ν_{max} 1115, 1239, 1724, 3318. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.32 (3H, s, CH_3), 3.42-3.68 (2H, m, CH_2CHCl),4.01 (3H, s, OCH_3), 5.10 (1H, d, J = 7.71 Hz, C*H*Cl), 5.12 (1H, d, J = 8.26, N*H*), 7.00 (2H, d, J = 8.81 Hz, 2 x CH_{arom}), 7.31 (2H, d, J = 8.26 Hz, 2 x CH_{arom}), 7.74 (2H, d, J = 8.26 Hz, 2 x CH_{arom}), 7.89 (2H, d, J = 8.81 Hz, 2 x CH_{arom}). **^{13}C NMR** (100.6

MHz, $CDCl_3$): δ 21.6 (CH_3), 45.0 (CH_2NH), 53.4 (OCH_3), 55.7 ($CHCl$), 114.2 (2 x CH_{arom}), 126.7 ($C_{arom,quat}$), 127.1 (2 x CH_{arom}), 130.0 (2 x CH_{arom}), 131.8 (2 x CH_{arom}), 137.0 ($C_{arom,quat}$), 143.9 ($C_{arom,quat}$), 164.6 ($C_{arom,quat}$), 191.2 (C=O). **MS** (ES, pos mode) *m/z* (%): 368 (100) $[M + H]^+$.

5.2.6 Synthesis of (R_S,*R*,*R*,)-methyl *N*-(*tert*-butylsulfinyl)-2-chloro-3-[(3,5-dimethoxyphenyl)(*p*-toluenesulfonylamino)methyl]propanimidate (R_S,*R*,*R*)-*anti*-325c

A solution of (R_S)-methyl *N*-*tert*-butanesulfinyl-2-chloroethanimidate (R_S)-**324** (1.5 equiv, 0.40 g, 1.9 mmol) in THF (5 mL) was cooled to -78 °C. A 1M solution of LiHMDS (1.5 equiv, 1.9 mL, 1.90 mmol) in THF was slowly added, and the resulting solution was stirred for 45 minutes at -78 °C. After deprotonation, a solution of *N*-(3,5-dimethoxybenzylidene)-4-methylbenzenesulfonamide **330** (1.0 equiv, 0.40 g, 1.26 mmol) in THF (5 mL) was added dropwise, and the reaction mixture was stirred at -78 ºC for 1 hour. To the reaction mixture was added a saturated solution NH_4Cl (2 mL), followed by a saturated solution of $NaHCO_3$ (10 mL). The aqueous phase was extracted with Et_2O (3 x 10 mL). The combined organic phases were dried ($MgSO_4$), filtered, and evaporated *in vacuo*. The crude product was purified by flash chromatography to yield 0.22 g (0.42 mmol, 33% yield) of pure (R_S,*R*,*R*,)-methyl *N*-(*tert*-butylsulfinyl)-2-chloro-3-[(3,5-dimethoxyphenyl)(*p*-toluenesulfonylamino)methyl]propanimidate (R_S,*R*,*R*)-*anti*-**325c**.



R_f = 0.13 (PE/Et_2O 7/3). Colorless oil, yield 33%. $[\alpha]_D$ -131.5 (*c* 0.3, $CHCl_3$). **IR** (cm^{-1}): ν_{max} 1058, 1154, 1157, 1295, 1456, 1598, 3105. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.40 (9H, s, *t*Bu), 2.29 (3H, s, CH_3), 3.67 (6H, s, 2 x OCH_3), 3.86 (3H, s, OCH_3), 4.54 (1H, t, *J* = 9.9 Hz, CHNH), 5.39 (1H, d, *J* = 9.9 Hz, C*H*Cl), 6.21 (1H, s, CH_{arom}), 6.24 (2H, s, CH_{arom}), 6.73 (1H, d, *J* = 9.9 Hz, CHN*H*), 7.00 (2H, d, *J* = 8.0 Hz, 2 x CH_{arom}), 7.38 (2H, d, *J* = 8.0 Hz, 2 x CH_{arom}). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ 21.4 (CH_3), 22.2 (3C, *t*Bu), 55.3 (2 x OCH_3), 55.6 (OCH_3), 56.7 (C_{quat}, *t*Bu), 58.2 (*C*HCl), 60.6 (*C*HNH), 100.2 (CH_{arom}), 105.8 (2 x CH_{arom}), 127.0 (2 x CH_{arom}), 128.9 (2 x CH_{arom}), 137.9 ($C_{arom,quat}$), 139.0 ($C_{arom,quat}$), 142.7 ($C_{arom,quat}$), 160.7 (2 x $C_{arom,quat}$), 167.1 (C=N). **MS** (ES, pos mode) *m/z* (%): 531/533 (100) $[M + H]^+$.

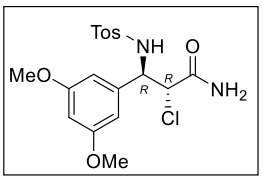
5.2.7 Synthesis of (*R*,*R*)-methyl-2-chloro-3-(3,5-dimethoxyphenyl)-3-[(4-methylphenyl)sulfonamido]propanoate 326c and (*R*,*R*)-2-chloro-3-(3,5-dimethoxyphenyl)-3-[(4-methylphenyl)sulfonamido]propanamide 331

Method A. To a solution of (R_S,*R*,*R*)-**325c** (0.38 g, 0.73 mmol) in MeOH (5 mL) was added a 3M solution of HCl in dioxane (30.0 equiv, 7.3 mL, 21.90 mmol) at room temperature. The mixture was allowed to stir for 18 hours at room temperature. Subsequently, the reaction mixture was poured into a saturated aqueous solution of $NaHCO_3$ (10 mL) and extracted with EtOAc (3 x 10 mL). The

combined organic phases were dried ($MgSO_4$), filtered and evaporated *in vacuo*. The crude mixture was purified by flash cromatography to yield pure ester (*R*,*R*)-*anti*-**326c** (23%) and amide (*R*,*R*)-*anti*-**331** (67%).

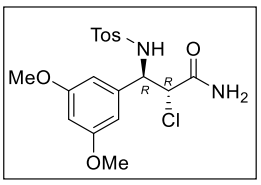
Method B (only for (*R*,*R*)-**331**). To a solution of (*R*$_S$,*R*,*R*)-**325c** (0.11 g, 0.21 mmol) in dioxane (3 mL) was added a 3M solution of HCl in dioxane (15.0 equiv, 1.03 mL, 3.11 mmol) at room temperature. The mixture was allowed to stir for 1 h at room temperature. Subsequently, the reaction mixture was concentrated *in vacuo*. Precipitation in diethyl ether/hexane (1:1) afforded pure (*R*,*R*)-*anti*-propanamide **331**.

(*R*,*R*)-Methyl-2-chloro-3-(3,5-dimethoxyphenyl)-3-[(4-methylphenyl)sulfonamido]propanoate 326c



R_f = 0.34 (PE/Et_2O 1/1). Pale yellow oil, yield 23% (method A). **[α]$_D$** -18.3 (*c* 0.3, $CHCl_3$). **IR** (cm^{-1}): ν_{max} 1154, 1332, 1598, 1747, 3264. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.34 (3H, s, C*H*$_3$), 3.66 (6H, s, 2 x C*H*$_3$), 3.70 (3H, s, OC*H*$_3$), 4.54 (1H, d, *J* = 6.6 Hz, C*H*Cl), 4.79 (1H, 2 x d, *J* = 7.15, 6.6 Hz, C*H*NH), 5.15 (1H, d, *J* = 7.15 Hz, CHN*H*), 6.20 (2H, s, 2 x C*H*$_{arom}$), 6.26 (1H, s, C*H*$_{arom}$), 7.19 (2H, d, *J* = 8.26 Hz, 2 x C*H*$_{arom}$), 7.58 (2H, d, *J* = 8.26 Hz, 2 x CH$_{arom}$). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ 21.5 (*C*H$_3$), 53.3 (O*C*H$_3$), 55.3 (2 x O*C*H$_3$), 58.9 (*C*HCl), 60.2 (*C*HNH), 100.6 (CH$_{arom}$), 105.2 (2 x CH$_{arom}$), 126.5 (CH$_{arom}$), 127.2 (CH$_{arom}$), 129.4 (CH$_{arom}$), 129.8 (CH$_{arom}$), 137.3 (C$_{arom,quat}$), 137.9 (C$_{arom,quat}$), 143.5 (C$_{arom,quat}$), 160.8 (2 x C$_{arom,quat}$), 168.2 (C=N). **MS** (ES, pos mode) *m/z* (%): 428/430 (100) $[M + H]^+$.

(*R*,*R*)-2-chloro-3-(3,5-dimethoxyphenyl)-3-[(4-methylphenyl)sulfonamido]propanamide 331

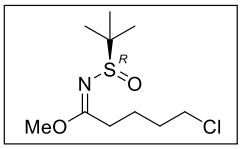


R_f = 0.05 (PE/Et_2O 1/2). White crystals, yield 67% (method A), yield 83% (method B). **Mp** 154.5-155.0 ºC. **[α]$_D$** -21.8 (*c* 0.4, DMF). **IR** (cm^{-1}): ν_{max} 1161, 1315, 1595, 1676, 3409, 3433. **^{1}H NMR** (400 MHz, $DMSO_{d6}$): δ 2.24 (3H, s, C*H*$_3$), 3.60 (6H, s, 2 x OC*H*$_3$), 4.33 (1H, d, *J* = 9.4 Hz, C*H*Cl), 4.67 (1H, t, *J* = 9.4 Hz, C*H*NH), 6.18 (1H, s, C*H*$_{arom}$), 6.24 (2H, s, 2 x C*H*$_{arom}$), 7.06 (2H, d, *J* = 8.3 Hz, 2 x C*H*$_{arom}$), 7.36 (2H, d, *J* = 8.3 Hz, 2 x C*H*$_{arom}$), 7.46 (1H, br s, N*H*(H)), 7.69 (1H, br s, N*H*(H)), 8.28 (1H, d, *J* = 9.4 Hz, CHN*H*). **^{13}C NMR** (100.6 MHz, $DMSO_{d6}$): δ 21.4 (*C*H$_3$), 55.6 (2 x O*C*H$_3$), 60.3 (*C*HCl), 60.4 (*C*HNH), 99.6 (CH$_{arom}$), 106.6 (2 x CH$_{arom}$), 127.0 (2 x CH$_{arom}$), 129.3 (2 x CH$_{arom}$), 138.7 (C$_{arom,quat}$), 139.4 (C$_{arom,quat}$), 142.6 (C$_{arom,quat}$), 160.4 (2 x C$_{arom,quat}$), 168.6 (C=N). **MS** (ES, pos mode) *m/z* (%): 413/415 (100) $[M + H]^+$.

5.2.8 Synthesis of (*E*)-methyl *N*-sulfinyl-5-chloropentanimidates (R_S)-26a-c

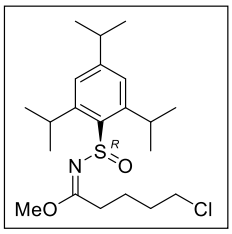
The synthesis of (R_S)-methyl *N*-*tert*-butanesulfinyl-5-chloropentanimidate (R_S)-**26a** is representative. To a round-bottomed flask charged with (R_S)-*tert*-butanesulfinamide (R_S)-**306** (13.17 g, 108.84 mmol) were added 5-chloro-1,1,1-trimethoxypentane **338** (1.5 equiv, 32.00 g, 163.96 mmol) and *p*-toluenesulfonic acid monohydrate (0.005 equiv, 0.10 g, 0.54 mmol). The reaction mixture was stirred for 20 h at 100 °C, and the volatile materials were removed *in vacuo*. The crude oil was purified *via* flash chromatography to yield pure (R_S)-methyl *N*-*tert*-butanesulfinyl-5-chloropentanimidate (R_S)-**26a**.

(*E*)-(R_S)-Methyl *N*-*tert*-butanesulfinyl-5-chloropentanimidate (R_S)-26a



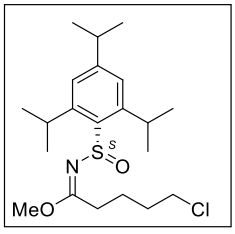
R_f = 0.15 (PE/Et_2O 1/1). Yellow oil, yield 87%. **[α]$_D$** -104.5 (*c* 0.4, $CHCl_3$). **IR** (cm^{-1}): ν_{max} 1074, 1282, 1607, 2948. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.20 (9H, s, *t*Bu), 1.74-1.88 (4H, m, CH_2CH_2CH_2Cl), 2.63-2.74 (2H, m, CH_2C=N), 3.51-3.60 (2H, m, CH_2Cl), 3.75 (3H, s, OCH_3). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ 21.8 (3C, *t*Bu), 23.5 (*C*H_2CH_2CH_2Cl), 31.7 (CH$_2$*C*H_2CH_2Cl), 31.9 (*C*H_2C=N), 44.2 (*C*H_2Cl), 54.1 (O*C*H_3), 55.8 (C_q, *t*Bu), 176.0 (*C*=N). **MS** (ES, pos mode) *m/z* (%): 254/256 (100) $[M + H]^+$. **HRMS**: calcd. for $C_{10}H_{21}ClNO_2S^+$ $[MH]^+$ 254.0976; found: 254.0974.

(*E*)-(*R*)-Methyl 5-chloro-*N*-[(2,4,6-triisopropylphenyl)sulfinyl]pentanimidate 26b



R_f = 0.28 (PE/Et_2O 1/1). Yellow oil, yield 80%. **[α]$_D$** +10.2 (*c* 0.6, $CHCl_3$). **IR** (cm^{-1}): ν_{max} 1078, 1308, 1458, 1600. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.26 (12H, 2 x d, *J* = 6.8, 5.8 Hz, 2 x CH(CH_3)$_2$), 1.31 (6H, d, *J* = 6.8 Hz, CH(CH_3)$_2$), 1.79-1.86 (4H, m, CH_2CH_2CH_2Cl), 2.66-2.86 (2H, m, CH_2C=N), 2.89 (1H, sep, *J* = 6.8 Hz, C*H*(CH$_3$)$_2$), 3.51-3.58 (2H, m, CH_2Cl), 3.76 (3H, s, OCH_3), 4.07-4.20 (2H, m, 2 x C*H*(CH$_3$)$_2$), 7.09 (2H, s, 2 x CH$_{arom}$). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ 23.4 (*C*H_2CH_2Cl), 23.8 (CH(*C*H_3)$_2$), 24.5 (2 x CH(*C*H_3)$_2$), 28.6 (2 x *C*H(CH$_3$)$_2$), 31.7 (*C*H_2CH_2CH_2Cl), 32.0 (*C*H_2C=N), 34.5 (*C*H(CH$_3$)$_2$), 44.4 (*C*H_2Cl), 54.5 (O*C*H$_3$), 122.9 (2 x CH$_{arom}$), 138.4 (C$_{arom,quat}$), 143.9 (C$_{arom,quat}$) 152.4 (2 x C$_{arom,quat}$), 174.1 (C=N). **MS** (ES, pos mode) *m/z*: 400/402 (100) $[M + H]^+$.

(*E*)-(*S*)-Methyl 5-chloro-*N*-[(2,4,6-triisopropylphenyl)sulfinyl]pentanimidate 26c



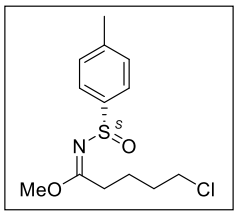
R_f = 0.28 (PE/Et_2O 1/1). Yellow oil, yield 76%. **[α]$_D$** -12.4 (*c* 0.5, $CHCl_3$). **IR** (cm^{-1}): ν_{max} 1078, 1308, 1458, 1600. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.26 (12H, 2 x d, *J* = 6.8, 5.8 Hz, 2 x CH(CH_3)$_2$), 1.31 (6H, d, *J* = 6.8 Hz, CH(CH_3)$_2$), 1.79-1.86 (4H, m, CH_2CH_2CH_2Cl), 2.66-2.86 (2H, m, CH_2C=N), 2.89 (1H, sep, *J* = 6.9 Hz, C*H*(CH$_3$)$_2$), 3.51-3.58 (2H, m, CH_2Cl), 3.76 (3H, s, OCH_3),

4.07-4.20 (2H, m, 2 x C*H*$(CH_3)_2$), 7.09 (2H, s, 2 x CH_{arom}). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ 23.4 (*C*H_2CH_2Cl), 23.8 (CH(*C*$H_3)_2$), 24.5 (2 x CH(*C*$H_3)_2$), 28.6 (2 x *C*H$(CH_3)_2$), 31.7 (*C*$H_2CH_2CH_2Cl$), 32.0 (*C*H_2C=N), 34.5 (*C*H$(CH_3)_2$), 44.4 (*C*H_2Cl), 54.5 (O*C*H_3), 122.9 (2 x CH_{arom}), 138.4 ($C_{arom,quat}$), 143.9 ($C_{arom,quat}$), 152.4 (2 x $C_{arom,quat}$), 174.1 (C=N). **MS** (ES, pos mode) *m/z*: 400/402 (100) $[M + H]^+$.

5.2.9 Synthesis of (*E*)-(*S*$_S$)-methyl 5-chloro-*N*-(p-tolylsulfinyl)pentanimidate 26d

To a solution of 5-chloro-1,1,1-trimethoxypentane **338** (0.50 g, 2.55 mmol) in dry CH_2Cl_2 (50 mL) was added (*S*$_S$)-*p*-tolylsulfinamide (*R*$_S$)-**216** (1.0 equiv, 0.16 g, 1.03 mmol), followed by addition of $MgSO_4$ (2.5 equiv, 0.31 g, 2.55 mmol). The reaction mixture was stirred for 3 h at room temperature. Subsequently, the reaction mixture was filtered through a Celite® pad and the filter cake was washed with a small amount of EtOAc. The solvent was evaporated and the crude mixture was purified by column chromatography, affording pure pentanimidate **26d**.

(*E*)-(*S*$_S$)-Methyl 5-chloro-*N*-(p-tolylsulfinyl)pentanimidate 26d



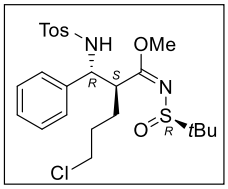
R_f = 0.19 (PE/Et_2O 6/4). Yellow oil, yield 61%. **[α]$_D$** +6.4 (*c* 0.6, $CHCl_3$). **IR** (cm^{-1}): ν_{max} 1076, 1286, 1610. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.80-1.89 (4H, m, C*H*$_2$C*H*$_2$CH$_2$Cl), 2.42 (3H, s, *p*C*H*$_3$), 2.76-2.82 (2H, m, C*H*$_2$C=N), 3.53-3.58 (2H, m, C*H*$_2$Cl), 3.78 (3H, s, OC*H*$_3$), 7.31 (2H, d, *J* = 8.3 Hz, 2 x CH_{arom}), 7.65 (2H, *J* = 8.3 Hz, 2 x CH_{arom}). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ 21.5 (*p*CH_3), 23.7 (*C*H_2CH_2Cl), 29.7 (*C*$H_2CH_2CH_2Cl$), 31.2 (*C*H_2C=N), 44.3 (*C*H_2Cl), 54.6 (O*C*H_3), 125.0 (2 x CH_{arom}), 129.7 (2 x CH_{arom}), 141.8 ($C_{quat,arom}$), 144.4 ($C_{arom,quat}$), 176.0 (C=N). **MS** (ES, pos mode) *m/z*: 288/290 (100) $[M + H]^+$.

5.2.10 Synthesis of δ-chloro-β-amino-*N*-sulfinyl imidates *anti*-339 and *anti*-340

The synthesis of (*R*$_S$,*S*,*R*)-δ-chloro-β-amino-(sulfonylamino)-*N*-sulfinyl imidates (*R*$_S$,*S*,*R*)-**339a** is representative. A solution of (*R*$_S$)-methyl *N*-*tert*-butanesulfinyl-5-chloropentanimidate (*R*$_S$)-**26a** (1.8 equiv, 2.00 g, 7.91 mmol) in THF (30 mL) was cooled to -78 °C. A 1M solution of LiHMDS (1.8 equiv, 7.91 mL, 7.91 mmol) in THF was slowly added, and the resulting solution was stirred for 45 minutes at -78 °C. After deprotonation, a solution of *N*-benzylidene-4-methylbenzenesulfonamide **27a** (1.0 equiv, 1.14 g, 4.39 mmol) in THF (10 mL) was added dropwise, and the reaction mixture was stirred at -78 ºC for 1 h. To the reaction mixture was added a saturated solution NH_4Cl (4 mL), followed by a saturated solution of $NaHCO_3$ (20 mL). The aqueous phase was extracted with Et_2O (3 x 20 mL). The combined organic phases were dried ($MgSO_4$), filtered, and evaporated *in vacuo*. The crude product was purified by flash chromatography to yield 1.95 g (7.23 mmol, 58% yield) of pure (*R*$_S$,*S*,*R*)-methyl 5-chloro-2-[(phenyl)(*p*-toluenesulfonylamino)methyl]-*N*-*tert*-

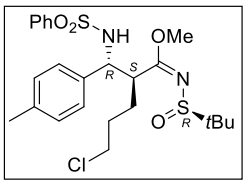
butanesulfinylpentanimidate (*R*$_S$,*S*,*R*)-*anti*-**339a**. In the synthesis of (*R*$_S$,*R*,*S*)-methyl 5-chloro-2-[(4-methoxyphenyl)(*p*-toluenesulfonylamino)methyl]-*N*-*tert*-butanesulfinylpentanimidate (*R*$_S$,*R*,*S*)-*anti*-**340b**, purification of the reaction mixture was performed *via* recrystallization from diethyl ether.

(*R*$_S$,*S*,*R*)-Methyl 5-chloro-2-[(phenyl)(*p*-toluenesulfonylamino)methyl]-*N*-*tert*-butanesulfinylpentanimidate (*R*$_S$,*S*,*R*)-339a



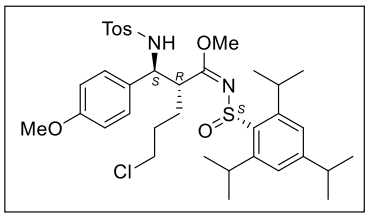
R_f = 0.09 (PE/Et_2O 1/1). White crystals, yield 58%. **Mp** 78.5-80.0 °C. **[α]$_D$** -89.4 (*c* 0.4, $CHCl_3$). **IR** (cm^{-1}): ν_{max} 1160, 1330, 1455, 1633, 2947. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.14 (9H, s, *t*Bu), 1.20-1.30 (1H, m, $CH_2CH(H)CH_2Cl$), 1.54-1.77 (3H, m, $CH(H)CH(H)CH_2Cl$), 2.30 (3H, s, *p*CH_3), 3.31-3.47 (2H, m, CH_2Cl), 3.74 (3H, s. OCH_3), 3.94 (1H, ddd, *J* = 13.7, 9.3, 4.2 Hz, $CHCH_2$), 4.48 (1H, d x d, *J* = 9.3, 9.8 Hz, C*H*NH), 5.67 (1H, d, *J* = 9.8 Hz, CHN*H*), 6.93-6.98 (2H, m, 2 x CH_{arom}), 7.03 (2H, d, *J* = 8.3 Hz, 2 x CH_{arom}), 7.07-7.12 (3H, m, 3 x CH_{arom}), 7.47 (2H, d, *J* = 8.3 Hz, 2 x CH_{arom}). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ 21.4 (*p*CH_3), 22.0 (3C, *t*Bu), 27.0 (CH_2CH_2Cl), 30.0 (CH_2CH), 44.4 (CH_2Cl), 47.7 (CH_2CH), 54.4 (OCH_3), 56.4 (C_q, *t*Bu), 60.0 (*C*HNH), 126.4 (2 x CH_{arom}), 127.0 (2 x CH_{arom}), 127.3 (CH_{arom}), 128.6 (2 x CH_{arom}), 129.2 (2 x CH_{arom}), 137.5 ($C_{arom,quat}$), 138.6 ($C_{arom,quat}$), 143.0 ($C_{arom,quat}$), 172.5 (C=N). **MS** (ES, pos mode) *m/z* (%): 513/515 (100) $[M + H]^+$. **HRMS**: calcd. for $C_{24}H_{34}ClN_2O_4S_2^+$ $[MH]^+$ 513.1643; found: 513.1655.

(*R*$_S$,*S*,*R*)-Methyl 5-chloro-2-[(benzenesulfonylamino)(*p*-tolyl)methyl]-*N*-*tert*-butanesulfinylpentanimidate (*R*$_S$,*S*,*R*)-339c



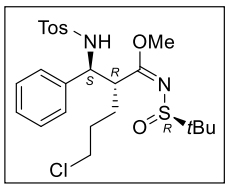
R_f = 0.07 (PE/Et_2O 1/1). White crystals, yield 45%. **Mp** 71.0-72.0 ºC. $[\alpha]_D$ -74.8 (*c* 0.4, $CHCl_3$). **IR** (cm^{-1}): ν_{max} 1039, 1163, 1242, 1326, 1447, 1633, 2958. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.79-0.93 (1H, m, C*H*(H)CH(H)CH_2Cl), 1.17 (9H, s, *t*Bu), 1.20-1.30 (1H, m, CH(H)C*H*(H)CH_2Cl), 1.63-1.76 (2H, m, CH(*H*)CH(*H*)CH_2Cl), 2.23 (3H, s, *p*CH_3), 3.30-3.45 (2H, m, CH_2Cl), 3.74 (3H, s, OCH_3), 3.89-4.01 (1H, m, $CHCH_2$), 4.43 (1H, d x d, *J* = 9.6, 9.6 Hz, C*H*NH), 5.66 (1H, d, *J* = 9.6 Hz, CHN*H*), 6.83 (2H, d, *J* = 8.0 Hz, 2 x CH_{arom}), 6.91 (2H, d, *J* = 8.0 Hz, 2 x CH_{arom}), 7.21-7.32 (1H, m, CH_{arom}), 7.36-7.44 (1H, m, CH_{arom}), 7.50-7.65 (3H, m, 3 x CH_{arom}). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ 21.1 (*p*CH_3), 22.2 (3C, *t*Bu), 27.0 (CH_2CH_2Cl), 30.1 (CH_2CH), 44.5 (CH_2Cl), 47.7 (CH_2CH), 54.5 (OCH_3), 56.5 (C_q, *t*Bu), 60.1 (*C*HNH), 126.2 (2 x CH_{arom}), 127.0 (2 x CH_{arom}), 128.6 (2 x CH_{arom}), 129.3 (2 x CH_{arom}), 132.1 ($C_{arom,quat}$), 135.4 ($C_{arom,quat}$), 137.6 ($C_{arom,quat}$), 140.5 ($C_{arom,quat}$), 172.5 (C=N). **MS** (ES, pos mode) *m/z* (%): 513/515 (100) $[M + H]^+$. **HRMS**: calcd. for $C_{24}H_{34}ClN_2O_4S_2^+$ $[MH]^+$ 513.1643; found: 513.1638.

(S_S,*R*,*S*)-Methyl 5-chloro-2-[(4-methoxyphenyl)(4-methylphenyl)sulfonamidomethyl]-*N*-(2,4,6-triisopropylphenyl)sulfinyl)pentanimidate 339i



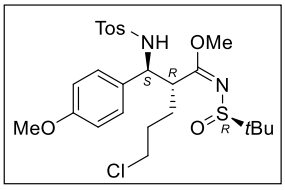
R_f = 0.16 (PE/Et_2O 1/1). White crystals, yield 10%. **Mp** 136.5-138.0 ºC. **[α]$_D$** +29.3 (*c* 0.3, $CHCl_3$). **IR** (cm^{-1}): ν_{max} 1035, 1072, 1157, 1266, 1510, 1628, 2961. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.22-1.27 (18H, m, 3 x CH(CH_3)$_2$), 1.63-1.82 (4H, $CH_2CH_2CH_2Cl$), 2.32 (3H, s, *p*CH_3), 2.88 (1H, sep, CH(CH_3)$_2$), 3.36-3.50 (3H, m, 2 x CH(CH_3)$_2$ and $CHCH_2$), 3.63 (3H, s, OCH_3), 3.74 (3H, s, OCH_3), 3.97-4.07 (2H, m, CH_2Cl), 4.50 (1H, dd, *J* = 9.5, 8.3 Hz, CHNH), 5.42 (1H, d, *J* = 9.5 Hz, CHNH), 6.66 (2H, d, *J* = 8.8 Hz, 2 x CH_{arom}), 6.93 (2H, d, *J* = 8.6 Hz, 2 x CH_{arom}), 7.04-7.08 (4H, m, 4 x CH_{arom}), 7.47 (2H, d, *J* = 8.6 Hz, 2 x CH_{arom}). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ 21.4 (*p*CH_3), 21.5 (CH_2CH_2Cl), 23.8 (2C, CH(CH_3)$_2$), 24.1 (2C, CH(CH_3)$_2$), 24.4 (2C, CH(CH_3)$_2$), 27.4 ($CHCH_2$), 29.7 (2 x CH(CH_3)$_2$), 30.2 ($CHCH_2$), 34.4 (CH(CH_3)$_2$), 44.4 (CH_2Cl), 48.2 (CHNH), 54.6 (OCH_3), 55.2 (OCH_3), 113.9 (2 x CH_{arom}), 126.4 ($C_{arom,quat}$), 127.0 (2 x CH_{arom}), 127.5 (2 x CH_{arom}), 129.2 (2 x CH_{arom}), 129.7 (2 x CH_{arom}), 130.8 ($C_{arom,quat}$), 137.6 ($C_{arom,quat}$), 138.3 ($C_{arom,quat}$), 142.9 ($C_{arom,quat}$), 152.2 (2 x $C_{arom,quat}$), 159.1 ($C_{arom,quat}$), 170.6 (C=N). **MS** (ES, pos mode) *m/z* (%): 689/691 (100) $[M + H]^+$.

***(R_S,R,S)*-Methyl 5-chloro-2-[(phenyl)(*p*-toluenesulfonylamino)methyl]-*N*-*tert*-butanesulfinyl-pentanimidate (*R_S*,*R*,*S*)-340a**



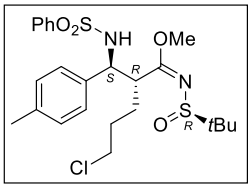
R_f = 0.39 (PE/Et_2O 1/1). Viscous colorless oil, yield 24%. $[\alpha]_D$ -124.4 (*c* 0.3, $CHCl_3$). **IR** (cm^{-1}): ν_{max} 1038, 1159, 1332, 1455, 1608, 2956. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.04-1.15 (1H, m, $CH_2CH(H)CH_2Cl$), 1.34 (9H, s, *t*Bu), 1.46-1.76 (3H, m, CH(*H*)CH(*H*)CH_2Cl), 2.25 (3H, s, *p*CH_3), 3.25-3.40 (2H, m, CH_2Cl), 3.54 (1H, td, *J* = 10.8, 3.7 Hz, $CHCH_2$), 3.78 (3H, s, OCH_3), 4.34 (1H, d x d, *J* = 10.8, 8.8 Hz, CHNH), 6.91 (2H, d, *J* = 8.3 Hz, 2 x CH_{arom}), 7.07-7.11 (5H, m, 5 x CH_{arom}), 7.15 (1H, d, *J* = 8.8 Hz, CHNH), 7.30 (2H, d, *J* = 8.3 Hz, 2 x CH_{arom}). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ 21.3 (*p*CH_3), 22.0 (3C, *t*Bu), 26.7 (CH_2CH_2Cl), 30.4 (CH_2CH), 43.9 (CH_2Cl), 50.2 (CH_2CH), 54.8 (OCH_3), 57.3 (C_q, *t*Bu), 59.4 (CHNH), 126.7 (2 x CH_{arom}), 127.4 (2 x CH_{arom}), 127.6 ($C_{quat,arom}$), 128.4 (2 x CH_{arom}), 128.8 (2 x CH_{arom}), 138.6 ($C_{arom,quat}$), 139.0 ($C_{arom,quat}$), 141.9 ($C_{arom,quat}$), 174.0 (C=N). **MS** (ES, pos mode) *m/z* (%): 513/515 (100) $[M + H]^+$. **HRMS**: calcd. for $C_{24}H_{34}ClN_2O_4S_2^+[MH]^+$ 513.1643; found: 513.1650.

(*R*S,*R*,*S*)-Methyl 5-chloro-2-[(4-methoxyphenyl)(*p*-toluenesulfonylamino)methyl]-*N*-*tert*-butane-sulfinylpentanimidate (*R*S,*R*,*S*)-340b



R_f = 0.27 (PE/Et_2O 1/1). White crystals, yield 69%. **Mp** 153.0-154.0 C. **[α]D** -151.2 (*c* 0.2, $CHCl_3$). **IR** (cm^{-1}): ν_{max} 1027, 1158, 1243, 1329, 1444, 1599, 2945, 3087. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.06-1.20 (1H, m, $CH_2CH(H)CH_2Cl$), 1.33 (9H, s, *t*Bu), 1.45-1.56 (2H, m, $CH(H)CH(H)CH_2Cl$), 1.60-1.77 (1H, m, $CH(H)CH_2CH_2Cl$), 2.27 (3H, s, pCH_3), 3.25-3.42 (2H, m, CH_2Cl), 3.50 (1H, td, *J* = 10.7, 3.6 Hz, $CHCH_2$), 3.73 (3H, s, OCH_3), 3.77 (3H, s, OCH_3), 4.32 (1H, d x d, *J* = 10.7, 8.8 Hz, CHNH), 6.59 (2H, d, *J* = 8.6 Hz, 2 x CH_{arom}), 6.94 (2H, d, *J* = 8.1 Hz, 2 x CH_{arom}), 6.99 (2H, d, *J* = 8.6 Hz, 2 x CH_{arom}), 7.08 (1H, d, *J* = 8.8 Hz, CHNH), 7.30 (2H, d, *J* = 8.1 Hz, 2 x CH_{arom}). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ 21.3 (pCH_3), 22.0 (3C, *t*Bu), 26.8 (CH_2CH_2Cl), 30.4 (CH_2CH), 43.9 (CH_2Cl), 50.3 (CH_2CH), 54.8 (OCH_3), 55.2 (OCH_3), 57.3 (C_q, *t*Bu), 59.0 (CHNH), 113.7 (2 x CH_{arom}), 126.7 (2 x CH_{arom}), 128.5 (2 x CH_{arom}), 128.8 (2 x CH_{arom}), 131.2 ($C_{arom,quat}$), 138.8 ($C_{arom,quat}$), 141.8 ($C_{arom,quat}$), 159.1 ($C_{arom,quat}$), 174.1 (C=N). **MS** (ES, pos mode) *m/z* (%): 543 (21) $[M + H]^+$, 372 (100). **HRMS**: calcd. for $C_{25}H_{36}ClN_2O_5S_2^+$ $[MH]^+$ 543.1749; found: 543.1746.

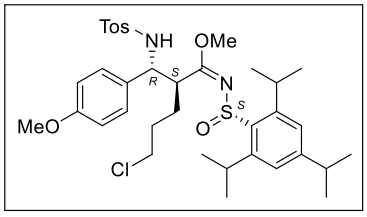
(*R*S,*R*,*S*)-Methyl 5-chloro-2-[(benzenesulfonylamino)(*p*-tolyl)methyl]-*N*-*tert*-butanesulfinyl-pentanimidate (*R*S,*R*,*S*)-340c



R_f = 0.40 (PE/Et_2O 1/1). White crystals, yield 38%. **Mp** 138.0-139.0 ºC. **[α]D** -128.4 (*c* 0.4, $CHCl_3$). **IR** (cm^{-1}): ν_{max} 1032, 1158, 1277, 1330, 1446, 1599, 2865, 3079. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.06-1.18 (1H, m, $CH_2CH(H)CH_2Cl$), 1.32 (9H, s, *t*Bu), 1.46-1.60 (2H, m, $CH(H)CH(H)CH_2Cl$), 1.67-1.78 (1H, m, $CH(H)CH_2CH_2Cl$), 2.22 (3H, s, pCH_3), 3.25-3.43 (2H, m, CH_2Cl), 3.52 (1H, td, *J* = 10.8, 3.7 Hz, $CHCH_2$), 3.76 (3H, s, OCH_3), 4.34 (1H, d x d, *J* = 10.8, 8.6 Hz, CHNH), 6.86 (2H, d, *J* = 8.0 Hz, 2 x CH_{arom}), 6.96 (2H, d, *J* = 8.0 Hz, 2 x CH_{arom}), 7.13 (2H, m, 2 x CH_{arom}), 7.20 (1H, d, *J* = 8.6 Hz, CHNH), 7.23-7.31 (1H, m, CH_{arom}), 7.39-7.45 (2H, m, 2 x CH_{arom}). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ 21.1 (pCH_3), 22.1 (3C, *t*Bu), 26.9 (CH_2CH_2Cl), 30.5 (CH_2CH), 44.0 (CH_2Cl), 50.2 (CH_2CH), 54.9 (OCH_3), 57.4 (C_q, *t*Bu), 59.4 (CHNH), 126.7 (2 x CH_{arom}), 127.3 (2 x CH_{arom}), 128.2 (2 x CH_{arom}), 129.1 (2 x CH_{arom}), 131.3 ($C_{arom,quat}$), 135.9 (CH_{arom}), 137.5 ($C_{arom,quat}$), 141.7 ($C_{arom,quat}$), 174.3 (C=N). *Crystal data:* $C_{24}H_{33}ClN_2O_4S_2$, *M* = 513.09, orthorhombic, space group $P2_12_12_1$ (No. 19), *a* = 8.9812(2) Å, *b* = 10.7105(2) Å, *c* = 26.6055(5) Å, *V* = 2559.30(9) $Å^3$, *Z* = 4, *T* = 100 K, ρ_{calc} = 1.332 g cm^{-3}, μ(Cu-Kα) = 3.114 mm^{-1}, *F*(000) = 1088, 21184 reflections measured, 5192 unique (R_{int} = 0.0553) which were used in all calculations. The final *R*1 was 0.0309 ($I > 2\sigma(I)$) and *wR*2 was 0.0790 (all data). **CCDC**: 1400317. **MS** (ES, pos mode)

m/z (%): 513/515 (100) $[M + H]^+$. **HRMS**: calcd. for $C_{24}H_{34}ClN_2O_4S_2^+$ $[MH]^+$ 513.1643; found: 513.1636.

(S_S,*S*,*R*)-Methyl 5-chloro-2-[(4-methoxyphenyl)(4-methylphenyl)sulfonamidomethyl]-*N*-(2,4,6-triisopropylphenyl)sulfinyl)pentanimidate 340i

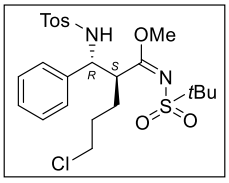


R_f = 0.16 (PE/Et_2O 1/1). Colorless viscous oil, yield 70%. **$[\alpha]_D$** +61.8 (*c* 0.2, $CHCl_3$). **IR** (cm^{-1}): ν_{max} 752, 1030, 1160, 1587, 3106. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.28 (12H, d, *J* = 6.9 Hz, 2 x $CH(CH_3)_2$), 1.37 (6H, d, *J* = 6.9 Hz, $CH(CH_3)_2$), 1.52-1.69 (2H, m, $CHCH(H)CH(H)$), 1.73-1.86 (2H, m, $CHCH(H)CH(H)$), 2.27 (3H, s, CH_3), 2.93 (1H, sep, *J* = 6.9 Hz, $CH(CH_3)_2$), 3.31-3.45 (2H, m, 2 x $CH(CH_3)_2$), 3.58 (1H, td, *J* = 10.7, 3.4 Hz, $CHCH_2$), 3.74 (3H, s, OCH_3), 3.82 (3H, s, OCH_3), 3.95-4.17 (2H, m, CH_2Cl), 4.46 (1H, 2 x d, *J* = 10.7, 9.5 Hz, CHNH), 6.62 (2H, d, *J* = 8.7 Hz, 2 x CH_{arom}), 6.93 (2H, d, *J* = 8.1 Hz, 2 x CH_{arom}), 7.05 (2H, d, *J* = 8.7 Hz, 2 x CH_{arom}), 7.10 (1H, d, *J* = 9.5 Hz, NH), 7.13 (2H, s, 2 x CH_{arom}), 7.28 (2H, d, *J* = 8.1 Hz, 2 x CH_{arom}). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ 21.3 (CH_3), 23.8 (4C, 2 x $CH(CH_3)_2$), 24.9 (2C, $CH(CH_3)_2$), 26.9 (CH_2CH_2Cl), 28.9 ($CHCH_2$), 30.5 ($CHCH_2$), 34.5 ($CH(CH_3)_2$), 43.8 (2 x $CH(CH_3)_2$), 49.8 (CH_2Cl), 55.2 (2 x OCH_3), 59.6 (CHNH), 113.2 (2 x CH_{arom}), 126.6 (2 x CH_{arom}), 128.6 (2 x CH_{arom}), 128.8 (4 x CH_{arom}), 131.0 ($C_{arom,quat}$), 136.3 ($C_{arom,quat}$), 138.9 ($C_{arom,quat}$), 141.8 ($C_{arom,quat}$), 152.9 (2 x $C_{arom,quat}$), 159.2 (2 x $C_{arom,quat}$), 176.0 (C=N). **MS** (ES, pos mode) *m/z* (%): 689/691 (100) $[M + H]^+$.

5.2.11 Synthesis of methyl 5-chloro-2-[(phenyl)(*p*-toluenesulfonylamino)methyl]-*N*-*tert*-butanesulfonylpentanimidates 342 and 343

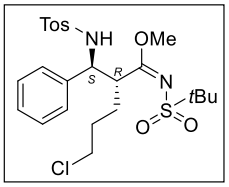
The synthesis of (*S*,*R*)-methyl 5-chloro-2-[(phenyl)(*p*-toluenesulfonylamino)methyl]-*N*-*tert*-butanesulfonylpentanimidate (*S*,*R*)-**342** is representative. To a solution of (R_S,*S*,*R*)-methyl 5-chloro-2-[(phenyl)(*p*-toluenesulfonylamino)methyl]-*N*-*tert*-butanesulfinylpentanimidate (R_S,*S*,*R*)-**339a** (0.07 g, 0.14 mmol) in CH_2Cl_2 (2.5 mL) was added *m*CPBA (1.5 equiv, 0.04 g, 0.21 mmol) in one portion at room temperature and the reaction mixture was stirred for 15 minutes. Subsequently, 40% aqueous sodium bisulfite (1.5 mL) was added. After stirring the mixture (5 minutes), the aqueous layer was separated and extracted with CH_2Cl_2 (3 x 4 mL). The organic phase was washed with saturated solution $NaHCO_3$ (2 x 5 mL), then with saturated aqueous solution NaCl (5 mL). The combined organic phases were dried ($MgSO_4$), filtered and evaporated *in vacuo*. The crude product was purified by flash chromatography to yield 0.05 g (0.10 mmol, 75% yield) of pure imidate (*S*,*R*)-**342**.

(*S,R*)-Methyl 5-chloro-2-[(phenyl)(*p*-toluenesulfonylamino)methyl]-*N*-*tert*-butanesulfonyl-pentanimidate (*S,R*)-342



R_f = 0.29 (PE/Et_2O 1/1). Colorless oil, yield 75%. **[α]$_D$** -8.7 (*c* 0.6, $CHCl_3$). **IR** (cm^{-1}): ν_{max} 694, 1114, 1159, 1276, 1612, 3274. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.12-1.25 (1H, m, $CH_2CH(H)CH_2Cl$), 1.53 (9H, s, *t*Bu), 1.58-1.72 (2H, m, $CH(H)CH(H)CH_2Cl$), 1.73-1.86 (1H, m, $CH(H)CH_2CH_2Cl$), 2.27 (3H, s, pCH_3), 3.27-3.38 (1H, m, $CH(H)Cl$), 3.39-3.50 (1H, m, $CH(H)Cl$), 3.80 (1H, td, *J* = 11.0, 3.6 Hz, $CHCH_2$), 3.87 (3H, s, OCH_3), 4.41 (1H, t, *J* = 10.3 Hz, CHNH), 6.38 (1H, d, *J* = 9.8 Hz, CHNH), 6.94 (2H, d, *J* = 8.1 Hz, 2 x CH_{arom}), 7.00-7.17 (5H, m, 5 x CH_{arom}), 7.31 (2H, d, *J* = 8.1 Hz, 2 x CH_{arom}). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ 21.3 (pCH_3), 24.0 (3C, *t*Bu), 26.7 (CH_2CH_2Cl), 30.0 (CH_2CH), 44.1 (CH_2Cl), 51.2 (CH_2CH), 55.8 (OCH_3), 59.3 (C_q, *t*Bu), 60.7 (CHNH), 126.7 (2 x CH_{arom}), 127.1 (2 x CH_{arom}), 127.9 (CH_{arom}), 128.6 (2 x CH_{arom}), 129.0 (2 x CH_{arom}), 138.1 ($C_{arom,quat}$), 138.4 ($C_{arom,quat}$), 142.5 ($C_{arom,quat}$), 176.8 (C=N). **MS** (ES, pos mode) *m/z* (%): 546/548 (100) $[M + NH_4]^+$.

