Ph.D. Thesis

Application of reductive amination for the stereocontrolled synthesis of functionalized azaheterocycles

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1. Introduction and aims

The chemistry of functionalized azaheterocycles have become a highly important topic in recent decades. They are widely distributed in nature and are essential to life in various ways, for instance alkaloids, antibiotics, amino acids, vitamins and a large number of synthetic drugs contain azaheterocyclic ring systems. The ring size as well as the nature and the stereochemical features of the substituents present in these heterocycles play a fundamental role in assessing their biological activity. Furthermore, a large number of pharmacologically active natural and synthetic *N*-heterocycles are in regular clinical use. They have been utilized as antibiotics, analgesics, antidepressants, anticancer, anti-HIV, and anti-HCV agents.

Fluorinated organic compounds are of particular interest in the field of functional materials science, pharmaceuticals, and agrochemicals, due to the unique characteristics of the fluorine atom, which can alter properties of organofluorines. Fluorine atom is undoubtedly one of the elements that has attracted high recent research interest in several aspects of chemistry. The incorporation of the fluorine atom or a certain fluorinated moiety into organic compounds has become a powerful tool to discover new chemical entities possessing unique physical, chemical and biological properties in comparison to those of nonfluorinated parent compounds. Recently, it has been estimated that about 30% of the newly approved drugs contained fluorine atoms.

In view of the importance of fluorination, fluorinated β-amino acids have received high attention. Therefore, incorporation of fluorine into cyclic β-amino acids and some functionalized cycloalkene derivatives became an important research topic in the Institute of Pharmaceutical Chemistry. The research used two common synthetic pathways. The first method (a direct fluorination approach) applies late-stage exchange of OH or oxo functions to fluorine by using various nucleophilic fluorinating reagents such as diethylaminosulfur trifluoride (DAST) or Deoxofluor. The other method is based on the application of fluorine-containing building blocks such as fluorinated amines.

The present PhD work focuses on the synthesis of various types of fluorinated functionalized azaheterocycles. The aim of the research was to expand the chemical space, to further extend and improve an efficient stereocontrolled procedure for the access of new fluorine-containing saturated *N*-heterocycles. The key step of this procedure is reductive amination of dialdehydes using fluorinated amines. The required dialdehydes were obtained from various cycloalkenes in two pathways. The first approach starts with OsO_4-mediated

dihydroxylation of the olefin bond of cycloalkenes, followed by oxidative cleavage of the diol intermediate using $NaIO_4$. In order to improve atom economy, reduce wastes and avoid the use of toxic heavy metal compounds, a second, "greener" approach has been developed which uses ozonolysis reaction (treatment with ozone, then reductive workup with dimethyl sulfide) to convert functionalized alkenes into the corresponding carbonyl compounds in a single step.

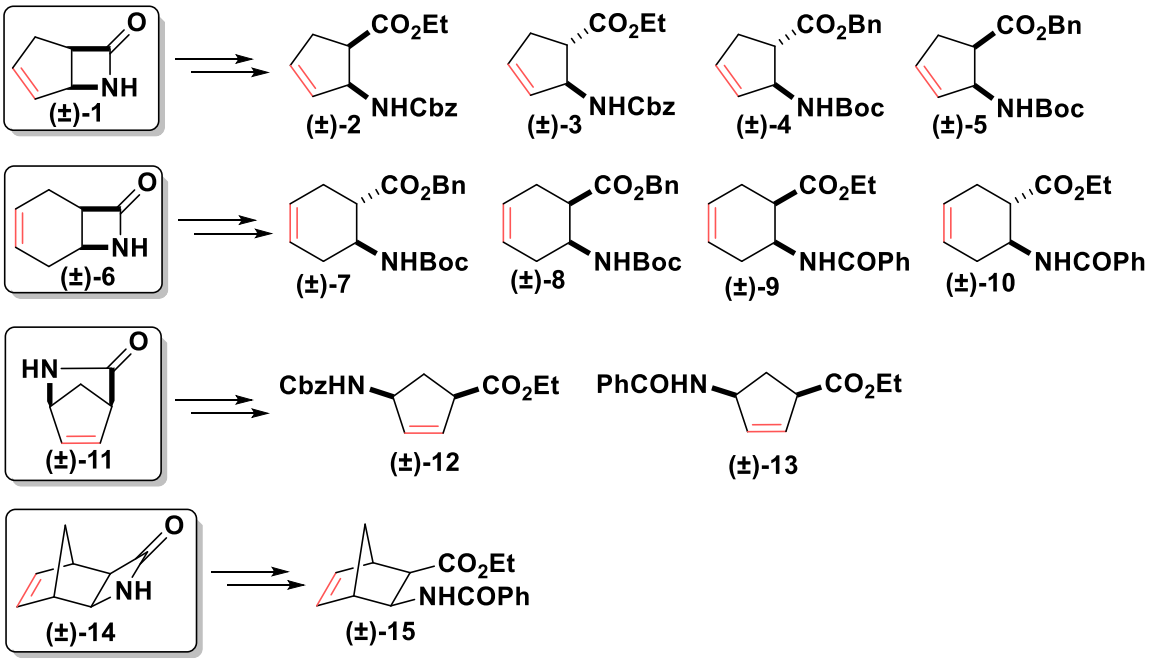
2. Methods

The synthesized compounds were separated and purified by column chromatography on silica gel. The newly prepared compounds were characterized by NMR spectroscopy, mass spectrometry, melting point measurement and elemental analysis. For determination of the structure and stereochemistry of the compounds, two-dimensional NMR techniques (COSY, HSQC, HMBC and NOESY) were applied.

3. Results and discussion

3.1 Synthesis of starting materials

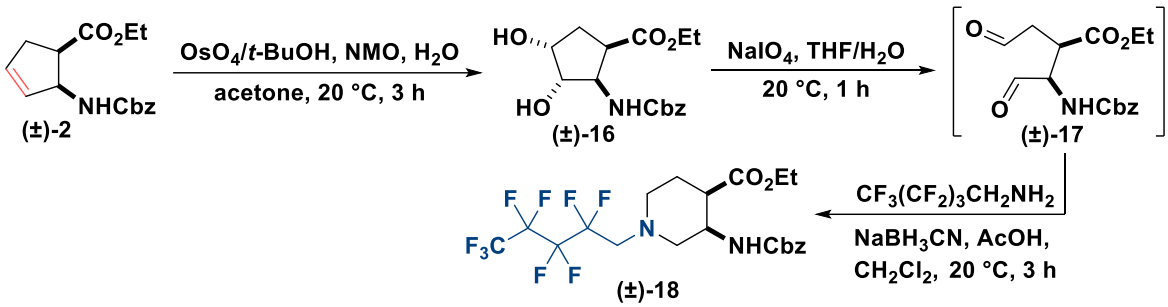
β- and γ-amino ester starting materials were synthesized from readily available unsaturated bicyclic β- and γ-lactams **(±)-1**, **(±)-6**, **(±)-11**, and **(±)-14** using simple, known literature methods. The primary products were *cis* amino esters: *N*-Cbz protected ethyl esters, *N*-benzoylated ethyl esters or *N*-Boc protected benzyl esters. Epimerization of monocyclic *cis*-β-amino esters led to corresponding *trans*-β-amino ester isomers (*Scheme 1*).



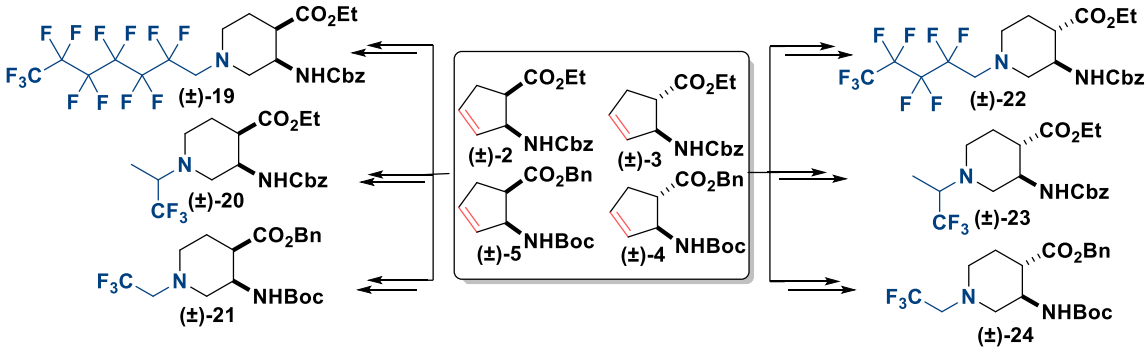
Scheme 1. Synthesis of *N*-protected β- and γ-amino ester starting model compounds

3.2 Synthesis of fluorine-containing piperidine β-amino esters

The synthetic route to fluorine-containing *cis* and *trans* piperidine β-amino esters started with oxidative ring cleavage of unsaturated *cis*- and *trans*-ethyl-β-aminocyclopentene-carboxylates. Reductive amination of the formed dialdehyde intermediates (addition of fluorinated amines, 10 min stirring, then addition of $NaBH_3CN$ and 2 drops of AcOH) resulted in the desired *N*-Cbz protected ethyl esters [**(±)-18, (±)-19, (±)-20**, **(±)-22** and **(±)-23**] and *N*-Boc protected benzyl esters [**(±)-21** and **(±)-24**] (*Scheme 2, Scheme 3*).