(*R,S*)-Methyl 5-chloro-2-[(phenyl)(*p*-toluenesulfonylamino)methyl]-*N*-*tert*-butanesulfonyl-pentanimidate (*R,S*)-343



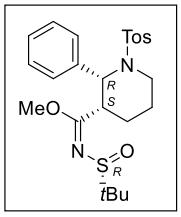
R_f = 0.29 (PE/Et_2O 1/1). Colorless oil, yield 71%. **[α]$_D$** +5.7 (*c* 0.7, $CHCl_3$). **IR** (cm^{-1}): ν_{max} 694, 1114, 1159, 1276, 1612, 3274. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.12-1.25 (1H, m, $CH_2CH(H)CH_2Cl$), 1.53 (9H, s, *t*Bu), 1.58-1.72 (2H, m, $CH(H)CH(H)CH_2Cl$), 1.73-1.86 (1H, m, $CH(H)CH_2CH_2Cl$), 2.27 (3H, s, pCH_3), 3.27-3.38 (1H, m, $CH(H)Cl$), 3.39-3.50 (1H, m, $CH(H)Cl$), 3.80 (1H, td, *J* = 11.0, 3.6 Hz, $CHCH_2$), 3.87 (3H, s, OCH_3), 4.41 (1H, t, *J* = 10.3 Hz, CHNH), 6.38 (1H, d, *J* = 9.8 Hz, CHNH), 6.94 (2H, d, *J* = 8.1 Hz, 2 x CH_{arom}), 7.00-7.17 (5H, m, 5 x CH_{arom}), 7.31 (2H, d, *J* = 8.1 Hz, 2 x CH_{arom}). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ 21.3 (pCH_3), 24.0 (3C, *t*Bu), 26.7 (CH_2CH_2Cl), 30.0 (CH_2CH), 44.1 (CH_2Cl), 51.2 (CH_2CH), 55.8 (OCH_3), 59.3 (C_q, *t*Bu), 60.7 (CHNH), 126.7 (2 x CH_{arom}), 127.1 (2 x CH_{arom}), 127.9 (CH_{arom}), 128.6 (2 x CH_{arom}), 129.0 (2 x CH_{arom}), 138.1 ($C_{arom,quat}$), 138.4 ($C_{arom,quat}$), 142.5 ($C_{arom,quat}$), 176.8 (C=N). **MS** (ES, pos mode) *m/z* (%): 546/548 (100) $[M + NH_4]^+$.

5.2.12 Synthesis of *cis*-methyl 2-aryl-1-sulfonylpiperidine-3-*N*-(*tert*-butylsulfinyl)-carbimidates *cis*-344 and *cis*-345

The synthesis of (R_S,*2R,3S*)-methyl *N*-*tert*-butanesulfinyl-2-phenyl-1-tosylpiperidine-3-carbimidate (R_S,*2R,3S*)-**344a** is representative. (R_S,*S,R*)-δ-Chloro-β-amino-*N*-sulfinylimidates (R_S,*S,R*)-**339a** (1.64 g, 3.20 mmol) was dissolved in acetonitrile (50 mL), and K_2CO_3 (3.0 equiv, 1.33 g, 9.61 mmol) was added in one portion. The reaction mixture was stirred for 20 hours at reflux and subsequently

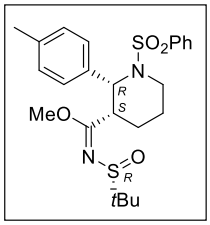
evaporated *in vacuo*. The reaction mixture was dissolved in EtOAc (30 mL), washed with brine (30 mL), dried ($MgSO_4$), filtered, and evaporated *in vacuo*. Purification *via* flash chromatography afforded 1.40 g (2.94 mmol, 92% yield) of pure (*R*$_S$,*2R,3S*)-*cis*-methyl 2-phenyl-1-(*p*-toluenesulfonyl)piperidine-3-*N*-(*tert*-butylsulfinyl)-carbimidate (*R*$_S$,*2R,3S*)-*cis*-**344a**.

(*R*$_S$,*2R,3S*)-*cis*-Methyl 2-phenyl-1-(*p*-toluenesulfonyl)piperidine-3-*N*-*tert*-butanesulfinylcarbimidate (*R*$_S$,*2R,3S*)-344a



R_f = 0.56 (PE/ethyl acetate 1/3). White crystals, yield 92%. **Mp** 132.0-134.0 C. **[α]$_D$** -182.8 (*c* 0.2, $CHCl_3$). **IR** (cm^{-1}): ν_{max} 1076, 1160, 1279, 1617, 2930. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.23 (9H, s, *t*Bu), 1.40-1.56 (1H, m, C*H*(H)CH_2CH_2N), 1.70-1.84 (2H, m, CH(*H*)C*H*(H)CH_2N), 2.01-2.14 (1H, m, CH_2CH(*H*)CH_2N), 2.34 (3H, s, *p*CH_3), 3.19-3.30 (1H, m, C*H*(H)N), 3.26 (3H, s, OCH_3), 3.75-3.89 (2H, m, CH(*H*)N and C*H*C=N), 5.59 (1H, d, *J* = 6.0 Hz, C*H*Ph), 7.07-7.26 (7H, m, 7 x CH_{arom}), 7.49 (2H, d, *J* = 8.3 Hz, 2 x CH_{arom}). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ 20.8 (*p*CH_3), 21.4 (*C*H_2CH_2N), 21.9 (3H, *t*Bu), 23.5 (*C*$H_2CH_2CH_2N$), 41.8 (*C*H_2N), 44.2 (*C*HC=N), 53.8 (O*C*H_3), 56.0 (C_q, *t*Bu), 56.9 (*C*HPh), 127.1 (2 x CH_{arom}), 127.7 (CH_{arom}), 128.0 (2 x CH_{arom}), 128.5 (2 x CH_{arom}), 129.4 (2 x CH_{arom}), 136.9 ($C_{arom,quat}$), 137.8 ($C_{arom,quat}$), 142.9 ($C_{arom,quat}$), 174.0 (C=N). *Crystal data:* $C_{24}H_{32}N_2O_4S_2$, *M* = 476.64, tetragonal, space group $P4_32_12$ (No. 96), *a* = *b* = 10.85357(10) Å, *c* = 42.3747(8) Å, *V* = 4991.74(13) Å^3, *Z* = 8, *T* = 100 K, ρ_{calc} = 1.268 g cm^{-3}, μ(Cu-Kα) = 2.193 mm^{-1}, *F*(000) = 2032, 23695 reflections measured, 5041 unique (R_{int} = 0.0795) which were used in all calculations. The final *R*1 was 0.0425 ($I > 2\sigma(I)$) and *wR*2 was 0.1001 (all data). **CCDC**: 1046634. **MS** (ES, pos mode) *m/z* (%): 477 (100) $[M + H]^+$. **HRMS**: calc for $C_{24}H_{33}N_2O_4S_2^+$ $[MH]^+$ 477.1876; found: 477.1874.

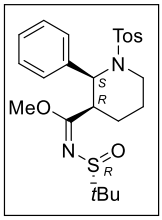
(*R*$_S$,*2R,3S*)-*cis*-Methyl 1-(benzenesulfonyl)-2-*p*-tolylpiperidine-3-*N*-*tert*-butylsulfinylcarbimidate (*R*$_S$,*2R,3S*)-344c



R_f = 0.23 (PE/Et_2O 1/1). Viscous colorless oil, yield 87%. **[α]$_D$** -127.9 (*c* 0.2, $CHCl_3$). **IR** (cm^{-1}): ν_{max} 1041, 1161, 1282, 1338, 1446, 1596, 2924. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.26 (9H, s, *t*Bu), 1.45-1.51 (1H, m, CH_2C*H*(H)CH_2N), 1.68-1.86 (2H, m, C*H*(H)CH(*H*)CH_2N), 1.98-2.18 (1H, m, CH(*H*)CH_2CH_2N), 2.28 (3H, s, *p*CH_3), 3.16-3.28 (1H, m, C*H*(H)N), 3.29 (3H, s, OCH_3), 3.70-3.89 (2H, m, CH(*H*)N and C*H*C=N), 5.56 (1H, d, *J* = 6.05 Hz, C*H*PhMe), 6.97 (2H, d, *J* = 8.1 Hz, 2 x CH_{arom}), 7.10 (2H, d, *J* = 8.1 Hz, 2 x CH_{arom}), 7.30-7.36 (2H, m, 2 x CH_{arom}), 7.42-7.48 (1H, m, CH_{arom}), 7.60-7.65 (2H, m, 2 x CH_{arom}). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ 20.7 (*p*CH_3), 21.1 (*C*H_2CH_2N), 22.0 (3C, *t*Bu), 23.6 (*C*$H_2CH_2CH_2N$), 41.8 (*C*H_2N), 44.3 (*C*HC=N), 53.9 (O*C*H_3), 56.1 (C_q, *t*Bu), 56.8 (*C*HPh), 127.2 (2 x CH_{arom}), 128.5 (2 x CH_{arom}), 128.7 (2 x CH_{arom}), 128.8 (2 x CH_{arom}),

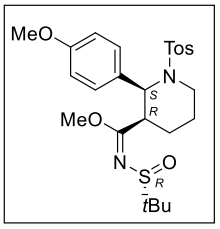
132.2 (2 x CH_{arom}), 134.7 ($C_{arom,quat}$), 137.5 ($C_{arom,quat}$), 139.9 ($C_{arom,quat}$), 175.0 (C=N). **MS** (ES, pos mode) *m/z* (%): 477 (100) $[M + H]^+$. **HRMS**: calcd. for $C_{24}H_{33}N_2O_4S_2^+[MH]^+$ 477.1876; found: 477.1899.

(R_S,2*S*,3*R*)-*cis*-Methyl 2-phenyl-1-(*p*-toluenesulfonyl)piperidine-3-*N*-*tert*-butanesulfinylcarbimidate (R_S,2*S*,3*R*)-345a



R_f = 0.63 (PE/EtOAc 1/3). White crystals, yield 87%. **Mp** 113.0-114.0 ºC. **[α]$_D$** +104.2 (*c* 0.2, $CHCl_3$). **IR** (cm^{-1}): ν_{max} 1077, 1160, 1292, 1340, 1593, 2972. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.22 (9H, s, *t*Bu), 1.52 (1H, ddddd, *J* = 13.5, 13.5, 9.1, 5.1, 4.0 Hz, $CH_2CH(H)CH_2N$), 1.65-1.73 (1H, m, $CH(H)CH_2CH_2N$), 1.80-1.90 (1H, m, $CH_2CH(H)CH_2N$), 2.07 (1H, dddd, *J* = 13.5, 13.5, 13.5, 3.6 Hz, $CH(H)CH_2CH_2N$), 2.33 (3H, s, pCH_3), 3.20 (3H, s, OCH_3), 3.34 (1H, td, *J* = 13.3, 3.6 Hz, CH(H)N), 3.52 (1H, ddd, *J* = 12.9, 6.2, 3.6 Hz, CHC=N), 3.99 (1H, d x d, *J* = 13.3, 4.0 Hz, CH(H)N), 5.81 (1H, d, *J* = 6.2 Hz, CHPh), 7.06 (2H, d, *J* = 8.3 Hz, 2 x CH_{arom}), 7.09-7.24 (5H, m, 5 x CH_{arom}), 7.51 (2H, d, *J* = 8.3 Hz, 2 x CH_{arom}). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ 21.0 (pCH_3), 21.4 (CH_2CH_2N), 21.9 (3C, *t*Bu), 23.9 ($CH_2CH_2CH_2N$), 42.2 (CH_2N), 45.8 (CHC=N), 53.7 (OCH_3), 56.2 (C_q, *t*Bu), 57.7 (CHPh), 127.3 (3 x CH_{arom}), 127.8 (2 x CH_{arom}), 128.7 (2 x CH_{arom}), 129.1 (2 x CH_{arom}), 137.1 ($C_{arom,quat}$), 138.2 ($C_{arom,quat}$), 142.5 ($C_{arom,quat}$), 174.2 (C=N). *Crystal data:* $C_{24}H_{32}N_2O_4S_2$, *M* = 476.64, tetragonal, space group $P4_12_12$ (No. 92), *a* = *b* = 10.87406(11) Å, *c* = 41.9807(7) Å, *V* = 4964.02(13) Å^3, *Z* = 8, *T* = 100 K, ρ_{calc} = 1.276 g cm^{-3}, μ(Cu-Kα) = 2.205 mm^{-1}, *F*(000) = 2032, 96397 reflections measured, 5145 unique (R_{int} = 0.1148) which were used in all calculations. The final *R*1 was 0.0435 ($I > 2\sigma(I)$) and *wR*2 was 0.0903 (all data). **CCDC**: 1046635. **MS** (ES, pos mode) *m/z* (%): 477 (100) $[M + H]^+$. **HRMS**: calcd. for $C_{24}H_{33}N_2O_4S_2^+$ $[MH]^+$ 477.1876; found: 477.1870.

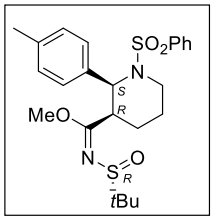
(R_S,2*S*,3*R*)-*cis*-Methyl 2-(4-methoxyphenyl)-1-(*p*-toluenesulfonyl)piperidine-3-*N*-*tert*-butylsulfinylcarbimidate (R_S,2*S*,3*R*)-345b



R_f = 0.16 (PE/Et_2O 1/1). White crystals, yield 97%. **Mp** 136.5-138.0 C. **[α]$_D$** +127.5 (*c* 0.4, $CHCl_3$). **IR** (cm^{-1}): ν_{max} 1035, 1072, 1157, 1266, 1510, 1628, 2961. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.21 (9H, s, *t*Bu), 1.43-1.60 (1H, m, $CH_2CH(H)CH_2N$), 1.63-1.74 (1H, m, $CH(H)CH_2CH_2N$), 1.78-1.88 (1H, m, $CH_2CH(H)CH_2N$), 2.09 (1H, dddd, *J* = 13.5, 13.5, 13.5, 3.4 Hz, $CH(H)CH_2CH_2N$), 2.34 (3H, s, pCH_3), 3.25 (3H, s, OCH_3), 3.26-3.34 (1H, m, CH(H)N), 3.44-3.56 (1H, m, CHC=N), 3.75 (3H, s, OCH_3), 3.91-4.01 (1H, m, CH(H)N), 5.76 (1H, d, *J* = 6.1 Hz, CHPhOMe), 6.65 (2H, d, *J* = 8.6 Hz, 2 x CH_{arom}), 7.08 (2H, d, *J* = 8.1 Hz, 2 x CH_{arom}), 7.15 (2H, d, *J* = 8.6 Hz, 2 x CH_{arom}), 7.51 (2H, d, *J* = 8.1 Hz, 2 x CH_{arom}). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ 21.1 (pCH_3), 21.4 (CH_2CH_2N), 21.9 (3C, *t*Bu), 23.9 ($CH_2CH_2CH_2N$), 41.9 (CH_2N), 45.7 (CHC=N), 53.9

(OCH_3), 55.2 (OCH_3), 56.1 (C_q, *t*Bu), 57.2 (*C*HPh), 113.1 (2 x CH_{arom}), 127.3 (2 x CH_{arom}), 129.1 (2 x CH_{arom}), 130.0 (2 x CH_{arom}), 130.4 ($C_{arom,quat}$), 137.2 ($C_{arom,quat}$), 142.4 ($C_{arom,quat}$), 158.8 ($C_{arom,quat}$), 174.3 (C=N). *Crystal data:* $C_{25}H_{34}N_2O_5S_2$, M = 506.66, orthorhombic, space group $P2_12_12_1$ (No. 19), a = 10.9791(2) Å, b = 15.0941(3) Å, c = 15.4399(3) Å, V = 2558.70(9) Å^3, Z = 4, T = 100 K, ρ_{calc} = 1.315 g cm^{-3}, μ(Cu-Kα) = 2.200 mm^{-1}, F(000) = 1080, 24610 reflections measured, 5216 unique (R_{int} = 0.0584) which were used in all calculations. The final R1 was 0.0324 ($I > 2\sigma(I)$) and wR2 was 0.0759 (all data). **CCDC**: 1046636. **MS** (ES, pos mode) *m/z* (%): 507 (100) $[M + H]^+$. **HRMS**: calcd. for $C_{25}H_{35}N_2O_5S_2^+$ $[MH]^+$507.1982; found: 507.1979.

(R_S,2S,3R)-*cis*-Methyl 1-(benzenesulfonyl)-2-*p*-tolylpiperidine-3-*N*-*tert*-butylsulfinylcarbimidate (R_S,2S,3R)-345c



R_f = 0.16 (PE/Et_2O 1/1). Viscous colorless oil, yield 89%. **$[\alpha]_D$** +105.1 (*c* 0.2, $CHCl_3$). **IR** (cm^{-1}): ν_{max} 949, 1042, 1161, 1283, 1340, 1446, 1594, 2947. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.22 (9H, s, *t*Bu), 1.45-1.60 (1H, m, $CH_2CH(H)CH_2N$), 1.64-1.74 (1H, m, $CH(H)CH_2CH_2N$), 1.81-1.90 (1H, m, $CH_2CH(H)CH_2N$), 2.01-2.14 (1H, m, $CH(H)CH_2CH_2N$), 2.25 (3H, s, pCH_3), 3.23 (3H, s, OCH_3), 3.33 (1H, td, J = 13.2, 3.9 Hz, $CH(H)N$), 3.50 (1H, ddd, J = 12.8, 6.2, 3.4 Hz, CHC=N), 3.93-4.04 (1H, m, $CH(H)N$), 5.79 (1H, d, J = 6.2 Hz, *CH*PhMe), 6.91 (2H, d, J = 8.1 Hz, 2 x CH_{arom}), 7.09 (2H, d, J = 8.1 Hz, 2 x CH_{arom}), 7.20-7.31 (2H, m, 2 x CH_{arom}), 7.38-7.43 (1H, m, CH_{arom}), 7.60-7.66 (2H, m, 2 x CH_{arom}). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ 20.9 (pCH_3), 21.0 (CH_2CH_2N), 22.0 (3C, *t*Bu), 24.0 ($CH_2CH_2CH_2N$), 42.2 (CH_2N), 45.8 (*C*HC=N), 53.8 (OCH_3), 56.2 (C_q, *t*Bu), 57.6 (*C*HPh), 127.3 (2 x CH_{arom}), 128.4 (2 x CH_{arom}), 128.5 (2 x CH_{arom}), 128.6 (2 x CH_{arom}), 131.8 (CH_{arom}), 135.0 ($C_{arom,quat}$), 137.0 ($C_{arom,quat}$), 140.1 ($C_{arom,quat}$), 174.2 (C=N). **MS** (ES, pos mode) *m/z* (%): 477 (100) $[M + H]^+$. **HRMS**: calcd. for $C_{24}H_{33}N_2O_4S_2^+$ $[MH]^+$ 477.1876; found: 477.1871.

5.2.13 Synthesis of 2-aryl-1-sulfonylpiperidine-3-carboxamide *cis*-347 and *cis*-348

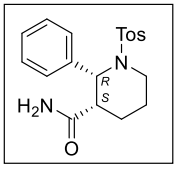
Method A (only for (2R,3S)-**347a** and **348a**). The synthesis of (2R,3S)-**347a** is representative. To a solution of (R_S,S,R)-**344a** (0.24 g, 0.47 mmol) in Et_2O (10 mL) was added a 3M solution of HCl in dioxane (15.0 equiv, 2.35 mL, 7.05 mmol) at 0 °C. The mixture was allowed to stir for 1 hour at °C. Subsequently, the reaction mixture was concentrated *in vacuo*. The resulting crude solid reaction mixture was heated under reflux in chlorophorm for 16 hours. After, the solvent was evaporated *in vacuo*. Precipitation in diethyl ether/hexane (1:1) afforded pure (2R,3S)-*cis*-2-phenyl-1-tosylpiperidine-3-carboxamide (2R,3S)-**347a**.

Method B. The synthesis of (2S,3R)-*cis*-2-(4-methoxyphenyl)-1-tosylpiperidine-3-carboxamide (2S,3R)-*cis*-**348b** is representative. To a solution of (R_S,2S,3R)-**345b** (1.4 g, 2.77 mmol) in dioxane (30 mL) was added a 3M solution of HCl in dioxane (15.0 equiv, 13.85 mL, 41.55 mmol) at room

temperature. The mixture was allowed to stir for 2 hours at room temperature. Subsequently, the reaction mixture was concentrated *in vacuo*. Precipitation in diethyl ether/hexane (1:1) afforded pure (*2S,3R*)-*cis*-2-(4-methoxyphenyl)-1-tosylpiperidine-3-carboxamide (*2S,3R*)-*cis*-**348b**.

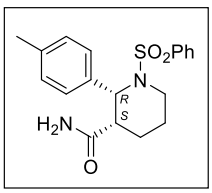
Method C. (Only for **347a**) To a solution of (*R*$_S$,*S*,*R*)-**344a** (0.20 g, 0.40 mmol) in dioxane (8 mL) was added a 3M solution of HCl in dioxane (15.0 equiv, 2.00 mL, 6.00 mmol) at 0 ºC. The mixture was allowed to stir for 2 hour at room temperature. Subsequently, the reaction mixture was concentrated *in vacuo*. The resulting crude solid reaction mixture was treated with K_2CO_3 (3.0 equiv, 0.20 g, 1.20 mmol) in CH_3CN (15 mL) at reflux for 15 hours. The solvent was evaporated *in vacuo*. The reactiom mixture was dissolved in EtOAc (15 mL), washed with brine (10 mL), dried $MgSO_4$, filtered and evaporated in vacuo. Precipitation in diethyl ether/hexane (1:1) afforded pure (*2R,3S*)-*cis*-2-phenyl-1-tosylpiperidine-3-carboxamide (*2R,3S*)-**347a**.

(*2R,3S*)-*cis*-2-Phenyl-1-tosylpiperidine-3-carboxamide (*2R,3S*)-347a



White crystals, yield 78% (method A), yield 99% (method B), yield 61% (method C). **Mp** 182.0-184.0 ºC. **[α]$_D$** +78.4 (*c* 0.3, $CHCl_3$). ee > 98%, **HPLC** (IB): hexane (80%)/ethanol (20%), 1 mL min $^{-1}$, 35 ºC, t_R = 9.28 min. **IR** (cm^{-1}): ν_{max} 1096, 1157, 1331, 1599, 1664, 3343. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.44-1.58 (1H, m, C*H*(H)CH_2N), 1.69-1.78 (1H, m, CH(*H*)CH_2N), 1.81-2.04 (2H, m, C$H_2CH_2CH_2$N), 2.38 (3H, s, *p*CH_3), 2.74 (1H, ddd, *J* = 12.6, 5.3, 4.1 Hz, C*H*C=O), 2.93 (1H, td, *J* = 13.7, 3.1 Hz, C*H*(H)N), 3.76-3.84 (1H, m, CH(*H*)N), 5.54 (1H, br s, N*H*(H)), 5.62 (1H, d, *J* = 5.3 Hz, C*H*Ph), 5.85 (1H, br s, NH(*H*)), 7.14-7.32 (7H, m, 7 x CH_{arom}), 7.55 (2H, d, *J* = 8.3 Hz, 2 x CH_{arom}). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ 20.9 (*p*CH_3), 21.5 (*C*H_2CH_2N), 24.1 (*C*$H_2CH_2CH_2$N), 41.2 (*C*H_2N), 45.4 (*C*HC=O), 57.1 (*C*HPh), 127.0 (2 x CH_{arom}), 127.6 (CH_{arom}), 128.4 (2 x CH_{arom}), 128.7 (2 x CH_{arom}), 129.6 (2 x CH_{arom}), 136.7 ($C_{arom,quat}$), 137.3 ($C_{arom,quat}$), 143.2 ($C_{arom,quat}$), 173.7 (C=O). *Crystal data:* $C_{19}H_{22}N_2O_3S$, 0.526(H_2O), *M* = 367.92, monoclinic, space group $P2_1$ (No. 4), *a* = 9.5068(3) Å, *b* = 10.2375(3) Å, *c* = 10.5226(3) Å, β = 114.558(4)°, *V* = 931.48(6) Å^3, *Z* = 2, *T* = 100 K, ρ_{calc} = 1.312 g cm^{-3}, μ(Cu-Kα) = 1.742 mm^{-1}, *F*(000) = 390.5, 9238 reflections measured, 3503 unique (R_{int} = 0.0507) which were used in all calculations. The final *R*1 was 0.0382 ($I > 2\sigma(I)$) and *wR*2 was 0.0897 (all data). **CCDC**: 1046637. **MS** (ES, pos mode) *m/z* (%): 359 (100) $[M + H]^+$. **HRMS**: calcd. for $C_{19}H_{23}N_2O_3S^+$ $[MH]^+$ 359.1424; found: 359.1437.

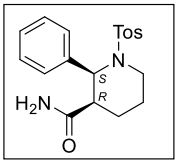
(*2R,3S*)-*cis*-1-(Phenylsulfonyl)-2-(*p*-tolyl)piperidine-3-carboxamide (*2R,3S*)-347c



White crystals, yield 94% (Method B). **Mp** 190.0-192.0 ºC. **[α]$_D$** +51.2 (*c* 0.3, $CHCl_3$). **IR** (cm^{-1}): ν_{max} 959, 1096, 1156, 1327, 1404, 1612, 1656, 3413. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.44-1.61 (1H, m, C*H*(H)CH_2N), 1.72-1.83 (1H, m, CH(*H*)CH_2N), 1.84-1.93 (1H, m, C*H*(H)CH_2CH_2N), 1.99 (1H, dddd, *J* = 12.9,

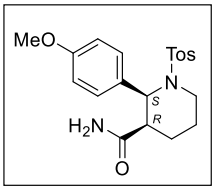
12.9, 12.9, 4.1 Hz, CH(*H*)CH_2CH_2N), 2.27 (3H, s, *p*CH_3), 2.76 (1H, ddd, *J* = 12.9, 5.3, 4.1 Hz, C*H*C=O), 2.96 (1H, td, *J* = 13.5, 3.0 Hz, C*H*(H)N), 3.76-3.87 (1H, m, CH(*H*)N), 5.42 (1H, br s, N*H*(H)), 5.57 (1H, d, *J* = 5.3 Hz, C*H*PhMe), 5.71 (1H, br s, NH(*H*)), 6.98 (2H, d, *J* = 8.1 Hz, 2 x CH_{arom}), 7.15 (2H, d, *J* = 8.1 Hz, 2 x CH_{arom}), 7.32-7.44 (2H, m, 2 x CH_{arom}), 7.44-7.54 (1H, m, CH_{arom}), 7.60-7.73 (2H, m, 2 x CH_{arom}). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ 20.9 (*p*CH_3), 21.0 (*C*H_2CH_2N), 24.2 (*C*$H_2CH_2CH_2N$), 41.2 (*C*H_2N), 45.7 (*C*HC=O), 57.1 (*C*HPhMe), 127.0 (2 x CH_{arom}), 128.6 (2 x CH_{arom}), 128.9 (2 x CH_{arom}), 129.1 (2 x CH_{arom}), 132.3 (CH_{arom}), 133.4 ($C_{arom,quat}$), 137.5 ($C_{arom,quat}$), 140.2 ($C_{arom,quat}$), 173.4 (C=O). **MS** (ES, pos mode) *m/z* (%): 359 (100) $[M + H]^+$. **HRMS**: calcd. for $C_{19}H_{23}N_2O_3S^+$ $[MH]^+$ 359.1424; found: 359.1431.

(*2S,3R*)-*cis*-2-Phenyl-1-tosylpiperidine-3-carboxamide (*2S,3R*)-348a



White crystals, yield 84% (method A), yield 98% (method B). **Mp** 178.0-180.0 ºC. **$[\alpha]_D$** -80.7 (*c* 0.4, $CHCl_3$). ee > 98%, **HPLC** (IB): hexane (80%)/ethanol (20%), 1 mL min $^{-1}$, 35 ºC, t_R = 8.04 min. **IR** (cm^{-1}): ν_{max} 1151, 1316, 1410, 1597, 1660, 3418. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.44-1.58 (1H, m, C*H*(H)CH_2N), 1.69-1.78 (1H, m, CH(*H*)CH_2N), 1.81-2.04 (2H, m, C$H_2CH_2CH_2N$), 2.38 (3H, s, *p*CH_3), 2.74 (1H, ddd, *J* = 12.6, 5.3, 4.1 Hz, C*H*C=O), 2.93 (1H, td, *J* = 13.7, 3.1 Hz, C*H*(H)N), 3.76-3.84 (1H, m, CH(*H*)N)), 5.54 (1H, br s, N*H*(H)), 5.62 (1H, d, *J* = 5.3 Hz, C*H*Ph), 5.88 (1H, br s, NH(*H*)), 7.14-7.32 (7H, m, 7 x CH_{arom}), 7.55 (2H, d, *J* = 8.3 Hz, 2 x CH_{arom}). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ 20.9 (*p*CH_3), 21.5 (*C*H_2CH_2N), 24.1 (*C*$H_2CH_2CH_2N$), 41.2 (*C*H_2N), 45.4 (*C*HC=O), 57.1 (*C*HPh), 127.0 (2 x CH_{arom}), 127.6 (CH_{arom}), 128.4 (2 x CH_{arom}), 128.7 (2 x CH_{arom}), 129.6 (2 x CH_{arom}), 136.7 ($C_{arom,quat}$), 137.3 ($C_{arom,quat}$), 143.2 ($C_{arom,quat}$), 173.7 (C=O). *Crystal data:* $C_{19}H_{22}N_2O_3S$, 0.576(H_2O), *M* = 368.82, monoclinic, space group $P2_1$ (No. 4), *a* = 9.5055(3) Å, *b* = 10.2450(2) Å, *c* = 10.5267(3) Å, β = 114.610(4)°, *V* = 932.01(5) Å^3, *Z* = 2, *T* = 100 K, ρ_{calc} = 1.314 g cm^{-3}, μ(Cu-Kα) = 1.744 mm^{-1}, *F*(000) = 391.5, 13909 reflections measured, 3716 unique (R_{int} = 0.0330) which were used in all calculations. The final *R*1 was 0.0289 ($I > 2\sigma(I)$) and *wR*2 was 0.0751 (all data). **CCDC**: 1046638. **MS** (ES, pos mode) *m/z* (%): 359 (100) $[M + H]^+$. **HRMS**: calcd. for $C_{19}H_{23}N_2O_3S^+$ $[MH]^+$ 359.1424; found: 359.1429.

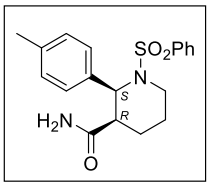
(*2S,3R*)-*cis*-2-(4-Methoxyphenyl)-1-tosylpiperidine-3-carboxamide (*2S,3R*)-348b



White crystals, yield 98% (Method B). **Mp** 196.0-198.0 ºC. **$[\alpha]_D$** -34.5 (*c* 0.3, $CHCl_3$). **IR** (cm^{-1}): ν_{max} 1096, 1155, 1246, 1325, 1513, 1608, 1660, 2940, 3426. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.39-1.55 (1H, m, C*H*(H)CH_2N), 1.67-1.76 (1H, m, CH(*H*)CH_2N), 1.80-1.88 (1H, m, C*H*(H)CH_2CH_2N), 1.96 (1H, dddd, *J* = 13.0, 13.0, 13.0, 4.0 Hz, CH(*H*)CH_2CH_2N), 2.37 (3H, s, *p*CH_3), 2.69 (1H, ddd, *J* = 13.0, 5.4, 4.0 Hz, C*H*C=O), 2.91 (1H, td, *J* = 13.4, 3.0 Hz, C*H*(H)N), 3.70-3.82 (1H, m, CH(*H*)N), 3.74 (3H, s, OCH_3), 5.58 (1H, d, *J* = 5.4 Hz, C*H*PhOMe), 5.64 (1H, br s, N*H*(H)), 6.04 (1H, br s, NH(*H*)), 6.70 (2H, d, *J*

= 8.8 Hz, 2 x C*H*$_{arom}$), 7.15 (2H, d, *J* = 8.3 Hz, 2 x C*H*$_{arom}$), 7.22 (2H, d, *J* = 8.8 Hz, 2 x C*H*$_{arom}$), 7.54 (2H, d, *J* = 8.3 Hz, 2 x C*H*$_{arom}$). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ 20.8 (*p*CH_3), 21.5 (*C*H_2CH_2N), 24.1 (*C*H_2CH_2CH_2N), 41.0 (*C*H_2N), 45.4 (*C*HC=O), 55.2 (O*C*H_3), 56.7 (*C*HPhOMe), 113.6 (2 x CH_{arom}), 127.0 (2 x CH_{arom}), 128.7 (CH_{arom}), 129.6 (2 x CH_{arom}), 130.0 (2 x CH_{arom}), 137.3 (C$_{arom,quat}$), 143.1 (C$_{arom,quat}$), 159.0 (C$_{arom,quat}$), 173.9 (C=O). *Crystal data:* $C_{20}H_{24}N_2O_4S$, *M* = 388.47, monoclinic, space group *P*2$_1$ (No. 4), *a* = 9.3435(2) Å, *b* = 10.02409(19) Å, *c* = 21.4346(5) Å, β = 101.916(2) °, *V* = 1964.31(7) Å^3, *Z* = 4, *T* = 100 K, ρ_{calc} = 1.314 g cm^{-3}, μ(Cu-Kα) = 1.699 mm^{-1}, *F*(000) = 824, 28131 reflections measured, 7867 unique (R_{int} = 0.0478) which were used in all calculations. The final *R*1 was 0.0514 ($I > 2\sigma(I)$) and *wR*2 was 0.1444 (all data). **CCDC**: 1046639. **MS** (ES, pos mode) *m/z* (%): 389 (100) $[M + H]^+$. **HRMS**: calcd. for $C_{20}H_{25}N_2O_4S^+$ $[MH]^+$ 389.1530; found: 389.1543.

(*2S,3R*)-*cis*-1-(Phenylsulfonyl)-2-(*p*-tolyl)piperidine-3-carboxamide (*2S,3R*)-348c



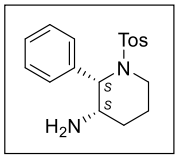
White crystals, yield 96% (Method B). **Mp** 186.0-188.0 ºC. **[α]$_D$** -51.3 (*c* 0.3, $CHCl_3$). **IR** (cm^{-1}): ν_{max} 959, 1096, 1155, 1326, 1446, 1611, 1656, 3413. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.44-1.61 (1H, m, C*H*(H)CH$_2$N), 1.72-1.83 (1H, m, CH(*H*)CH$_2$N), 1.84-1.93 (1H, m, C*H*(H)CH$_2$CH$_2$N), 1.99 (1H, dddd, *J* = 12.9, 12.9, 12.9, 4.1 Hz, CH(*H*)CH$_2$CH$_2$N), 2.27 (3H, s, *p*C*H*$_3$), 2.76 (1H, ddd, *J* = 12.9, 5.3, 4.1 Hz, C*H*C=O), 2.96 (1H, td, *J* = 13.5, 3.0 Hz, C*H*(H)N), 3.76-3.87 (1H, m, CH(*H*)N), 5.57 (1H, d, *J* = 5.3 Hz, C*H*PhMe), 5.66 (2H, br s, N*H*$_2$), 6.98 (2H, d, *J* = 8.1 Hz, 2 x C*H*$_{arom}$), 7.15 (2H, d, *J* = 8.1 Hz, 2 x C*H*$_{arom}$), 7.32-7.44 (2H, m, 2 x C*H*$_{arom}$), 7.44-7.54 (1H, m, C*H*$_{arom}$), 7.60-7.73 (2H, m, 2 x C*H*$_{arom}$). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ 20.9 (*p*CH_3), 21.0 (*C*H_2CH_2N), 24.2 (*C*H_2CH_2CH_2N), 41.2 (*C*H_2N), 45.7 (*C*HC=O), 57.1 (*C*HPhMe), 127.0 (2 x CH_{arom}), 128.6 (2 x CH_{arom}), 128.9 (2 x CH_{arom}), 129.1 (2 x CH_{arom}), 132.3 (CH_{arom}), 133.4 (C$_{arom,quat}$), 137.5 (C$_{arom,quat}$), 140.2 (C$_{arom,quat}$), 173.4 (C=O). **MS** (ES, pos mode) *m/z* (%): 359 (100) $[M + H]^+$. **HRMS**: calcd. for $C_{19}H_{23}N_2O_3S^+$ $[MH]^+$ 359.1424; found: 359.1437.

5.2.14 Synthesis of 3-amino-2-aryl-1-sulfonylpiperidine *cis*-350 and *cis*-351

The synthesis of (*2S,3S*)-3-amino-2-phenyl-1-tosylpiperidine (*2S,3S*)-*cis*-**350** is representative. To a cooled (-5 °C) solution of NaOH (0.01 g, 0.35 mmol) in water (1.0 mL) was added bromine (1.1 equiv, 0.02 g, 0.15 mmol). The mixture was stirred for 30 minutes and (*2R,3S*)-*cis*-2-phenyl-1-tosylpiperidine-3-carboxamide (*2R,3S*)-*cis*-**347a** (1.0 equiv, 0.05 g, 0.14 mmol) in acetonitrile/water 2:1 (5 mL) was added. The reaction mixture was stirred at 55 °C for 1 hour until completion of the reaction (LC-MS). Subsequently, the reaction mixture was extracted with ethyl acetate (3 x 8 mL). The combined organic layers were washed with 3M HCl (15 mL). The water layer was then made alkaline (pH = 9) with 10% NaOH and extracted with ethyl acetate. The combined organic phases

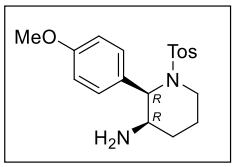
were dried (Na_2SO_4), filtered, and evaporated *in vacuo* and afforded 0.03 g (0.09 mmol, 60% yield) of (*2S,3S*)-3-amino-2-phenyl-1-tosylpiperidine (*2S,3S*)-*cis*-**350**.

(*2S,3S*)-*cis*-3-Amino-2-phenyl-1-tosylpiperidine (*2S,3S*)-350



R_f = 0.48 (EtOAc/MeOH 95/5). Viscous yellow oil, yield 60%. **[α]$_D$** -17.0 (*c* 0.3, CH_2Cl_2). **IR** (cm^{-1}): ν_{max} 1153, 1330, 2937. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.07 (2H, br s, N*H*$_2$), 1.51-1.65 (1H, m, C*H*(H)CH$_2$N), 1.69-1.83 (2H, m, C*H*$_2$CH$_2$CH$_2$N), 1.84-1.93 (1H, m, CH(*H*)CH$_2$N), 2.31 (3H, s, *p*C*H*$_3$), 3.11 (1H, td, *J* = 13.0, 3.5 Hz, C*H*(H)N), 3.18 (1H, ddd, *J* = 12.3, 6.2, 4.0 Hz, C*H*NH$_2$), 3.82 (1H, dd, *J* = 13.0, 3.5 Hz, CH(*H*)N), 5.11 (1H, d, *J* = 6.2 Hz, C*H*Ph), 7.00 (2H, d, *J* = 8.0 Hz, 2 x C*H*$_{arom}$), 7.14-7.31 (7H, m, 7 x C*H*$_{arom}$). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ 21.4 (*p*C*H*$_3$), 24.5 (*C*H$_2$CH$_2$N), 28.4 (*C*H$_2$CH$_2$CH$_2$N), 41.3 (*C*H$_2$N), 51.4 (*C*HNH$_2$), 62.3 (*C*HPh), 127.0 (2 x CH$_{arom}$), 127.7 (CH$_{arom}$), 128.2 (2 x CH$_{arom}$), 129.0 (2 x CH$_{arom}$), 130.0 (2 x CH$_{arom}$), 136.5 (C$_{arom,quat}$), 136.7 (C$_{arom,quat}$), 142.5 (C$_{arom,quat}$). **MS** (ES, pos mode) *m/z* (%): 331 (100) $[M + H]^+$. **HRMS**: calcd. for $C_{18}H_{23}N_2O_2S^+$ $[MH]^+$ 331.1148; found: 331.1483.

(*2R,3R*)-*cis*-3-Amino-2-(4-methoxyphenyl)-1-tosylpiperidine (*2R,3R*)-351



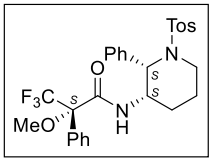
R_f = 0.56 (EtOAc/MeOH 95/5). Viscous yellow oil, yield 75%. **[α]$_D$** +26.7 (*c* 0.3, CH_2Cl_2). **IR** (cm^{-1}): ν_{max} 1156, 1249, 1331, 1510, 1608, 3356. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.22 (2H, br s, N*H*$_2$), 1.49-1.63 (1H, m, C*H*(H)CH$_2$N), 1.66-1.81 (2H, m, C*H*$_2$CH$_2$CH$_2$N), 1.82-1.92 (1H, m, CH(*H*)CH$_2$N), 2.32 (3H, s, *p*C*H*), 3.07 (1H, td, *J* = 12.7, 3.4 Hz, C*H*(H)N), 3.16 (1H, ddd, *J* = 12.3, 6.2, 4.0 Hz, C*H*NH$_2$), 3.73-3.81 (1H, m, CH(*H*)N), 3.77 (3H, s, OC*H*$_3$), 5.07 (1H, d, *J* = 6.2 Hz, C*H*PhOMe), 6.71 (2H, d, *J* = 8.7 Hz, 2 x CH$_{arom}$), 7.01 (2H, d, *J* = 8.2 Hz, 2 x CH$_{arom}$), 7.17 (2H, d, *J* = 8.7 Hz, 2 x CH$_{arom}$), 7.30 (2H, d, *J* = 8.2 Hz, 2 x CH$_{arom}$). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ 21.4 (*p*C*H*$_3$), 24.5 (*C*H$_2$CH$_2$N), 28.4 (*C*H$_2$CH$_2$CH$_2$N), 41.2 (*C*H$_2$N), 51.4 (*C*HNH$_2$), 55.3 (OC*H*$_3$), 61.7 (*C*HPh), 113.6 (2 x CH$_{arom}$), 127.1 (2 x CH$_{arom}$), 128.7 (CH$_{arom}$), 129.0 (2 x CH$_{arom}$), 131.1 (2 x CH$_{arom}$), 136.6 (C$_{arom,quat}$), 142.4 (C$_{arom,quat}$), 142.3 (C$_{arom,quat}$). **MS** (ES, pos mode) *m/z* (%): 361 (100) $[M + H]^+$. **HRMS**: calcd. for $C_{19}H_{25}N_2O_3S^+$ $[MH]^+$ 361.1580; found: 361.1592.

5.2.15 Synthesis of 3,3,3-trifluoro-2-methoxy-2-phenyl-*N*-((*2S,3S*)-2-phenyl-1-tosyl-piperidin-3-yl)propanamides 352 and 353

The synthesis of (*S*)-3,3,3-trifluoro-2-methoxy-2-phenyl-*N*-((*2S,3S*)-2-phenyl-1-tosylpiperidin-3-yl)propanamide **352** is representative. In a screw-capped 4 mL glass vial, fitted with a magnetic stir bar, (*2S,3S*)-3-amino-2-phenyl-1-tosylpiperidine (*2S,3S*)-**350** (5.1 mg, 0.016 mmol) was dissolved in dry CH_2Cl_2 (1 mL) and dry pyridine (3.1 equiv, 4 µL) was added at room temperature. To the

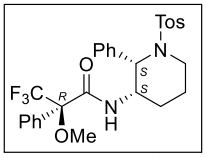
resulting mixture was added (*R*)-MTPA-Cl (1.8 equiv, 7.1 mg, 0.028 mmol) and the reaction was stirred at room temperature for 2 hours (TLC control). After reaction completion, H_2O (1 mL) was added and mixture was extracted with Et_2O (3 x 2 mL). The organic layers were combined and dried (Na_2SO_4). The filtration, evaporation of solvent *in vacuo* and purification *via* preparative thin layer chromatography afforded pure (*S*)-3,3,3-trifluoro-2-methoxy-2-phenyl-*N*-((*2S,3S*)-2-phenyl-1-tosylpiperidin-3-yl)propanamide **352**.