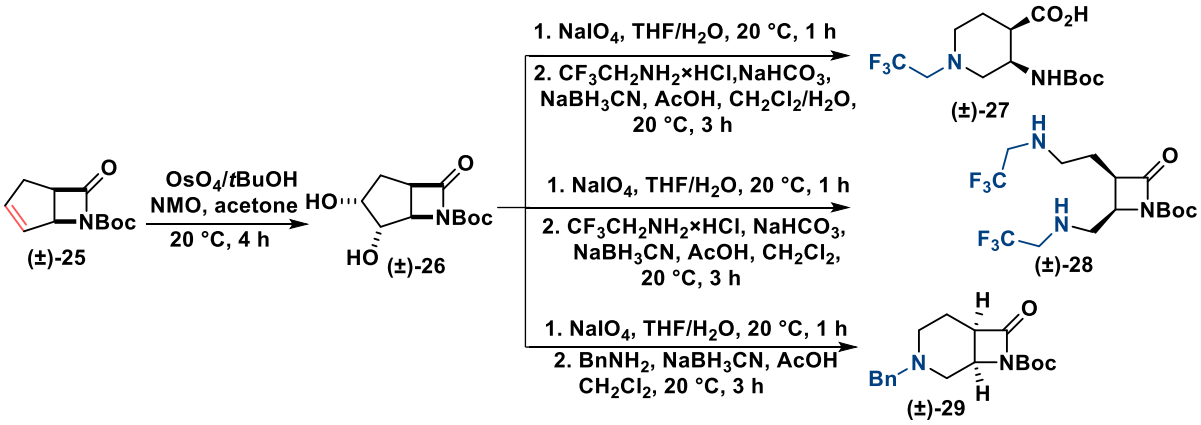


Scheme 2. Synthesis of fluorine-containing piperidine *cis*-β-amino ester **(±)-18**



Scheme 3. Synthesis of fluorinated piperidine *cis*- and *trans*-β-amino esters

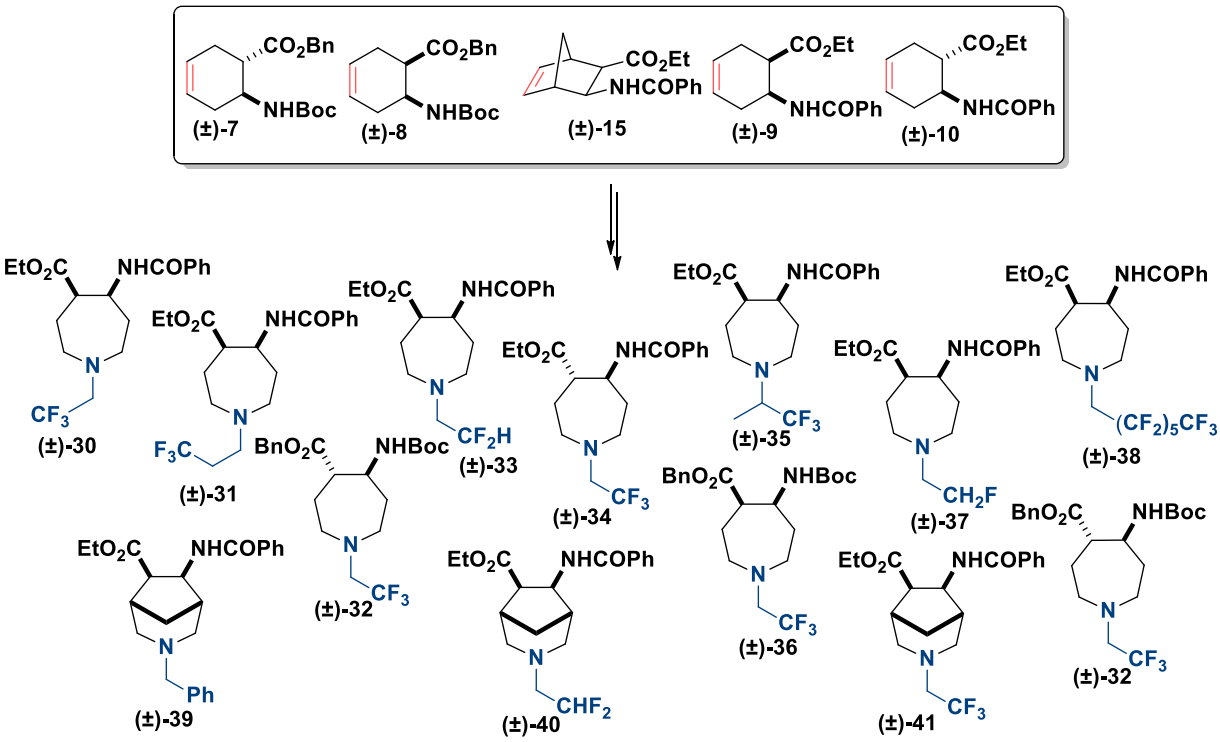
Synthesis of compounds **(±)-27, (±)-28** and **(±)-29** was accomplished from bicyclic β-lactam **(±)-25** through oxidative ring cleavage/reductive ring closing protocol (*Scheme 4*).