(*S*)-*cis*-3,3,3-trifluoro-2-methoxy-2-phenyl-*N*-((*2S,3S*)-2-phenyl-1-tosylpiperidin-3-yl)propanamide 352



R_f = 0.61 (PE/EA 1/1). Viscous colorless oil, yield 86%. **[α]$_D$** -45.7 (*c* 0.1, CH_3Cl). **IR** (cm^{-1}): ν_{max} 1138, 1164, 1325, 1648, 3058. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.65-1.91 (4H, m, C*H*(*H*)C*H*(*H*)CH_2N), 2.33 (3H, s, CH_3 in Tos), 3.06 (3H, s, OCH_3), 3.15-3.25 (1H, m, C*H*(H)N), 3.79-3.86 (1H, m, CH(*H*)N), 4.30-4.40 (1H, m, C*H*N), 5.42 (1H, d, *J* = 6.4 Hz, C*H*Ph), 6.23 (1H, d, *J* = 8.6 Hz, CHN*H*), 7.07 (2H, d, *J* = 8.0 Hz, 2 x CH_{arom}), 7.20-7.44 (12H, m, 12 x CH_{arom}). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ 21.4 (CH_3, Tos), 23.8 (*C*$H_2CH_2CH_2$N), 25.3 (*C*H_2CH_2N), 41.3 (*C*H_2N), 48.5 (*C*HNH), 54.8 (O*C*H_3), 58.3 (*C*HPh), 83.8 (*C*CF_3, d, *J* = 26.3 Hz), 123.4 (*C*F_3, q, *J* = 291.2 Hz), 127.1 (2 x CH_{arom}), 127.4 (2 x CH_{arom}), 128.2 (CH_{arom}), 128.5 (2 x CH_{arom}), 128.6 (2 x CH_{arom}), 129.3 (2 x CH_{arom}), 129.4 (2 x CH_{arom}), 129.6 (2 x CH_{arom}), 132.6 ($C_{arom,quat}$), 136.7 (C=O, d, *J* = 20.9 Hz), 142.8 ($C_{arom,quat}$), 165.3 ($C_{arom,quat}$). **^{19}F NMR** (282 MHz, $CDCl_3$): δ -68.44 (3F, s, CF_3). **MS** (ES, pos mode) *m/z*: 547 (100) $[M + H]^+$. **HRMS**: calcd for $C_{28}H_{30}F_3N_2O_4S^+$ $[MH]^+$ 547.1873; found: 547.1877.

(*R*)-*cis*-3,3,3-trifluoro-2-methoxy-2-phenyl-*N*-((*2S,3S*)-2-phenyl-1-tosylpiperidin-3-yl)propanamide 353

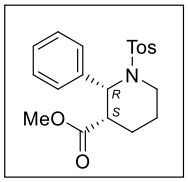


R_f = 0.61 (PE/EA 1/1). Viscous colorless oil, yield 71%. **[α]$_D$** -62.6 (*c* 0.1, CH_3Cl). **IR** (cm^{-1}): ν_{max} 1134, 1158, 1330, 1654, 3042. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.66-1.91 (4H, m, C*H*(*H*)C*H*(*H*)CH_2N), 2.33 (3H, s, CH_3 in Tos), 3.11 (3H, s, OCH_3), 3.16-3.25 (1H, m, C*H*(H)N), 3.79-3.86 (1H, m, CH(*H*)N), 4.31-4.40 (1H, m, C*H*N), 5.29 (1H, d, *J* = 6.4 Hz, C*H*Ph), 6.29 (1H, d, *J* = 8.6 Hz, CHN*H*), 7.05-7.16 (6H, m, 6 x CH_{arom}), 7.21-7.25 (1H, m, CH_{arom}), 7.34-7.45 (7H, m, 7 x CH_{arom}). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ 21.4 (CH_3, Tos), 23.8 (*C*$H_2CH_2CH_2$N), 25.4 (*C*H_2CH_2N), 41.4 (*C*H_2N), 48.2 (*C*HNH), 54.6 (O*C*H_3), 58.3 (*C*HPh), 83.7 (*C*CF_3, d, *J* = 26.2 Hz), 123.6 (*C*F_3, q, *J* = 299.4 Hz), 127.0 (2 x CH_{arom}), 127.7 (2 x CH_{arom}), 128.0 (CH_{arom}), 128.4 (2 x CH_{arom}), 128.6 (2 x CH_{arom}), 129.3 (2 x CH_{arom}), 129.4 (2 x CH_{arom}), 129.5 (2 x CH_{arom}), 131.8 ($C_{arom,quat}$), 136.6 (C=O, d, *J* = 25.7 Hz), 142.9 ($C_{arom,quat}$), 165.2 ($C_{arom,quat}$). **^{19}F NMR** (282 MHz, $CDCl_3$): δ -69.25 (3F, s, CF_3). **MS** (ES, pos mode) *m/z*: 547 (100) $[M + H]^+$. **HRMS**: calcd for $C_{28}H_{30}F_3N_2O_4S^+$ $[MH]^+$ 547.1873; found: 547.1875.

5.2.16 Synthesis of methyl 2-aryl-1-sulfonylpiperidine-3-carboxylates *cis*-354 and *cis*-355

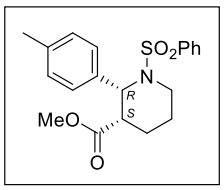
The synthesis of (*2S,3R*)-*cis*-methyl 2-(4-methoxyphenyl)-1-tosylpiperidine-3-carboxylate (*2S,3R*)-**355b** is representative. To a solution of (*R*$_S$,*2S,3R*)-**345b** (0.25 g, 0.51 mmol) in methanol (15 mL) was added 3M HCl in methanol (80.0 equiv, 13.7 mL, 41.1 mmol) at room temperature. The mixture was stirred for 24 hours at room temperature and subsequently poured in saturated aqueous $NaHCO_3$ (20 mL) and extracted with EtOAc (3 x 10 mL). The combined organic phases were dried ($MgSO_4$), filtered, and evaporated *in vacuo*. The crude product was purified by flash chromatography to yield 0.11 g (0.27 mmol, 65% yield) of pure (*2S,3R*)-methyl 2-(4-methoxyphenyl)-1-tosylpiperidine-3-carboxylate (*2S,3R*)-*cis*-**355b**.

(*2R,3S*)-*cis*-Methyl 2-phenyl-1-tosylpiperidine-3-carboxylate (*2R,3S*)-354a



R_f = 0.32 (PE/Et_2O 1/1). Colorless oil, yield 58%. **[α]$_D$** +78.4 (*c* 0.1, $CHCl_3$). ee > 98%, **HPLC** (IA): hexane (95%)/ethanol (5%), 1 mL min $^{-1}$, 35 ºC, t_R = 15.65 min. **IR** (cm^{-1}): ν_{max} 1157, 1337, 1733, 2950. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.37-1.51 (1H, m, C*H*(H)CH_2N), 1.63-1.72 (1H, m, CH(*H*)CH_2N), 1.92-2.02 (2H, m, C*H*$_2$$CH_2$$CH_2$N), 2.40 (3H, s, *p*C*H*$_3$), 2.74-2.82 (1H, m, C*H*C=O), 2.87 (1H, td, *J* = 13.8, 3.0 Hz, C*H*(H)N), 3.57 (3H, s, OC*H*$_3$), 3.77-3.85 (1H, m, CH(*H*)N), 5.68 (1H, d, *J* = 5.4 Hz, C*H*Ph), 7.17-7.25 (7H, m, 7 x CH_{arom}), 7.61 (2H, d, *J* = 8.3 Hz, 2 x CH_{arom}). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ 20.7 (*p*CH_3), 21.5 (*C*$H_2$$CH_2$N), 24.0 (*C*$H_2$$CH_2$$CH_2$N), 41.2 (*C*$H_2$N), 43.9 (*C*HC=O), 51.9 (OCH_3), 56.4 (*C*HPh), 127.0 (2 x CH_{arom}), 127.5 (CH_{arom}), 128.3 (2 x CH_{arom}), 128.4 (2 x CH_{arom}), 129.6 (2 x CH_{arom}), 137.1 ($C_{arom,quat}$), 137.7 ($C_{arom,quat}$), 143.1 ($C_{arom,quat}$), 172.6 (C=O). **MS** (ES, pos mode) *m/z* (%): 374 (100) $[M + H]^+$. **HRMS**: calcd. for $C_{20}H_{24}NO_4S^+$ $[MH]^+$ 374.1426; found: 374.1415.

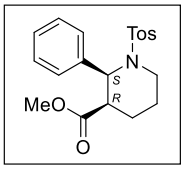
(*2R,3S*)-*cis*-Methyl 1-(phenylsulfonyl)-2-(*p*-tolyl)piperidine-3-carboxylate (*2R,3S*)-354c



R_f = 0.24 (PE/ Et_2O 7/3). Colorless oil, yield 63%. **[α]$_D$** +48.3 (*c* 0.2, $CHCl_3$). **IR** (cm^{-1}): ν_{max} 950, 1094, 1157, 1309, 1446, 1731, 2954. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.44-1.54 (1H, m, C*H*(H)CH_2N), 1.64-1.75 (1H, m, CH(*H*)CH_2N), 1.91-2.02 (2H, m, C*H*$_2$$CH_2$$CH_2$N), 2.28 (3H, s, *p*C*H*$_3$), 2.74-2.83 (1H, m, C*H*C=O), 2.89 (1H, td, *J* = 13.6, 3.8 Hz, C*H*(H)N), 3.57 (3H, s, OC*H*$_3$), 3.79-3.88 (1H, m, CH(*H*)N), 5.65 (1H, d, *J* = 5.5 Hz, C*H*PhMe), 7.00 (2H, d, *J* = 8.2 Hz, 2 x CH_{arom}), 7.09 (2H, d, *J* = 8.2 Hz, 2 x CH_{arom}), 7.34-7.42 (2H, m, 2 x CH_{arom}), 7.47-7.53 (1H, m, CH_{arom}), 7.66-7.74 (2H, m, 2 x CH_{arom}). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ 20.7 (*p*CH_3), 20.9 (*C*$H_2$$CH_2$N), 24.1 (*C*$H_2$$CH_2$$CH_2$N), 41.2 (*C*$H_2$N), 44.2 (*C*HC=O), 51.8 (OCH_3), 56.3 (*C*HPh), 127.0 (2 x CH_{arom}), 128.2 (2 x CH_{arom}), 129.0 (2 x CH_{arom}), 129.1 (2 x CH_{arom}), 132.3 (CH_{arom}), 133.9 ($C_{arom,quat}$), 137.3 ($C_{arom,quat}$), 140.6 ($C_{arom,quat}$),

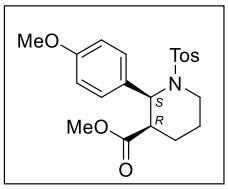
172.5 (C=O). **MS** (ES, pos mode) *m/z* (%): 374 (100) $[M + H]^+$. **HRMS**: calcd. for $C_{20}H_{24}NO_4S^+$ $[MH]^+$ 374.1426; found: 374.1419.

(*2S,3R*)-*cis*-Methyl 2-phenyl-1-tosylpiperidine-3-carboxylate (*2S,3R*)-355a



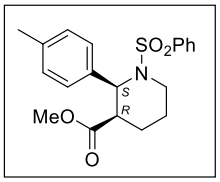
R_f = 0.32 (PE/ Et_2O 1/1). Colorless oil, yield 54 %. **$[\alpha]_D$** -76.2 (*c* 0.1, $CHCl_3$). ee > 98%, **HPLC** (IA): hexane (95%)/ethanol (5%), 1 mL min^{-1}, 35 °C, t_R = 14.27 min. **IR** (cm^{-1}): ν_{max} 1160, 1138, 1734, 2952. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.37-1.51 (1H, m, C*H*(H)CH_2N), 1.63-1.72 (1H, m, CH(*H*)CH_2N), 1.92-2.02 (2H, m, C$H_2$$CH_2$$CH_2$N), 2.40 (3H, s, *p*C$H_3$), 2.74-2.82 (1H, m, C*H*C=O), 2.87 (1H, td, *J* = 13.8, 3.0 Hz, C*H*(H)N), 3.57 (3H, s, OCH_3), 3.77-3.85 (1H, m, CH(*H*)N), 5.68 (1H, d, *J* = 5.4 Hz, C*H*Ph), 7.17-7.25 (7H, m, 7 x CH_{arom}), 7.61 (2H, d, *J* = 8.3 Hz, 2 x CH_{arom}). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ 20.7 (*p*CH_3), 21.5 (*C*$H_2$$CH_2$N), 24.0 (*C*$H_2$$CH_2$$CH_2$N), 41.2 (*C*$H_2$N), 43.9 (*C*HC=O), 51.9 (O*C*H_3), 56.4 (*C*HPh), 127.0 (2 x CH_{arom}), 127.5 (CH_{arom}), 128.3 (2 x CH_{arom}), 128.4 (2 x CH_{arom}), 129.6 (2 x CH_{arom}), 137.1 ($C_{arom,quat}$), 137.7 ($C_{arom,quat}$), 143.1 ($C_{arom,quat}$), 172.6 (C=O). **MS** (ES, pos mode) *m/z* (%): 374 (100) $[M + H]^+$. **HRMS**: calcd. for $C_{20}H_{24}NO_4S^+$ $[MH]^+$ 374.1426; found: 374.1425.

(*2S,3R*)-*cis*-Methyl 2-(4-methoxyphenyl)-1-tosylpiperidine-3-carboxylate (*2S,3R*)-355b



R_f = 0.27 (PE/Et_2O 1/1). Colorless oil, yield 65%. **$[\alpha]_D$** -50.9 (*c* 0.1, $CHCl_3$). **IR** (cm^{-1}): ν_{max} 1157, 1459, 1513, 1734, 2923. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.37-1.55 (1H, m, C*H*(H)CH_2N), 1.64-1.73 (1H, m, CH(*H*)CH_2N), 1.91-2.00 (2H, m, C$H_2$$CH_2$$CH_2$N), 2.38 (3H, s, *p*C$H_3$), 2.73-2.82 (1H, m, C*H*C=O), 2.88 (1H, td, *J* = 13.6, 3.0 Hz, C*H*(H)N), 3.56 (3H, s, OCH_3), 3.76 (3H, s, OCH_3), 3.77-3.83 (1H, m, CH(*H*)N), 5.62 (1H, d, *J* = 5.5 Hz, C*H*PhOMe), 6.73 (2H, d, *J* = 8.8 Hz, 2 x CH_{arom}), 7.15 (2H, d, *J* = 8.8 Hz, 2 x CH_{arom}), 7.19 (2H, d, *J* = 8.2 Hz, 2 x CH_{arom}), 7.59 (2H, d, *J* = 8.2 Hz, 2 x CH_{arom}). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ 20.7 (*p*CH_3), 21.5 (*C*$H_2$$CH_2$N), 24.0 (*C*$H_2$$CH_2$$CH_2$N), 41.0 (*C*$H_2$N), 44.1 (*C*HC=O), 51.8 (O*C*H_3), 55.2 (O*C*H_3), 56.0 (*C*HPh), 113.7 (2 x CH_{arom}), 127.0 (2 x CH_{arom}), 129.0 ($C_{arom,quat}$), 129.6 (4 x CH_{arom}), 137.7 ($C_{arom,quat}$), 143.0 ($C_{arom,quat}$), 158.9 ($C_{arom,quat}$), 172.6 (C=O). **MS** (ES, pos mode) *m/z* (%): 404 (97) $[M + H]^+$, 372 (100). **HRMS**: calcd. for $C_{21}H_{26}NO_5S^+$ $[MH]^+$ 404.1526; found: 404.1534.

(*2S,3R*)-*cis*-Methyl 1-(phenylsulfonyl)-2-(*p*-tolyl)piperidine-3-carboxylate (*2S,3R*)-355c



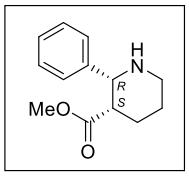
R_f = 0.24 (PE/Et_2O 7/3). Colorless oil, yield 68%. **$[\alpha]_D$** -52.1 (*c* 0.2, $CHCl_3$). **IR** (cm^{-1}): ν_{max} 951, 1095, 1157, 1309, 1446, 1731, 2953. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.44-1.54 (1H, m, C*H*(H)CH_2N), 1.64-1.75 (1H, m, CH(*H*)CH_2N), 1.91-2.02 (2H, m, C$H_2$$CH_2$$CH_2$N), 2.28 (3H, s, *p*C$H_3$), 2.74-2.83 (1H, m, C*H*C=O), 2.89 (1H, td, *J* = 13.6, 3.8 Hz, C*H*(H)N), 3.57 (3H, s, OCH_3), 3.79-3.88 (1H, m, CH(*H*)N), 5.65 (1H, d, *J* = 5.5 Hz, C*H*PhMe), 7.00 (2H, d, *J* = 8.2 Hz, 2 x CH_{arom}), 7.09 (2H, d, *J* = 8.2 Hz, 2 x

CH_{arom}), 7.34-7.42 (2H, m, 2 x CH_{arom}), 7.47-7.53 (1H, m, CH_{arom}), 7.66-7.74 (2H, m, 2 x CH_{arom}). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ 20.7 (*p*CH_3), 20.9 (*C*H_2CH_2N), 24.1 (*C*H_2CH_2CH_2N), 41.2 (*C*H_2N), 44.2 (*C*HC=O), 51.8 (O*C*H_3), 56.3 (*C*HPh), 127.0 (2 x CH_{arom}), 128.2 (2 x CH_{arom}), 129.0 (2 x CH_{arom}), 129.1 (2 x CH_{arom}), 132.3 (CH_{arom}), 133.9 ($C_{arom,quat}$), 137.3 ($C_{arom,quat}$), 140.6 ($C_{arom,quat}$), 172.5 (C=O). **MS** (ES, pos mode) *m/z* (%): 374 (100) $[M + H]^+$. **HRMS**: calcd. for $C_{20}H_{24}NO_4S^+$ $[MH]^+$ 374.1426; found: 374.1427.

5.2.17 Synthesis of methyl 2-arylpiperidine-3-carboxylates *cis*-356 and *cis*-357

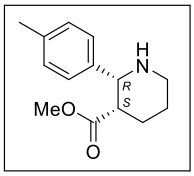
The synthesis of (*2R,3S*)-*cis*-methyl 2-phenylpiperidine-3-carboxylate (*2R,3S*)-*cis*-**356a** is representative. A mixture of magnesium turnings (60.0 equiv, 0.15 g, 6.43 mmol) in dry MeOH (15 mL) was sonicated at 40 °C for 10 minutes. Subsequently, a solution of piperidine-3-carboxylate (*2R,3S*)-**354a** (0.04 g, 0.11 mmol) in MeOH (5 mL) was added dropwise and the resulting suspension was sonicated for six hours at 40 °C. Next, the reaction mixture was concentrated under reduced pressure to afford a white powder which was redissolved in 10 mL aqueous NH_4Cl (sat.) and extracted with EtOAc (3 x 10 mL). The combined organic phases were dried ($MgSO_4$), filtered, and evaporated *in vacuo*. The crude product was purified by flash chromatography to yield 0.009 g (0.04 mmol, 37% yield) of pure (*2R,3S*)-methyl 2-phenyl-1-tosylpiperidine-3-carboxylate (*2R,3S*)-**356a**. For the synthesis of (*2R,3S*)-*cis*-methyl 2-(*p*-tolyl)piperidine-3-carboxylate (*2R,3S*)-*cis*-**356c** and (*2S,3R*)-*cis*-methyl 2-(*p*-tolyl)piperidine-3-carboxylate (*2S,3R*)-*cis*-**357c**, 20.0 equivalents of Mg was used and the reaction time was reduced to 1.5 hours.

(*2R,3S*)-*cis*-Methyl 2-phenylpiperidine-3-carboxylate (*2R,3S*)-356a



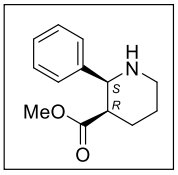
R_f = 0.15 (EtOAc/MeOH 95/5). Pale yellow oil, yield 37%. **[α]$_D$** +82.5 (*c* 0.2, $CHCl_3$). **IR** (cm^{-1}): ν_{max} 1161, 1436, 1723, 2936. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.46-1.53 (1H, m, C*H*(H)CH_2N), 1.72-2.01 (2H, m, C*H*(H)CH(*H*)CH_2N), 2.04 (1H, br s, NH), 2.11-2.22 (1H, m, CH(*H*)CH_2CH_2N), 2.81 (1H, td, *J* = 12.5, 3.1 Hz, C*H*(H)N), 2.93-3.04 (1H, m, C*H*C=O), 3.30-3.39 (1H, m, CH(*H*)N), 3.41 (3H, s, OC*H*$_3$), 3.95 (1H, d, *J* = 3.5 Hz, C*H*Ph), 7.17-7.24 (1H, m, CH_{arom}), 7.27-7.33 (4H, m, 4 x CH_{arom}). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ 22.0 (*C*H_2CH_2N), 27.9 (*C*H_2CH_2CH_2N), 44.8 (*C*HC=O), 47.2 (*C*H_2N), 51.0 (O*C*H_3), 61.4 (*C*HPh), 126.0 (2 x CH_{arom}), 126.8 (CH_{arom}), 128.1 (2 x CH_{arom}), 142.3 ($C_{arom,quat}$), 174.0 (C=O). **MS** (ES, pos mode) *m/z* (%): 220 (100) $[M + H]^+$. **HRMS**: calcd. for $C_{13}H_{18}NO_2^+$ $[MH]^+$ 220.1332; found: 220.1353.

(*2R,3S*)-*cis*-Methyl 2-(*p*-tolyl)piperidine-3-carboxylate (*2R,3S*)-356c



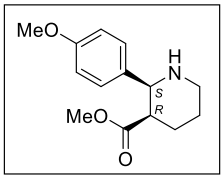
R_f = 0.14 (EtOAc/MeOH 95/5). Pale yellow oil, yield 52%. **[α]$_D$** +87.5 (*c* 0.2, $CHCl_3$). **IR** (cm^{-1}): ν_{max} 808, 1190, 1436, 1726, 2934. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.42-1.53 (1H, m, C*H*(H)CH_2N), 1.75-1.99 (2H, m, C*H*(H)CH(*H*)CH_2N), 2.11-2.20 (1H, m, CH(*H*)CH_2CH_2N), 2.31 (3H, s, *p*C*H*$_3$), 2.80 (1H, td, *J* = 12.7, 2.9 Hz, C*H*(H)N), 2.90-2.98 (1H, m, C*H*C=O), 3.29-3.36 (1H, m, CH(*H*)N), 3.45 (3H, s, OC*H*$_3$), 3.91 (1H, d, *J* = 3.4 Hz, C*H*Ph), 7.10 (2H, d, *J* = 8.1 Hz, 2 x CH_{arom}), 7.17 (2H, d, *J* = 8.1 Hz, 2 x CH_{arom}). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ 21.0 (*p*CH_3), 22.0 (*C*H_2CH_2N), 27.8 (*C*H_2CH_2CH_2N), 44.6 (*C*HC=O), 47.1 (*C*H_2N), 51.1 (O*C*H_3), 61.1 (*C*HPhMe), 125.8 (2 x CH_{arom}), 128.8 (2 x CH_{arom}), 136.2 ($C_{arom,quat}$), 139.3 ($C_{arom,quat}$), 174.1 (C=O). **MS** (ES, pos mode) *m/z* (%): 234 (100) $[M + H]^+$. **HRMS**: calcd. for $C_{14}H_{20}NO_2^+$ $[MH]^+$ 234.1489; found: 234.1491.

(*2S,3R*)-*cis*-Methyl 2-phenylpiperidine-3-carboxylate (*2S,3R*)-357a



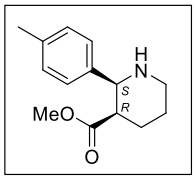
R_f = 0.15 (EtOAc/MeOH 95/5). Pale yellow oil, yield 35%. **[α]$_D$** -76.4 (*c* 0.1, $CHCl_3$). **IR** (cm^{-1}): ν_{max} 1161, 1436, 1724, 2930. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.46-1.53 (1H, m, C*H*(H)CH_2N), 1.72-2.01 (2H, m, C*H*(H)CH(*H*)CH_2N), 2.11-2.22 (1H, m, CH(*H*)CH_2CH_2N), 2.81 (1H, td, *J* = 12.5, 3.1 Hz, C*H*(H)N), 2.93-3.04 (1H, m, C*H*C=O), 3.30-3.39 (1H, m, CH(*H*)N), 3.41 (3H, s, OC*H*$_3$), 3.95 (1H, d, *J* = 3.5 Hz, C*H*Ph), 7.17-7.24 (1H, m, CH_{arom}), 7.27-7.33 (4H, m, 4 x CH_{arom}). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ 22.0 (*C*H_2CH_2N), 27.9 (*C*H_2CH_2CH_2N), 44.8 (*C*HC=O), 47.2 (*C*H_2N), 51.0 (O*C*H_3), 61.4 (*C*HPh), 126.0 (2 x CH_{arom}), 126.8 (CH_{arom}), 128.1 (2 x CH_{arom}), 142.3 ($C_{arom,quat}$), 174.0 (C=O). **MS** (ES, pos mode) *m/z* (%): 220 (100) $[M + H]^+$. **HRMS**: calcd. for $C_{13}H_{18}NO_2^+$ $[MH]^+$ 220.1332; found: 220.1331.

(*2S,3R*)-*cis*-Methyl 2-(4-methoxyphenyl)piperidine-3-carboxylate (*2S,3R*)-357b



R_f = 0.14 (EtOAc/MeOH 95/5). Pale yellow oil, yield 44%. **[α]$_D$** -67.4 (*c* 0.2, $CHCl_3$). **IR** (cm^{-1}): ν_{max} 1158, 1250, 1513, 1731, 2928. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.44-1.54 (1H, m, C*H*(H)CH_2N), 1.69-1.98 (3H, m, C*H*(H)CH(*H*)CH_2N and N*H*), 2.03-2.20 (1H, m, CH(*H*)CH_2CH_2N), 2.79 (1H, td, *J* = 12.6, 3.1 Hz, C*H*(H)N), 2.89-2.97 (1H, m, C*H*C=O), 3.27-3.40 (1H, m, CH(*H*)N), 3.45 (3H, s, OC*H*$_3$), 3.78 (3H, s, OC*H*$_3$), 3.90 (1H, d, *J* = 3.4 Hz, C*H*PhOMe), 6.83 (2H, d, *J* = 8.6 Hz, 2 x CH_{arom}), 7.20 (2H, d, *J* = 8.6 Hz, 2 x CH_{arom}). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ 22.0 (*C*H_2CH_2N), 27.8 (*C*H_2CH_2CH_2N), 44.6 (*C*HC=O), 47.1 (*C*H_2N), 51.1 (O*C*H_3), 55.2 (O*C*H_3), 60.8 (*C*HPhOMe), 113.5 (2 x CH_{arom}), 127.0 (2 x CH_{arom}), 128.5 ($C_{arom,quat}$), 134.5 ($C_{arom,quat}$), 174.1 (C=O). **MS** (ES, pos mode) *m/z* (%): 250 (100) $[M + H]^+$. **HRMS**: calcd. for $C_{14}H_{20}NO_3^+$ $[MH]^+$ 250.1438; found: 250.1443.

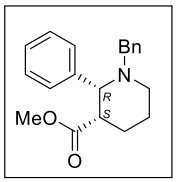
(*2S,3R*)-*cis*-Methyl 2-(*p*-tolyl)piperidine-3-carboxylate (*2S,3R*)-357c



R_f = 0.16 (EtOAc/MeOH 95/5). Pale yellow oil, yield 50%. **[α]$_D$** -80.3 (*c* 0.3, $CHCl_3$). **IR** (cm^{-1}): ν_{max} 1162, 1436, 1726, 2930. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.42-1.53 (1H, m, C*H*(H)CH_2N), 1.75-1.99 (2H, m, C*H*(H)CH(*H*)CH_2N), 2.11-2.20 (1H, m, CH(*H*)CH_2CH_2N), 2.31 (3H, s, *p*C*H*$_3$), 2.80 (1H, td, *J* = 12.7, 2.9 Hz, C*H*(H)N), 2.90-2.98 (1H, m, C*H*C=O), 3.29-3.36 (1H, m, CH(*H*)N), 3.45 (3H, s, OC*H*$_3$), 3.91 (1H, d, *J* = 3.4 Hz, C*H*Ph), 7.10 (2H, d, *J* = 8.1 Hz, 2 x CH_{arom}), 7.17 (2H, d, *J* = 8.1 Hz, 2 x CH_{arom}). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ 21.0 (*p*CH_3), 22.0 (*C*H_2CH_2N), 27.8 (*C*$H_2CH_2CH_2$N), 44.6 (*C*HC=O), 47.1 (*C*H_2N), 51.1 (O*C*H_3), 61.1 (*C*HPhMe), 125.8 (2 x CH_{arom}), 128.8 (2 x CH_{arom}), 136.2 ($C_{arom,quat}$), 139.3 ($C_{arom,quat}$), 174.1 (C=O). **MS** (ES, pos mode) *m/z* (%): 234 (100) $[M + H]^+$, 235 (15). **HRMS**: calcd. for $C_{14}H_{20}NO_2^+$ $[MH]^+$ 234.1489; found: 234.1487.

5.2.18 Synthesis of (*2R,3S*)-*cis*-methyl 1-benzyl-2-phenylpiperidine-3-carboxylate 358

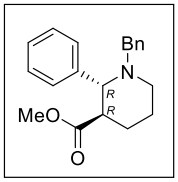
To a solution of (*2R,3S*)-*cis*-methyl 2-phenylpiperidine-3-carboxylate **356a** (0.18 g, 0.84 mmol) in dry THF (10 mL), Et_3N (1.1 equiv, 0.09 g, 0.92 mmol) and benzylbromide (1.0 equiv, 0.14 g, 0.84 mmol) were added at 0 °C. The reaction mixture was stirred at room temperature for 18 hours. Subsequently, the reaction mixture was quenched with 1M HCl (1 mL), and 10 mL H_2O was added, followed by extraction with Et_2O (3 x 10 mL). The organic phases were combined and washed with $NaHCO_3$ (2 x 10 mL) and brine (1 x 10 mL), then dried ($MgSO_4$). Filtration, evaporation of the solvent *in vacuo* and purification *via* column chromatography afforded (*2R,3S*)-*cis*-**358**.



R_f = 0.49 (PE/Et_2O 2/1). Pale yellow oil, yield 33%. **[α]$_D$** +40.9 (*c* 0.2, $CHCl_3$). **IR** (cm^{-1}): ν_{max} 1255 1731. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.52-1.62 (1H, m, C*H*(H)CH_2N), 1.70-1.81 (1H, m, C*H*(H)CH_2CH_2N), 2.00-2.10 (1H, m, CH(*H*)CH_2CH_2N), 2.11-2.24 (2H, m, CH(*H*)C*H*(H)N), 2.92-2.98 (1H, m, C*H*C=O), 2.98-3.04 (1H, m, CH_2CH(*H*)N), 3.12 (1H, d, *J* = 14.3 Hz, C*H*(H)Ph), 3.36 (3H, s, OC*H*$_3$), 3.73 (1H, d, *J* = 14.3 Hz, CH(*H*)Ph), 3.75 (1H, *J* = 5.6 Hz, NC*H*Ph), 7.19-7.40 (10H, m, C*H*$_{arom}$). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ 22.3 (*C*H_2CH_2N), 25.2 (*C*$H_2CH_2CH_2$N), 46.6 (C*H*C=O), 50.6 (*C*H_2N), 50.9 (O*C*H_3), 59.4 (*C*H_2Ph), 66.9 (N*C*HPh), 126.7 (CH_{arom}), 127.3 (CH_{arom}), 128.1 (4CH_{arom}), 128.5 (4CH_{arom}), 139.3 ($C_{arom,quat}$), 140.8 ($C_{arom,quat}$), 173.5 (C=O). **MS** (ES, pos mode) *m/z*: 310 (100) $[M + H]^+$. **HRMS**: calcd for $C_{20}H_{24}NO_2^+$ $[MH]^+$ 310.1802; found: 310.1811.

5.2.19 Synthesis of (*2R,3R*)-*trans*-methyl 1-benzyl-2-phenylpiperidine-3-carboxylate 359

To a solution of (*2R,3S*)-*cis*-methyl 1-benzyl-2-phenylpiperidine-3-carboxylate **358** (0.10 g, 0.32 mmol) in dry THF (5 mL), potassium *tert*-butoxide (0.32 mmol, 0.32 mL of a 1 M solution in THF) and *tert*-butyl acetate (10 mmol, 3.2 mL) were added at room temperature. The reaction mixture was stirred for 48 hours at ambient temperature under nitrogen flow and subsequently was passed through a plug of silica gel and washed with THF followed by ethyl acetate. The eluent was evaporated and the crude mixture was purified by thin layer chromatography, affording *trans*-**359**.



R_f = 0.16 (PE/Et_2O 9/1). Pale yellow oil, yield 43%. **[α]$_D$** -10.5 (*c* 0.3, $CHCl_3$). **IR** (cm^{-1}): ν_{max} 1254, 1732. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.59-1.73 (3H, m, C*H*(H)C*H*(*H*)CH_2N), 1.97-2.07 (2H, m, CH(*H*)CH_2C*H*(H)N), 2.66-2.75 (1H, m, C*H*C=O), 2.82 (1H, d, *J* = 13.7 Hz, C*H*(H)Ph), 2.92-3.00 (1H, m, C*H*(H)N), 3.36 (3H, s, OC*H*$_3$), 3.37 (1H, d, *J* = 10.1 Hz, NC*H*Ph), 3.71 (1H, d, *J* = 13.7 Hz, CH(*H*)Ph), 7.17-7.47 (10H, m, C*H*$_{arom}$). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ 24.7 (*C*H_2CH_2N), 28.7 (*C*$H_2CH_2CH_2$N), 51.2 (O*C*H_3), 52.2 (C*H*C=O), 52.5 (*C*H_2N), 59.2 (*C*H_2Ph), 69.9 (N*C*HPh), 126.7 (CH_{arom}), 127.5 (CH_{arom}), 128.1 ($2CH_{arom}$), 128.2 ($2CH_{arom}$), 128.4 ($2CH_{arom}$), 128.6 ($2CH_{arom}$), 139.5 ($C_{arom,quat}$), 141.9 ($C_{arom,quat}$), 174.5 (C=O). **MS** (ES, pos mode) *m/z*: 310 (100) $[M + H]^+$. **HRMS**: calcd for $C_{20}H_{24}NO_2^+$ $[MH]^+$ 310.1802; found: 310.1809.

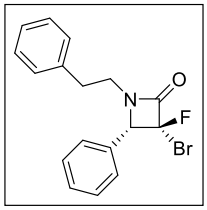
5.2.20 Synthesis of α-bromo-α-fluoro-β-lactams 363

The synthesis of 1-benzyl-3-bromo-3-fluoro-4-phenylazetidin-2-one **363a** is representative. Ethyl dibromofluoroacetate **34** (1.86 g, 9.2 mmol) was added to a solution of imine **362a** (0.6 g, 3.1 mmol) in Et_2O (20 mL) at -10 °C and then 1M Et_2Zn in hexane (3.0 equiv, 9.2 mL) was slowly added to the mixture at -10 °C. The resulting mixture was stirred at the same temperature for 1 hour. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ (9 mL), and the mixture was filtered through a Celite pad and the filter cake was rinsed with a small amount of EtOAc (10 mL). The filtrate was extracted with EtOAc (3 x 15 mL), and then the organic phase was washed with brine (2 x 20 mL) and dried over $MgSO_4$. Filtration, removal of solvent *in vacuo* and purification *via* column chromatography afforded 1-benzyl-3-bromo-3-fluoro-4-phenylazetidin-2-one **363a** in 57% yield.

β-Lactams **363a-e** are known compounds and all spectroscopic data were in good agreement with reported data.[204i]

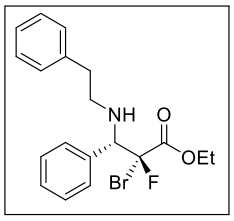
When imine **365a** was used, only ethyl *trans*-1-benzyl-2-fluoro-3-methylaziridine-2-carboxylate **366** was formed. When imine **365b** was used, a mixture of *cis*-**363f**, *syn*-**367** and *cis*-**368** was formed. When aldimine **27a** was used, diastereomeric mixture **370** was formed in a ratio 1/1.

***cis*-3-Bromo-3-fluoro-1-phenethyl-4-phenylazetidin-2-one 363f**



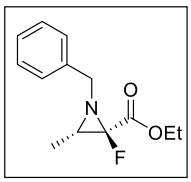
R_f = 0.18 (PE/Et_2O 8/2). White crystals, yield 36%. **Mp** 73.2-74.2 °C. **IR** (cm^{-1}): ν_{max} 697, 756, 969, 1777. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.96 (2H, t, J = 7.1 Hz, NCH(H)C*H*(*H*)Ph), 3.18 (1H, dt, J = 14.1, 7.1 Hz, NC*H*(H)CH(H)Ph), 3.89 (1H, dt, J = 14.1, 7.1 Hz, NCH(*H*)CH(H)Ph), 4.63 (1H, d, J = 10.3 Hz, C*H*CF), 7.05-7.17 (4H, m, CH_{arom}), 7.23-7.45 (6H, m, C*H*$_{arom}$). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ 33.6 (NCH_2CH_2Ph), 42.4 (NCH_2CH_2Ph), 70.8 (d, J = 25.0 Hz, *C*HPh), 106.3 (d, J = 299.4 Hz, *C*F), 127.0 (CH_{arom}), 127.8 (2 x CH_{arom}), 128.6 (2 x CH_{arom}), 128.7 (2 x CH_{arom}), 128.8 (2 x CH_{arom}), 129.7 (CH_{arom}), 132.4 ($C_{arom,quat}$), 137.5 ($C_{arom,quat}$), 161.3 (C=O, d, J = 25.6 Hz). **^{19}F NMR** (376.5 MHz, $CDCl_3$): δ -117.2 (CFCH, d, J = 10.3 Hz). **MS** (ES, pos. mode): *m/z* (%): 348/350 (100) $[M+H]^+$. **HRMS**: calcd for $C_{17}H_{16}BrFNO^+$ $[MH]^+$ 348.0394; found: 348.0398.

***syn*-Ethyl 2-bromo-2-fluoro-3-(phenethylamino)-3-phenylpropanoate 367**



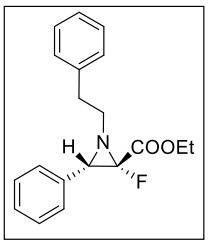
R_f = 0.37 (PE/Et_2O 8/2). (*syn*-**5g**/ unidentified prod 81/19). Pale yellow oil, yield 15%. **IR** (cm^{-1}): ν_{max} 697, 1144, 1257, 1764, 3028. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.12 (3H, t, J = 7.1 Hz, OCH_2CH_3), 2.02 (1H, br s, NH), 2.73-2.85 (4H, m, CH_2CH_2Ph), 4.04-4.17 (2H, m, OCH_2CH_3), 4.33 (1H, d, J = 23.1 Hz, C*H*CF), 7.11-7.37 (10H, m, 10 x C*H*$_{arom}$). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ 13.7 (OCH_2CH_3), 36.2 (NCH_2CH_2Ph), 48.8 (NCH_2CH_2Ph), 62.9 (OCH_2CH_3), 68.9 (*C*HCF, d, J = 17.2 Hz), 100.8 (CH*C*F, d, J = 274.1 Hz), 126.2 (CH_{arom}), 128.4 (2 x CH_{arom}), 128.5 (2 x CH_{arom}), 128.7 (2 x CH_{arom}), 128.8 (CH_{arom}), 129.1 (2 x CH_{arom}), 135.3, ($C_{arom,quat}$) 139.6 ($C_{arom,quat}$), 165.1 (C=O, d, J = 25.8 Hz). **^{19}F NMR** (376.5 MHz, $CDCl_3$): δ -127.7 (1F, d, J = 23.1 Hz, CHCF). **MS** (ES, pos. mode): *m/z* (%): 394/396 (100) $[M+H]^+$. **HRMS**: calcd for $C_{19}H_{22}BrFNO_2^+$ $[MH]^+$ 394.0813; found: 394.0817.

***trans*-Ethyl 1-benzyl-2-fluoro-3-methylaziridine-2-carboxylate 366**



R_f = 0.59 (PE/Et_2O 6/1). Yellow oil, yield 37 %, purity 94%. **IR** (cm^{-1}): ν_{max} 649, 1105, 1257, 1762. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.29-1.31 (6H, m, C*H*$_3$CH$_2$O and C*H*$_3$CH), 2.32-2.44 (1H, m, CH$_3$C*H*), 3.89 (1H, d, J = 13.8 Hz, C*H*(H)Ph), 3.99 (1H, d, J = 13.8 Hz, CH(*H*)Ph), 4.25-4.36 (2H, m, CH$_3$C*H*$_2$O), 7.23-7.38 (5H, m, C*H*$_{arom}$). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ 14.1 (2C, *C*H$_3$CH$_2$O and *C*H$_3$CH), 44.9 (CH$_3$*C*H, d, J = 17.5 Hz), 52.9 (*C*H$_2$Ph), 62.2 (CH$_3$*C*H$_2$O), 85.3 (*C*F, d, J = 257.4 Hz), 127.2 (CH_{arom}), 127.8 (2 x CH_{arom}), 128.4 (2 x CH_{arom}), 138.0 ($C_{arom,quat}$), 166 (C=O, d, J = 34.6 Hz). **^{19}F NMR** (376.5 MHz, $CDCl_3$): δ -119.07 (1F, d, J = 11.1 Hz, C*F*COOEt). **MS** (ES, pos. mode): *m/z* (%): 238 (100) $[M+H]^+$. **HRMS**: calcd for $C_{13}H_{17}FNO_2^+$ $[MH]^+$ 238.1238; found: 238.1242.

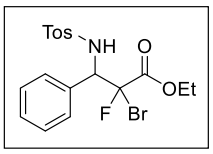
***cis*-Ethyl 2-fluoro-1-phenethyl-3-phenylaziridine-2-carboxylate 368**



R_f = 0.46 (PE/Et_2O 8/2). Yellow oil, yield 11%. **IR** (cm^{-1}): ν_{max} 696, 1139, 1289, 1703, 1732. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.34 (3H, t, J = 7.1 Hz, OCH_2CH_3), 2.90 (2H, m, CH_2CH_2Ph), 3.03-3.12 (1H, m, $CH(H)CH_2Ph$), 3.15-3.24 (1H, m, $CH(H)CH_2Ph$), 4.37 (1H, d, J = 4.4 Hz, CHCF), 4.23-4.36 (2H, m, OCH_2CH_3), 7.14-7.40 (10H, m, 10 x CH_{arom}). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ 14.2 (OCH_2CH_3), 36.0 (NCH_2CH_2Ph), 51.2 (CHCF, d, J = 12.3 Hz), 52.8 (NCH_2CH_2Ph), 62.5 (OCH_2CH_3), 84.8 (CHCF, d, J = 253.9 Hz), 126.3 (CH_{arom}), 127.8 (2 x CH_{arom}), 128.0 (CH_{arom}), 128.1 (2 x CH_{arom}), 128.4 (2 x CH_{arom}), 128.9 (2 x CH_{arom}), 133.7 ($C_{arom,quat}$) 139.1 ($C_{arom,quat}$), 165.2 (C=O, d, J = 35.9 Hz). **^{19}F NMR** (376.5 MHz, $CDCl_3$): δ -68.8 (1F, d, J = 4.4 Hz, CHCF). **MS** (ES, pos. mode): *m/z* (%): 294 (100) $[M-F]^-$. **HRMS**: calcd for $C_{19}H_{21}FNO_2^+$ $[MH]^+$ 314.1551; found: 314.1553.

Ethyl 2-bromo-2-fluoro-3-((4-methylphenyl)sulfonamido)-3-phenylpropanoate 370

Spectral data were obtained from a mixture of two diastereomers in a 1/1 ratio



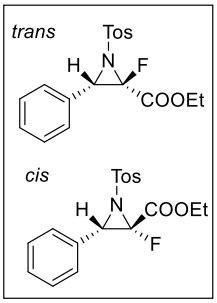
R_f = 0.30 (PE/Et_2O 1/1). Yellow amorphous solid, yield 65%. **IR** (cm^{-1}): ν_{max} 700, 921, 1146, 1160, 1254, 1328, 1458, 1463, 1763, 3239. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.11 (3H, t, J = 7.1 Hz, $OCH_2CH_{3,isomer\ 1}$), 1.36 (3H, t, J = 7.1 Hz, $OCH_2CH_{3,isomer\ 2}$), 2.30 (3H, s, $CH_{3\ isomer\ 1}$, Tos), 2.31 (3H, s, $CH_{3\ isomer\ 2}$, Tos), 4.02-4.16 (2H, m, $OCH_2CH_{3\ isomer\ 1}$), 4.28-4.37 (2H, m, $OCH_2CH_{3\ isomer\ 2}$), 5.10 (1H, dd, J = 24.3, 9.3 Hz, $CHCF_{isomer\ 1}$), 5.11 (1H, dd, J = 22.3, 10.7 Hz, $CHCF_{isomer\ 2}$), 5.60 (1H, d, J = 9.3 Hz, $NHCH_{isomer\ 1}$), 5.70 (1H, d, J = 10.7 Hz, $NHCH_{isomer\ 2}$), 6.99-7.28 (14H, m, 7 x $CH_{arom,isomer\ 1}$ and 7 x $CH_{arom,isomer\ 2}$), 7.44 (2H, 2 x $CH_{arom,isomer\ 1}$), 7.53 (2H, 2 x $CH_{arom,isomer\ 2}$). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ 13.6 ($OCH_2CH_{3\ isomer\ 1}$), 13.8 ($OCH_2CH_{3\ isomer\ 2}$), 21.4 (2 x $CH_{3\ isomer\ 1\ and\ 2}$, Tos), 63.4 ($OCH_2CH_{3\ isomer\ 1}$), 63.8 ($OCH_2CH_{3\ isomer\ 2}$), 64.0 ($CHPh_{isomer\ 1}$, d, J = 20.8 Hz), 64.3 ($CHPh_{isomer\ 1}$, d, J = 17.7 Hz), 97.4 ($CHCF_{isomer\ 1}$, d, J = 268.7 Hz), 97.4 ($CHCF_{isomer\ 2}$, d, J = 270.4 Hz), 127.0 and 127.1 (2 x $CH_{arom,\ isomer\ 1\ and\ 2}$), 128.3 (2 x $CH_{arom,\ isomer\ 1\ and\ 2}$), 128.5 (4 x $CH_{arom,\ isomer\ 1\ and\ 2}$), 128.7 (4 x $CH_{arom,\ isomer\ 1\ and\ 2}$), 129.0 (2 x $CH_{arom,\ isomer\ 1\ and\ 2}$), 129.3 (4 x $CH_{arom,\ isomer\ 1\ and\ 2}$), 133.2 (2 x $C_{arom,quat,\ isomer\ 1\ and\ 2}$), 136.7 and 137.1 (2 x $C_{arom,quat\ isomer\ 1\ and\ 2}$), 143.4 (2 x $C_{arom,quat,\ isomer\ 1\ and\ 2}$), 164.0 ($C=O_{isomer\ 1}$, d, J = 28.8 Hz), 164.9 ($C=O_{isomer\ 2}$, d, J = 27.5 Hz). **^{19}F NMR** (376.5 MHz, $CDCl_3$): δ -129.3 (1F, d, J = 24.3 Hz, $CHCF_{isomer\ 1}$), -131 (1F, d, J = 22.3 Hz, $CHCF_{isomer\ 2}$). **MS** (ES, pos. mode): *m/z* (%): 461/463 (100) $[M+NH_4]^+$.

5.2.21 Synthesis of 2-fluoro-3-phenyl-1-tosylaziridine-2-carboxylates 371 and 372

To a solution of ethyl 2-bromo-2-fluoro-3-((4-methylphenyl)sulfonamido)-3-phenylpropanoate **370** (122.6 mg, 0.28 mmol) in CH_3CN (10 mL), K_2CO_3 (3.0 equiv, 115.9 mg, 0.84 mmol) was added in

one portion. The reaction mixture was stirred for 1 hour at room temperature. Then, the solvent was removed *in vacuo* and EtOAc was added to the residue, followed by filtration. The filter cake was rinsed with a small amount of EtOAc and the solvents were removed *in vacuo*. Purification of the crude mixture *via* column chromatography afforded a mixture of **371**/**372** in overall yield of 30%.

Ethyl 2-fluoro-3-phenyl-1-tosylaziridine-2-carboxylates *cis*-371 and *trans*-372



Yellow oil, yield 12% (mixture *trans*/*cis* 34/66) and 18% (mixture *trans*/*cis* 97/3). <u>*trans*-**372**</u>: R_f = 0.37 (PE/Et_2O 6/4). **IR** (cm^{-1}): ν_{max} 760, 957, 1163, 1339, 1748. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.99 (3H, t, J = 7.1 Hz, OCH_2CH_3), 2.46 (3H, s, CH_3 in Tos), 3.98-4.14 (2H, m, OCH_2CH_3), 4.54 (1H, d, J = 8.1 Hz, C*H*Ph), 7.19-7.31 (5H, m, 5 x CH_{arom}), 7.36 (2H, d, J = 8.2 Hz, 2 x CH_{arom}), 7.93 (2H, d, J = 8.2 Hz, 2 x CH_{arom}). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ 13.6 (OCH_2CH_3), 21.7 (CH_3, Tos), 50.8 (*C*HPh, d, J = 19.3 Hz), 62.8 (OCH_2CH_3), 84.6 (CF, d, J = 276.0 Hz), 127.2 (2 x CH_{arom}), 128.2 (2 x CH_{arom}), 128.3 (2 x CH_{arom}), 128.9 (CH_{arom}), 129.6 ($C_{arom,quat}$), 129.9 (2 x CH_{arom}), 135.2 ($C_{arom,quat}$), 145.4 ($C_{arom,quat}$), 160.9 (C=O, d, J = 34.2 Hz). **^{19}F NMR** (376.5 MHz, $CDCl_3$): δ -165.3 (1F, d, J = 8.1 Hz, C*F*). **MS** (ES, pos. mode): *m/z* (%): 364 (100) $[M+H]^+$. **HRMS**: calcd for $C_{18}H_{19}FNO_4S^+$ $[MH]^+$ 364.1013; found: 364.1017.

<u>*cis*-**371**</u>: R_f = 0.40 (PE/Et_2O 6/4). **IR** (cm^{-1}): ν_{max} 760, 957, 1163, 1339, 1748. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.44 (3H, t, J = 7.2 Hz, OCH_2CH_3), 2.43 (3H, s, CH_3 in Tos), 4.41-4.52 (2H, m, OCH_2CH_3), 4.87 (1H, d, J = 2.5 Hz, C*H*Ph), 7.20-7.38 (5H, m, 5 x CH_{arom}), 7.33 (2H, d, J = 8.4 Hz, 2 x CH_{arom}), 7.84 (2H, d, J = 8.4 Hz, 2 x CH_{arom}). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ 13.9 (OCH_2CH_3), 21.7 (CH_3, Tos), 52.2 (*C*HPh, d, J = 19.3 Hz), 63.8 (OCH_2CH_3), 82.9 (*C*F, d, J = 269.1 Hz), 127.3 (2 x CH_{arom}), 127.7 (CH_{arom}), 128.5 (2 x CH_{arom}), 128.9 (CH_{arom}), 129.2 (CH_{arom}), 129.7 ($C_{arom,quat}$), 129.8 (2 x CH_{arom}), 137.1 ($C_{arom,quat}$), 144.8 ($C_{arom,quat}$), 162.3 (C=O, d, J = 35.3 Hz). **^{19}F NMR** (376.5 MHz, $CDCl_3$): δ -161.1 (1F, d, J = 2.5 Hz, C*F*). **MS** (ES, pos. mode): *m/z* (%): 364 (100) $[M+H]^+$. **HRMS**: calcd for $C_{18}H_{19}FNO_4S^+$ $[MH]^+$ 364.1013; found: 364.1017.

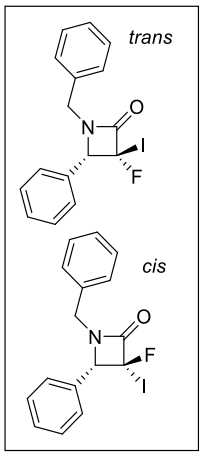
5.2.22 Synthesis of 1-benzyl-3-fluoro-3-iodo-4-phenylazetidin-2-ones 387

To a solution of 3-fluoro-2-azetidin-2-one **386** (0.39 g, 1.5 mmol) in THF (8 mL), a 1M solution of LiHMDS in hexanes (2.0 equiv, 3.1 mL) was added dropwise at -78 °C and the reaction mixture was stirred at the same temperature for 45 min. Then, a solution of iodine (1.1 equiv, 0.43 g, 1.7 mmol) in THF (4 mL) was added slowly to the reaction mixture. The resulting mixture was stirred at -78 °C for 1 h and subsequently quenched with aqueous NH_4Cl. The reaction mixture was poured into an aqueous saturated $NaHCO_3$ and extracted with Et_2O (3 x 10 mL). The organic phase was washed with brine (2 x 5 mL) and dried over $MgSO_4$. Filtration, removal of the solvent *in vacuo*, and purification by column chromatography afforded 3-fluoro-3-iodo-2-azetidinone **387** in 31% yield.

The side product *trans*-1-benzyl-3-fluoro-4-phenylazetidin-2-one **388**, which is an isomer of starting *cis*-**386**, was isolated in 15% yield.

***trans*- and *cis*-1-Benzyl-3-fluoro-3-iodo-4-phenylazetidin-2-ones 387**

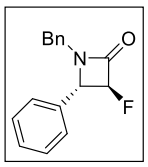
Spectral data were obtained from a mixture of two diastereomers in 85/15 ratio.



R_f = 0.40 (PE/Et_2O 7/3). Yellow amorphous solid, yield 31%. **IR** (cm^{-1}): ν_{max} 696, 1771. <u>*trans*-**387**</u>: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 3.91 (1H, d, J = 14.8 Hz, C*H*(H)Ph), 4.91 (1H, d, J = 14.8 Hz, CH(*H*)Ph), 4.95 (1H, d, J = 2.8 Hz, C*H*Ph), 7.08-7.48 (10H, m, CH_{arom}). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ 44.3 (*C*H_2Ph), 74.3 (*C*HPh, d, J = 23.2 Hz), 79.44 (*C*F, d, J = 311.9 Hz), 128.1 (CH_{arom}), 128.4 (4 x CH_{arom}), 129.1 (4 x CH_{arom}), 129.9 (CH_{arom}), 130.9 ($C_{arom,quat}$), 133.3 ($C_{arom,quat}$), 162.3 (C=O, d, J = 24.2 Hz). **^{19}F NMR** (376.5 MHz, $CDCl_3$): δ -130.71 (CHC*F*, d, J = 2.8 Hz). **MS** (ES, pos. mode): *m/z* (%): 382 (100) $[M+H]^+$. **HRMS**: calcd for $C_{16}H_{14}FINO^+$ $[MH]^+$ 382.0099; found: 382.0111.

<u>*cis*-**387**</u>: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 3.89 (1H, d, J = 14.8 Hz, C*H*(H)Ph), 4.63 (1H, d, J = 11.4 Hz, C*H*Ph), 4.97 (1H, d, J = 14.8 Hz, CH(*H*)Ph), 7.08-7.48 (10H, m, CH_{arom}). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ 45.1 (*C*H_2Ph), 69.4 (*C*HPh, d, J = 24.7 Hz), 90.67 (*C*F, d, J = 301.1 Hz), 127.6 (CH_{arom}), 128.4 (2 x CH_{arom}), 128.7 (2 x CH_{arom}), 128.9 (2 x CH_{arom}), 129.1 (2 x CH_{arom}), 129.8 (CH_{arom}), 133.5 ($C_{arom,quat}$), 134.3 ($C_{arom,quat}$), 162.2 (C=O, d, J = 24.3 Hz). **^{19}F NMR** (376.5 MHz, $CDCl_3$): δ -118.4 (CHC*F*, d, J = 11.4 Hz). **MS** (ES, pos. mode): *m/z* (%): 382 (100) $[M+H]^+$. **HRMS**: calcd for $C_{16}H_{14}FINO^+$ $[MH]^+$ 382.0099; found: 382.0111.

***trans*-1-Benzyl-3-fluoro-4-phenylazetidin-2-one 388**

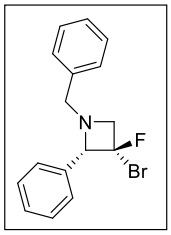


R_f = 0.25 (PE/Et_2O 7/3). Yellow oil, yield 15%. **IR** (cm^{-1}): ν_{max} 720, 1766. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 3.78 (1H, d, J = 14.9 Hz, C*H*(H)Ph), 4.47 (1H, d, J = 11.0 Hz, C*H*CHF), 4.88 (1H, d, J = 14.9 Hz, CH(*H*)Ph), 5.24 (1H, d, J = 54.2 Hz, CHC*H*F), 7.10-7.22 (4H, m, 4 x CH_{arom}), 7.27-7.44 (6H, m, 6 x CH_{arom}). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ 44.5 (*C*H_2Ph), 62.5 (*C*HCHF, d, J = 24.0 Hz), 97.9 (*C*HF, d, J = 226.1 Hz), 126.8 (2 x CH_{arom}), 128.1 (CH_{arom}), 128.6 (2 x CH_{arom}), 128.9 (2 x CH_{arom}), 129.2 (2 x CH_{arom}), 129.3 (CH_{arom}), 134.2 ($C_{arom,quat}$), 134.3 ($C_{arom,quat}$), 163.6 (C=O, d, J = 22.8 Hz). **^{19}F NMR** (376.5 MHz, $CDCl_3$): δ -189.5 (1F, d x d, J = 54.5, 11.0 Hz, C*H*F). **MS** (ES, pos. mode): *m/z* (%): 256 (100) $[M+H]^+$. **HRMS**: calcd for $C_{19}H_{21}FNO_2^+$ $[MH]^+$ 256.1132; found: 256.1136.

5.2.23 Synthesis of *cis*-3-bromo-3-fluoro-2-phenylazetidines 373 and *trans*-1-benzyl-3-fluoro-3-iodo-2-phenylazetidine 383

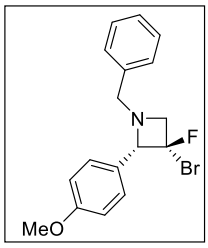
The synthesis of 3-bromo-3-fluoro-2-phenylazetidine **373a** is representative. To a solution of aluminium(III) chloride (3.0 equiv, 0.12 g, 0.90 mmol) in 5 mL of dry Et_2O was added lithium aluminium hydride (3.0 equiv, 0.03 g, 0.90 mmol) at 0 °C. The reaction mixture was stirred for 10 minutes at 0 °C and was subsequently refluxed during 30 minutes. 1-Benzyl-3-bromo-3-fluoro-4-phenylazetidin-2-one **363a** (0.10 g, 0.30 mmol) in 4 mL of dry Et_2O was added dropwise, and after the addition was complete, reflux was maintained during 4 hours. The reaction was cooled to 0 °C and 8 mL of water was carefully added. The aqueous phase was extracted with EtOAc (3 x 10 mL) and the combined organic phases were dried over $MgSO_4$. Filtration, evaporation of solvent and recrystallization of the crude mixture afforded pure *cis*-1-benzyl-3-bromo-3-fluoro-2-phenylazetidine **373a** in 98% yield. The reaction time was shortened to 2 hours for the synthesis of azetidine **383**. The crude oils were purified *via* column chromatography.

***cis*-1-Benzyl-3-bromo-3-fluoro-2-phenylazetidine 373a**



R_f = 0.44 (PE/Et_2O 9/1). White crystals, yield 98%. **Mp** 48.5-49.5 °C. **IR** (cm^{-1}): ν_{max} 696, 1219, 1450. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 3.43-3.62 (1H, m, C*H*(H)CFBr), 3.52 (1H, d, *J* = 13.1 Hz, C*H*(H)Ph), 3.91 (1H, t, *J* = 8.8 Hz, CH(*H*)CFBr), 4.02 (1H, d, *J* = 13.1 Hz, CH(*H*)Ph), 4.52 (1H, d, *J* = 20.2 Hz, C*H*N), 7.18-7.60 (10H, m, CH_{arom}). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 60.3 (*C*H_2Ph), 68.1 (*C*H_2CFBr, d, *J* = 19.6 Hz), 80.4 (*C*HN, d, *J* = 20.8 Hz), 102.5 (*C*FBr, d, *J* = 291.9 Hz), 127.6 (CH_{arom}), 127.7 (2 x CH_{arom}), 128.4 (2 x CH_{arom}), 128.6 (2 x CH_{arom}), 128.7 (CH_{arom}), 128.8 (2 x CH_{arom}), 136.8 ($C_{arom,quat}$), 137.0 ($C_{arom,quat}$). **^{19}F NMR** (282 MHz, $CDCl_3$): δ -90.53 (1F, td, *J* = 20.2, 8.8 Hz, CBr*F*). **MS** (ES, pos. mode): *m/z* (%): 320/322 (100) $[M+H]^+$. **HRMS**: calcd for $C_{16}H_{16}BrFN^+$ $[MH]^+$ 320.0444; found: 320.0454.

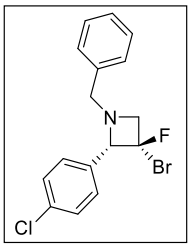
***cis*-1-Benzyl-3-bromo-3-fluoro-2-(4-methoxyphenyl)azetidine 373b**



R_f = 0.29 (PE/Et_2O 9/1). White crystals, yield 95%. **Mp** 50.3-51.3 °C. **IR** (cm^{-1}): ν_{max} 696, 1219, 1450. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 3.49-3.58 (1H, m, C*H*(H)CFBr), 3.49 (1H, d, *J* = 13.2 Hz, C*H*(H)Ph), 3.83 (3H, s, OMe), 3.88 (1H, t, *J* = 8.8 Hz, CH(*H*)CFBr), 3.88 (1H, d, *J* = 13.2 Hz, CH(*H*)Ph), 4.44 (1H, d, *J* = 20.0 Hz, C*H*N), 6.93 (2H, d, *J* = 8.6 Hz, CH_{arom}), 7.26-7.36 (5H, m, CH_{arom}), 7.41 (2H, d, *J* = 8.6 Hz, CH_{arom}). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 55.4 (O*C*H_3), 60.1 (*C*H_2Ph), 67.9 (*C*H_2CFBr, d, *J* = 18.5 Hz), 80.1 (*C*HN, d, *J* = 20.8 Hz), 103.3 (*C*FBr, d, *J* = 290.8 Hz), 113.7 (2 x CH_{arom}), 127.6 (CH_{arom}), 128.6 (2 x CH_{arom}), 128.8 (2 x CH_{arom}), 129.1 (3 x CH_{arom}), 136.9 ($C_{arom,quat}$), 160.0 ($C_{arom,quat}$). **^{19}F NMR** (282 MHz, $CDCl_3$): δ -90.75 (1F, td, *J* = 20.0, 8.8 Hz, CBr*F*). **MS** (ES,

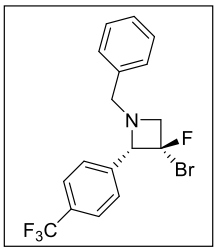
pos. mode): *m/z* (%): 350/352 (100) $[M+H]^+$. **HRMS**: calcd for $C_{17}H_{18}BrFNO^+$ $[MH]^+$ 350.0550; found: 350.0547.

***cis*-1-Benzyl-3-bromo-2-(4-chlorophenyl)-3-fluoroazetidine 373c**



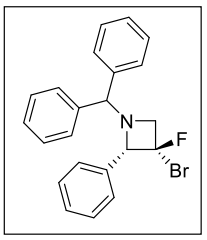
R_f = 0.35 (PE/Et_2O 9/1). White cryst, yield 98%. **Mp** 68.5-69.5 °C. **IR** (cm^{-1}): ν_{max} 697, 1222, 1488. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 3.54 (1H, d, *J* = 13.1 Hz, C*H*(H)Ph), 3.58 (1H, dd, *J* = 20.8, 9.0 Hz, C*H*(H)CFBr), 3.90 (1H, t, *J* = 9.0 Hz, CH(*H*)CFBr), 3.96 (1H, d, *J* = 13.1 Hz, CH(*H*)Ph), 4.47 (1H, *J* = 20.8 Hz, C*H*N), 7.24-7.42 (9H, m, CH_{arom}). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ 60.2 (*C*H_2Ph), 68.0 (*C*H_2CFBr, d, *J* = 19.2 Hz), 79.7 (*C*HN, d, *J* = 20.7 Hz), 102.0 (*C*F, d, *J* = 292.1 Hz), 127.7 (CH_{arom}), 128.5 (4 x CH_{arom}), 128.8 (2 x CH_{arom}), 129.0 (2 x CH_{arom}), 134.4 ($C_{arom,quat}$), 135.4 ($C_{arom,quat}$), 136.4 ($C_{arom,quat}$). **^{19}F NMR** (376.5 MHz, $CDCl_3$): δ -90.70 (1F, td, *J* = 20.8, 9.0 Hz, CBr*F*). **MS** (ES, pos. mode): *m/z* (%): 354/356/358 (100) $[M+H]^+$. **HRMS**: calcd for $C_{16}H_{15}BrClFN^+$ $[MH]^+$ 354.0055; found: 354.0055.

***cis*-1-Benzyl-3-bromo-3-fluoro-2-(4-(trifluoromethyl)phenyl)azetidine 373d**



R_f = 0.60 (PE/Et_2O 9/1). White crystals, yield 85%. **Mp** 55.0-56.0 °C. **IR** (cm^{-1}): ν_{max} 747, 1094, 1323. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 3.58 (1H, d, *J* = 13.0 Hz, C*H*(H)Ph), 3.63 (1H, dd, *J* = 20.4, 9.5 Hz, C*H*(H)CFBr), 3.94 (1H, t, *J* = 9.5 Hz, CH(*H*)CFBr), 3.98 (1H, d, *J* = 13.0 Hz, CH(*H*)Ph), 4.57 (1H, *J* = 20.4 Hz, C*H*Ph), 7.26-7.36 (5H, m, CH_{arom}), 7.57 (2H, d, *J* = 8.3 Hz, CH_{arom}), 7.65 (2H, d, *J* = 8.3 Hz, CH_{arom}). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ 60.3 (*C*H_2Ph), 68.1 (*C*H_2CFBr, d, *J* = 19.2 Hz), 79.8 (*C*HN, d, *J* = 20.8 Hz), 101.4 (*C*F, d, *J* = 292.4 Hz), 124.2 (*C*F_3, q, *J* = 272.1 Hz), 125.3 (2 x CF_3*C*CH, q, *J* = 3.8 Hz), 127.6 (CH_{arom}), 128.0 (2 x CH_{arom}), 128.6 (2 x CH_{arom}), 128.8 (2 x CH_{arom}), 130.7 (CF_3*C*CH, q, *J* = 32.4 Hz), 136.3 ($C_{arom,quat}$), 140.8 ($C_{arom,quat}$). **^{19}F NMR** (376.5 MHz, $CDCl_3$): δ -90.58 (1F, td, *J* = 20.4, 9.5 Hz, CBr*F*), -62.48 (3F, s, CF_3). **MS** (ES, pos. mode): *m/z* (%): 388/390 (100) $[M+H]^+$. **HRMS**: calcd for $C_{17}H_{15}BrF_4N^+$ $[MH]^+$ 388.0319; found: 388.0320.

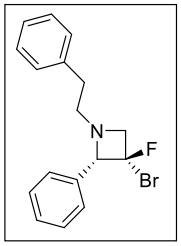
***cis*-1-Benzhydryl-3-bromo-3-fluoro-2-phenylazetidine 373e**



R_f = 0.63 (PE/Et_2O 9/1). White crystals, yield 87%. **Mp** 69.0-70.0 °C. **IR** (cm^{-1}): ν_{max} 697, 1207, 1491. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 3.57 (1H, dd, *J* = 21.7, 10.6 Hz, C*H*(H)CF), 4.10 (1H, t, *J* = 10.6 Hz, CH(*H*)CF), 4.53 (1H, d, *J* = 21.7 Hz, C*H*Ph), 4.71 (1H, s, C*H*Ph_2), 6.93-7.04 (3H, m, CH_{arom}), 7.16-7.31 (8H, m, CH_{arom}), 7.33-7.45 (4H, m, CH_{arom}). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ 68.0 (*C*H_2CF, d, *J* = 19.6 Hz), 75.4 (*C*HPh_2), 80.0 (*C*HPh, d, *J* = 20.8 Hz), 103.3 (*C*F, d, *J* = 290.9 Hz), 127.4 (CH_{arom}), 127.5 (2 x CH_{arom}), 127.6 (CH_{arom}), 127.9 (2 x CH_{arom}), 128.0 (2 x CH_{arom}), 128.1 (CH_{arom}), 128.2 (2 x CH_{arom}), 128.6 (2 x CH_{arom}), 128.7 (2 x CH_{arom}), 137.3 ($C_{arom,quat}$), 140.1

($C_{arom,quat}$), 140.2 ($C_{arom,quat}$). **^{19}F NMR** (376.5 MHz, $CDCl_3$): δ -88.7 (1F, td, *J* = 21.7, 10.6 Hz, CBr*F*). **MS** (ES, pos. mode): *m/z* (%): 396/398 (100) $[M+H]^+$. **HRMS**: calcd for $C_{22}H_{20}BrFN^+$ $[MH]^+$ 396.0758; found: 396.0763.

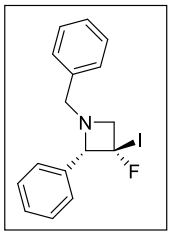
***cis*-3-Bromo-3-fluoro-1-phenethyl-2-phenylazetidine 373f**



R_f = 0.33 (PE/Et_2O 9/1). Pale yellow oil, yield 92%. **IR** (cm^{-1}): ν_{max} 695, 1213, 1486. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.69 (2H, t, *J* = 7.6 Hz, NCH(H)C*H*(*H*)Ph), 2.73-2.81 (1H, m, NC*H*(H)CH(H)Ph), 2.92-3.00 (1H, m, NCH(*H*)CH(H)Ph), 3.54 (1H, dd, *J* = 20.3, 9.0 Hz, C*H*(H)CF), 4.02 (1H, t, *J* = 9.0 Hz, CH(*H*)CF), 4.40 (1H, d, *J* = 20.3 Hz, C*H*Ph), 7.12-7.28 (5H, m, C*H*$_{arom}$), 7.32-7.39 (5H, m, C*H*$_{arom}$). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ 34.8 (NCH_2CH_2Ph), 59.1 (NCH_2CH_2Ph), 68.9 (CH_2CFBr, d, *J* = 19.0 Hz), 81.3 (*C*HPh, d, *J* = 19.9 Hz), 102.2 (*C*FBr, d, *J* = 292.1 Hz), 126.2 (CH_{arom}), 127.5 (2 x CH_{arom}), 128.2 (2 x CH_{arom}), 128.4 (2 x CH_{arom}), 128.5 (CH_{arom}), 128.6 (2 x CH_{arom}), 137.2 ($C_{arom,quat}$), 139.4 ($C_{arom,quat}$). **^{19}F NMR** (376.5 MHz, $CDCl_3$): δ -89.96 (1F, td, *J* = 20.3, 9.0 Hz, CBr*F*). **MS** (ES, pos. mode): *m/z* (%): 334/336 (100) $[M+H]^+$. **HRMS**: calcd for $C_{17}H_{18}BrFN^+$ $[MH]^+$ 334.0601; found: 334.0606.

***trans*-1-Benzyl-3-fluoro-3-iodo-2-phenylazetidine 383**

Spectral data were obtained from a mixture of *trans*/*cis* isomers in 96/4 ratio.



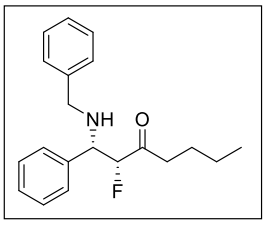
R_f = 0.69 (PE/Et_2O 8/2). Yellow oil, yield 78% (*trans*/*cis* 96/4). **IR** (cm^{-1}): ν_{max} 720, 743, 1157, 1452. *Trans*-**24**: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 3.65 (1H, d, *J* = 12.9 Hz, C*H*(H)Ph), 3.89 (1H, dd, *J* = 23.4, 9.8 Hz, C*H*(H)CF), 4.01 (1H, d, *J* = 12.9 Hz, CH(*H*)Ph), 4.19 (1H, dd, *J* = 15.7, 9.8 Hz, CH(*H*)CF), 5.09 (1H, d, *J* = 15.7 Hz, C*H*Ph), 7.22-7.45 (10H, m, CH_{arom}). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ 60.9 (CH_2Ph), 70.4 (CH_2CF, d, *J* = 22.0 Hz), 73.1 (CF, d, *J* = 292.4 Hz), 85.11 (*C*HCF, d, *J* = 20.7 Hz), 127.5 (CH_{arom}), 127.7 (2 x CH_{arom}), 128.4 (2 x CH_{arom}), 128.5 (2 x CH_{arom}), 128.6 (2 x CH_{arom}), 128.7 (CH_{arom}), 134.2 ($C_{arom,quat}$), 137.0 ($C_{arom,quat}$). **^{19}F NMR** (376.5 MHz, $CDCl_3$): δ -120.53 (1F, dt, *J* = 23.4, 15.7 Hz, CH*F*). **MS** (ES, pos. mode): *m/z* (%): 368 (100) $[M+H]^+$. **HRMS**: calcd for $C_{16}H_{16}FIN^+[MH]^+$ 368.0306; found: 368.0317.

5.2.24 Synthesis of *syn*-1-(benzylamino)-2-fluoro-1-phenylheptan-3-one 389

To a solution of 1-benzyl-3-fluoro-4-phenylazetidin-2-one **386** (117.1 mg, 0.46 mmol) in THF (10 mL) was added at -78 °C a 1.7M solution of *n*-butyllithium in hexanes (2 equiv, 0.53 mL) and the mixture was stirred at the same temperature for 45 minutes. The resulting mixture was added to a solution of iodine (1.1 equiv, 127.8 mg, 0.51 mmol) in THF (5 mL) at -78 °C. This mixture was stirred for 1 hour and subsequently quenched with a solution of $NH_4Cl_{(aq)}$. Saturated aqueous of

$NaHCO_3$ (10 mL) was added and the mixture was extracted with EtOAc (2 x 10 mL). The organic phase was washed with a saturated aqueous sodium thiosulfate (2 x 8 mL) and brine (10 mL). Filtration, evaporation of solvent, and purification by column chromatography afforded 1-(benzylamino)-2-fluoro-1-phenylheptan-3-one **389** in 85% yield.

***syn*-1-(Benzylamino)-2-fluoro-1-phenylheptan-3-one 389**



R_f = 0.56 (PE/Et_2O 1/1). Yellow oil, yield 85%. **IR** (cm^{-1}): ν_{max} 710, 1065, 1453, 1715, 3359. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.91 (3H, t, *J* = 7.3 Hz, C*H*$_3$), 1.26 (1H, br. s, N*H*), 1.27-1.37 (2H, m, C*H*$_2$CH$_3$), 1.52-1.61 (2H, m, C*H*$_2$CH$_2$CH$_3$), 2.46-2.64 (2H, m, C*H*$_2$C=O), 3.47 (1H, d, *J* = 13.1 Hz, C*H*(H)Ph), 3.69 (1H, d, *J* = 13.1 Hz, CH(*H*)Ph), 4.11 (1H, dd, *J* = 28.3, 2.9 Hz, C*H*NH), 4.79 (1H, dd, *J* = 49.2, 2.9 Hz, C*H*F), 7.17-7.43 (10H, m, C*H*$_{arom}$). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ 13.9 (*C*H$_3$), 22.2 (*C*H$_2$CH$_3$), 24.6 (*C*H$_2$CH$_2$CH$_3$), 39.4 (*C*H$_2$C=O), 50.9 (*C*H$_2$Ph), 63.0 (*C*HNH, d, *J* = 18.3 Hz), 98.5 (*C*HF, d, *J* = 191.6 Hz), 127.1 (CH$_{arom}$), 121.7 (2 x CH$_{arom}$), 128.0 (CH$_{arom}$), 128.2 (2 x CH$_{arom}$), 128.3 (2 x CH$_{arom}$), 128.8 (2 x CH$_{arom}$), 138.4 (C$_{arom,quat}$), 139.6 (C$_{arom,quat}$), 209.0 (*C*=O, d, *J* = 25.0 Hz). **^{19}F NMR** (376.5 MHz, $CDCl_3$): δ -203.76 (1F, dd, *J* = 49.2, 28.3 Hz, CH*F*). **MS** (ES, pos. mode): *m/z* (%): 314 (100) $[M+H]^+$. **HRMS**: calcd for $C_{20}H_{25}FNO^+$ $[MH]^+$ 314.1915; found: 314.1927.

5.2.25 Synthesis of 1-benzyl-3-fluoro-2-arylazetidine-2-carbonitriles 377 and 1-benzyl-3,3-dimethoxy-2-arylazetidines 378

The synthesis of 1-benzyl-3-fluoro-2-phenyl-2-carbonitrile **377a** is representative.

Method A.

1-Benzyl-3-bromo-3-fluoro-2-phenylazetidine **373a** (0.11 g, 0.34 mmol) was dissolved in dry DMSO (5 mL) and potassium cyanide (4.0 equiv, 0.09 g, 1.38 mmol) was added to the solution in one portion. The resulting mixture was heated at 100 °C and after completion of reaction (20 hours, TLC-monitoring) quenched with water (10 mL). This mixture was extracted with Et_2O (3 x 5 mL). The combined organic phases were washed with brine (3 x 5 mL) and water (1 x 5 mL), and were dried over $MgSO_4$. Filtration, evaporation of solvent and purification *via* column chromatography afforded 1-benzyl-3-fluoro-2-phenyl-2-carbonitrile **377a** in 34% yield.

Method B.

In a microwave vial, 1-benzyl-3-bromo-3-fluoro-2-phenylazetidine **373a** (0.20 g, 0.63 mmol) was dissolved in dry DMSO (6 mL) after which potassium cyanide (2.0 equiv, 0.08 g, 1.25 mmol) was added to the solution in one portion. The mixture was heated for 10 minutes at 125 °C with

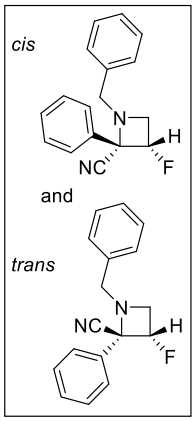
microwave irradiation. After completion of the reaction (10 minutes, LC-MS monitoring), 10 mL of water was added and extracted with Et_2O (3 x 10 mL). The organic phase was washed with brine (3 x 5 mL) and water (1 x 5 mL), dried over $MgSO_4$, and filtered. Removal of solvent *in vacuo* and purification *via* column chromatography afforded azetidine **377a** in 24% yield.

Method C.

In a microwave vial, 1-benzyl-3-bromo-3-fluoro-2-phenylazetidine **373a** (0.10 g, 0.31 mmol) was dissolved in dry MeOH (3 mL) and potassium cyanide (4.3 equiv, 0.09 g, 1.38 mmol) was added to the solution in one portion. The mixture was heated for 30 min at 100 °C with microwave irradiation. After completion of the reaction (30 minutes, LC-MS monitoring), MeOH was removed *in vacuo* and EtOAc (10 mL) was added to the resulting residue. The resulting suspension was filtered and the filter cake was rinsed with a small amount of EtOAc. Evaporation and purification of the crude mixture *via* preparative thin layer chromatography **377a** and **378a** in 46% and 37% yield, respectively.

1-Benzyl-3-fluoro-2-phenyl-2-carbonitrile 377a

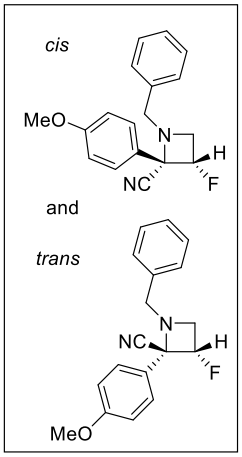
Spectral data were obtained from a mixture of *cis*/*trans* isomers in 84/16 ratio.



R_f = 0.51 (PE/Et_2O 8/2). Yellow oil, yield 34% (method A), 24% (method B), 46% (method C). **IR** (cm^{-1}): ν_{max} 1180, 1359, 1449. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 3.00-4.00 (4H, m, 2 x C*H*$_2$CHF$_{cis \text{ and } trans}$, 2 x C*H*$_2Ph_{cis \text{ and } trans}$), 4.86 (1H, dt, J = 54.5 Hz, 6.1 Hz, C*H*F$_{cis}$), 5.29 (1H, dt, J = 55.6 Hz, 2.8 Hz, C*H*F$_{trans}$), 7.10-7.80 (20H, m, 10 x CH$_{arom,cis}$ and 10 x CH$_{arom,trans}$). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ 56.6 (*C*H$_2$CF$_{trans}$, d, J = 23.1 Hz), 56.8 (*C*H$_2$CF$_{cis}$, d, J = 20.8 Hz), 57.1 (2 x *C*H$_2$Ph$_{cis \text{ and } trans}$), 72.0 (*C*CN$_{trans}$, d, J = 26.5 Hz), 72.2 (*C*CN$_{cis}$, d, J = 18.5 Hz), 87.9 (*C*F$_{cis}$, d, J = 230.8 Hz), 88.8 (*C*F$_{trans}$, d, J = 223.8 Hz), 114.8 (C*C*N$_{cis}$, d, J = 6.9 Hz), 116.4 (C*C*N$_{trans}$, d, J = 5.8 Hz), 126.0, 127.5, 127.8, 128.6, 128.7, 128.8, 129.1 and 129.7 (10 x *C*H$_{arom,cis \text{ and } trans}$), 135.3 (C$_{arom,quat,cis \text{ and } trans}$), 135.9 (C$_{arom,quat,cis \text{ and } trans}$). **^{19}F NMR** (376.5 MHz, $CDCl_3$): δ -176.2 (1F, ddd, J = 55.3, 19.7, 7.9 Hz, CH*F*$_{cis}$), -191.2 (1F, ddd, J = 55.3, 27.6, 19.7 Hz, CH*F*$_{trans}$). **MS** (ES, pos. mode): *m/z* (%): 267 (100) $[M+H]^+$.

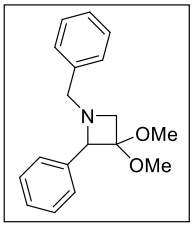
1-Benzyl-3-fluoro-2-(4-methoxyphenyl)azetidine-2-carbonitrile 377b

Spectral data were obtained from a mixture of *cis*/*trans* isomers in 85/15 ratio.



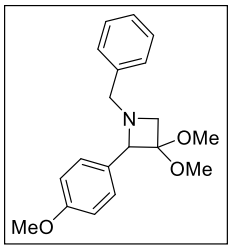
R_f = 0.54 (PE/Et_2O 7/3). Yellow oil, yield 36%. **IR** (cm^{-1}): ν_{max} 696, 1174, 1250, 1511, 1690. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 3.16-3.32 (1H, m, C*H*(H)CHF$_{cis\ and\ trans}$), 3.42-3.54 (1H, m, CH(*H*)CHF$_{trans}$), 3.63 (1H, q, *J* = 6.6 Hz, CH(*H*)CHF$_{cis}$), 3.69 (1H, d, *J* = 12.8 Hz, C*H*(H)Ph$_{trans}$), 3.71 (1H, d, *J* = 12.7 Hz, C*H*(H)Ph$_{cis}$), 3.81 (3H, s, OC*H*$_{3,trans}$), 3.83 (3H, s, OC*H*$_{3,cis}$), 3.89 (1H, d, *J* = 12.8 Hz, CH(*H*)Ph$_{trans}$), 3.91 (1H, d, *J* = 12.7 Hz, CH(*H*)Ph$_{cis}$), 4.82 (1H, dt, *J* = 55.2 Hz, 6.4 Hz, C*H*F$_{cis}$), 5.25 (1H, dd, *J* = 55.3 Hz, 4.6 Hz, C*H*F$_{trans}$), 6.91-6.99 (2H, m, 2 x CH$_{arom,cis\ and\ trans}$), 7.22-7.49 (5H, m, 5 x CH$_{arom,cis\ and\ trans}$), 7.54-7.69 (2H, m, 2 x CH$_{arom,cis\ and\ trans}$). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ 55.3 (OC$H_{3,\ trans}$), 55.4 (OC$H_{3,cis}$), 56.4 (*C*H_2CF$_{trans}$, d, *J* = 23.4 Hz), 56.5 (*C*H_2CF$_{cis}$, d, *J* = 21.5 Hz), 56.7 (*C*H_2Ph$_{trans}$), 56.8 (*C*H_2Ph$_{cis}$), 71.6 (*C*CN$_{trans}$, d, *J* = 27.0 Hz), 74.8 (*C*CN$_{cis}$, d, *J* = 17.9 Hz), 88.1 (*C*HF$_{cis}$, d, *J* = 222.1 Hz), 88.8 (*C*HF$_{trans}$, d, *J* = 230.3 Hz), 114.0 (2 x CH$_{arom,trans}$), 114.3 (2 x CH$_{arom,cis}$), 114.9 (C*C*N$_{cis}$, d, *J* = 7.0 Hz), 116.4 (C*C*N$_{trans}$, d, *J* = 5.9 Hz), 127.2, 127.3, 127.6, 127.7, 128.5, 128.7, 128.8 (7 x CH$_{arom,cis\ and\ trans}$), 136.0 (C$_{arom,quat,cis\ and\ trans}$), 160.7 (C$_{arom,quat,cis\ and\ trans}$). **^{19}F NMR** (376.5 MHz, $CDCl_3$): δ -176.7 (1F, ddd, *J* = 55.2, 17.9, 6.8 Hz, CH*F*$_{cis}$), -192.2 (1F, ddd, *J* = 55.3, 26.2, 20.1 Hz, CH*F*$_{trans}$). **MS** (ES, pos. mode): *m/z* (%): 314 (100) $[M+NH_4]^+$.

1-Benzyl-3,3-dimethoxy-2-phenylazetidine 378a



R_f = 0.24 (PE/Et_2O 8/2). Colorless amorphous solid, yield 36%. **IR** (cm^{-1}): ν_{max} 1046, 1239, 1508. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.88 (1H, d, *J* = 7.9 Hz, C*H*(H)C(OCH_3)$_2$), 2.96 (3H, s, OC*H*$_3$), 3.23 (3H, s, OC*H*$_3$), 3.46 (1H, d, *J* = 13.0 Hz, C*H*(H)Ph), 3.55 (1H, d, *J* = 7.9 Hz, CH(*H*)C(OCH_3)$_2$), 3.91 (1H, d, *J* = 13.0 Hz, CH(*H*)Ph), 4.22 (1H, s, C*H*Ph), 7.17-7.59 (10H, m, 10 x CH$_{arom}$). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ 49.4 (OCH_3), 49.7 (OCH_3), 60.0 (*C*H_2C(OCH_3)$_2$), 61.3 (N*C*H_2Ph), 77.5 (*C*HPh), 100.5 (CH$_2$*C*(OCH_3)$_2$), 126.8 (CH$_{arom}$), 127.7 (CH$_{arom}$), 128.0 (2 x CH$_{arom}$), 128.2 (2 x CH$_{arom}$), 128.7 (4 x CH$_{arom}$), 137.4 (C$_{arom,quat}$), 138.2 (C$_{arom,quat}$). **MS** (ES, pos. mode): *m/z* (%): 284 (100) $[M+H]^+$.

1-Benzyl-3,3-dimethoxy-2-(4-methoxyphenyl)azetidine 378b

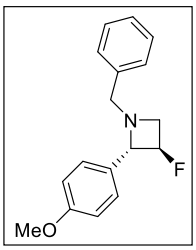


R_f = 0.27 (PE/Et_2O 8/2). Colorless amorphous solid, yield 41% (method C). **IR** (cm^{-1}): ν_{max} 1031, 1245, 1510. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.86 (1H, d, J = 8.0 Hz, C*H*(H)C(OCH_3)$_2$), 2.99 (3H, s, OCH_3), 3.21 (3H, s, OCH_3), 3.44 (1H, d, J = 13.2 Hz, C*H*(H)Ph), 3.53 (1H, d, J = 8.0 Hz, CH(*H*)C(OCH_3)$_2$), 3.81 (3H, s, OCH_3), 3.90 (1H, d, J = 13.2 Hz, CH(*H*)Ph), 4.15 (1H, s, C*H*N), 6.89 (2H, d, J = 8.8 Hz, CH_{arom}), 7.16-7.37 (5H, m, CH_{arom}), 7.49 (2H, d, J = 8.8 Hz, CH_{arom}). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ 49.5 (OCH_3), 49.8 (OCH_3), 55.3 (OCH_3), 59.9 (*C*H_2C(OCH_3)$_2$), 61.3 (N*C*H_2Ph), 77.0 (N*C*H), 100.7 (CH_2*C*(OCH_3)$_2$), 113.5 (2 x CH_{arom}), 127.1 (CH_{arom}), 128.3 (2 x CH_{arom}), 128.8 (2 x CH_{arom}), 129.7 ($C_{arom,quat}$), 130.0 (2 x CH_{arom}), 138.4 ($C_{arom,quat}$), 159.3 ($C_{arom,quat}$). **MS** (ES, pos. mode): *m/z* (%): 314 (100) $[M+H]^+$.

5.2.26 Synthesis of 1-benzyl-3-fluoro-2-arylazetidines 380

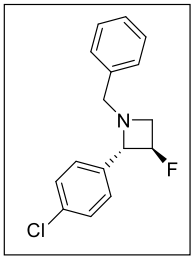
The synthesis of 1-benzyl-3-fluoro-2-(4-methoxyphenyl)azetidine **380b** is representative. To a solution of 1-benzyl-3-bromo-3-fluoro-2-(4-methoxyphenyl)azetidine **373b** (50 mg, 0.14 mmoL) in THF (3 mL) was added at -90 °C a 1.4M solution of *sec*-butyllithium in cyclohexane (1.4 equiv, 0.14 mL), and the reaction mixture was stirred at the same temperature for 30 min. Subsequently, 0.013 mL of water (5.0 equiv) was added at -90 °C and the reaction was slowly warmed up to room temperature. Then, a saturated aqueous NH_4Cl (1 mL) was added and the mixture was extracted with Et_2O (3 x 5 mL). The organic phase was washed with brine (2 x 2 mL) and dried over $MgSO_4$. Filtration, evaporation and purification by preparative thin layer chromatography afforded 1-benzyl-3-fluoro-2-(4-methoxyphenyl)azetidine **380b** in 27% yield.

***trans*-1-Benzyl-3-fluoro-2-(4-methoxyphenyl)azetidine 380b**



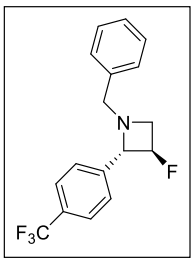
R_f = 0.24 (PE/Et_2O 4/1). Colorless oil, yield 27%. **IR** (cm^{-1}): ν_{max} 1086, 1248, 1513. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.94 (1H, dt, J = 22.0, 7.3 Hz, C*H*(H)CHF), 3.48 (1H, d, J = 12.8 Hz, C*H*(H)Ph), 3.64 (1H, q, J = 7.3 Hz, CH(*H*)CHF), 3.81 (3H, s, OCH_3), 3.93 (1H, d, J = 12.8 Hz, CH(*H*)Ph), 4.08 (1H, dd, J = 22.0, 7.3 Hz, C*H*CHF), 4.78 (1H, dq, J = 57.1, 7.3 Hz, C*H*F), 6.89 (2H, d, J = 8.7 Hz, 2 x CH_{arom}), 7.19-7.33 (5H, m, 5 x CH_{arom}), 7.36 (2H, d, J = 8.7 Hz, 2 x CH_{arom}). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ 55.3 (O*C*H_3), 57.5 (*C*H_2CHF, d, J = 19.9 Hz), 61.6 (*C*H_2Ph), 75.0 (*C*HCHF, d, J = 20.3 Hz), 88.6 (*C*HF, d, J = 213.2 Hz), 113.9 (2 x CH_{arom}), 127.2 (CH_{arom}), 128.2 (2 x CH_{arom}), 128.3 (2 x CH_{arom}), 128.8 (2 x CH_{arom}), 131.4 ($C_{arom,quat}$), 137.4 ($C_{arom,quat}$), 159.4 ($C_{arom,quat}$). **^{19}F NMR** (376.5 MHz, $CDCl_3$): δ -176.1 (1F, dddd, J = 57.1, 22.0, 22.0, 7.3 Hz). **MS** (ES, pos. mode): *m/z* (%): 272 (25) $[M+H]^+$, 120 (100).

***trans*-1-Benzyl-2-(4-chlorophenyl)-3-fluoroazetidine 380c**



R_f = 0.54 (PE/Et_2O 4/1). Pale yellow oil, yield 30%. **IR** (cm^{-1}): ν_{max} 691, 1080, 1250, 1514. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.97 (1H, dt, *J* = 22.1, 6.8 Hz, C*H*(H)CHF), 3.50 (1H, d, *J* = 12.8 Hz, C*H*(H)Ph), 3.60-3.69 (1H, m, CH(*H*)CHF), 3.89 (1H, d, *J* = 12.8 Hz, CH(*H*)Ph), 4.11 (1H, dd, *J* = 22.1, 5.2 Hz, C*H*CHF), 4.73 (1H, dq, *J* = 56.9, 5.7 Hz, C*H*F), 7.21-7.43 (9H, m, 9 x CH_{arom}). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ 57.7 (*C*H_2CHF, d, *J* = 19.9 Hz), 61.8 (*C*H_2Ph), 74.8 (*C*HCHF, d, *J* = 20.4 Hz), 88.4 (*C*HF, d, *J* = 214.1 Hz), 127.3 (CH_{arom}), 128.2 (2 x CH_{arom}), 128.4 (2 x CH_{arom}), 128.6 (2 x CH_{arom}), 128.8 (2 x CH_{arom}), 133.6 ($C_{arom,quat}$), 137.2 ($C_{arom,quat}$), 137.9 ($C_{arom,quat}$, d, *J* = 2.4 Hz). **^{19}F NMR** (376.5 MHz, $CDCl_3$): δ -176.1 (1F, dddd, *J* = 56.9, 22.1, 22.1, 9.0 Hz). **MS** (ES, pos. mode): *m/z* (%): 276/278 (100) $[M+H]^+$.

***trans*-1-Benzyl-3-fluoro-2-(4-(trifluoromethyl)phenyl)azetidine 380d**

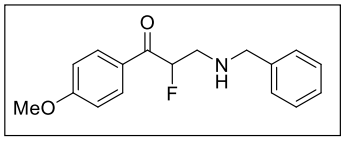


R_f = 0.57 (PE/Et_2O 4/1). Colorless oil, yield 35%. **IR** (cm^{-1}): ν_{max} 1098, 1054, 1245, 1511. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 3.02 (1H, dt, *J* = 22.1, 6.8 Hz, C*H*(H)CHF), 3.55 (1H, d, *J* = 12.8 Hz, C*H*(H)Ph), 3.65-3.72 (1H, m, CH(*H*)CHF), 3.90 (1H, d, *J* = 12.8 Hz, CH(*H*)Ph), 4.22 (1H, dd, *J* = 22.1, 5.2 Hz, C*H*CHF), 4.76 (1H, dq, *J* = 56.9, 5.7 Hz, C*H*F), 7.22-7.33 (5H, m, 5 x CH_{arom}), 7.53 (2H, d, *J* = 8.3 Hz, 2 x CH_{arom}), 7.60 (2H, d, *J* = 8.3 Hz, 2 x CH_{arom}). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ 57.8 (*C*H_2CHF, d, *J* = 19.9 Hz), 61.2 (*C*H_2Ph), 74.8 (*C*HCHF, d, *J* = 20.4 Hz), 88.2 (*C*HF, d, *J* = 214.6 Hz), 124.1 (*C*F_3, q, *J* = 270.0 Hz), 125.4 (2 x CF_3C*C*H, q, *J* = 3.8 Hz), 127.0 (2 x CH_{arom}), 127.4 (CH_{arom}), 128.4 (2 x CH_{arom}), 128.8 (2 x CH_{arom}), 130.1(CF_3*C*CH, q, *J* = 32.3 Hz), 137.0 ($C_{arom,quat}$), 143.4 ($C_{arom,quat}$). **^{19}F NMR** (376.5 MHz, $CDCl_3$): δ -62.5 (3F, s, C*F*$_3$), -176.1 (1F, dddd, *J* = 56.9, 22.1, 22.1, 9.4 Hz). **MS** (ES, pos. mode): *m/z* (%): 310 (100) $[M+H]^+$.

5.2.27 Synthesis of 3-(benzylamino)-2-fluoro-1-(4-methoxyphenyl)propan-1-one 382

Sodium hydride (70 mg, 2.87 mmol, 60% dispersion in oil) was washed two times with 3 mL of pentane and evaporated to dryness. Dry DMSO (4 mL) was added and the mixture was stirred for 15 min at room temperature to generate dimsyl sodium in DMSO. Then, 1-benzyl-3-bromo-3-fluoro-2-(4-methoxyphenyl)azetidine **373b** (500 mg, 1.43 mmol), dissolved in dry DMSO (5 mL), was added dropwise at room temperature. After the addition was completed, the mixture was stirred at 75 °C for 2 h. After cooling, 8 mL of water was added and the water phase was extracted with Et_2O (3 x 8 mL). The combined organic phases were dried over $MgSO_4$ and after filtration, evaporation of the solvent and purification by chromatography, 3-(benzylamino)-2-fluoro-1-(4-methoxyphenyl)propan-1-one **382** was isolated in 21% yield.

3-(Benzylamino)-2-fluoro-1-(4-methoxyphenyl)propan-1-one 382



R_f = 0.32 (PE/Et_2O 2/1). Yellow oil, yield 21%, **IR** (cm^{-1}): ν_{max} 1027, 1174, 1250, 1509, 1600, 1682, 3029. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 3.16 (2H, dd, J = 25.3, 5.0 Hz, CH_2CHF), 3.57-4.00 (3H, m, CH_2Ph and N*H*), 3.89 (3H, s, OCH_3), 5.72 (1H, dt, J = 49.5, 5.0 Hz, C*H*F), 6.93 (2H, d, J = 8.8 Hz, 2 x CH_{arom}), 7.08-7.40 (5H, m, 5 x CH_{arom}), 7.94 (2H, d, J = 8.8 Hz, 2 x CH_{arom}). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 50.7 (*C*H_2CF, d, J = 20.8 Hz), 53.6 (*C*H_2Ph), 55.6 (O*C*H_3), 93.3 (CF, d, J = 182.3 Hz), 114.1 (2 x CH_{arom}), 127.3 (CH_{arom}), 128.2 (2 x CH_{arom}), 128.6 (2 x CH_{arom}), 131.2 ($C_{arom,quat}$), 131.4 (2 x CH_{arom}), 139.6 ($C_{arom,quat}$), 164.2 ($C_{arom,quat}$), 194.0 (C=O, d, J = 18.5 Hz). **^{19}F NMR** (282 MHz, $CDCl_3$): δ -192.23 (1F, dt, J = 49.5, 25.3 Hz, CH_2C*F*). **MS** (ES, pos. mode): *m/z* (%): 288 (100) $[M+H]^+$.

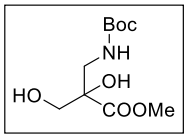
5.2.28 Synthesis of alkyl dihydroxy(aminomethyl)propanoates 43

The synthetic procedure is reported in a preliminary research.[50] For the synthesis of propanoate **43b**, the reaction time was extended to 18 hours and purification was performed *via* column chromatography. CAUTION: vapors of osmium tetroxide (OsO_4) are highly toxic; all work with osmium must be carried out in a well-ventilated fume hood.

Ethyl 2,3-dihydroxy-2-[((4-methylbenzene)sulfonamido)methyl]propanoate 43a

Yield 82%. Spectral data of ethyl 2,3-dihydroxy-2-[((4-methylbenzene)sulfonamido)methyl]propanoate **43a** corresponded with described data in the literature.[50]

Methyl 2,3-dihydroxy-2-[(*tert*-butoxycarbonylamino)methyl]propanoate 43b



R_f = 0.07 (PE/EtOAc 1/1). Colorless oil, yield 89%. IR (cm^{-1}): $\nu_{OH,NH}$ = 3379, $\nu_{C=O}$ = 1710. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.43 (9H, s, *t*Bu), 3.36 (1H, dd, J = 14.3, 5.5 Hz, C*H*(H)NH), 3.52 (1H, dd, J = 14.3, 7.5 Hz, CH(*H*)NH), 3.66 (1H, dd, J = 11.7, 5.6 Hz, C*H*(H)OH), 3.77 (1H, dd, J = 11.7, 8.2 Hz, CH(*H*)OH), 3.82 (3H, s, OCH_3), 5.13 (1H, br s, J = 6.3, 5.0 Hz, NH). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ 28.2 (3C, *t*Bu), 44.3 (*C*H_2NH), 53.1 (O*C*H_3), 65.1 (*C*H_2OH), 78.3 (*C*OH), 80.1 (*C*$(CH_3)_3$), 156.7 (C=O, Boc), 174.0 (C=O). **MS** (ES, pos. mode): *m/z* (%): 272 (100) $[M+Na]^+$. **HRMS**: calcd for $C_{13}H_{19}NO_6SNa^+$ $[M+Na]^+$ 272.1105; found: 272.1101.

5.2.29 Synthesis of alkyl 2-(aminomethyl)oxirane-2-carboxylates 44

Method A

The synthetic procedure starting from aminodiols **43** is reported in a preliminary research.[50] For the synthesis of epoxide **44b** a reaction time of 27 hours was applied.

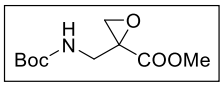
Method B

The synthetic procedure starting from monomesylated aminodiols **400** is reported in preliminary research.[50]

Ethyl 2-[((4-methylbenzene)sulfonamido)methyl]oxirane-2-carboxylate 44a

Yield 80%. (Method B). Spectral data of ethyl 2-[((4-methylbenzene)sulfonamido)methyl]oxirane-2-carboxylate **44a** corresponded with described data in the literature.[50]

Methyl 2-[(*tert*-butoxycarbonylamino)methyl]oxirane-2-carboxylate 44b



R_f = 0.59 (PE/EtOAc 1/1). Colorless oil, yield 34% (Method A), yield 80% (Method B). **IR** (cm^{-1}): ν_{NH} = 3385, $\nu_{C=O}$ = 1708. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.44 (9H, s, *t*Bu), 2.94 (1H, d, *J* = 5.8 Hz, C*H*(H)O), 3.11 (1H, d, *J* = 5.8 Hz, CH(*H*)O), 3.57 (1H, dd, *J* = 14.9, 5.9 Hz, C*H*(H)NH), 3.78 (3H, s, OCH_3), 3.76-3.86 (1H, m, CH(*H*)NH), 4.81 (1H, br s, NH). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ 28.3 (3C, *t*Bu), 40.3 (CH_2NH), 50.2 (CH_2O), 52.8 (OCH_3), 55.5 (CCH_2), 79.8 ($C(CH_3)_3$), 155.8 (C=O, Boc), 169.9 (C=O). **MS** (ES, pos. mode): *m/z* (%): 176 (100) $[(M-C_4H_8)+H]^+$. **HRMS**: calcd for $C_5H_{10}NO_3^+$ $[(M-Boc)+H]^+$ 132.0655; found: 132.0656.

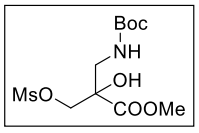
5.2.30 Synthesis of alkyl 2-aminomethyl-2-hydroxy-3-(methanesulfonyloxy)propanoates 400

The synthesis of ethyl 2-hydroxy-3-methanesulfonyloxy-2-[((4-methylbenzene)sulfonamido)methyl]-propanoate **400a** is representative. To a mixture of ethyl 2,3-dihydroxy-2-[((4-methylbenzene)sulfonamido)methyl]propanoate **43a** (107 mg, 0.34 mmol) and triethylamine (37 mg, 0.37 mmol) in dry THF (10 mL), a solution of methanesulfonyl chloride (46 mg, 0.37 mmol) in dry THF (3 mL) was added dropwise at 0 °C under N_2. The reaction mixture was stirred at room temperature for 6 hours. After completion, the resulting reaction mixture was quenched with water (5 mL) and extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with brine (2 × 5 mL) and water (5 mL). Drying ($MgSO_4$), filtration, evaporation of the solvent under reduced pressure and purification by flash chromatography on silica gel (petroleum ether/Et_2O 3/7) afforded pure compound **400a**.

Ethyl 2-hydroxy-3-methanesulfonyloxy-2-[((4-methylbenzene)sulfonamido)methyl]-propanoate 400a

Yield 97%. Spectral data of ethyl 2-hydroxy-3-methanesulfonyloxy-2-[((4-methylbenzene)sulfonamido)methyl]-propanoate **400a** corresponded with described data in the literature.[50]

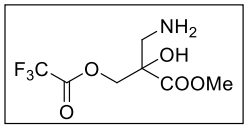
Methyl 2-[(*tert*-butoxycarbonylamino)methyl]-2-hydroxy-3-(methanesulfonyloxy)propanoate 400b



R_f = 0.20 (PE/EtOAc 1/1). White crystals, yield 94%. **Mp**. 94.5-95.0 °C. **IR** (cm^{-1}): $\nu_{OH,NH}$ = 3426, $\nu_{C=O}$ = 1742, $\nu_{C=O}$ = 1693, $\nu_{S=O}$ = 1160. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.43 (9H, s, *t*Bu), 3.06 (3H, s, SO_3CH_3), 3.37 (1H, dd, J = 14.2, 6.1 Hz, C*H*(H)NH), 3.57 (1H, dd, J = 14.2, 7.4 Hz, CH(*H*)NH), 3.85 (3H, s, OCH_3), 4.04 (1H, br s, OH), 4.34 (1H, d, J = 10.8 Hz, C*H*(H)OMs), 4.44 (1H, d, J = 10.8 Hz, CH(*H*)OMs), 4.90 (1H, br s, NH). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ 28.2 (3C, *t*Bu), 37.8 (SO_3CH_3), 44.7 (*C*H_2NH), 53.7 (O*C*H_3), 71.0 (*C*H_2OMs), 77.2 (*C*OH), 80.4 (*C*$(CH_3)_3$), 156.3 (C=O), 172.1 (C=O). **MS** (ES, pos. mode): *m/z* (%): 228 (100) $[(M\text{-Boc})+H]^+$. **HRMS**: calcd for $C_6H_{14}NO_6S^+$ $[(M\text{-Boc})+H]^+$ 228.0536; found: 228.0536.

5.2.31 Synthesis of methyl 3-amino-2-hydroxy-2-[(2,2,2-trifluoroacetoxy)methyl]propanoate 401

To a solution of methyl 2-[(*tert*-butoxycarbonyl)aminomethyl]-2-hydroxy-3-(methylsulfonyloxy)propanoate **400b** (147 mg, 0.45 mmol) in dry CH_2Cl_2 (2 mL) was slowly added trifluoroacetic acid (1 mL) at 0 ºC and then the reaction mixture was warmed up to room temperature. After 15 minutes, the reaction mixture was cooled down to 0 ºC, quenched by slowly adding aqueous saturated $NaHCO_3$ and extracted with EtOAc (3 × 5 mL). After drying (Na_2CO_3), filtration and evaporation of the solvent under reduced pressure, the resulting crude product was dissolved in CH_3CN and powdered K_2CO_3 (1.5 equiv, 93 mg, 0.66 mmol) was added in one portion. The resulting reaction mixture was stirred at 60 ºC for 2 h. Then the solvent was removed under reduced pressure and EtOAc was added. The resulting solution was filtered and the filter cake was washed with small portions of EtOAc. Evaporation of the solvent under reduced pressure afforded crude **401**.



R_f = 0.08 (EtOAc 100%). Pale yellow oil, yield 67% (crude). **IR** (cm^{-1}): ν_{NH} = 3311, $\nu_{C=O}$ = 1667. **^{1}H NMR** (400 MHz, CD_3OD): δ 3.51 (1H, d, J = 13.8 Hz, C*H*(H)NH_2), 3.61 (1H, d, J = 5.8 Hz, CH(*H*)O), 3.65 (1H, d, J = 13.8 Hz, CH(*H*)NH_2), 3.75 (3H, s, OCH_3), 3.73-3.78 (1H, m, CH(*H*)O). **^{13}C NMR** (100.6 MHz, CD_3OD): δ 43.2 (*C*H_2NH), 51.8 (O*C*H_3), 65.0 (*C*H_2O), 77.8 (*C*CH_2), 116.9 (*C*F_3, q, J = 293.0 Hz), 161.7 (CF_3*C*=O, q, J = 34.2 Hz), 173.2 (C=O). **MS** (ES, pos. mode): *m/z* (%): 132 (100), 246 (43) $[M+H]^+$.

5.2.32 Synthesis of alkyl 2,3-bis-methanesulfonyloxy-2-(aminomethyl)propanoates 403

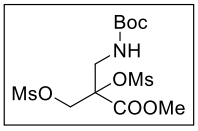
The synthetic procedure is reported in a preliminary research.[50]

For the synthesis of compound **403b** dry THF was used instead of dry CH_2Cl_2.

Ethyl 2,3-bis-methanesulfonyloxy-2-[((4-methylbenzene)sulfonamido)methyl]-propanoate 403a

Yield 27%. **HRMS**: calcd for $C_{15}H_{27}N_2O_{10}S_3^+$ $[M+NH_4]^+$ 491.0822; found: 491.0828. Spectral data of ethyl 2,3-bis-methanesulfonyloxy-2-[((4-methylbenzene)sulfonamido)methyl]-propanoate **403a** corresponded with described data in the literature.[50]

Methyl 2-[(*tert*-butoxycarbonylamino)methyl]-2,3-bis-(methanelsulfonyloxy)propanoate 403b



R_f = 0.37 (PE/EtOAc 1/1). White crystals, yield 59%. **Mp** 104.5-106.0 ºC. **IR** (cm^{-1}): ν_{NH} = 3417, $\nu_{C=O}$ = 1748, $\nu_{C=O}$ = 1712, $\nu_{S=O}$ = 1178. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.43 (9H, s, *t*Bu), 3.12 (3H, s, SO_3CH_3), 3.27 (3H, s, SO_3CH_3), 3.68 (1H, dd, J = 14.9, 6.5 Hz, C*H*(H)NH), 3.84 (3H, s, OCH_3), 3.88 (1H, dd, J = 14.9, 7.4 Hz, CH(*H*)NH), 4.70 (2H, s, C*H*(*H*)OMs), 5.03 (1H, br s, NH). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ 28.2 (3C, *t*Bu), 37.7 (SO_3CH_3), 40.7 (SO_3CH_3), 43.3 (*C*H_2NH), 53.7 (O*C*H_3), 67.6 (*C*H_2OMs), 80.4 (*C*$(CH_3)_3$), 86.3 (*C*OMs), 155.7 (C=O), 167.0 (C=O). **MS** (ES, pos. mode): *m/z* (%): 306 (100) $[(M\text{-Boc})+H]^+$. **HRMS**: calcd for $C_7H_{16}NO_8S_2^+$ $[(M\text{-Boc})+H]^+$ 306.0312; found: 306.0333.

5.2.33 Synthesis of ethyl 2-methanesulfonyloxymethyl-1-(4-methylbenzenesulfonyl)aziridine-2-carboxylate 45a

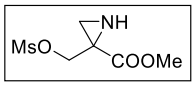
The synthetic procedure is reported in a preliminary research.[50]

HRMS: calcd for $C_{14}H_{20}NO_7S_2^+$ $[MH]^+$ 378.0676; found: 378.0684. Spectral data of ethyl 2-methanesulfonyloxymethyl-1-(4-methylbenzenesulfonyl)aziridine-2-carboxylate **45a** corresponded with described data in the literature.[50]

5.2.34 Synthesis of methyl 2-[(methanesulfonyloxy)methyl]aziridine-2-carboxylate 405

To a solution of methyl 2-[(*tert*-butoxycarbonyl)aminomethyl)-2,3-bis-(methanesulfonyloxy)propanoate **403b** (70 mg, 0.17 mmol) in dry CH_2Cl_2 (1.5 mL) was slowly added trifluoroacetic acid (0.6 mL) at 0 ºC, and then the reaction mixture was warmed up to room temperature. After 15 minutes, the reaction mixture was cooled down to 0 ºC, quenched by slowly adding aqueous saturated $NaHCO_3$ and extracted with EtOAc (3 × 5 mL). Drying (Na_2CO_3), filtration and evaporation of the solvent under reduced pressure afforded intermediate **404**. Crude deprotected amine **404** was dissolved in CH_3CN and powdered K_2CO_3 (3.0 equiv, 0.51 mmol, 70 mg) was added

in one portion. The resulting reaction mixture was stirred at 60 ºC for 1 h. Then the solvent was removed under reduced pressure and EtOAc (5 mL) was added. The resulting solution was filtered and the filter cake was washed with small portions of EtOAc. Evaporation of the solvent under reduced pressure and purification *via* preparative HPLC afforded compound **405** contaminated with starting material **404** (**405**/**404** = 80/20).



R_f = 0.10 (PE/EtOAc 1/9). Colorless oil, yield 34%. **IR** (cm^{-1}): ν_{NH} = 3358, $\nu_{C=O}$ = 1672, $\nu_{S=O}$ = 1174. **^{1}H NMR** (400 MHz, CD_3OD): δ 2.00 (1H, s, C*H*(H)NH), 2.29 (1H, s, CH(*H*)NH), 3.12 (3H, s, SO_3CH_3), 3.81 (3H, s, OCH_3), 4.09 (1H, d, *J* = 11.0 Hz, C*H*(H)OMs), 4.73 (1H, d, *J* = 11.0 Hz, CH(*H*)OMs). **^{13}C NMR** (100.6 MHz, CD_3OD): δ 30.6 (*C*H_2NH), 35.9 (SO_3CH_3), 45.0 (*C*CH_2), 52.2 (O*C*H_3), 70.7 (*C*H_2OMs), 170.7 (C=O). **MS** (ES, pos. mode): *m/z* (%): 210 (100) $[M+H]^+$. **HRMS**: calcd. for $C_6H_{12}NO_5S^+$ $[MH]^+$ 210.0431; found: 210.0435.

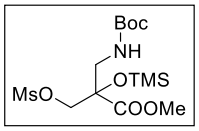
5.2.35 Synthesis of alkyl 2-aminomethyl-3-methanesulfonyloxy-2-(trimethylsilanyloxy)propanoates 406

The synthetic procedure is reported in a preliminary research.[50]

Ethyl 3-methanesulfonyloxy-2-[((4-methylbenzene)sulfonamido)methyl]-2-(trimethyl-silanyloxy)propanoate 406a

Yield 90%. Spectral data of ethyl 3-methanesulfonyloxy-2-[((4-methylbenzene)sulfonamido)methyl]-2-(trimethyl-silanyloxy)propanoate **406a** corresponded with described data in the literature.[50]

Methyl 2-[(*tert*-butoxycarbonylamino)methyl]-3-methanesulfonyloxy-2-(trimethylsilanyloxy) propanoate 406b



R_f = 0.48 (PE/EtOAc 2/1). White crystals, yield 94%. **Mp** 90.3-91.3 ºC. **IR** (cm^{-1}): ν_{NH} = 3351, $\nu_{C=O}$ = 1753, $\nu_{C=O}$ = 1691, ν_{Si-C} = 1249, $\nu_{S=O}$ = 1165. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.19 (9H, s, $Si(CH_3)_3$), 1.44 (9H, s, *t*Bu), 3.05 (3H, s, SO_3CH_3), 3.47 (2H, d, *J* = 6.6 Hz, C*H*(*H*)NH), 3.79 (3H, s, OCH_3), 4.30 (1H, d, *J* = 10.2 Hz, CH(*H*)OMs), 4.39 (1H, d, *J* = 10.2 Hz, CH(*H*)OMs), 4.81 (1H, br s, NH). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ 1.95 (3C, OTMS), 28.3 (3C, *t*Bu), 37.5 (SO_3CH_3), 45.4 (*C*H_2NH), 52.8 (O*C*H_3), 70.9 (*C*H_2OMs), 78.5 (*C*OTMS), 79.9 (*C*$(CH_3)_3$), 155.7 (C=O), 171.0 (C=O). **MS** (ES, pos. mode): *m/z* (%): 300 (100) $[(M-Boc)+H]^+$. **HRMS**: calcd for $C_9H_{22}NO_6SSi^+$ $[(M-Boc)+H]^+$ 300.0932; found: 300.0931.

5.2.36 Synthesis of ethyl 1-(4-methylbenzenesulfonyl)-3-(trimethylsilanyloxy)azetidine-3-carboxylate 407a

The synthetic procedure is reported in a preliminary research.[50]

Yield 95%. Spectral data of ethyl 1-(4-methylbenzenesulfonyl)-3-(trimethylsilanyloxy)azetidine-3-carboxylate **407a** corresponded with described data in the literature.[50]

5.2.37 Synthesis of ethyl 3-hydroxy-1-(4-methylbenzenesulfonyl)azetidine-3-carboxylate 46a

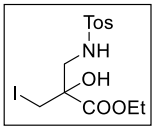
The synthetic procedure is reported in a preliminary research.[50]

Yield 90%. Spectral data of ethyl 3-hydroxy-1-(4-methylbenzenesulfonyl)azetidine-3-carboxylate **46a** corresponded with described data in the literature.[50]

5.2.38 Synthesis of ethyl 2-hydroxy-3-iodo-2-[((4-methylbenzene)sulfonamido)-methyl]propanoate 409

Triphenylphosphine (1.2 equiv, 0.40 mmol, 105 mg) and imidazole (1.2 equiv, 0.40 mmol, 27 mg) were dissolved in dry dichloromethane with stirring under nitrogen. Iodine (1.2 equiv, 0.40 mmol, 102 mg) was added slowly and after 5 minutes a solution of the ethyl 3-hydroxy-1-(4-methylbenzenesulfonyl)azetidine-3-carboxylate **46a** (1 equiv, 0.33 mmol, 100 mg) in dry dichlorometane was added and the reaction mixture was stirred at room temperature for 48 hours. Then, the solvent was evaporated under reduced pressure. The residue was filtered through a short layer of silica gel eluting with ethyl acetate, and the filtrate was concentrated to give crude mixture of product **409** and **42a**. Purification *via* column chromatography afforded the mixture of **409**/**42a** in a ratio of 75/25.

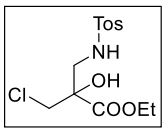
Spectral data were obtained from a mixture of **409**/**42a** isomers in 75:25 ratio.



R_f = 0.53 (PE/EtOAc 1/1). Pale yellow oil, yield 27% (calculated). **IR** (cm^{-1}): ν_{max} 1090, 1156, 1326, 1732, 3266, 3524. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.32 (3H, t, J = 7.1 Hz, OCH_2CH_3), 2.43 (3H, s, *p*-CH_3), 3.14 (1H, dd, J = 12.5, 5.0 Hz, C*H*(H)NH), 3.34 (1H, d, J = 10.4 Hz, C*H*(H)I), 3.42 (1H, d, J = 10.4 Hz, CH(*H*)I), 3.43 (1H, dd, J = 12.5, 8.5 Hz, CH(*H*)NH), 4.18-4.35 (2H, m, OCH_2CH_3), 5.10 (1H, dd, J = 8.5, 5.0 Hz, N*H*), 7.31 (2H, d, J = 8.5 Hz, 2 × CH_{arom}), 7.72 (2H, d, J = 8.5 Hz, 2 × CH_{arom}). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ 9.6 (CH_2I), 14.1 (OCH_2CH_3), 21.5 (*p*-CH_3), 48.2 (CH_2NH), 63.5 (OCH_2CH_3), 76.0 (*C*OH), 127.0 (2 × CH_{arom}), 129.8 (2 × CH_{arom}), 136.6 ($C_{arom,quat}$), 143.8 ($C_{arom,quat}$), 171.6 (C=O). **MS** (ES, pos. mode): *m/z* (%): 428 (100) $[M+H]^+$. **HRMS**: calcd for $C_{13}H_{19}INO_5S^+$ $[MH]^+$ 428.0023; found: 428.0004.

5.2.39 Synthesis of ethyl 3-chloro-2-hydroxy-2-[((4-methylbenzene)sulfonamido)-methyl]propanoate 412

To a solution of ethyl 3-hydroxy-1-(4-methylbenzenesulfonyl)azetidine-3-carboxylate **46a** (0.10 g, 0.33 mmol) in dry CH_2Cl_2 (4 mL), thionyl chloride (1.2 equiv, 0.03 mL, 0.40 mmol) was added dropwise at 0 °C and the reaction mixture was slowly warmed up to room temperature. Then triethylamine (1 equiv, 34 mg, 0.33 mmol) was added and the reaction was stirred at room temperature for 30 minutes. After completion of the reaction (TLC-monitoring), the solvent was evaporated and the crude mixture was purified *via* column chromatography (PE/EtOAc 3/1) to give ethyl 3-chloro-2-hydroxy-2-[((4-methylbenzene)sulfonamido)methyl]propanoate **412**.



R_f = 0.48 (PE/EtOAc 1/1). Colorless amorphous solid, yield 78 %. **IR** (cm^{-1}): ν_{max} 1089, 1146, 1240, 1319, 1733, 3271, 3541. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.31 (3H, t, J = 7.1 Hz, OCH_2CH_3), 2.43 (3H, s, p-CH_3), 3.12 (1H, dd, J = 12.5, 5.3 Hz, C*H*(H)NH), 3.35 (1H, dd, J = 12.5, 8.1 Hz, CH(*H*)NH), 3.62 (1H, d, J = 11.4 Hz, C*H*(H)Cl), 3.73 (1H, d, J = 11.4 Hz, CH(*H*)Cl), 4.18-4.35 (2H, m, OCH_2CH_3), 4.83 (1H, dd, J = 8.1, 5.3 Hz, N*H*), 7.32 (2H, d, J = 7.8 Hz, 2 × CH_{arom}), 7.72 (2H, d, J = 7.8 Hz, 2 × CH_{arom}). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ 14.1 (OCH_2CH_3), 21.5 (p-CH_3), 47.6 (CH_2NH), 47.7 (CH_2Cl), 63.4 (OCH_2CH_3), 76.9 (*C*OH), 127.1 (2 × CH_{arom}), 129.9 (2 × CH_{arom}), 136.4 ($C_{arom,quat}$), 143.9 ($C_{arom,quat}$), 171.2 (C=O). **MS** (ES, pos. mode): *m/z* (%): 336/338 (100) $[M+H]^+$. **HRMS**: calcd for $C_{13}H_{19}ClNO_5S^+$ $[MH]^+$ 336.0667; found: 336.0659.

5.2.40 Synthesis of ethyl 3-methanesulfonyloxy-1-(4-methylbenzenesulfonyl)azetidine-3-carboxylate 413

The synthetic procedure is reported in a preliminary research.[50] Dry THF was used as solvent instead of CH_2Cl_2.

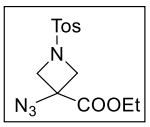
Yield 95%. Spectral data of ethyl 3-methanesulfonyloxy-1-(4-methylbenzenesulfonyl)azetidine-3-carboxylate **413** corresponded with described data in the literature.[50]

5.2.41 Synthesis of ethyl 3-azido-1-tosylazetidine-3-carboxylate 414

To a solution of ethyl 3-methanesulfonyloxy-1-(4-methylbenzenesulfonyl)azetidine-3-carboxylate **413** (522 mg, 1.38 mmol) in absolute DMSO (15 mL), sodium iodide (622 mg, 4.15 mmol) was added at room temperature and the reaction mixture was stirred for 15 minutes. Subsequently, sodium azide (270 mg, 4.15 mmol) was added in one portion and the solution was heated at 85 °C for 20 hours. After cooling, the reaction mixture was poured into water (10 mL) and extracted with Et_2O (3 × 20 mL). The combined organic extracts were washed with brine (2 × 15 mL) and water (15 mL). The combined organic phases were dried ($MgSO_4$), filtered and evaporated *in vacuo*. The crude

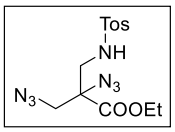
product was purified by column chromatography to give ethyl 3-azido-1-tosylazetidine-3-carboxylate **414** (96 mg, 0.30 mmol, 21%). Starting material **413** was isolated and subsequently used again for the synthesis of compound **414** *via* the above described procedure. When the reaction was performed with 4.0 equiv NaI and 4.0 equiv NaN_3 at 110 °C for 24 h, the formation of the side product ethyl 2,3-diazido-2-[((4-methylbenzene)sulfonamide)methyl]propanoate **415**, which can be isolated by flash chromatography in 5% yield, was observed. CAUTION: strict safety measurements have to be applied for reactions with NaN_3 to avoid risk of explosions (safety shield).

Ethyl 3-azido-1-tosylazetidine-3-carboxylate 414



R_f = 0.23 (PE/Et_2O 7/3). Yellow viscous oil, yield 56%. **IR** (cm^{-1}): ν_{N3} = 2116, $\nu_{C=O}$ = 1732, $\nu_{S=O}$ = 1161. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.24 (3H, t, J = 7.1 Hz, OCH_2CH_3), 2.47 (3H, s, *p*-CH_3), 3.82 (2H, d, J = 9.8 Hz, C*H*(H)NC*H*(H)), 4.19 (2H, d, J = 9.8 Hz, CH(*H*)NCH(*H*)), 4.20 (2H, q, J = 7.1 Hz, OCH_2CH_3), 7.40 (2H, d, J = 8.2 Hz, 2 × CH_{arom}), 7.74 (2H, d, J = 8.2 Hz, 2 × CH_{arom}). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ 13.9 (OCH_2CH_3), 21.6 (*p*-CH_3), 58.2 (CCH_2), 58.4 (CH_2NCH_2), 63.0 (OCH_2CH_3), 128.4 (2 × CH_{arom}), 130.0 (2 × CH_{arom}), 131.2 ($C_{arom,quat}$), 144.7 ($C_{arom,quat}$), 167.9 (C=O). **MS** (ES, pos. mode): *m/z* (%): 325 (100) $[M+H]^+$. **HRMS**: calcd for $C_{13}H_{17}N_4O_4S^+$ $[MH]^+$ 325.0965; found: 325.0956.

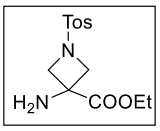
Ethyl 2,3-diazido-2-[((4-methylbenzene)sulfonamide)methyl]propanoate 415



R_f = 0.13 (PE/Et_2O 7/3). Pale yellow oil, yield 5%. **IR** (cm^{-1}): ν_{NH} = 3276, ν_{N3} = 2106, $\nu_{C=O}$ = 1739, $\nu_{S=O}$ = 1161. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.33 (3H, t, J = 7.1 Hz, OCH_2CH_3), 2.44 (3H, s, *p*-CH_3), 3.16 (1H, dd, J = 13.2, 6.9 Hz, C*H*(H)NH), 3.25 (1H, dd, J = 13.2, 6.9 Hz, CH(*H*)NH), 3.64 (1H, d, J = 12.6 Hz, C*H*(H)N_3), 3.77 (1H, d, J = 12.6 Hz, CH(*H*)N_3), 4.25-4.33 (2H, m, OCH_2CH_3), 4.88 (1H, t, J = 6.9 Hz, NH), 7.33 (2H, d, J = 8.2 Hz, 2 × CH_{arom}), 7.73 (2H, d, J = 8.2 Hz, 2 × CH_{arom}). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ 14.1 (OCH_2CH_3), 21.6 (*p*-CH_3), 46.0 (CH_2NH), 54.3 (CH_2N_3), 63.3 (OCH_2CH_3), 68.3 (CN_3), 127.0 (2 × CH_{arom}), 130.0 (2 × CH_{arom}), 136.5 ($C_{arom,quat}$), 144.0 ($C_{arom,quat}$), 168.2 (C=O). **MS** (ES, pos. mode): *m/z* (%): 368 (100) $[M+H]^+$. **HRMS**: calcd for $C_{13}H_{18}N_7O_4S^+$ $[MH]^+$ 368.1136; found: 368.1122.

5.2.42 Synthesis of ethyl 3-amino-1-tosylazetidine-3-carboxylate 47a

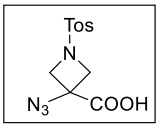
To a solution of ethyl 3-azido-1-tosylazetidine-3-carboxylate **414** (9 mg, 0.03 mmol) in EtOH (1 mL), Pd (3 mg, 10 wt.% on carbon) was added and the reaction mixture was stirred under H_2 atmosphere (1 bar) at room temperature for 1.5 h. Subsequently, the reaction mixture was filtered over Celite® and the filter cake was washed with a small portion of EtOH. Evaporation of the solvent under reduced pressure and purification of the crude mixture by preparative TLC on silica gel afforded pure compound **47a**.



R_f = 0.39 (PE/EtOAc 5/95). Yellow oil, yield 83%. **IR** (cm^{-1}): ν_{NH} = 3358, $\nu_{C=O}$ = 1730, $\nu_{S=O}$ = 1152. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.18 (3H, t, J = 7.1 Hz, OCH_2CH_3), 1.26 (2H, br s, NH_2), 2.43 (3H, s, p-CH_3), 3.64 (2H, d, J = 9.0 Hz, C*H*(H)NC*H*(H)), 4.11 (2H, q, J = 7.1 Hz, OCH_2CH_3), 4.15 (2H, d, J = 9.0 Hz, CH(*H*)NCH(*H*)), 7.38 (2H, d, J = 8.2 Hz, 2 × CH_{arom}), 7.75 (2H, d, J = 8.2 Hz, 2 × CH_{arom}). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ 13.9 (OCH_2CH_3), 21.6 (p-CH_3), 53.0 (CCH_2), 62.01 (OCH_2CH_3), 62.04 (CH_2NCH_2), 128.5 (2 × CH_{arom}), 129.8 (2 × CH_{arom}), 131.6 ($C_{arom,quat}$), 144.3 ($C_{arom,quat}$), 171.8 (C=O). **MS** (ES, pos. mode): *m/z* (%): 299 (100) $[M+H]^+$. **HRMS**: calcd for $C_{13}H_{19}N_2O_4S$ $[MH]^+$ 299.1060; found: 299.1068.

5.2.43 Synthesis of 3-azido-1-tosylazetidine-3-carboxylic acid 48a

To a solution of ethyl 3-azido-1-tosylazetidine-3-carboxylate **414** (30 mg, 0.09 mmol) in MeOH (2 mL) was added dropwise at 0 °C 2M $NaOH_{(aq)}$ (2 mL), and the reaction mixture was stirred at room temperature for 2 h. The reaction mixture was acidified with 1M HCl aq. solution till pH = 7 and extracted with EtOAc (3 × 5 mL). The combined organic phases were dried ($MgSO_4$), filtered and evaporated *in vacuo*. The crude product was purified by column chromatography to give 3-azido-1-tosylazetidine-3-carboxylic acid **48a**.

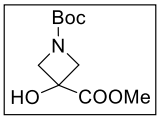


R_f = 0.19 (PE/Et_2O 1/1). Yellow oil, yield 80%. **IR** (cm^{-1}): ν_{OH} = 3221, ν_{N3} = 2108, $\nu_{C=O}$ = 1731, $\nu_{S=O}$ = 1157. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.48 (3H, s, p-CH_3), 3.83 (2H, d, J = 9.5 Hz, C*H*(H)NC*H*(H)), 4.21 (2H, d, J = 9.5 Hz, CH(*H*)NCH(*H*)), 7.40 (2H, d, J = 8.2 Hz, 2 × CH_{arom}), 7.74 (2H, d, J = 8.2 Hz, 2 × CH_{arom}). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ 21.7 (p-CH_3), 58.2 (CCH_2), 58.4 (CH_2NCH_2), 128.4 (2 × CH_{arom}), 130.0 (2 × CH_{arom}), 131.2 ($C_{arom,quat}$), 144.7 ($C_{arom,quat}$), 168.5 (C=O). **MS** (ES, pos. mode): *m/z* (%): 297 (100) $[M+H]^+$. **HRMS**: calcd for $C_{11}H_{11}N_4O_4S^-$ $[M-H^+]$ 295.0507; found: 295.0516.

5.2.44 Synthesis of methyl *N*-(*tert*-butoxycarbonyl)-3-hydroxyazetidine-3-carboxylate 46b

A mixture of magnesium powder (33 mg, 1.37 mmol) in dry MeOH (1 mL) was stirred at room temperature for 10 min. The reaction mixture was cooled down to 0 °C and a solution of ethyl 3-hydroxy-1-(4-methylbenzenesulfonyl)azetidine-3-carboxylate **46a** (41 mg, 0.13 mmol) in dry MeOH (2 mL) was added dropwise. Subsequently, the resulting suspension was allowed to warm up to room temperature. After 16 h, a second portion of magnesium powder (16 mg, 0.68 mmol) was added. The suspension was stirred for another 2 h at room temperature. Subsequently, the reaction mixture was cooled down to 0 °C and Et_3N (14 mg, 0.14 mmol) was added dropwise followed by addition of a solution of di-*tert*-butyl dicarbonate (31 mg, 0.14 mmol) in MeOH (0.5 mL). The ice bath was removed and the resulting suspension was stirred at room temperature for 3 h. Subsequently, the reaction mixture was concentrated under reduced pressure to afford a gray suspension which was

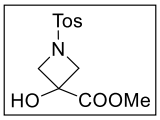
dissolved in aqueous NH_4Cl and extracted with EtOAc (3 × 5 mL). The combined organic phases were dried ($MgSO_4$), filtered and evaporated *in vacuo*. The purification of the crude mixture by preparative TLC on silica gel afforded pure methyl *N*-(*tert*-butoxycarbonyl)-3-hydroxyazetidine-3-carboxylate **46b**. CAUTION: strict safety measurements have to be applied for Mg-promoted reactions to avoid risk of violent reactions, fires or explosions (safety shield).



R_f = 0.27 (PE/Et_2O 3/7). Colorless oil, yield 54%. **IR** (cm^{-1}): ν_{OH} = 3387, $\nu_{C=O}$ = 1740, $\nu_{C=O}$ = 1675. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.46 (9H, s, *t*Bu), 3.63 (1H, s, OH), 3.90 (3H, s, OCH_3), 4.01 (2H, d, *J* = 9.9 Hz, C*H*(H)NC*H*(H)), 4.26 (2H, d, *J* = 9.9 Hz, CH(*H*)NCH(*H*)). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ 28.3 (3C, *t*Bu), 53.6 (OCH_3), 60.8 (*C*H_2N*C*H2), 69.2 (*C*CH_2), 80.1 (*C*$(CH_3)_3$), 156.1 (C=O), 174.0 (C=O). **MS** (ES, pos. mode): *m/z* (%): 132 (100) $[(M\text{-Boc})+H]^+$. **HRMS**: calcd for $C_5H_{10}NO_5^+$ $[(M\text{-Boc})+H]^+$ 132.0655; found: 132.0656.

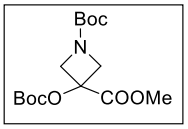
Compounds **46c**, **417** and **418** were formed as a side products during the optimization of *N*-deprotection reaction of ethyl 3-hydroxy-1-(4-methylbenzenesulfonyl)azetidine-3-carboxylate **46a** (See table 17). The spectral data of the pure isolated compounds are given below:

Methyl 3-hydroxy-1-(4-methylbenzenesulfonyl)azetidine-3-carboxylate 46c



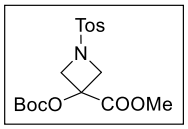
R_f = 0.15 (PE/Et_2O 3/7). White crystals, yield 15%. **Mp** 105.5-106.5 ºC. **IR** (cm^{-1}): ν_{OH} = 3410, $\nu_{C=O}$ = 1739, $\nu_{S=O}$ = 1156. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.47 (3H, s, *p*-CH_3), 3.55 (1H, s, OH), 3.80 (3H, s, OCH_3), 3.82 (2H, d, *J* = 9.2 Hz, C*H*(H)NC*H*(H)), 4.17 (2H, d, *J* = 9.0 Hz, CH(*H*)NCH(*H*)), 7.39 (2H, d, *J* = 8.2 Hz, 2 × CH_{arom}), 7.75 (2H, d, *J* = 8.2 Hz, 2 × CH_{arom}). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ 21.6 (*p*-CH_3), 53.8 (OCH_3), 61.8 (*C*H_2N*C*H_2), 67.8 (*C*CH_2), 128.4 (2 × CH_{arom}), 129.8 (2 × CH_{arom}), 131.3 ($C_{arom,quat}$), 144.3 ($C_{arom,quat}$), 173.1 (C=O). **MS** (ES, pos. mode): *m/z* (%): 286 (100) $[M+H]^+$. **HRMS** Calcd for $C_{12}H_{16}NO_5S^+$ $[MH]^+$ 286.0744; found: 286.0751.

1-(*tert*-Butoxycarbonyl) methyl 3-[(*tert*-butoxycarbonyl)oxy]azetidine-3-carboxylate 417



R_f = 0.50 (PE/Et_2O 1/1). Yellow oil, yield 8%. **IR** (cm^{-1}): $\nu_{C=O}$ = 1743, $\nu_{C=O}$ = 1706. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.45 (9H, s, *t*Bu), 1.50 (9H, s, *t*Bu), 3.84 (3H, s, OCH_3), 4.09 (2H, d, *J* = 10.1 Hz, C*H*(H)NC*H*(H)), 4.38 (2H, d, *J* = 10.1 Hz, CH(*H*)NCH(*H*)). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ 27.6 (3C, *t*Bu), 28.3 (3C, *t*Bu), 53.1 (O*C*H_3), 57.6, 73.3 (*C*CH_2), 80.4 (C$(CH_3)_3$), 84.2 (C$(CH_3)_3$), 151.2 (C=O), 155.9 (C=O), 169.3 (C=O). **MS** (ES, pos. mode): *m/z* (%): 220 (100) $[(M\text{-}C_8H_{16})+H]^+$. **HRMS**: calcd for $C_5H_{10}NO_3^+$ $[(M\text{-2xBoc})+H]^+$ 132.0655; found: 132.0657.

Methyl 3-[(tert-butoxycarbonyl)oxy]-1--(4-methylbenzenesulfonyl)azetidine-3-carboxylate 27

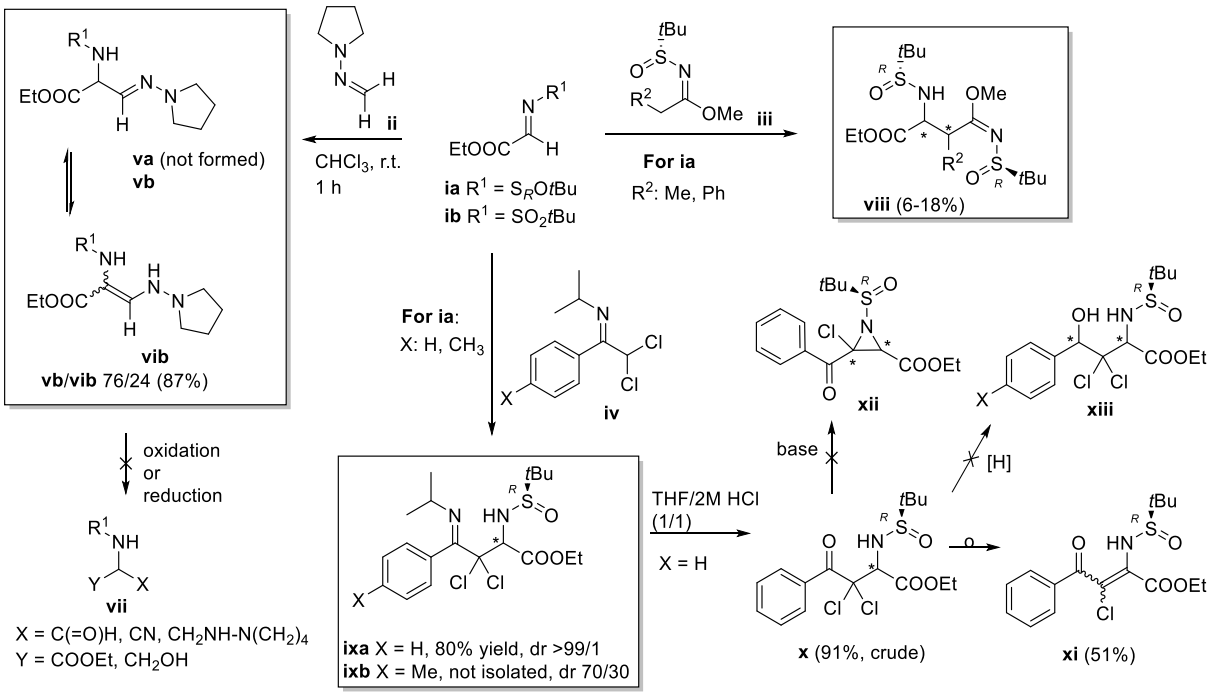


R_f = 0.33 (PE/Et_2O 1/1). Pale yellow oil, yield 5%. **IR** (cm^{-1}): $\nu_{C=O}$ = 1740, $\nu_{S=O}$ = 1160. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.45 (9H, s, *t*Bu), 2.48 (3H, s, *p*-CH_3), 3.70 (3H, s, O*C*H_3), 4.00 (2H, d, *J* = 9.7 Hz, C*H*(H)NC*H*(H)), 4.26 (2H, d, *J* = 9.7 Hz, CH(*H*)NCH(*H*)), 7.39 (2H, d, *J* = 8.3 Hz, 2 × CH_{arom}), 7.75 (2H, d, *J* = 8.3 Hz, 2 × CH_{arom}). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ 21.7 (*p*-CH_3), 27.5 (3C, *t*Bu), 53.2 (O*C*H_3), 58.6 (*C*H_2N*C*H_2), 72.1 (*C*CH_2), 84.5 (C(CH_3)$_3$), 128.4 (2 × CH_{arom}), 129.9 (2 × CH_{arom}), 131.7 ($C_{arom,quat}$), 144.5 ($C_{arom,quat}$), 151.4 (C=O), 168.2 (C=O). **MS** (ES, pos. mode): *m/z* (%): 330 (100) $[(M\text{-}C_4H_8)+H]^+$. **HRMS**: calcd for $C_{13}H_{19}N_2O_7S^+$ $[(M\text{-}C_4H_8)+NH_4]^+$ 374.0908; found: 347.0923.

6 Summary

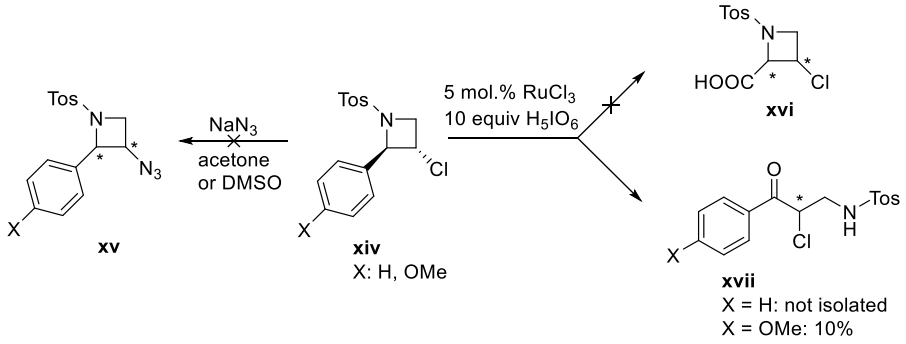
The discovery of non-proteinogenic amino acids among natural products has significantly increased interest in this class of compounds as they may possess interesting biological activity and could also serve as valuable building blocks in the synthesis of new classes of bioactive compounds as well as for the synthesis and design of peptides. Some natural non-proteinogenic amino acids were proposed as neurotoxic compounds which play a role in neurodegenerative diseases. The misincorporation of some non-proteinogenic amino acids into proteins in place of canonical amino acids causes toxic effect and has been implicated in the pathophysiology of a wide range of diseases, including amyotrophic lateral sclerosis (ALS) and Alzheimer's disease. In that respect, the synthesis of new derivatives of non-proteinogenic α- and β-amino acids, including acyclic and cyclic scaffolds, was the subject of the present research.

In the first part of this PhD thesis, iminoacetates **i** were used for (asymmetric) synthesis of non-proteinogenic diamino acid derivatives (Scheme 110). The condensation of iminoacetates **i** with 1-(methylenamino)pyrrolidine **ii**, *N*-sulfinyl imidates **iii** and 3,3-dichloroketimines **iv** afforded adducts **v/vi**, **viii** and **ix**, respectively. Unfortunately, further transformations of the mixture **vb**/**vib** towards the desired amino acid derivatives **vii** could not be realized due to instability of the adducts. Adduct **ixa** was tested as a possible precursor for the asymmetric synthesis of aziridine-2-carboxylic acid derivative **xii** or chlorinated amino alcohol **xiii** without success, however.



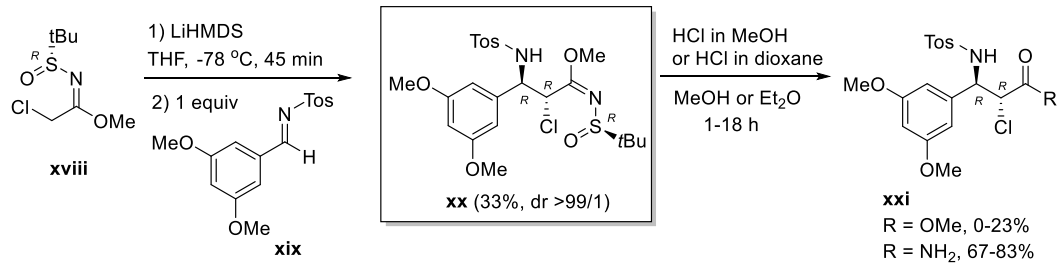
Scheme 110

In the next part of the research, the synthesis of 3-chloroazetidine-2-carboxylic acid **xvi** from enantiomerically pure 2-arylazetidines **xiv** was attempted (Scheme 111). The latter azetidines were synthesized *via* an earlier described procedure based on a Mannich-type reaction of methyl α-chloro-*N*-sulfinyl acetimidate across aromatic aldimines. However, the oxidation of the 2-aryl substituent failed, giving the ring opened product **xvii** (only **xviib** was isolated). Nucleophilic substitution of chloride to an azido group could also not be achieved (Scheme 111).



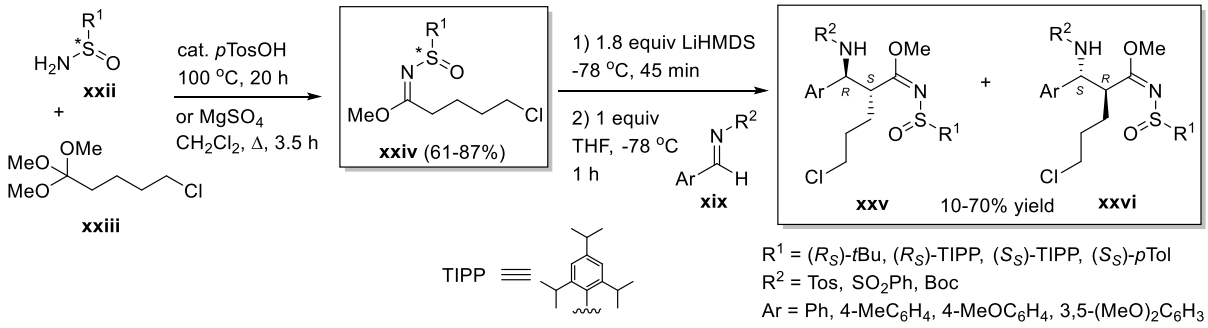
Scheme 111

A modification of the aromatic substituent to a 3,5-dimethoxyphenyl moiety was investigated to facilitate the oxidation process. However, the selectivity and efficiency of the key step involving the formation of imidate **xx** (Scheme 112) dropped significantly when aldimine **xix** was used as starting material. Subsequent *N*-sulfinyl deprotection, en route towards the corresponding azetidine, afforded undesired amide **xxi** (R = NH_2) as main product instead of ester **xxi** (R = OMe).



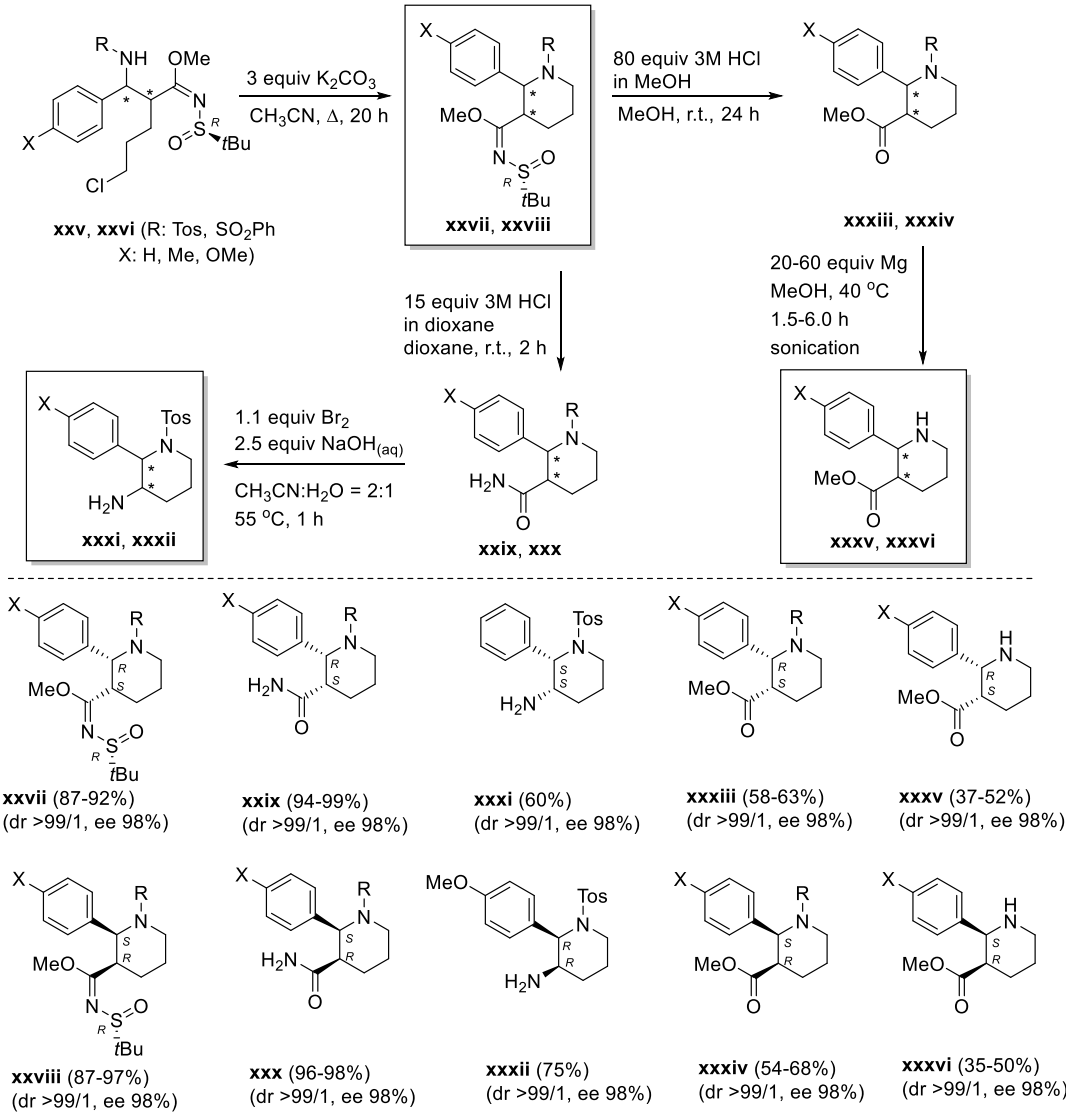
Scheme 112

Furthermore, the use of δ-chloro *N*-sulfinyl imidates **xxiv** in the addition reaction across aromatic aldimines led to the synthesis of new chiral β-aryl-δ-chloro-substituted β-amino acid derivatives **xxv** and **xxvi** as potential building blocks of enantiopure functionalized piperidines (Scheme 113).



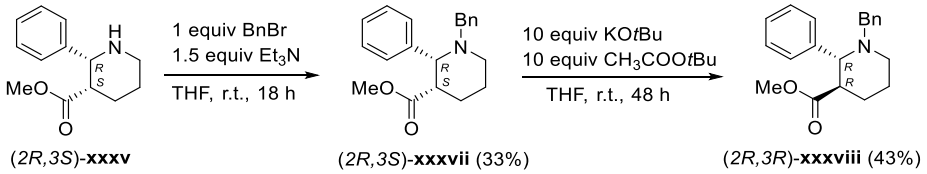
Scheme 113

Diastereomers **xxv** and **xxvi** were separated and selected derivatives were subjected to further transformations (Scheme 114). The base-promoted cyclization of imidates **xxv** and **xxvi** afforded piperidines **xxvii** and **xxviii**. The latter were *N*-deprotected leading to the formation of amides (**xxix** and **xxx**) or esters (**xxxiii** and **xxxiv**). Hofmann rearrangement of the amides **xxix** and **xxx** provided the enantiomerically pure 3-amino-2-arylpiperidines **xxxi** and **xxxii**. The *N*-detosylation of esters **xxxiii** and **xxxiv** gave the piperidine-3-carboxylic acid derivatives **xxxv** and **xxxvi**.



Scheme 114

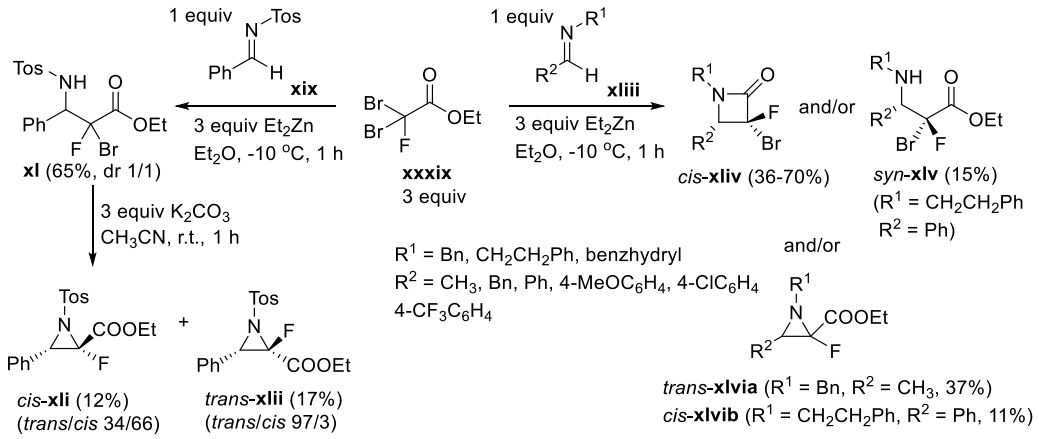
The *N*-benzyl protection of the *cis*-piperidine-3-carboxylate **xxxv** and subsequent treatment with a base afforded the *trans*-derivative **xxxviii** (Scheme 115).



Scheme 115

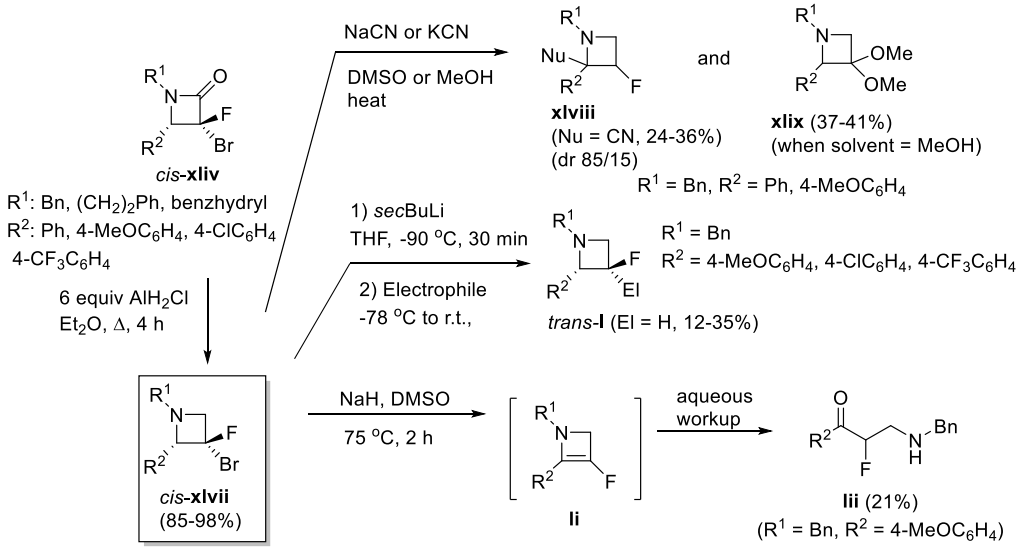
In the third part of this PhD, fluorinated azetidines were synthesized and their reactivity was investigated. The synthesis of key precursor *cis*-**xliv** was performed *via* Reformatsky-type reaction of dibromofluoroacetate **xxxix** and aldimines **xliii** (Scheme 116). The formation of adducts **xlv** and aziridines **xlvi** was observed in some cases. When aldimine **xix,** bearing an electron-withdrawing

group at nitrogen, was subjected to the condensation with acetate **xxxix**, adduct **xl** was obtained which was further cyclized towards aziridines **xli** and **xlii**.



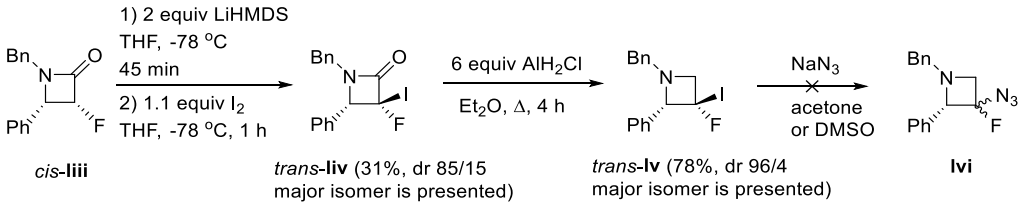
Scheme 116

The reduction of *cis*-β-lactams **xliv** was accomplished using chloroalane in Et_2O, affording *cis*-2-aryl-3-bromo-3-fluoroazetidines **xlvii**, exclusively (Scheme 117). In the next step, the reactivity of the fluorinated azetidines **xlvii** was investigated (Scheme 117). The unexpected nucleophilic attack at the C-2 position of the azetidine ring afforded 2-aryl-2-cyano-3-fluoroazetidine **xlviii** and side product **xlix**, when the reaction was performed in methanol. Furthermore, the azetidines **xlvii** were used in a halogen-lithium exchange strategy. When water was used as an electrophile, *trans*-2-aryl-3-fluoroazetidines **l** were formed. Other electrophilic reagents did not lead to the desired substitution. The treatment of azetidine **xlvii** (R^2 = 4-$MeOC_6H_4$) with NaH in DMSO followed by aqueous work-up afforded the ring opened product, *i.e.* β-amino-α-fluoroketone **lii**.



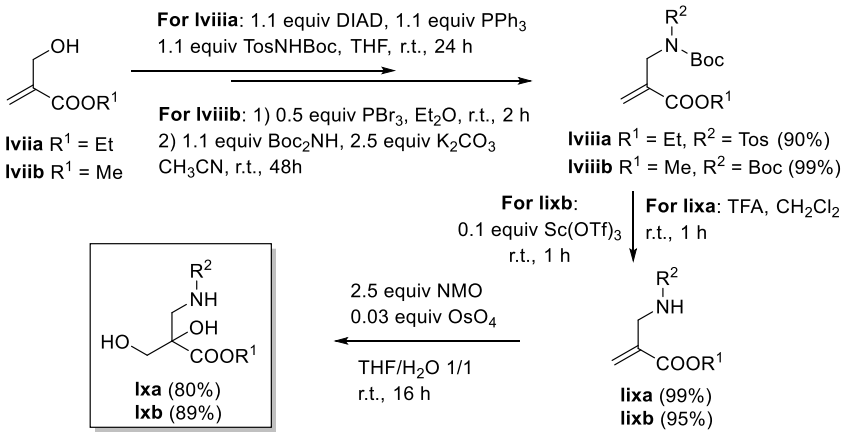
Scheme 117

Furthermore, the influence of substrate structure on the reactivity of 3-fluorinated azetidines **xlvii** was investigated. Thus, *trans*-3-fluoro-3-iodo-2-phenylazetidine **lv** was prepared *via* reduction of β-lactam **liv** (Scheme 118). Despite several attempts, the nucleophilic substitution of iodide in azetidine **lv** using sodium azide in different solvents was not successful.



Scheme 118

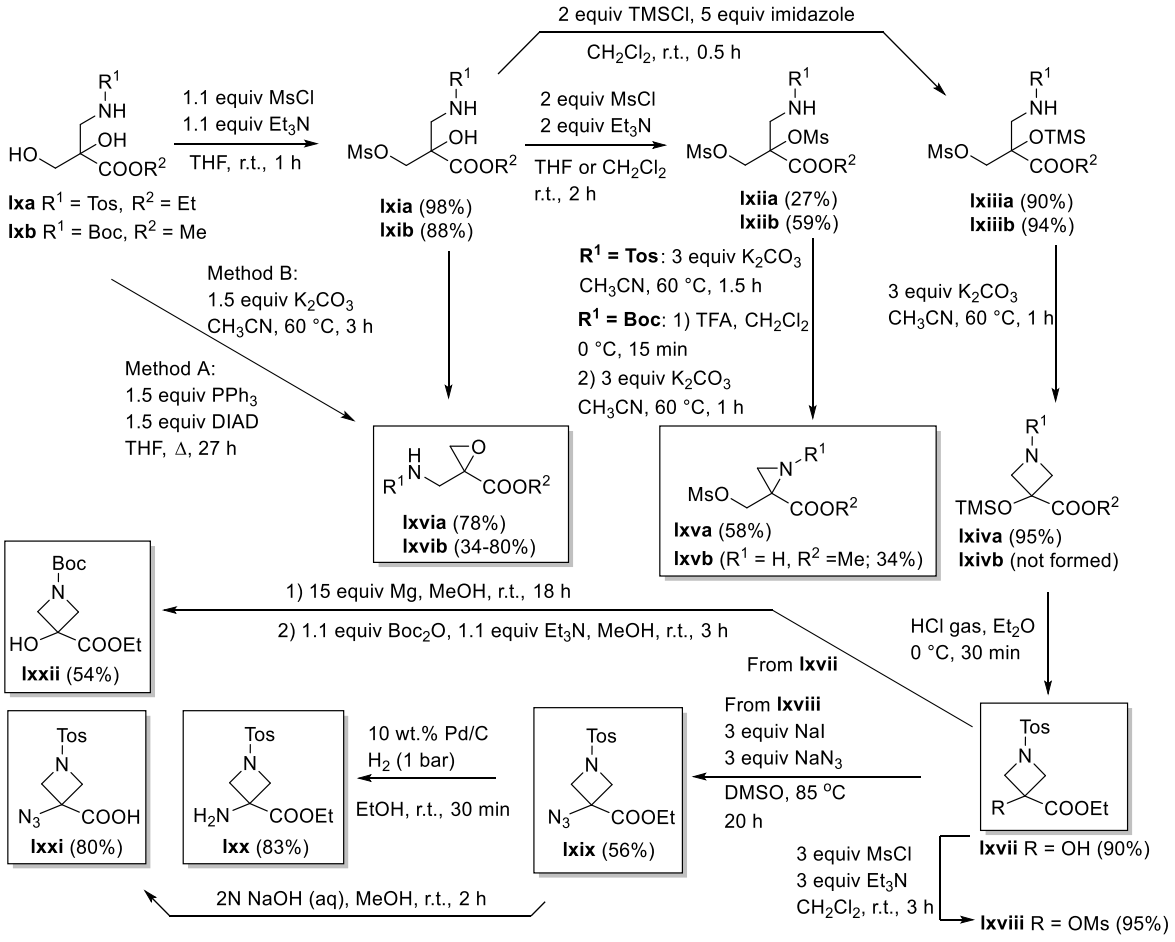
In the last part of this PhD thesis, aminodiols **lx** were elaborated towards small membered amino acid derivatives bearing an aziridine, azetidine and epoxide scaffold. The starting aminodiols **lx** were synthesized from the functionalized allylamines **lix** by OsO_4-catalyzed dihydroxylation (Scheme 119).



Scheme 119

The cyclization of aminodiol **lxb** under Mitsunobu conditions afforded epoxide **lxvib** (Scheme 120). A more efficient synthesis of epoxides **lxvi** was accomplished *via* a monomesylation/cyclization sequence. When bismesylated aminodiols **lxii** were treated with potassium carbonate, the cyclization towards aziridine **lxva** occurred smoothly but prior *N*-Boc deprotection was necessary in order to obtain aziridine **lxvb**. The tertiary hydroxyl group of monomesylated substrates **lxi** was TMS-protected, affording mesylates **lxiii**. Only *N*-Tos protected mesylate **lxiiia** was cyclized to the azetidine **lxiva**. The *O*-deprotection and subsequent mesylation of the hydroxyl group of azetidine **lxiva** afforded mesylate **lxviii**. Azetidine **lxviii** was elaborated towards the 3-azidoazetidine **lxix**, while reduction or hydrolysis of the latter afforded the 3-aminoazetidine-3-carboxylate **lxx** or

azetidine-3-carboxylic acid **lxxi**, respectively. Additional transformation of azetidine **lxvii** towards *N*-Boc protected azetidine **lxxii** was performed *via* an *N*-detosylation/*N*-protection sequence.



Scheme 120

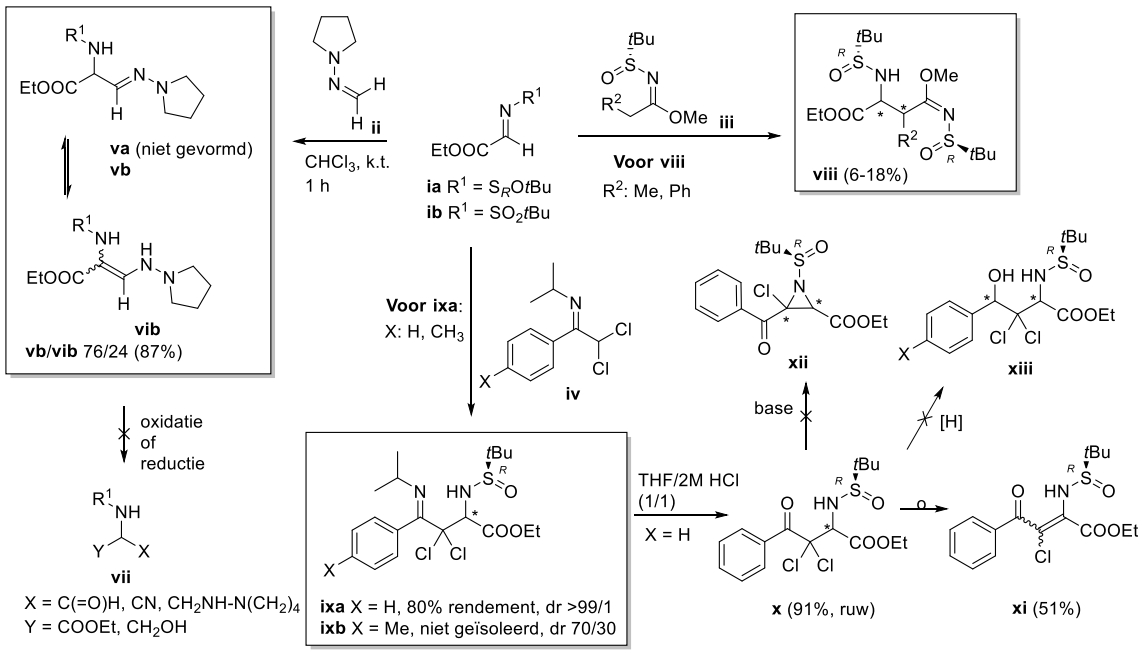
In conclusion, this PhD work resulted in the preparation of diverse acyclic and cyclic non-proteinogenic amino acid derivatives such as aziridines, epoxides, azetidines and piperidines with different types of substitution, including some enantiomerically enriched compounds.

Some of the established synthetic approaches provide great potential in the synthesis of various biologically relevant compounds.

7 Samenvatting

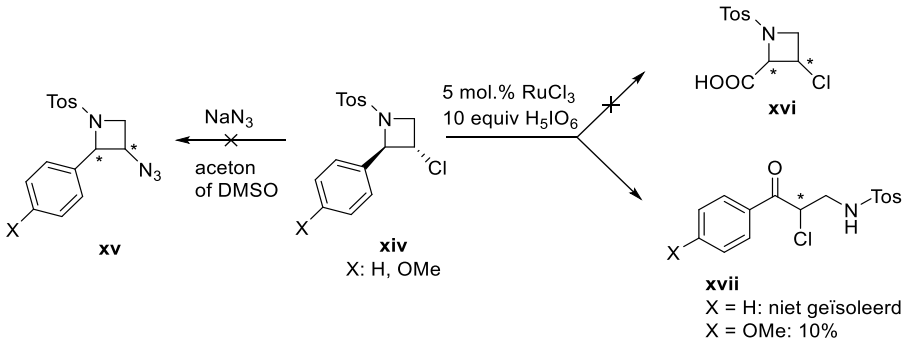
De ontdekking van niet-proteïnogene aminozuren in natuurlijke producten deed de belangstelling voor deze klasse van verbindingen aanzienlijk toenemen. Naast een mogelijk interessante biologische activiteit, kunnen ze een waardevolle rol spelen als bouwstenen bij de synthese van nieuwe klassen van bioactieve verbindingen en bij de synthese en het ontwerp van peptiden. Sommige natuurlijk voorkomende niet-proteïnogene aminozuren worden beschouwd als neurotoxische verbindingen met een rol in neurodegeneratieve ziektes. De foutieve incorporatie van een aantal niet-proteïnogene aminozuren in plaats van de canonieke aminozuren in eiwitten brengt toxische effecten teweeg en is betrokken bij de pathofysiologie van een brede waaier ziekten, zoals amyotrofische laterale sclerose (ALS) en de ziekte van Alzheimer. Vanuit dit oogpunt was de synthese van nieuwe derivaten van niet-proteïnogene α- en β-aminozuren, waaronder acyclische en cyclische derivaten, een relevant onderwerp voor het huidige onderzoek.

In het eerste deel van dit proefschrift werden iminoacetaten **i** gebruikt voor de (asymmetrische) synthese van niet-proteïnogene diaminozuurderivaten (Schema 1). De condensatie van iminoacetaten **i** met 1-(methyleenamino)pyrrolidine **ii**, *N*-sulfinyl imidaten **iii** en 3,3-dichloorketiminen **iv** gaf de adducten **v/vi**, **viii** en **ix**, respectievelijk. Verdere omzettingen van het mengsel **v/vi** naar de gewenste aminozuurderivaten **vii** kon jammerlijk niet worden gerealiseerd vanwege de instabiliteit van de adducten. Adduct **ixa** werd getest als een mogelijke precursor voor de asymmetrische synthese van het aziridine-2-carbonzuurderivaat **xii** of het gechloreerde aminoalcohol **xiii**, maar dit evenwel zonder succes.



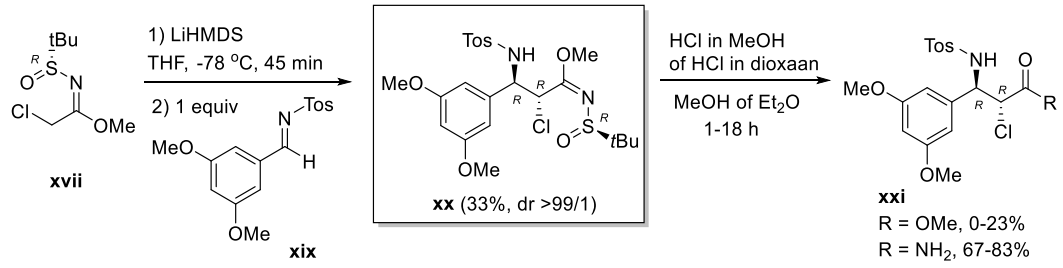
Schema 1

In het volgende deel van dit onderzoek werd de synthese van 3-chloorazetidine-2-carbonzuur **xvi** vanuit enantiomeer zuivere 2-arylazetidines **xiv** beoogd (Schema 2). De azetidines **xiv** werden gesynthetiseerd *via* een eerder beschreven procedure op basis van een Mannich-type reactie van methyl α-chloor-*N*-sulfinyl acetimidaat en een aromatisch aldimine. De oxidatie van de 2-arylsubstituent mislukte, waardoor het geringopend product **xvii** (alleen **xviib** werd geïsoleerd) bekomen werd. De nucleofiele substitutie van het chlooratoom met een azidogroep was evenmin succesvol (Schema 2).



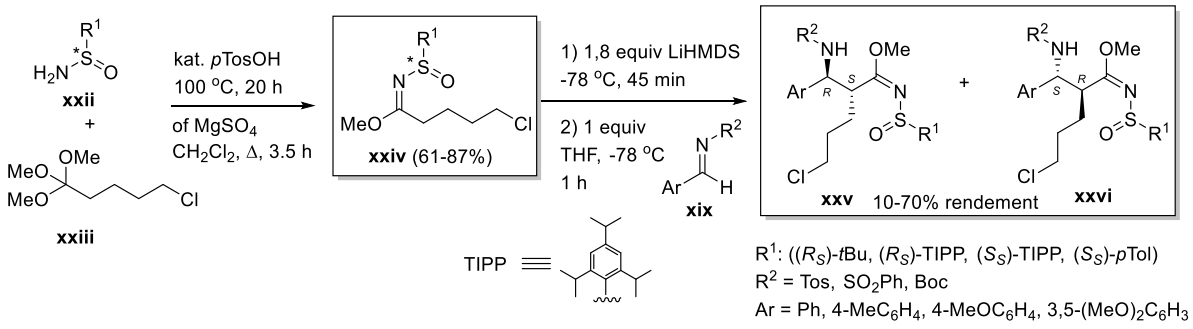
Schema 2

De wijziging van de aromatische substituent naar een 3,5-dimethoxyfenyl-groep werd geëvalueerd om de oxidatie te vergemakkelijken. Echter, hierdoor daalde de selectiviteit en de efficiëntie van de vorming van imidaat **xx** (Schema 3) aanzienlijk wanneer aldimine **xix** werd gebruikt als uitgangsmateriaal. Daaropvolgende *N*-sulfinyl ontscherming, om het overeenkomstige azetidine te bekomen, leverde het ongewenste amide **xxi** (R = NH_2) als hoofdproduct in plaats van het ester **xxi** (R = OMe).



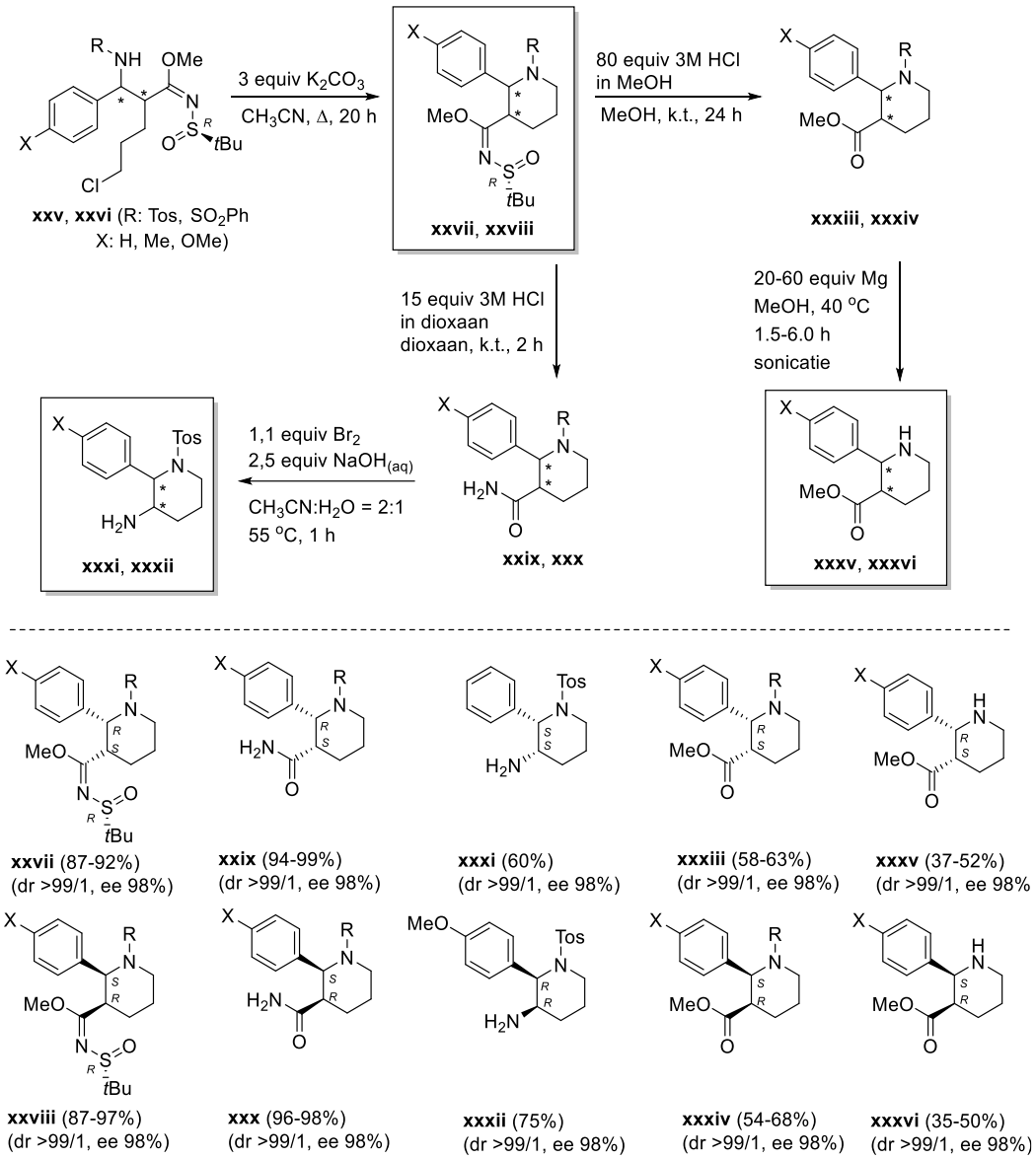
Schema 3

Het gebruik van δ-chloor-*N*-sulfinyl imidaten **xxiv** in de additiereactie met aromatische aldiminen leidde tot de synthese van de nieuwe, chirale β-aryl-δ-chloor-gesubstitueerde β-aminozuurderivaten **xxv** en **xxvi** als mogelijke bouwstenen voor enantiomeer zuivere, gefunctionaliseerde piperidinen (Schema 4).



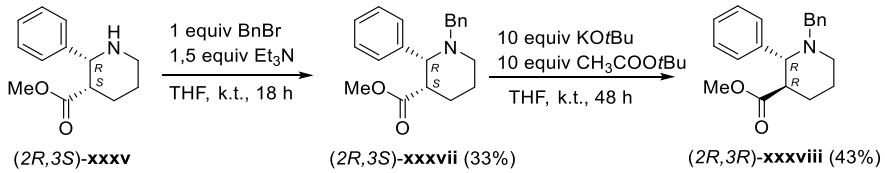
Schema 4

Diastereomeren **xxv** en **xxvi** werden gescheiden en geselecteerde derivaten werden gebruikt voor verdere transformaties (Schema 5). De base bevorderde ringsluiting van imidaten **xxv** en **xxvi** leidde tot piperidinen **xxvii** en **xxviii**. Deze laatste werden *N*-ontschermd tot de amiden (**xxix** en **xxx**) of esters (**xxxiii** en **xxxiv**). Hofmann-omlegging van de amiden **xxix** en **xxx** gaf de enantiomeer zuivere 3-amino-2-arylpiperidinen **xxxi** en **xxxii**. De *N*-detosylering van de esters **xxxiii** en **xxxiv** gaf piperidine-3-carbonzuurderivaten **xxxv** en **xxxvi**.



Schema 5

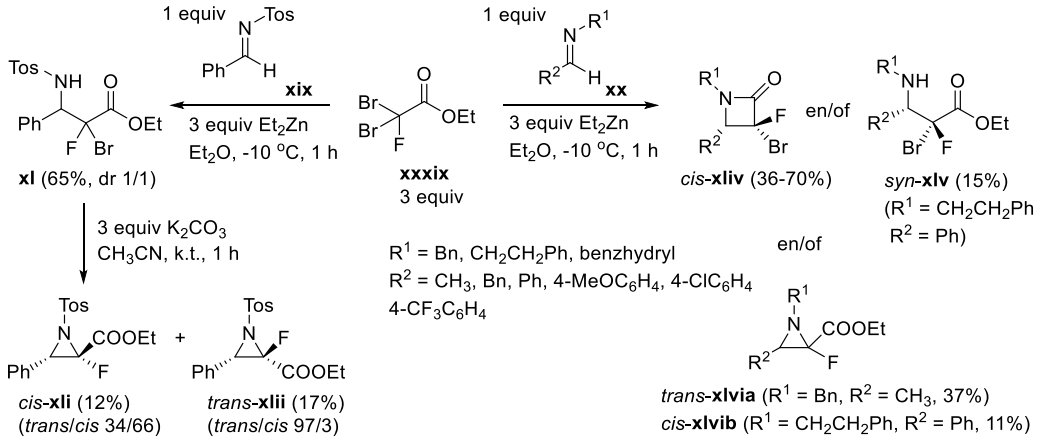
De *N*-benzyl bescherming van *cis*-piperidine-3-carboxylaat **xxxv** en de daaropvolgende behandeling met een base leverde het *trans*-derivaat **xxxviii** op (Schema 6).



Schema 6

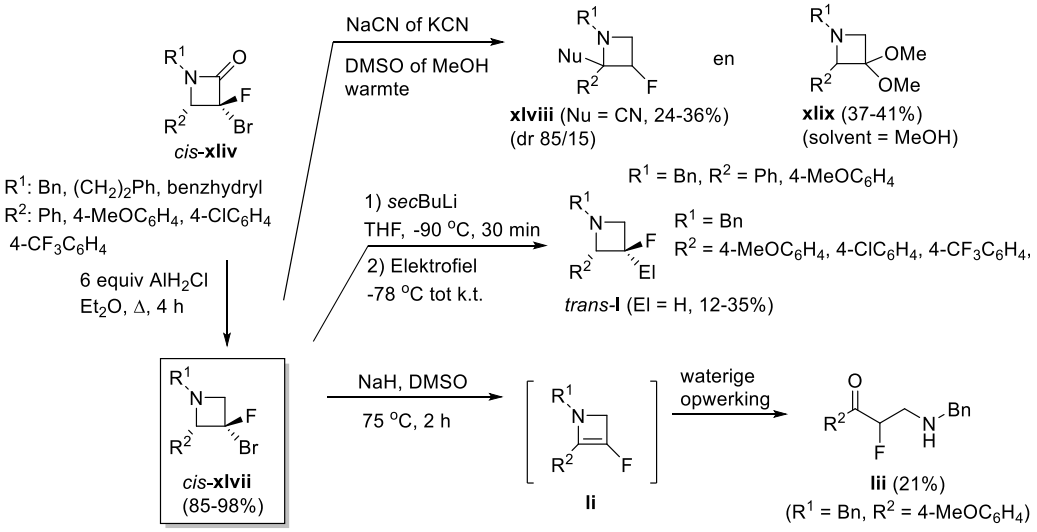
In een derde luik van dit doctoraat werden gefluoreerde azetidinen gesynthetiseerd en werd hun reactiviteit onderzocht. De synthese van de belangrijkste precursor *cis*-**xliv** gebeurde *via* een Reformatsky-type reactie met dibroomfluoracetaat **xxxix** en aldiminen **xliii** (Schema 7). De vorming

van adducten **xlv** en aziridinen **xlvia,b** werd geobserveerd in sommige gevallen. Wanneer aldimine **xixa**, voorzien van een elektronenzuigende groep op het stikstofatoom, werd onderworpen aan een condensatiereactie met acetaat **xxxix**, werd adduct **xl** verkregen, dat werd gecycliseerd tot aziridines **xli** and **xlii**.



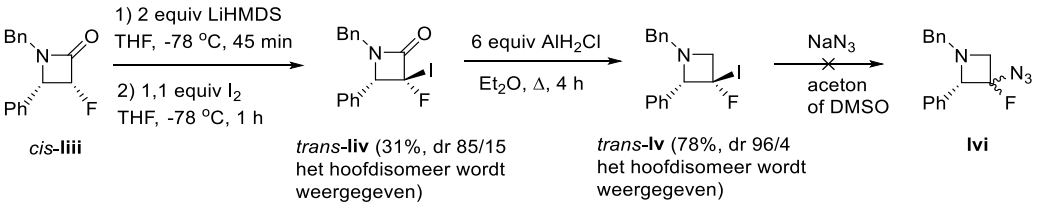
Schema 7

De reductie van *cis*-β-lactam **xliv** werd bewerkstelligd met behulp van chlooralaan in Et_2O en gaf uitsluitend aanleiding tot *cis*-2-aryl-3-broom-3-fluorazetidines **xlvii** (Schema 8). In de volgende stap werd de reactiviteit van de verkregen gefluoreerde azetidines **xlvii** onderzocht (Schema 8). Een onverwachte nucleofiele aanval trad op aan de C-2 positie van de azetidinering, wat aanleiding gaf tot 2-aryl-2-cyaan-3-fluorazetidine **xlviii** en nevenproduct **xlix** wanneer de reactie werd uitgevoerd in methanol. Azetidines **xlvii** werden ook gebruikt in een halogeen-lithium-uitwisselingsstrategie. Wanneer water werd gebruikt als elektrofiel, werden *trans*-2-aryl-3-fluorazetidines **l** gevormd. Andere elektrofiele reagentia leidden niet tot de gewenste substitutie. De behandeling van azetidine **xlvii** (R^2 = 4-$MeOC_6H_4$) met NaH in DMSO, gevolgd door een waterige opwerking bewerkstelligde ringopening tot β-amino-α-fluorketon **lii**.



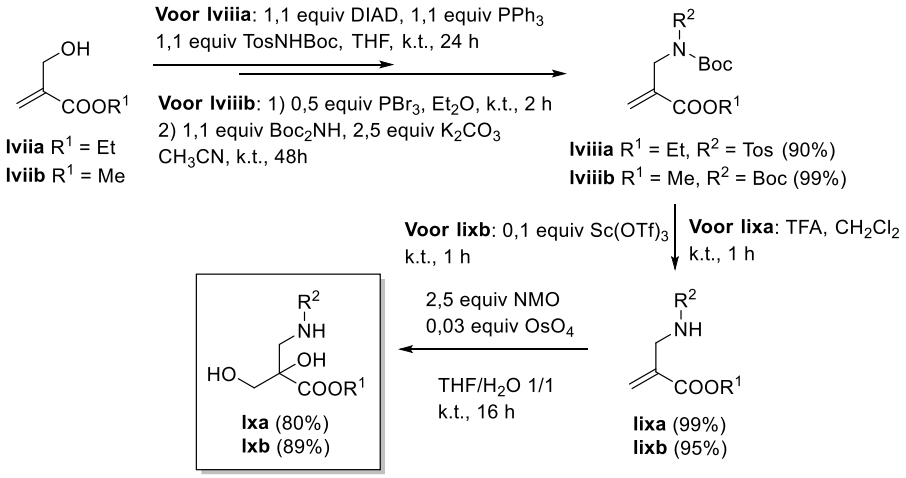
Schema 8

Vervolgens werd de invloed van de substraatstructuur op de reactiviteit van 3-gefluoreerde azetidines **xlvii** onderzocht. Aldus werd *trans*-3-fluor-3-jood-2-fenylazetidine **lv** bereid *via* de reductie van β-lactam **liv** (Schema 9). Ondanks verschillende pogingen, faalde de nucleofiele substitutie van het joodatoom in azetidine **lv** gebruik makende van natriumazide en dit in verschillende solventen.



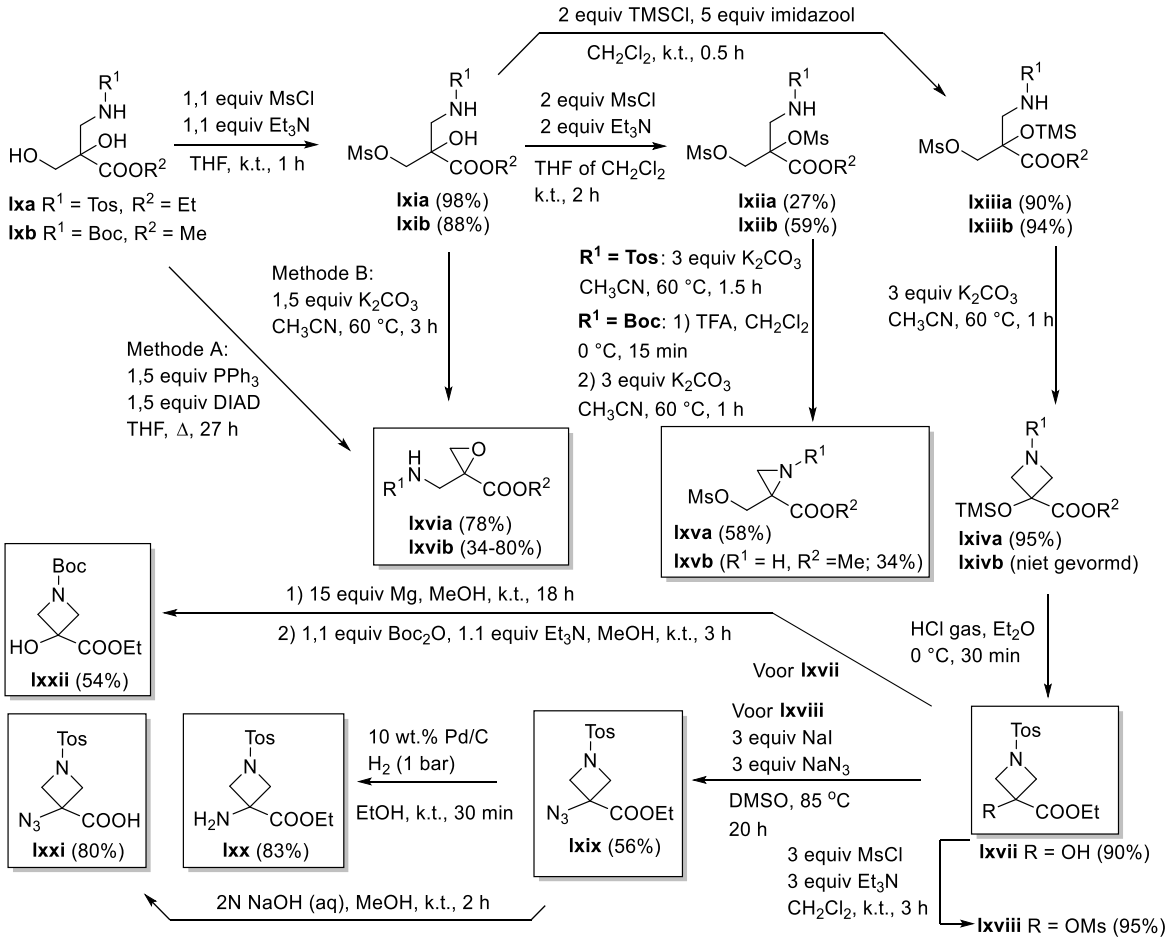
Schema 9

In het laatste deel van dit proefschrift werden aminodiolen **lx** verder omgezet tot aminozuurderivaten voorzien van een aziridine, azetidine of epoxide-eenheid. De benodigde aminodiolen **lx** werden gesynthetiseerd uit gefunctionaliseerde allylamines **lix** *via* een OsO_4 gekatalyseerde dihydroxylering (Schema 10).



Schema 10

De ringsluiting van aminodiol **lxb** onder Mitsunobu-condities gaf epoxide **lxvib** (Schema 11). Een efficiëntere synthese van epoxiden **lxvi** werd bekomen *via* een monomesylering/ringsluitingssequentie. Wanneer bisgemesyleerde aminodiolen **lxii** met kaliumcarbonaat behandeld werden, ging de ringsluiting tot aziridine **lxva** vlot door, alhoewel een voorafgaande *N*-Boc-ontscherming noodzakelijk was om aziridine **lxvb** te verkrijgen. De tertiaire hydroxylgroep van monogemesyleerde substraten **lxi** werd TMS-beschermd, met als resultaat mesylaten **lxiii**. Alleen het *N*-Tos beschermde mesylaat **lxiiia** werd gecycliseerd tot het azetidine **lxiva**. De *O*-ontscherming en daaropvolgende mesylering van de hydroxylgroep van azetidine **lxiva** gaf mesylaat **lxviii**. Azetidine **lxviii** werd verder omgezet tot 3-azidoazetidine **lxix**. Reductie of hydrolyse van het laatstgenoemde azetidine leverde het 3-aminoazetidine-3-carboxylaat **lxx** of het azetidine-3-carbonzuur **lxxi**, respectievelijk. Een extra transformatie van azetidine **lxvii** tot het *N*-Boc beschermde azetidine **lxxii** werd uitgevoerd *via* een *N*-detosylering/*N*-beschermingssequentie.



Schema 11

Samengevat, resulteerde dit onderzoek in de synthese van verschillende acyclische en cyclische niet-proteïnogene aminozuurderivaten zoals aziridinen, epoxiden, azetidinen en piperidines met verschillende substituties, waaronder ook enkele enantiomeer aangerijkte verbindingen. Enkele van de ontwikkelde synthetische protocollen hebben een groot potentieel in de synthese van verschillende biologisch relevante verbindingen.

8 References

[1] Kasperkiewicz, P.; Gajda, A. D.; Drag, M. *Biol. Chem.* **2012**, *393*, 843-851.

[2] a) Walsh, C. T.; Brien, R. V. O.; Khosla, C. *Angew. Chem. Int. Ed.* **2013**, *52*, 7098-7124; b) Alladoum, J.; Dechoux, L. *Tetrahedron Lett.* **2005**, *46*, 8203-8205.

[3] Vranova, V.; Rejsek, K.; Skene, K. R.; Formanek, P. *Plant Soil* **2011**, *342*, 31-48.

[4] a) Mach, J. *Plant Cell* **2015**, *27*, 949-949; b) Xu, M. M.; Galhano, R.; Wiemann, P.; Bueno, E.; Tiernan, M.; Wu, W.; Chung, I. M.; Gershenzon, J.; Tudzynski, B.; Sesma, A.; Peters, R. J. *New. Phytol.* **2012**, *193*, 570-575.

[5] Huang, T. F.; Jander, G.; de Vos, M. *Phytochemistry* **2011**, *72*, 1531-1537.

[6] Aravinda, S.; Shamala, N.; Roy, R. S.; Balaram, P. *P. Indian. AS-Chem. Sci.* **2003**, *115*, 373-400.

[7] Dasuri, K.; Ebenezer, P. J.; Uranga, R. M.; Gavilan, E.; Zhang, L.; Fernandez-Kim, S. O. K.; Bruce-Keller, A. J.; Keller, J. N. *J. Neurosci. Res.* **2011**, *89*, 1471-1477.

[8] Rodgers, K. J. *Exp. Neurol.* **2014**, *253*, 192-196.

[9] Vega, A.; Bell, E. A. *Phytochemistry* **1967**, *6*, 759-762.

[10] Cox, P. A.; Banack, S. A.; Murch, S. J.; Rasmussen, U.; Tien, G.; Bidigare, R. R.; Metcalf, J. S.; Morrison, L. F.; Codd, G. A.; Bergman, B. *P. Natl. Acad. Sci. USA* **2005**, *102*, 9734-9734.

[11] a) Banack, S. A.; Johnson, H. E.; Cheng, R.; Cox, P. A. *Mar. Drugs* **2007**, *5*, 180-196; b) Brand, L. E.; Pablo, J.; Compton, A.; Hammerschlag, N.; Mash, D. C. *Harmful Algae* **2010**, *9*, 620-635; c) Esterhuizen, M.; Downing, T. G. *Ecotox. Environ. Safe* **2008**, *71*, 309-313.

[12] Mondo, K.; Hammerschlag, N.; Basile, M.; Pablo, J.; Banack, S. A.; Mash, D. C. *Mar. Drugs* **2012**, *10*, 509-520.

[13] a) Spencer, P. S.; Nunn, P. B.; Hugon, J.; Ludolph, A. C.; Ross, S. M.; Roy, D. N.; Robertson, R. C. *Science* **1987**, *237*, 517-522; b) Cox, P. A.; Sacks, O. W. *Neurology* **2002**, *58*, 956-959.

[14] Banack, S. A.; Caller, T. A.; Stommel, E. W. *Toxins* **2010**, *2*, 2837-2850.

[15] Duncan, M. W.; Steele, J. C.; Kopin, I. J.; Markey, S. P. *Neurology* **1990**, *40*, 767-772.

[16] Murch, S. J.; Cox, P. A.; Banack, S. A.; Steele, J. C.; Sacks, O. W. *Acta Neurol. Scand.* **2004**, *110*, 267-269.

[17] Cox, P. A.; Banack, S. A.; Murch, S. J. *P. Natl. Acad. Sci. USA* **2003**, *100*, 13380-13383.

[18] Lobner, D.; Piana, P. M. T.; Salous, A. K.; Peoples, R. W. *Neurobiol. Dis.* **2007**, *25*, 360-366.

[19] Bridges, R. J.; Natale, N. R.; Patel, S. A. *Brit. J. Pharmacol.* **2012**, *165*, 20-34.

[20] Lobner, D. *Amyotroph. Lateral Sc.* **2009**, *10*, 56-60.

[21] Dunlop, R. A.; Cox, P. A.; Banack, S. A.; Rodgers, K. J. *Plos One* **2013**, *8*.

[22] a) Rao, S. L. N.; Sarma, P. S.; Adiga, P. R. *Biochemistry* **1964**, *3*, 432-&; b) Murti, V. V. S.; Seshadri, T. R.; Venkitasubramanian, T. A. *Phytochemistry* **1964**, *3*, 73-78.

[23] a) Lambein, F.; Ongena, G.; Kuo, Y. H. *Phytochemistry* **1990**, *29*, 3793-3796; b) Lambein, F.; Kuo, Y. H.; Kusama-Eguchi, K.; Ikegami, F. *Arkivoc* **2007**, 45-52; c) Akalu, G.; Johansson, G.; Nair, B. M. *Food Chem.* **1998**, *62*, 233-237.

[24] Van Moorhem, M.; Lambein, F.; Leybaert, L. *Food Chem. Toxicol.* **2011**, *49*, 550-555.

[25] Singh, S. S.; Rao, S. L. N. *Indian J. Med. Res.* **2013**, *138*, 31-36.

[26] Bell, E. A.; Odonovan, J. P. *Phytochemistry* **1966**, *5*, 1211-1219.

[27] Bell, E. A. *J. Agric. Food Chem.* **2003**, *51*, 2854-2865.

[28] a) Rubenstein, E. *J. Neuropath. Exp. Neur.* **2008**, *67*, 1035-1040; b) Bessonov, K.; Bamm, V. V.; Harauz, G. *Phytochemistry* **2010**, *71*, 502-507; c) Bessonov, K.; Vassall, K. A.; Harauz, G. *J. Mol. Graph. Model.* **2013**, *39*, 118-125; d) Rubenstein, E.; McLaughlin, T.; Winant, R. C.; Sanchez, A.; Eckart, M.; Krasinska, K. M.; Chien, A. *Phytochemistry* **2009**, *70*, 100-104; e) Fowden, L. *Biochem. J.* **1956**, *64*, 323-332.

[29] a) Gustafsson, D.; Nystrom, J. E.; Carlsson, S.; Bredberg, U.; Eriksson, U.; Gyzander, E.; Elg, M.; Antonsson, T.; Hoffmann, K. J.; Ungell, A. L.; Sorensen, H.; Nagard, S.; Abrahamsson, A.; Bylund, R. *Thromb. Res.* **2001**, *101*, 171-181; b) Bach, T. M. H.; Takagi, H. *Appl. Microbiol. Biot.* **2013**, *97*, 6623-6634.

[30] Hecht, S.; Huc, I. *Foldamers: Structure, Properties, and Applications*, Wiley - VCH, Weinheim, **2007**.

[31] a) Seebach, D.; Abele, S.; Schreiber, J. V.; Martinoni, B.; Nussbaum, A. K.; Schild, H.; Schulz, H.; Hennecke, H.; Woessner, R.; Bitsch, F. *Chimia* **1998**, *52*, 734-739; b) Seebach, D.; Overhand, M.; Kuhnle, F. N. M.; Martinoni, B.; Oberer, L.; Hommel, U.; Widmer, H. *Helv. Chim. Acta* **1996**, *79*, 913-941; c) Lelais, G.; Seebach, D. *Biopolymers* **2004**, *76*, 206-243; d) Frackenpohl, J.; Arvidsson, P. I.; Schreiber, J. V.; Seebach, D. *Chembiochem* **2001**, *2*, 445-455.

[32] a) Gellman, S. H. *Acc. Chem. Res.* **1998**, *31*, 173-180; b) Appella, D. H.; Christianson, L. A.; Karle, I. L.; Powell, D. R.; Gellman, S. H. *J. Am. Chem. Soc.* **1996**, *118*, 13071-13072; c) Fülöp, F.; Forró, E.; Toth, M. K. *Org. Lett.* **2004**, *6*, 4239-4241; d) Forró, E.; Fülöp, F. *Mini-Rev. Org. Chem.* **2004**, *1*, 93-102; e) Cheng, R. P.; Gellman, S. H.; DeGrado, W. F. *Chem. Rev.* **2001**, *101*, 3219-3232.

[33] a) Appella, D. H.; Barchi, J. J.; Durell, S. R.; Gellman, S. H. *J. Am. Chem. Soc.* **1999**, *121*, 2309-2310; b) Appella, D. H.; Christianson, L. A.; Klein, D. A.; Powell, D. R.; Huang, X. L.; Barchi, J. J.; Gellman, S. H. *Nature* **1997**, *387*, 381-384; c) Appella, D. H.; Christianson, L. A.; Klein, D. A.; Richards, M. R.; Powell, D. R.; Gellman, S. H. *J. Am. Chem. Soc.* **1999**, *121*, 7574-7581; d) Applequist, J.; Bode, K. A.; Appella, D. H.; Christianson, L. A.; Gellman, S. H. *J. Am. Chem. Soc.* **1998**, *120*, 4891-4892; e) Raguse, T. L.; Porter, E. A.; Weisblum, B.; Gellman, S. H. *J. Am. Chem. Soc.* **2002**, *124*, 12774-12785; f) Porter, E. A.; Wang, X. F.; Lee, H. S.; Weisblum, B.; Gellman, S. H. *Nature* **2000**, *404*, 565-565.

[34] a) Chung, Y. J.; Huck, B. R.; Christianson, L. A.; Stanger, H. E.; Krauthauser, S.; Powell, D. R.; Gellman, S. H. *J. Am. Chem. Soc.* **2000**, *122*, 3995-4004; b) Huck, B. R.; Fisk, J. D.; Gellman, S. H. *Org. Lett.* **2000**, *2*, 2607-2610.

[35] Halab, L.; Lubell, W. D. *J. Org. Chem.* **1999**, *64*, 3312-3321.

[36] Gilbertson, S. R.; Pawlick, R. V. *Angew. Chem. Int. Ed. Eng.* **1996**, *35*, 902-904.

[37] Huck, B. R.; Langenhan, J. M.; Gellman, S. H. *Org. Lett.* **1999**, *1*, 1717-1720.

[38] a) Burke, M. D.; Schreiber, S. L. *Angew. Chem. Int. Ed.* **2004**, *43*, 46-58; b) Nielsen, T. E.; Schreiber, S. L. *Angew. Chem. Int. Ed.* **2008**, *47*, 48-56; c) Schreiber, S. L. *Science* **2000**, *287*, 1964-1969.

[39] Brehme, R.; Enders, D.; Fernandez, R.; Lassaletta, J. M. *Eur. J. Org. Chem.* **2007**, 5629-5660.

[40] Davis, F. A.; McCoull, W. *J. Org. Chem.* **1999**, *64*, 3396-3397.

[41] a) Davis, F. A.; Zhou, P.; Chen, B. C. *Chem. Soc. Rev.* **1998**, *27*, 13-18; b) Robak, M. T.; Herbage, M. A.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 3600-3740.

[42] Weinreb, S. M. *Top. Curr. Chem.* **1997**, *190*, 131-184.

[43] Enders, D.; Lochtman, R.; Meiers, M.; Muller, S.; Lazny, R. *Synlett* **1998**, 1182-1184.

[44] a) Rudinger, J.; Poduska, K.; Zaoral, M. *Collect. Czech. Chem. Commun.* **1960**, *25*, 2022-2028; b) Haskell, B. E.; Bowlus, S. B. *J. Org. Chem.* **1976**, *41*, 159-160.

[45] a) Aelterman, W.; De Kimpe, N.; Declercq, J. P. *J. Org. Chem.* **1998**, *63*, 6-11; b) Dejaegher, Y.; Mangelinckx, S.; De Kimpe, N. *J. Org. Chem.* **2002**, *67*, 2075-2081.

[46] Mangelinckx, S.; Van Speybroeck, V.; Vansteenkiste, P.; Waroquier, M.; De Kimpe, N. *J. Org. Chem.* **2008**, *73*, 5481-5488.

[47] Colpaert, F.; Mangelinckx, S.; De Brabandere, S.; De Kimpe, N. *J. Org. Chem.* **2011**, *76*, 2204-2213.

[48] a) Smart, B. E. *J. Fluorine Chem.* **2001**, *109*, 3-11; b) 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.

[49] Tarui, A.; Kawashima, N.; Sato, K.; Omote, M.; Miwa, Y.; Minami, H.; Ando, A. *Tetrahedron Lett.* **2010**, *51*, 2000-2003.

[50] Žukauskaitė, A. *Doctoral dissertation*, Synthesis and study of the reactivity of functionalized small-membered azaheterocyclic amino acid derivatives, *Ghent University*, **2012**.

[51] a) Žukauskaitė, A.; Moretto, A.; Peggion, C.; De Zotti, M.; Šačkus, A.; Formaggio, F.; De Kimpe, N.; Mangelinckx, S. *Eur. J. Org. Chem.* **2014**, *2014*, 2312-2321; b) Maity, P.; Konig, B. *Biopolymers* **2008**, *90*, 8-27; c) Maffucci, I.; Pellegrino, S.; Clayden, J.; Contini, A. *J. Phys. Chem. B* **2015**, *119*, 1350-1361.

[52] a) Couty, F. *Amino Acids* **1999**, *16*, 297-320; b) Li, Y. B.; Tang, F. X.; Meng, C.; Guo, Y. H. *Chinese J. Org. Chem.* **2009**, *29*, 1068-1081; c) Couty, F.; Evano, G. *Org. Prep. Proced. Int.* **2006**, *38*, 427-465; d) Cochi, A.; Pardo, D. G.; Cossy, J. *Eur. J. Org. Chem.* **2013**, 809-829.

[53] Zacharius, R. M.; Thompson, J. F.; Steward, F. C. *J. Am. Chem. Soc.* **1954**, *76*, 2908-2912.

[54] Bartolozzi, A.; Cirillo, P. F.; Berry, A. K.; Hickey, E. R.; Thomson, D. S.; Wu, L. F.; Zindell, R.; Albrecht, C.; Ceci, A.; Gemkow, M. J.; Nagaraja, N. V.; Romig, H.; Sauer, A.; Riether, D. *Bioorg. Med. Chem. Lett.* **2015**, *25*, 587-592.

[55] Miller, S. P.; Zhong, Y. L.; Liu, Z. J.; Simeone, M.; Yasuda, N.; Limanto, J.; Chen, Z.; Lynch, J.; Capodanno, V. *Org. Lett.* **2014**, *16*, 174-177.

[56] a) Tang, J.; Majeti, J. W.; Sudom, A.; Xiong, Y. M.; Lu, M.; Liu, Q.; Higbee, J.; Zhang, Y.; Wang, Y.; Wang, W.; Cao, P.; Xia, Z.; Johnstone, S.; Min, X. S.; Yang, X. P.; Shao, H.; Yu, T.; Sharkov, N.; Walker, N.; Tu, H.; Shen, W. Y.; Wang, Z. L. *J. Biol. Chem.* **2013**, *288*, 1307-1316; b) Xia, G. X.; Liu, L.; Liu, H. Y.; Yu, J. X.; Xu, Z. M.; Chen, Q.; Ma, C.; Li, P.; Xiong, B.; Liu, X. J.; Shen, J. K. *Chemmedchem* **2013**, *8*, 577-581; c) Xia, G. X.; You, X. D.; Liu, L.; Liu, H. Y.; Wang, J. F.; Shi, Y. F.; Li, P.; Xiong, B.; Liu, X. J.; Shen, J. K. *Eur. J. Med. Chem.* **2013**, *62*, 1-10.

[57] Scott, J. D.; Williams, R. M. *Tetrahedron Lett.* **2000**, *41*, 8413-8416.

[58] a) Gatto, G. J.; Boyne, M. T.; Kelleher, N. L.; Walsh, C. T. *J. Am. Chem. Soc.* **2006**, *128*, 3838-3847; b) Wu, X. H.; Wang, L. S.; Han, Y. H.; Regan, N.; Li, P. K.; Vilaona, M. A.; Hu, X. C.; Briesewitz, R.; Pei, D. H. *ACS Comb. Sci.* **2011**, *13*, 486-495.

[59] Ding, C. Y.; Bremer, N. M.; Smith, T. D.; Seitz, P. K.; Anastasio, N. C.; Cunningham, K. A.; Zhou, J. *ACS Chem. Neurosci.* **2012**, *3*, 538-545.

[60] a) Lamarre, D.; Croteau, G.; Wardrop, E.; Bourgon, L.; Thibeault, D.; Clouette, C.; Vaillancourt, M.; Cohen, E.; Pargellis, C.; Yoakim, C.; Anderson, P. *Antimicrob. Agents Chemother.* **1997**, *41*, 965-971; b) Maxson, T.; Deane, C. D.; Molloy, E. M.; Cox, C. L.; Markley, A. L.; Lee, S. W.; Mitchell, D. A. *ACS Chem. Biol.* **2015**, *10*, 1217-1226.

[61] a) Occhiato, E. G.; Casini, A.; Guarna, A.; Scarpi, D. *Eur. J. Org. Chem.* **2011**, 6544-6552; b) Sernissi, L.; Petrovic, M.; Scarpi, D.; Guarna, A.; Trabocchi, A.; Bianchini, F.; Occhiato, E. G. *Chem. Eur. J.* **2014**, *20*, 11187-11203.

[62] Zampella, A.; Sepe, V.; Luciano, P.; Bellotta, F.; Monti, M. C.; D'Auria, M. V.; Jepsen, T.; Petek, S.; Adeline, M. T.; Laprevote, O.; Aubertin, A. M.; Debitus, C.; Poupat, C.; Ahond, A. *J. Org. Chem.* **2008**, *73*, 5319-5327.

[63] Wang, Z. Y.; Wang, C.; Zhou, L.; Sun, J. *Org. Biomol. Chem.* **2013**, *11*, 787-797.

[64] El-Deen, A. A. A.; El-Askalany, A. E.; Halaoui, R.; Jean-Claude, B. J.; Butler, I. S.; Mostafa, S. I. *J. Mol. Struct.* **2013**, *1036*, 161-167.

[65] a) Ehara, T.; Irie, O.; Kosaka, T.; Kanazawa, T.; Breitenstein, W.; Grosche, P.; Ostermann, N.; Suzuki, M.; Kawakami, S.; Konishi, K.; Hitomi, Y.; Toyao, A.; Gunji, H.; Cumin, F.; Schiering, N.; Wagner, T.; Rigel, D. F.; Webb, R. L.; Maibaum, J.; Yokokawa, F. *ACS Med. Chem. Lett.* **2014**, *5*, 787-792; b) Mori, Y.; Ogawa, Y.; Mochizuki, A.; Nakamura, Y.; Fujimoto, T.; Sugita, C.; Miyazaki, S.; Tamaki, K.; Nagayama, T.; Nagai, Y.; Inoue, S.; Chiba,

K.; Nishi, T. *Bioorg. Med. Chem.* **2013**, *21*, 5907-5922; c) Mori, Y.; Iwamoto, M.; Mori, K.; Yoshida, M.; Honda, T.; Nagayama, T.; Nishi, T. *Heterocycles* **2014**, *89*, 1413-1426; d) Mori, Y.; Ogawa, Y.; Mochizuki, A.; Nakamura, Y.; Sugita, C.; Miyazaki, S.; Tamaki, K.; Matsui, Y.; Takahashi, M.; Nagayama, T.; Nagai, Y.; Inoue, S.; Nishi, T. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 7677-7682; e) Corminboeuf, O.; Bezencon, O.; Grisostomi, C.; Remen, L.; Richard-Bildstein, S.; Bur, D.; Prade, L.; Hess, P.; Strickner, P.; Fischli, W.; Steiner, B.; Treiber, A. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 6286-6290; f) Corminboeuf, O.; Bezencon, O.; Remen, L.; Grisostomi, C.; Richard-Bildstein, S.; Bur, D.; Prade, L.; Strickner, P.; Hess, P.; Fischli, W.; Steiner, B.; Treiber, A. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 6291-6296; g) Shieh, W. C.; Du, Z. M.; Kim, H.; Liu, Y. G.; Prashad, M. *Org. Process Res. Dev.* **2014**, *18*, 1339-1344.

[66] a) Sindelar, M.; Lutz, T. A.; Petrera, M.; Wanner, K. T. *J. Med. Chem.* **2013**, *56*, 1323-1340; b) Quandt, G.; Hofner, G.; Wanner, K. T. *Bioorg. Med. Chem.* **2013**, *21*, 3363-3378.

[67] a) Kiss, L.; Forró, E.; Fülöp, F. *Tetrahedron Lett.* **2006**, *47*, 2855-2858; b) Kiss, L.; Kazi, B.; Forró, E.; Fülöp, F. *Tetrahedron Lett.* **2008**, *49*, 339-342; c) Chen, Z. P.; Ye, Z. S.; Chen, M. W.; Zhou, Y. G. *Synthesis* **2013**, *45*, 3239-3244; d) Porter, E. A.; Weisblum, B.; Gellman, S. H. *J. Am. Chem. Soc.* **2002**, *124*, 7324-7330; e) Gais, H. J.; Loo, R.; Roder, D.; Das, P.; Raabe, G. *Eur. J. Org. Chem.* **2003**, 1500-1526; f) Masesane, I. B.; Steel, P. G. *Tetrahedron Lett.* **2004**, *45*, 5007-5009; g) Miyata, O.; Muroya, K.; Kobayashi, T.; Yamanaka, R.; Kajisa, S.; Koide, J.; Naito, T. *Tetrahedron* **2002**, *58*, 4459-4479; h) Martinek, T. A.; Otvos, F.; Dervarics, M.; Toth, G.; Fülöp, F. *J. Med. Chem.* **2005**, *48*, 3239-3250; i) Banerjee, A.; Sergienko, E.; Vasile, S.; Gupta, V.; Vuori, K.; Wipf, P. *Org. Lett.* **2009**, *11*, 65-68; j) Dervarics, M.; Otvos, F.; Martinek, T. A. *J. Chem. Inf. Model.* **2006**, *46*, 1431-1438.

[68] Setterholm, N. A.; McDonald, F. E.; Boatright, J. H.; Iuvone, P. M. *Tetrahedron Lett.* **2015**, *56*, 3413-3415.

[69] Bell, J. L.; Haak, A. J.; Wade, S. M.; Kirchhoff, P. D.; Neubig, R. R.; Larsen, S. D. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 3826-3832.

[70] Sharma, R.; Soman, S. S. *Eur. J. Med. Chem.* **2015**, *90*, 342-350.

[71] Wiles, J. A.; Phadke, A. S.; Bradbury, B. J.; Pucci, M. J.; Thanassi, J. A.; Deshpande, M. *J. Med. Chem.* **2011**, *54*, 3418-3425.

[72] a) Rubenstein, E.; Zhou, H. L.; Krasinska, K. M.; Chien, A.; Becker, C. H. *Phytochemistry* **2006**, *67*, 898-903; b) Baek, S. H.; Lee, J. G.; Park, S. Y.; Piao, X. L.; Kim, H. Y.; Bae, O. N.; Park, J. H. *J. Food Compos. Anal.* **2012**, *25*, 137-141.

[73] a) Altmayer-Henzien, A.; Declerck, V.; Guillot, R.; Aitken, D. J. *Tetrahedron Lett.* **2013**, *54*, 802-805; b) Altmayer-Henzien, A.; Declerck, V.; Merlet, D.; Baltaze, J. P.; Farjon, J.; Guillot, R.; Aitken, D. J. *J. Org. Chem.* **2013**, *78*, 6031-6039; c) Drouillat, B.; Wright, K.; Marrot, J.; Couty, F. *Tetrahedron-Asymm.* **2012**, *23*, 690-696.

[74] a) Budesinsky, M.; Budzikiewicz, H.; Prochazka, Z.; Ripperger, H.; Romer, A.; Scholz, G.; Schreiber, K. *Phytochemistry* **1980**, *19*, 2295-2297; b) Fushiya, S.; Takahashi, K.; Nakatsuyama, S.; Sato, Y.; Nozoe, S.; Takagi, S. *Phytochemistry* **1982**, *21*, 1907-1908.

[75] a) Takemoto, T.; Nomoto, K.; Fushiya, S.; Ouchi, R.; Kusano, G.; Hikino, H.; Takagi, S. I.; Matsuura, Y.; Kakudo, M. *P. Jpn. Acad. B-Phys.* **1978**, *54*, 469-473; b) Sugiura, Y.; Mino, Y.; Iwashita, T.; Nomoto, K. *J. Am. Chem. Soc.* **1985**, *107*, 4667-4669.

[76] Murakami, T.; Ise, K.; Hayakawa, M.; Kamei, S.; Takagi, S. I. *Chem. Lett.* **1989**, 2137-2140.

[77] Fushiya, S.; Tamura, T.; Tashiro, T.; Nozoe, S. *Heterocycles* **1984**, *22*, 1039-1040.

[78] Bondada, L.; Rondla, R.; Pradere, U.; Liu, P.; Li, C. W.; Bobeck, D.; McBrayer, T.; Tharnish, P.; Courcambeck, J.; Halfon, P.; Whitaker, T.; Amblard, F.; Coats, S. J.; Schinazi, R. F. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 6325-6330.

[79] Phillips, D. P.; Gao, W. Q.; Yang, Y.; Zhang, G. B.; Lerario, I. K.; Lau, T. L.; Jiang, J. Q.; Wang, X.; Nguyen, D. G.; Bhat, B. G.; Trotter, C.; Sullivan, H.; Welzel, G.; Landry, J.; Chen, Y. L.; Joseph, S. B.; Li, C.; Gordon, W. P.; Richmond, W.; Johnson, K.; Bretz, A.; Bursulaya, B.; Pan, S. F.; McNamara, P.; Seidel, H. M. *J. Med. Chem.* **2014**, *57*, 3263-3282.

[80] a) Ernstsson, S.; Betz, R.; Lagercrantz, S.; Larsson, C.; Ericksson, S.; Cederberg, A.; Carlsson, P.; Enerback, S. *Genomics* **1997**, *46*, 78-85; b) Kirk, I., *WO2000041716*, **2000**.

[81] Song, X. X.; Liu, A. X.; Liu, S. S.; Gao, W. C.; Wang, M. C.; Chang, J. B. A. *Tetrahedron* **2014**, *70*, 1464-1470.

[82] Parsy, C.; Alexandre, F. R.; Brandt, G.; Caillet, C.; Cappelle, S.; Chaves, D.; Convard, T.; Derock, M.; Gloux, D.; Griffon, Y.; Lallos, L.; Leroy, F.; Liuzzi, M.; Loi, A. G.; Moulat, L.; Musiu, C.; Rahali, H.; Roques, V.; Seifer, M.; Standring, D.; Surleraux, D. *Bioorg. Med. Chem. Lett.* **2014**, *24*, 4444-4449.

[83] Cee, V. J.; Frohn, M.; Lanman, B. A.; Golden, J.; Muller, K.; Neira, S.; Pickrell, A.; Arnett, H.; Buys, J.; Gore, A.; Fiorino, M.; Horner, M.; Itano, A.; Lee, M. R.; McElvain, M.; Middleton, S.; Schrag, M.; Rivenzon-Segal, D.; Vargas, H. M.; Xu, H.; Xu, Y.; Zhang, X. X.; Siu, J.; Wong, M.; Burli, R. W. *ACS Med. Chem. Lett.* **2011**, *2*, 107-112.

[84] Pan, S. F.; Gray, N. S.; Gao, W. Q.; Mi, Y.; Fan, Y.; Wang, X.; Tuntland, T.; Che, J. W.; Lefebvre, S.; Chen, Y.; Chu, A.; Hinterding, K.; Gardin, A.; End, P.; Heining, P.; Bruns, C.; Cooke, N. G.; Nuesslein-Hildesheim, B. *ACS Med. Chem. Lett.* **2013**, *4*, 333-337.

[85] a) Lanman, B. A.; Cee, V. J.; Cheruku, S. R.; Frohn, M.; Golden, J.; Lin, J. A.; Lobera, M.; Marantz, Y.; Muller, K. M.; Neira, S. C.; Pickrell, A. J.; Rivenzon-Segal, D.; Schutz, N.; Sharadendu, A.; Yu, X. A.; Zhang, Z. D.; Buys, J.; Fiorino, M.; Gore, A.; Horner, M.; Itano, A.; McElvain, M.; Middleton, S.; Schrag, M.; Vargas, H. M.; Xu, H.; Xu, Y.; Zhang, X. X.; Siu, J.; Burli, R. W. *ACS Med. Chem. Lett.* **2011**, *2*, 102-106; b) Kurata, H.; Kusumi, K.; Otsuki, K.; Suzuki, R.; Kurono, M.; Tokuda, N.; Takada, Y.; Shioya, H.; Mizuno, H.; Komiya,

T.; Ono, T.; Hagiya, H.; Minami, M.; Nakade, S.; Habashita, H. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 144-148.

[86] Rajulu, G. G.; Naik, H. S. B.; Kumar, G. C.; Ramaraj, S.; Sambasivam, G.; Koppolu, K. P. *Med. Chem. Res.* **2014**, *23*, 2856-2868.

[87] Chavan, S. P.; Harale, K. R.; Dumare, N. B.; Kalkote, U. R. *Tetrahedron-Asymm.* **2011**, *22*, 587-590.

[88] Iida, H.; Yamazaki, N.; Kibayashi, C. *J. Org. Chem.* **1987**, *52*, 3337-3342.

[89] Koulocheri, S. D.; Magiatis, P.; Skaltsounis, A. L.; Haroutounian, S. A. *Tetrahedron* **2002**, *58*, 6665-6671.

[90] Chavan, S. P.; Harale, K. R.; Pawar, K. P. *Tetrahedron Lett.* **2013**, *54*, 4851-4853.

[91] a) Fowler, L. S.; Thomas, L. H.; Ellis, D.; Sutherland, A. *Chem. Commun.* **2011**, *47*, 6569-6571; b) Daly, M.; Cant, A. A.; Fowler, L. S.; Simpson, G. L.; Senn, H. M.; Sutherland, A. *J. Org. Chem.* **2012**, *77*, 10001-10009.

[92] Vu, H. D.; Renault, J.; Toupet, L.; Uriac, P.; Gouault, N. *Eur. J. Org. Chem.* **2013**, *2013*, 6677-6686.

[93] Mallick, A.; Kumari, N.; Roy, R.; Palanivel, A.; Vankar, Y. D. *Eur. J. Org. Chem.* **2014**, 5557-5563.

[94] Reddy, B. G.; Madhusudanan, K. P.; Vankar, Y. D. *J. Org. Chem.* **2004**, *69*, 2630-2633.

[95] Sadiq, A.; Sewald, N. *Arkivoc* **2012**, 28-36.

[96] Baldwin, J. E.; Herchen, S. R.; Johnson, B. L.; Jung, M.; Usher, J. J.; Wan, T. *J. Chem. Soc., Perkin Trans. 1* **1981**, 2253-2257.

[97] Purkayastha, N.; Shendage, D. M.; Frohlich, R.; Haufe, G. *J. Org. Chem.* **2010**, *75*, 222-225.

[98] Pansare, S. V.; Paul, E. K. *Org. Biomol. Chem.* **2012**, *10*, 2119-2125.

[99] List, B. *Tetrahedron* **2002**, *58*, 5573-5590.

[100] Kumar, I.; Ramaraju, P.; Mir, N. A.; Singh, D.; Gupta, V. K.; Rajnikanth *Chem. Commun.* **2013**, *49*, 5645-5647.

[101] a) Terada, M. *Synthesis* **2010**, 1929-1982; b) Bergonzini, G.; Gramigna, L.; Mazzanti, A.; Fochi, M.; Bernardi, L.; Ricci, A. *Chem. Commun.* **2010**, *46*, 327-329.

[102] Zhong, S.; Nieger, M.; Bihlmeier, A.; Shi, M.; Brase, S. *Org. Biomol. Chem.* **2014**, *12*, 3265-3270.

[103] Zarate, A.; Orea, L.; Juarez, J. R.; Castro, A.; Mendoza, A.; Gnecco, D.; Teran, J. L. *Synth. Commun.* **2014**, *44*, 2838-2847.

[104] Moustafa, M. M. A.; Pagenkopf, B. L. *Org. Lett.* **2010**, *12*, 4732-4735.

[105] Baar, M. R.; Ballesteros, P.; Roberts, B. W. *Tetrahedron Lett.* **1986**, *27*, 2083-2086.

[106] Harada, S.; Sakai, T.; Takasu, K.; Yamada, K.; Yamamoto, Y.; Tomioka, K. *J. Org. Chem.* **2012**, *77*, 7212-7222.

[107] Menendez, J. C. *Curr. Org. Chem.* **2013**, *17*, 1919-1919.

[108] Liu, H.; Zhou, Z. Q.; Sun, Q.; Li, Y.; Li, Y.; Liu, J. L.; Yan, P. Y.; Wang, D. D.; Wang, C. D. *ACS Comb. Sci.* **2012**, *14*, 366-371.

[109] Hall, D. G.; Laplante, C.; Manku, S.; Nagendran, J. *J. Org. Chem.* **1999**, *64*, 698-699.

[110] Suryavanshi, P. A.; Sridharan, V.; Maiti, S.; Menendez, J. C. *Chem. Eur. J.* **2014**, *20*, 8791-8799.

[111] Noole, A.; Borissova, M.; Lopp, M.; Kanger, T. *J. Org. Chem.* **2011**, *76*, 1538-1545.

[112] Lensen, N.; Marais, J.; Brigand, T. *Org. Lett.* **2015**, *17*, 342-345.

[113] Biswas, T.; Mukherjee, J. P.; Chattopadhyay, S. K. *Tetrahedron-Asymm.* **2012**, *23*, 1416-1422.

[114] Tafesse, L.; Tsuno, N., *WO2013080036*, **2012**.

[115] Pradhan, T. K.; Krishnan, K. S.; Vasse, J. L.; Szymoniak, J. *Org. Lett.* **2011**, *13*, 1793-1795.

[116] Callebaut, G.; Mangelinckx, S.; Kiss, L.; Sillanpaa, R.; Fülöp, F.; De Kimpe, N. *Org. Biomol. Chem.* **2012**, *10*, 2326-2338.

[117] Kano, T.; Sakamoto, R.; Mii, H.; Wang, Y. G.; Maruoka, K. *Tetrahedron* **2010**, *66*, 4900-4904.

[118] Kern, N.; Felten, A. S.; Weibel, J. M.; Pale, P.; Blanc, A. *Org. Lett.* **2014**, *16*, 6104-6107.

[119] He, G.; Zhao, Y. S.; Zhang, S. Y.; Lu, C. X.; Chen, G. *J. Am. Chem. Soc.* **2012**, *134*, 3-6.

[120] Declerck, V.; Aitken, D. J. *J. Org. Chem.* **2011**, *76*, 708-711.

[121] Ye, Y.; Wang, H.; Fan, R. H. *Org. Lett.* **2010**, *12*, 2802-2805.

[122] Zhang, H. H.; Luo, Y. C.; Wang, H. P.; Chen, W.; Xu, P. F. *Org. Lett.* **2014**, *16*, 4896-4899.

[123] a) Fritz, S. P.; Mumtaz, A.; Yar, M.; McGarrigle, E. M.; Aggarwal, V. K. *Eur. J. Org. Chem.* **2011**, 3156-3164; b) McGarrigle, E. M.; Fritz, S. P.; Favereau, L.; Yar, M.; Aggarwal, V. K. *Org. Lett.* **2011**, *13*, 3060-3063.

[124] Fritz, S. P.; Moya, J. F.; Unthank, M. G.; McGarrigle, E. M.; Aggarwal, V. K. *Synthesis* **2012**, *44*, 1584-1590.

[125] Yadav, L. D. S.; Srivastava, V. P.; Patel, R. *Tetrahedron Lett.* **2008**, *49*, 5652-5654.

[126] Van Hende, E.; Verniest, G.; Deroose, F.; Thuring, J. W.; Macdonald, G.; De Kimpe, N. *J. Org. Chem.* **2009**, *74*, 2250-2253.

[127] a) Mangelinckx, S.; Žukauskaitė, A.; Buinauskaité, V.; Šačkus, A.; De Kimpe, N. *Tetrahedron Lett.* **2008**, *49*, 6896-6900; b) Žukauskaitė, A.; Mangelinckx, S.; Buinauskaitė, V.; Šačkus, A.; De Kimpe, N. *Amino Acids* **2011**, *41*, 541-558; c) Žukauskaitė, A.; Mangelinckx, S.; Šačkus, A.; De Kimpe, N. *Heterocycles* **2014**, *88*, 731-740.

[128] Guihua, L.; Song, F.; Peng, C. F., L, *CN2000109992*, **2001**.

[129] Hu, Z.; Lingling, W.; Zhangwan, L., *CN200510020257*, **2006**.

[130] Hu, Y. L.; Ziffer, H. *J. Labelled. Compd. Rad.* **1990**, *28*, 581-586.

[131] Moura, S.; Pinto, E. *Tetrahedron Lett.* **2007**, *48*, 2325-2327.

[132] Arevalo-Garcia, E. B.; Colmenares, J. C. *Tetrahedron Lett.* **2014**, *55*, 2335-2336.

[133] Kovács, J.; Bruckner, V.; Kovács, K. *J. Chem. Soc.* **1953**, 145-147.

[134] Adamson, D. W. *J. Chem. Soc.* **1939**, 1564-1568.

[135] Karrer, P.; Escher, K.; Widmer, H. *Helv. Chim. Acta* **1926**, *3*, 301-323.

[136] Talbot, G.; Gaudry, R.; Berlinguet, L. *Can. J. Chem.* **1958**, *36*, 593-596.

[137] Solladie-Cavallo, A.; Simon, M. C. *Tetrahedron Lett.* **1989**, *30*, 6011-6014.

[138] Dixon, D. J.; Tillman, A. L. *Synlett* **2005**, 2635-2638.

[139] Liu, G. C.; Cogan, D. A.; Owens, T. D.; Tang, T. P.; Ellman, J. A. *J. Org. Chem.* **1999**, *64*, 1278-1284.

[140] Pareja, C.; Martin-Zamora, E.; Fernandez, R.; Lassaletta, J. M. *J. Org. Chem.* **1999**, *64*, 8846-8854.

[141] Fernandez, R.; Martin-Zamora, E.; Pareja, C.; Alcarazo, M.; Martin, J.; Lassaletta, J. M. *Synlett* **2001**, 1158-1160.

[142] Schleusner, M.; Koep, S.; Gunter, M.; Tiwari, S. K.; Gais, H. J. *Synthesis* **2004**, 967-969.

[143] Enders, D.; Schubert, H. *Angew. Chem. Int. Ed. Eng.* **1984**, *23*, 365-366.

[144] Bycroft, B. W.; Chhabra, S. R.; Grout, R. J.; Crowley, P. J. *J. Chem. Soc., Chem. Comm.* **1984**, 1156-1157.

[145] Breitler, S.; Carreira, E. M. *J. Am. Chem. Soc.* **2015**, *137*, 5296-5299.

[146] a) Crespo-Pena, A.; Martin-Zamora, E.; Fernandez, R.; Lassaletta, J. M. *Chem. Asian. J.* **2011**, *6*, 2287-2290; b) Maji, B.; Troshin, K.; Mayr, H. *Angew. Chem. Int. Ed.* **2013**, *52*, 11900-11904.

[147] a) Hashimoto, T.; Hirose, M.; Maruoka, K. *J. Am. Chem. Soc.* **2008**, *130*, 7556-7557; b) Hashimoto, T.; Kimura, H.; Maruoka, K. *Tetrahedron-Asymm.* **2010**, *21*, 1187-1188.

[148] De Kimpe, N.; Sulmon, P.; Schamp, N. *Angew. Chem. Int. Ed. Eng.* **1985**, *24*, 881-882.

[149] Giubellina, N.; Mangelinckx, S.; Tornroos, K. W.; De Kimpe, N. *J. Org. Chem.* **2006**, *71*, 5881-5887.

[150] De Kimpe, N.; Coppens, W.; Welch, J.; Decorte, B. *Synthesis* **1990**, 675-677.

[151] a) Kobayashi, S.; Ishitani, H. *Chem. Rev.* **1999**, *99*, 1069-1094; b) Ueno, M.; Kobayashi, S. in *Enantioselective Synthesis of β-Amino Acids*, 2nd ed. (Eds.: Juaristi, E., Soloshonok, V. A.), Wiley, New York, **2005**, pp. 139-157.

[152] a) Nakano, J.; Masuda, K.; Yamashita, Y.; Kobayashi, S. *Angew. Chem. Int. Ed.* **2012**, *51*, 9525-9529; b) Matsubara, R.; Berthiol, F.; Nguyen, H. V.; Kobayashi, S. *Bull. Chem. Soc. Jpn.* **2009**, *82*, 1083-1102; c) Matsubara, R.; Berthiol, F.; Kobayashi, S. *J. Am. Chem. Soc.* **2008**, *130*, 1804-1805.

[153] a) Ellman, J. A. *Pure Appl. Chem.* **2003**, *75*, 39-46; b) Kochi, T.; Mukade, T.; Ellman, J. A. *J. Syn. Org. Chem. Jpn.* **2004**, *62*, 128-139; c) Davis, F. A.; Prasad, K. R.; Nolt, M. B.; Wu, Y. Z. *Org. Lett.* **2003**, *5*, 925-927; d) Xu, H. C.; Chowdhury, S.; Ellman, J. A. *Nat. Protoc.* **2013**, *8*, 2271-2280; e) Colpaert, F.; Mangelinckx, S.; De Kimpe, N. *Org. Lett.* **2010**, *12*, 1904-1907; f) Zhou, P.; Chen, B. C.; Davis, F. A. *Tetrahedron* **2004**, *60*, 8003-8030; g) Foubelo, F.; Yus,

M. *Eur. J. Org. Chem.* **2014**, *2014*, 485-491; h) Morton, D.; Stockman, R. A. *Tetrahedron* **2006**, *62*, 8869-8905; i) Si, C. M.; Huang, W.; Du, Z. T.; Wei, B. G.; Lin, G. Q. *Org. Lett.* **2014**, *16*, 4328-4331.

[154] a) Wang, J. F.; Zhou, Y.; Zhang, L.; Li, Z.; Chen, X. J.; Liu, H. *Org. Lett.* **2013**, *15*, 1508-1511; b) Wang, H.; Tang, P.; Zhou, Q.; Zhang, D.; Chen, Z.; Huang, H.; Qin, Y. *J. Org. Chem.* **2015**, *80*, 2494-2502.

[155] a) Kochi, T.; Ellman, J. A. *J. Am. Chem. Soc.* **2004**, *126*, 15652-15653; b) Colpaert, F.; Mangelinckx, S.; Verniest, G.; De Kimpe, N. *J. Org. Chem.* **2009**, *74*, 3792-3797; c) Colpaert, F.; Mangelinckx, S.; De Kimpe, N. *J. Org. Chem.* **2011**, *76*, 234-244.

[156] Bartrum, H. E.; Viceriat, A.; Carret, S.; Poisson, J. F. *Org. Lett.* **2014**, *16*, 1972-1975.

[157] a) Mander, L. N.; Williams, C. M. *Tetrahedron* **2003**, *59*, 1105-1136; b) Nunez, M. T.; Martin, V. S. *J. Org. Chem.* **1990**, *55*, 1928-1932.

[158] a) Kasai, M.; Ziffer, H. *J. Org. Chem.* **1983**, *48*, 2346-2349; b) Miranda, L. S. M.; Vasconcellos, M. L. A. A. *Synthesis* **2004**, 1767-1770; c) Kawasaki, M.; Hayashi, Y.; Kakuda, H.; Toyooka, N.; Tanaka, A.; Goto, M.; Kawabata, S.; Kometani, T. *Tetrahedron-Asymm.* **2005**, *16*, 4065-4072.

[159] Kobayashi, K.; Jadhav, P. K.; Zydowsky, T. M.; Floss, H. G. *J. Org. Chem.* **1983**, *48*, 3510-3512.

[160] Duran-Galvan, M.; Connell, B. T. *Tetrahedron* **2011**, *67*, 7901-7908.

[161] a) Davis, F. A.; Chao, B.; Andemichael, Y. W.; Mohanty, P. K.; Fang, T. N.; Burns, D. M.; Rao, A.; Szewczyk, J. M. *Heteroatom Chem.* **2002**, *13*, 486-492; b) Bols, M. *Acc. Chem. Res.* **1998**, *31*, 1-8; c) Enders, D.; Tiebes, J.; De Kimpe, N.; Keppens, M.; Stevens, C.; Smagghe, G.; Betz, O. *J. Org. Chem.* **1993**, *58*, 4881-4884; d) Keppens, M.; De Kimpe, N. *Synlett* **1994**, 285-286; e) Keppens, M.; De Kimpe, N. *J. Org. Chem.* **1995**, *60*, 3916-3918; f) Reynolds, T. *Phytochemistry* **2005**, *66*, 1399-1406.

[162] a) Butters, T. D.; Dwek, R. A.; Platt, F. M. *Chem. Rev.* **2000**, *100*, 4683-4696; b) Nara, S.; Tanaka, R.; Eishima, J.; Hara, M.; Takahashi, Y.; Otaki, S.; Foglesong, R. J.; Hughes, P. F.; Turkington, S.; Kanda, Y. *J. Med. Chem.* **2003**, *46*, 2467-2473; c) He, R.; Kurome, T.; Giberson, K. M.; Johnson, K. M.; Kozikowski, A. P. *J. Med. Chem.* **2005**, *48*, 7970-7979; d) Watson, P. S.; Jiang, B.; Scott, B. *Org. Lett.* **2000**, *2*, 3679-3681; e) Lapuyade, G.; Schlewer, G.; Wermuth, C. G. *Bull. Soc. Chim. Fr.* **1986**, 663-668; f) Lapuyade, G.; Schlewer, G.; Ngoka, V.; Vernieres, J. C.; Chambon, J. P.; Lagrange, J.; Lagrange, P.; Wermuth, C. G. *Eur. J. Med. Chem.* **1987**, *22*, 383-391; g) Bourbeau, M. P.; Bartbergen, M. D. *J. Med. Chem.* **2015**, *58*, 525-536.

[163] a) Cochi, A.; Pardo, D. G.; Cossy, J. *Heterocycles* **2012**, *86*, 89-116; b) Davis, F. A.; Zhang, Y. F. *Tetrahedron Lett.* **2009**, *50*, 5205-5207; c) Pansare, S. V.; Paul, E. K. *Org. Biomol. Chem.*

2012, *10*, 2119-2125; d) Calvez, O.; Langlois, N. *Tetrahedron Lett.* **1999**, *40*, 7099-7100; e) D'hooghe, M.; Dejaegher, Y.; De Kimpe, N. *Tetrahedron* **2008**, *64*, 4575-4584.

[164] a) Harrison, S.; Geppetti, P. *Int. J. Biochem. Cell B* **2001**, *33*, 555-576; b) Datar, P.; Srivastava, S.; Coutinho, E.; Govil, G. *Curr. Top. Med. Chem.* **2004**, *4*, 75-103; c) Mclean, S.; Ganong, A.; Seymour, P. A.; Snider, R. M.; Desai, M. C.; Rosen, T.; Bryce, D. K.; Longo, K. P.; Reynolds, L. S.; Robinson, G.; Schmidt, A. W.; Siok, C.; Heym, J. *Regul. Peptides* **1992**, S120-S120; d) Desai, M. C.; Rosen, T. J., *WO1993001170 A1*, **1991**; e) Desai, M. C.; Lefkowitz, S. L.; Thadeio, P. F.; Longo, K. P.; Snider, R. M. *J. Med. Chem.* **1992**, *35*, 4911-4913.

[165] a) Laube, B.; Hirai, H.; Sturgess, M.; Betz, H.; Kuhse, J. *Neuron* **1997**, *18*, 493-503; b) Leach, M. J.; Marden, C. M.; Canning, H. M. *Eur. J. Pharmacol.* **1986**, *121*, 173-179; c) Leach, M. J.; Hollox, K. J.; Odonnell, R. A.; Miller, A. A. *Eur. J. Pharmacol.* **1988**, *152*, 189-192; d) Claesson, A.; Swahn, B. M.; Edvinsson, K. M.; Molin, H.; Sandberg, M. *Bioorg. Med. Chem. Lett.* **1992**, *2*, 1247-1250; e) Agami, C.; Kadouripuchot, C.; Leguen, V.; Vaissermann, J. *Tetrahedron Lett.* **1995**, *36*, 1657-1660; f) Agami, C.; Hamon, L.; KadouriPuchot, C.; LeGuen, V. *J. Org. Chem.* **1996**, *61*, 5736-5742.

[166] a) Garrido, N. M.; Sanchez, M. R.; Diez, D.; Sanz, F.; Urones, J. G. *Tetrahedron-Asymm.* **2011**, *22*, 872-880; b) Boks, G. J.; Tollenaere, J. P.; Kroon, J. *Bioorg. Med. Chem.* **1997**, *5*, 535-547.

[167] a) Davis, F. A.; Theddu, N. *J. Org. Chem.* **2010**, *75*, 3814-3820; b) Satyanarayanajois, S.; Villalba, S.; Liu, J. C.; Lin, G. M. *Chem. Biol. Drug. Des.* **2009**, *74*, 246-257; c) Balamurugan, D.; Muraleedharan, K. M. *Chem. Eur. J.* **2012**, *18*, 9516-9520.

[168] a) Sultane, P. R.; Bhat, R. G. *J. Org. Chem.* **2012**, *77*, 11349-11354; b) Calosso, M.; Wagner, M.; Gendrineau, T.; Petit, M.; Kadouri-Puchot, C.; Dechoux, L. *Lett. Org. Chem.* **2007**, *4*, 4-6; c) Noel, R.; Vanucci-Bacque, C.; Fargeau-Bellassoued, M. C.; Lhommet, G. *Eur. J. Org. Chem.* **2007**, 476-486; d) Chandrasekhar, S.; Mohanty, P. K. *Tetrahedron Lett.* **1999**, *40*, 5071-5072.

[169] Yamazaki, N.; Atobe, M.; Kibayashi, C. *Tetrahedron Lett.* **2002**, *43*, 7979-7982.

[170] a) Kokotos, C. G.; Aggarwal, V. K. *Org. Lett.* **2007**, *9*, 2099-2102; b) Kokotos, C. G.; Aggarwal, V. K. *Chem. Commun.* **2006**, 2156-2158.

[171] a) Garrido, N. M.; Garcia, M.; Diez, D.; Sanchez, M. R.; Sanz, F.; Urones, J. G. *Org. Lett.* **2008**, *10*, 1687-1690; b) Ahari, M.; Perez, A.; Menant, C.; Vasse, J. L.; Szymoniak, J. *Org. Lett.* **2008**, *10*, 2473-2476.

[172] Mangelinckx, S.; De Sterck, B.; Colpaert, F.; Catak, S.; Jacobs, J.; Rooryck, S.; Waroquier, M.; Van Speybroeck, V.; De Kimpe, N. *J. Org. Chem.* **2012**, *77*, 3415-3425.

[173] Sulmon, P.; De Kimpe, N.; Schamp, N. *Tetrahedron* **1989**, *45*, 3907-3922.

[174] Pedersen, C. M.; Bols, M. *Tetrahedron* **2005**, *61*, 115-122.

[175] Coombs, T. C.; Lushington, G. H.; Douglas, J.; Aube, J. *Angew. Chem. Int. Ed.* **2011**, *50*, 2734-2737.

[176] Burdzhiev, N.; Stanoeva, E. *C. R. Chimie* **2010**, *13*, 1443-1449.

[177] Hoye, T. R.; Jeffrey, C. S.; Shao, F. *Nat. Protoc.* **2007**, *2*, 2451-2458.

[178] a) Ojima, I. *J. Org. Chem.* **2013**, *78*, 6358-6383; b) Rowley, M.; Hallett, D. J.; Goodacre, S.; Moyes, C.; Crawforth, J.; Sparey, T. J.; Patel, S.; Marwood, R.; Patel, S.; Thomas, S.; Hitzel, L.; O'Connor, D.; Szeto, N.; Castro, J. L.; Hutson, P. H.; MacLeod, A. M. *J. Med. Chem.* **2001**, *44*, 1603-1614; c) Campbell, N. H.; Smith, D. L.; Reszka, A. P.; Neidle, S.; O'Hagan, D. *Org. Biomol. Chem.* **2011**, *9*, 1328-1331; d) Bohm, H. J.; Banner, D.; Bendels, S.; Kansy, M.; Kuhn, B.; Muller, K.; Obst-Sander, U.; Stahl, M. *Chembiochem* **2004**, *5*, 637-643.

[179] a) O'Hagan, D. *Chem. Soc. Rev.* **2008**, *37*, 308-319; b) Hu, X. G.; Hunter, L. *Beilstein J. Org. Chem.* **2013**, *9*, 2696-2708; c) Gooseman, N. E. J.; O'Hagan, D.; Slawin, A. M. Z.; Teale, A. M.; Tozer, D. J.; Young, R. J. *Chem. Commun.* **2006**, 3190-3192.

[180] Holmgren, S. K.; Taylor, K. M.; Bretscher, L. E.; Raines, R. T. *Nature* **1998**, *392*, 666-667.

[181] a) Lemal, D. M. *J. Org. Chem.* **2004**, *69*, 1-11; b) Hunter, L. *Beilstein J. Org. Chem.* **2010**, *6*; c) Thibaudeau, C.; Plavec, J.; Chattopadhyaya, J. *J. Org. Chem.* **1998**, *63*, 4967-4984.

[182] a) Piron, K.; Verniest, G.; Van Hende, E.; De Kimpe, N. *Arkivoc* **2012**, 6-15; b) Van Brabandt, W.; Verniest, G.; De Smaele, D.; Duvey, G.; De Kimpe, N. *J. Org. Chem.* **2006**, *71*, 7100-7102; c) Van Brabandt, W.; De Kimpe, N. *Synlett* **2006**, 2039-2042; d) Ferraris, D.; Belyakov, S.; Li, W. X.; Oliver, E.; Ko, Y. S.; Calvin, D.; Lautar, S.; Thomas, B.; Rojas, C. *Curr. Top. Med. Chem.* **2007**, *7*, 597-608.

[183] a) Schjoeth-Eskesen, C.; Hansen, P. R.; Kjaer, A.; Gillings, N. *Chemistryopen* **2015**, *4*, 65-71; b) Lu, P. F. *Tetrahedron* **2010**, *66*, 2549-2560; c) Stankovic, S.; Catak, S.; D'hooghe, M.; Goossens, H.; Tehrani, K. A.; Bogaert, P.; Waroquier, M.; Van Speybroeck, V.; De Kimpe, N. *J. Org. Chem.* **2011**, *76*, 2157-2167; d) Verniest, G.; Colpaert, F.; Van Hende, E.; De Kimpe, N. *J. Org. Chem.* **2007**, *72*, 8569-8572; e) Van Hende, E.; Verniest, G.; Surmont, R.; De Kimpe, N. *Org. Lett.* **2007**, *9*, 2935-2937; f) Yudin, A. K. *Aziridines and Epoxides in Organic Synthesis*, Wiley, **2006**; g) Kusei, E. Y.; Novikov, M. S.; Khlebnikov, A. F. *Russ. J. Gen. Chem.* **2005**, *75*, 1643-1647; h) Konev, A. S.; Novikov, M. S.; Khlebnikov, A. F.; Tehrani, K. A. *J. Fluorine Chem.* **2007**, *128*, 114-119.

[184] Tarui, A.; Kawashima, N.; Sato, K.; Omote, M.; Ando, A. *Tetrahedron Lett.* **2010**, *51*, 4246-4249.

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

[186] Dolbier, W. R. *Guide to fluorine NMR for organic chemists*, Wiley, **2009**.

[187] a) De Kimpe, N.; De Smaele, D.; Hofkens, A.; Dejaegher, Y.; Kesteleyn, B. *Tetrahedron* **1997**, *53*, 10803-10816; b) Soloshonok, V. A.; Ono, T. *Tetrahedron* **1996**, *52*, 14701-14712; c)

Soloshonok, V. A.; Ono, T. *Synlett* **1996**, 919-&; d) Ono, T.; Kukhar, V. P.; Soloshonok, V. A. *J. Org. Chem.* **1996**, *61*, 6563-6569; e) Smith, P. A. S.; Vandang, C. *J. Org. Chem.* **1976**, *41*, 2013-2015; f) Jaeger, D. A.; Broadhurst, M. D.; Cram, D. J. *J. Am. Chem. Soc.* **1979**, *101*, 717-732.

[188] Alvernhe, G.; Laurent, A.; Touhami, K.; Bartnik, R.; Mloston, G. *J. Fluorine Chem.* **1985**, *29*, 363-384.

[189] a) Higgins, R. H.; Cromwell, N. H. *J. Heterocycl. Chem.* **1971**, *8*, 1059-1062; b) Higgins, R. H.; Cromwell, N. H.; Paudler, W. W. *J. Heterocycl. Chem.* **1971**, *8*, 961; c) Higgins, R. H.; Doomes, E.; Cromwell, N. H. *J. Heterocycl. Chem.* **1971**, *8*, 1063-1067.

[190] Araki, K.; Wichtowski, J. A.; Welch, J. T. *Tetrahedron Lett.* **1991**, *32*, 5461-5464.

[191] Kurth, M. J.; Green, C. B.; Mount, M. E.; Jackson, D. Y. *Int. J. Pept. Protein Res.* **1988**, *31*, 388-395.

[192] Kunzi, S. A.; Morandi, B.; Carreira, E. M. *Org. Lett.* **2012**, *14*, 1900-1901.

[193] Kawecki, R.; Welch, J. T. *Tetrahedron Lett.* **1993**, *34*, 3087-3090.

[194] Jonet, S.; Cherouvrier, F.; Brigaud, T.; Portella, C. *Eur. J. Org. Chem.* **2005**, 4304-4312.

[195] Dembitsky, V. M.; Terent'ev, A. O.; Levitsky, D. O. *Natural Products* **2013**, 977-1006.

[196] a) Arfaoui, A.; Beji, F.; Amri, H. *Synth. Commun.* **2010**, *40*, 766-771; b) A., Ž.; Mangelinckx, S.; Callebaut, G.; Wybon, C.; Šačkus, A.; De Kimpe, N. *Tetrahedron* **2013**, *69*, 3437-3443.

[197] a) Lakner, F. J.; Hager, L. P. *Tetrahedron-Asymm.* **1997**, *8*, 3547-3550; b) Sun, B. F.; Hong, R.; Kang, Y. B.; Deng, L. *J. Am. Chem. Soc.* **2009**, *131*, 10384-10385; c) Russo, A.; Galdi, G.; Croce, G.; Lattanzi, A. *Chem. Eur. J.* **2012**, *18*, 6152-6157.

[198] Krasnova, L. B.; Yudin, A. K. *Org. Lett.* **2006**, *8*, 2011-2014.

[199] Lai, J. Y.; Wang, F. S.; Guo, G. Z.; Dai, L. X. *J. Org. Chem.* **1993**, *58*, 6944-6946.

[200] a) Li, G. G.; Kotti, S. R. S. S.; Timmons, C. *Eur. J. Org. Chem.* **2007**, 2745-2758; b) Wei, H. X.; Kim, S. H.; Li, G. G. *Tetrahedron* **2001**, *57*, 3869-3873; c) Li, G. G.; Wei, H. X.; Kim, S. H.; Neighbors, M. *Org. Lett.* **1999**, *1*, 395-397; d) Li, G. G.; Wei, H. X.; Kim, S. H. *Tetrahedron* **2001**, *57*, 8407-8411.

[201] a) Hajra, S.; Sinha, D.; Bhowmick, M. *Tetrahedron Lett.* **2006**, *47*, 7017-7019; b) Saikia, I.; Phukan, P. *Tetrahedron Lett.* **2009**, *50*, 5083-5087.

[202] a) Pringle, W.; Sharpless, K. B. *Tetrahedron Lett.* **1999**, *40*, 5151-5154; b) Ma, Z. W.; Naylor, B. C.; Loertscher, B. M.; Hafen, D. D.; Li, J. M.; Castle, S. L. *J. Org. Chem.* **2012**, *77*, 1208-1214.

[203] a) Kolb, H. C.; Vannieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483-2547; b) Feng, Z. X.; Zhou, W. S. *Tetrahedron Lett.* **2003**, *44*, 493-495.

[204] a) Habaue, S.; Baraki, H.; Okamoto, Y. *Polym. J.* **1997**, *29*, 872-874; b) Baraki, H.; Habaue, S.; Okamoto, Y. *Polym. J.* **1999**, *31*, 1260-1266; c) Galeazzi, R.; Martelli, G.; Mobbili, G.; Orena, M.; Rinaldi, S. *Org. Lett.* **2004**, *6*, 2571-2574; d) Galeazzi, R.; Martelli, G.; Mobbili,

G.; Orena, M.; Rinaldi, S. *Tetrahedron* **2006**, *62*, 10450-10455; e) Buchholz, R.; Hoffmann, H. M. R. *Helv. Chim. Acta* **1991**, *74*, 1213-1220; f) March, T. L.; Johnston, M. R.; Duggan, P. J.; Gardiner, J. *Chem. Biodivers.* **2012**, *9*, 2410-2441; g) Luhr, S.; Holz, J.; Zayas, O.; Seidelmann, O.; Domke, L.; Borner, A. *Tetrahedron-Asymm.* **2013**, *24*, 395-401; h) Welch, J. T.; Araki, K.; Kawecki, R.; Wichtowski, J. A. *J. Org. Chem.* **1993**, *58*, 2454-2462; i) Tarui, A.; Kawashima, N.; Kawakita, T.; Sato, K.; Omote, M.; Ando, A. *J. Org. Chem.* **2013**, *78*, 7903-7911; j) Luo, X. B.; Dong, R. Z.; Luo, S. L.; Zhan, Y. C.; Tu, X. M.; Yang, L. X. *J. Appl. Polym. Sci.* **2013**, *127*, 2884-2890; k) Zou, G. F.; Pan, F.; Liao, W. W. *Org. Biomol. Chem.* **2013**, *11*, 7080-7083; l) Ablikim, M.; Achasov, M. N.; Ai, X. C.; Albayrak, O.; Albrecht, M.; Ambrose, D. J.; Amoroso, A.; An, F. F.; An, Q.; Bai, J. Z.; Ferroli, R. B.; Ban, Y.; Bennett, D. W.; Bennett, J. V.; Bertani, M.; Bettoni, D.; Bian, J. M.; Bianchi, F.; Boger, E.; Bondarenko, O.; Boyko, I.; Briere, R. A.; Cai, H.; Cai, X.; Cakir, O.; Calcaterra, A.; Cao, G. F.; Cetin, S. A.; Chang, J. F.; Chelkov, G.; Chen, G.; Chen, H. S.; Chen, H. Y.; Chen, J. C.; Chen, M. L.; Chen, S. J.; Chen, X.; Chen, X. R.; Chen, Y. B.; Cheng, H. P.; Chu, X. K.; Cibinetto, G.; Cronin-Hennessy, D.; Dai, H. L.; Dai, J. P.; Dbeyssi, A.; Dedovich, D.; Deng, Z. Y.; Denig, A.; Denysenko, I.; Destefanis, M.; De Mori, F.; Ding, Y.; Dong, C.; Dong, J.; Dong, L. Y.; Dong, M. Y.; Du, S. X.; Duan, P. F.; Fan, J. Z.; Fang, J.; Fang, S. S.; Fang, X.; Fang, Y.; Fava, L.; Feldbauer, F.; Felici, G.; Feng, C. Q.; Fioravanti, E.; Fritsch, M.; Fu, C. D.; Gao, Q.; Gao, Y.; Garzia, I.; Goetzen, K.; Gong, W. X.; Gradl, W.; Greco, M.; Gu, M. H.; Gu, Y. T.; Guan, Y. H.; Guo, A. Q.; Guo, L. B.; Guo, T.; Guo, Y.; Guo, Y. P.; Haddadi, Z.; Hafner, A.; Han, S.; Han, Y. L.; Harris, F. A.; He, K. L.; He, Z. Y.; Held, T.; Heng, Y. K.; Hou, Z. L.; Hu, C.; Hu, H. M.; Hu, J. F.; Hu, T., et al. *Phys. Rev. D* **2015**, *91*.

[205] a) Toniolo, C.; Formaggio, F.; Kaptein, B.; Broxterman, Q. B. *Synlett* **2006**, 1295-1310; b) Gatos, M.; Formaggio, F.; Crisma, M.; Toniolo, C.; Bonora, G. M.; Benedetti, Z.; Di Blasio, B.; Iacovino, R.; Santini, A.; Saviano, M.; Kamphuis, J. *J. Pept. Sci.* **1997**, *3*, 110-122.

[206] a) Hennequin, L. F. A.; Ballard, P.; Boyle, F. T.; Delouvrie, B.; Ellston, R. P. A.; Halsall, C. T.; Harris, C. S.; Hudson, K.; Kendrew, J.; Pearse, J. E.; Ross, H. S.; Smith, P.; Vincent, J. L. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2672-2676; b) Kozikowski, A. P.; Fauq, A. H. *Synlett* **1991**, 783-784; c) Albrecht, B. K.; Audia, J. E.; Cote, A.; Gehling, V. S.; Harmange, J.-C.; Hewitt, M. C.; Nanveschuk, C. G.; Taylor, A. M.; Vasange, R. G., *WO2012075456A1*, **2012**.

[207] a) Cardillo, G.; Gentilucci, L.; Tolomelli, A. *Aldrichim. Acta* **2003**, *36*, 39-50; b) Cardillo, G.; Gentilucci, L.; Tolomelli, A. *Mini-Rev. Med. Chem.* **2006**, *6*, 293-304; c) Fülöp, F.; Martinek, T. A.; Toth, G. K. *Chem. Soc. Rev.* **2006**, *35*, 323-334; d) Lee, W. K.; Ha, H. J. *Aldrichim. Acta* **2003**, *36*, 57-U55; e) Lucarini, S.; Tomasini, C. *J. Org. Chem.* **2001**, *66*, 727-732.

[208] Kiss, L.; Fülöp, F. *Chem. Rev.* **2014**, *114*, 1116-1169.

[209] a) Kazi, B.; Kiss, L.; Forró, E.; Fülöp, F. *Tetrahedron Lett.* **2010**, *51*, 82-85; b) Park, K. H.; Kurth, M. J. *Tetrahedron* **2002**, *58*, 8629-8659.

[210] a) Cramay, C.; Degueil-Castaing, M.; Maillard, B. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3573-3577; b) Luisi, R.; Capriati, V.; Degennaro, L.; Florio, S. *Org. Lett.* **2003**, *5*, 2723-2726; c) Marastoni, M.; McDonald, J.; Baldisserotto, A.; Canella, A.; De Risi, C.; Pollini, G. P.; Tomatis, R. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1965-1968.

[211] a) Nielsen, L. P. C.; Jacobsen, E. N. *Aziridines and Epoxides in Organic synthesis* Wiley-VCH, Weinheim, **2006**; b) Lauret, C. *Tetrahedron-Asymm.* **2001**, *12*, 2359-2383.

[212] Huck, J.; Duru, C.; Roumestant, M. L.; Martinez, J. *Synthesis* **2003**, 2165-2168.

[213] Aciro, C.; Claridge, T. D. W.; Davies, S. G.; Roberts, P. M.; Russell, A. J.; Thomson, J. E. *Org. Biomol. Chem.* **2008**, *6*, 3751-3761.

[214] Hunter, C.; Jackson, R. F. W.; Rami, H. K. *J. Chem. Soc., Perkin Trans. 1* **2000**, 219-223.

[215] Kumar, M.; Pandey, S. K.; Gandhi, S.; Singh, V. K. *Tetrahedron Lett.* **2009**, *50*, 363-365.

[216] a) Ghorai, M. K.; Shukla, D.; Bhattacharyya, A. *J. Org. Chem.* **2012**, *77*, 3740-3753; b) Ghorai, M. K.; Kumar, A.; Tiwari, D. P. *J. Org. Chem.* **2010**, *75*, 137-151; c) Ghorai, M. K.; Das, K.; Shukla, D. *J. Org. Chem.* **2007**, *72*, 5859-5862; d) Ghorai, M. K.; Kumar, A.; Das, K. *Org. Lett.* **2007**, *9*, 5441-5444; e) Couty, F.; David, O.; Durrat, F.; Evano, G.; Lakhdar, S.; Marrot, J.; Vargas-Sanchez, M. *Eur. J. Org. Chem.* **2006**, 3479-3490.

[217] Wang, Z. B.; Sheong, F. K.; Sung, H. H. Y.; Williams, I. D.; Lin, Z. Y.; Sun, J. W. *J. Am. Chem. Soc.* **2015**, *137*, 5895-5898.

[218] Minakata, S.; Okada, Y.; Oderaotoshi, Y.; Komatsu, M. *Org. Lett.* **2005**, *7*, 3509-3512.

[219] a) Zefirov, N. S.; Makhonkov, D. I. *Chem. Rev.* **1982**, *82*, 615-624; b) Grinblat, J.; Ben-Zion, B.; Hoz, S. *J. Am. Chem. Soc.* **2001**, *123*, 10738-10739.

[220] Fu, J.; Karur, S.; Madera, A. M.; Pecchi, S.; Sweeney, Z. K.; Tjandra, M.; Yifru, A., *WO2014160649*, **2014**.

[221] Kvaerno, L.; Werder, M.; Hauser, H.; Carreira, E. M. *J. Med. Chem.* **2005**, *48*, 6035-6053.

[222] O'Dowd, H.; Lewis, J. G.; Trias, J.; Asano, R.; Blais, J.; Lopez, S. L.; Park, C. K.; Wu, C.; Wang, W.; Gordeev, M. F. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 2645-2648.

[223] Caille, J. C.; Farnier, M.; Guilard, R.; Aubry, A.; Lecomte, C. *Can. J. Chem.* **1986**, *64*, 831-836.

[224] Taylor, F.; Huffman, M. D.; Macedo, A. F.; Moore, T. H. M.; Burke, M.; Smith, G. D.; Ward, K.; Ebrahim, S. *Cochrane Database Syst. Rev.* **2013**.

[225] Stritzke, K.; Schulz, S.; Nishida, R. *Eur. J. Org. Chem.* **2002**, 3884-3892.

[226] O'Reilly, E.; Pes, L.; Ortin, Y.; Muller-Bunz, H.; Paradisi, F. *Amino Acids* **2013**, *44*, 511-518.

[227] a) Baldauf, C.; Gunther, R.; Hofmann, H. J. *J. Org. Chem.* **2004**, *69*, 6214-6220; b) Baldauf, C.; Gunther, R.; Hofmann, H. J. *Peptide Revolution: Genomics, Proteomics & Therapeutics* **2004**, 439-440; c) Baldauf, C.; Gunther, R.; Hofmann, H. J. *Peptide Revolution: Genomics, Proteomics & Therapeutics* **2004**, 441-442.

[228] Liu, J.; Hu, J. B. *Future Med. Chem.* **2009**, *1*, 875-888.

[229] a) Bensemhoun, J.; Rudi, A.; Kashman, Y.; Gaydou, E. M.; Vacelet, J.; Aknin, M. *Nat. Prod. Commun.* **2010**, *5*, 259-260; b) Kashman, Y.; Bishara, A.; Aknin, M. *Mar. Drugs* **2010**, *8*, 2810-2836.

[230] Heaney, F.; Fenlon, J.; McArdle, P.; Cunningham, D. *Org. Biomol. Chem.* **2003**, *1*, 1122-1132.

[231] Agilent Technologies, *1.171.37.31*.

[232] Dolomanov, O. V.; Bourhis, L. J.; Gildea, R. J.; Howard, J. A. K.; Puschmann, H. *J. Appl. Crystallogr.* **2009**, *42*, 339-341.

[233] Sheldrick, G. M. *Acta. Crystallogr. A* **2008**, *64*, 112-122.

9 Curriculum Vitae

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Education

2011-2015 *Ghent, Belgium*	**PhD**: (Bioscience) Engineering Department of Sustainable Organic Chemistry and Technology Faculty of Bioscience Engineering Ghent University Promoters: Prof. Dr. ir. Norbert De Kimpe Prof. Dr. ir. Sven Mangelinckx **Thesis:** Synthesis of new cyclic and acyclic biologically relevant amino acids derivatives
2009-2011 *Moscow, Russia*	**M.Sc.**: Organic chemistry Department of Organic Chemistry Faculty of Natural Science Lomonosov State Academy of Fine Chemical Technology Promoter: Prof. Dr. Anatoly D. Shutalev **Thesis:** Enantioselective synthesis of novel 1,2,3,4-tetrahydropyrimidine-2-thiones/ones
2005-2009 *Moscow, Russia*	**B.Sc.**: Chemistry Department of Organic Chemistry Faculty of Natural Science Lomonosov State Academy of Fine Chemical Technology Promoter: Prof. Dr. Anatoly D. Shutalev **Thesis:** Base mediated transformation of *N*-[(2-chloro-1-tosyl)ethyl]urea. Synthesis of novel captodative alkenes
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Publications in international journals with peer-review

1. E. Semina, F. Colpaert, K. Van Hecke, N. De Kimpe, S. Mangelinckx, Asymmetric Synthesis of δ-chloro-β-amino-*N*-sulfinyl imidates as versatile chiral building blocks for the synthesis of 2,3-disubstituted piperidines. *Eur. J. Org. Chem.* **2015**, *22*, 4847-4859.
2. T. Malcomson, K. Yelekci, M. T. Borrello, A. Ganesan, E. Semina, N. De Kimpe, S. Mangelinckx, R. R. Ramsay, *cis*-Cyclopropylamines as mechanism-based inhibitors of monoamine oxidases. *FEBS Journal* **2015**, *16*, 3190–3198.
3. S. Mangelinckx, S. T. Kadam, E. Semina, G. Callebaut, F. Colpaert, D. De Smaele, N. De Kimpe, Synthesis of *cis*-2-alkoxycyclopropylamines *via* intramolecular cyclisation of 2-azaallylic anions derived from alkoxybrominated *N*-(arylidene)-2-methyl-2-propenylamines. *Tetrahedron* **2013**, *69*, 3728-3735

Conferences and meetings

1. Green Chemistry for the 21*st* Century Chemical Industries, *The Educational Workshop*. Antwerp, Belgium, 2015.

2. E. Semina, F. Colpaert, K. Van Hecke, N. De Kimpe, S. Mangelinckx. Stereoselective synthesis of 3-functionalized 2-arylpiperidines using *N*-*tert*-butanesulfinyl δ-chloro imidates. 18th Sigma Aldrich Organic Synthesis Meeting, Duinse Polders, Blankenberge, Belgium, 2014, P28.

3. 16th Sigma Aldrich Organic Synthesis Meeting, Sol Cress, Spa, Belgium, 2012

4. E. Semina, O. Kuzmina, V. Mikhaylov. The solvation of carboxylic acids monomers and dimmers in organic solvents. // Program and Abstracts. 4-th International Conference Extraction of Organic Compounds, Voronezh, Russia, 2010, p. 378.

5. E. Semina, I. Zamilatskov, D. Albov, E. Savinkina, A. Shutalev. Synthesis of 5-acyl-1,2,3,4-tetrahydropyrimidine-2-thiones/ones and their complexes with 2B group metals// Program and Abstracts. XXIVth European Colloquium on Heterocyclic Chemistry, Vienna, Austria , 2010, PO-109.