Scheme 4. Transformations of bicyclic β-lactam **(±)-25**

3.3 Synthesis of fluorine-containing azepane β-amino esters

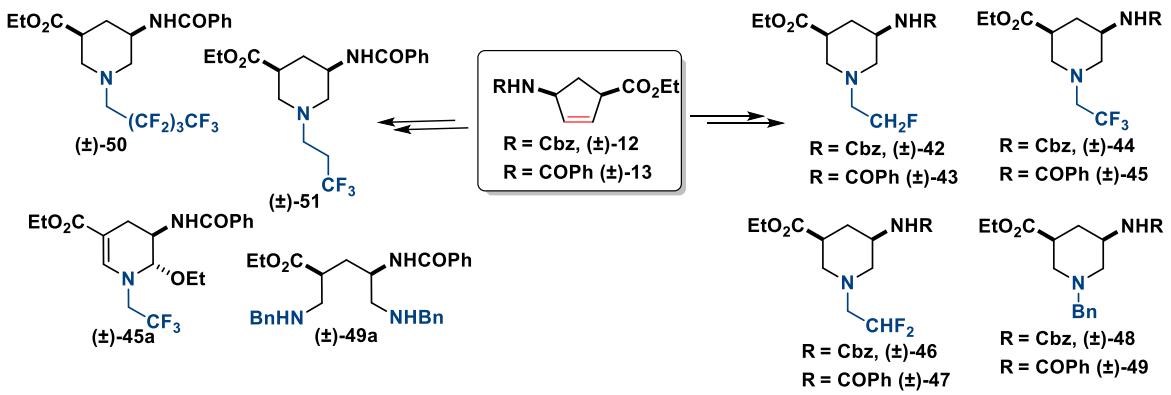
The above synthetic approach was applied for the stereocontrolled synthesis of fluorine-containing azepane β-amino esters [**(±)-30-38**] from unsaturated cyclohexene β-amino esters [**(±)-7-10**]. Bridged azepane β-amino esters **(±)-39**, **(±)-40** and **(±)-41** were prepared from **(±)-15** (*Scheme 5*).



Scheme 5. Synthesis of azepane and methylene bridged azepane β-amino esters

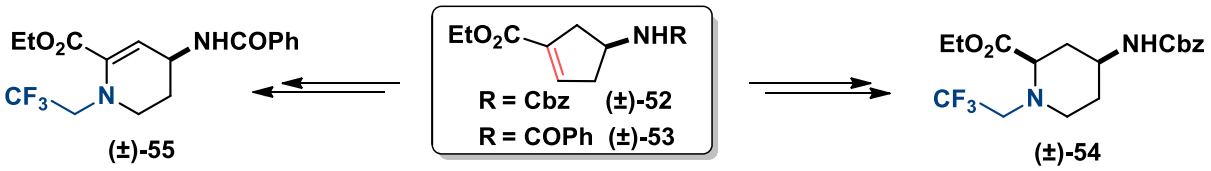
3.4 Synthesis of fluorine-containing piperidine γ-amino esters

Unsaturated cis γ-amino esters **(±)-12** and **(±)-13** were transformed, with the conservation of the relative stereochemistry, into *cis*-γ-amino esters **(±)-42-51** with piperidine skeleton. The protocol involved the earlier described steps, namely oxidative ring opening and stereocontrolled ring expansion through ring-closing across double reductive amination with various fluorine-containing amines and benzylamine (*Scheme 6*). The protocol was sensitive to slight changes. For example, solvent change (EtOH instead of CH_2Cl_2) resulted in compound **(±)-45a** instead of compound **(±)-45**. Addition of $NaBH_3CN$ and AcOH together with benzylamine (and not 10 min later) yielded open-chain product **(±)-49a** instead of compound **(±)-49**.



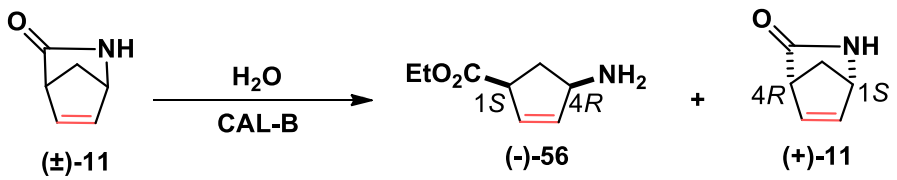
Scheme 6. Synthesis of piperidine γ-amino esters

Synthesis of novel regioisomeric trifluoromethyl-containing piperidine *cis* γ-amino esters **(±)-54** and **(±)-55** was also accomplished (*Scheme 7*).



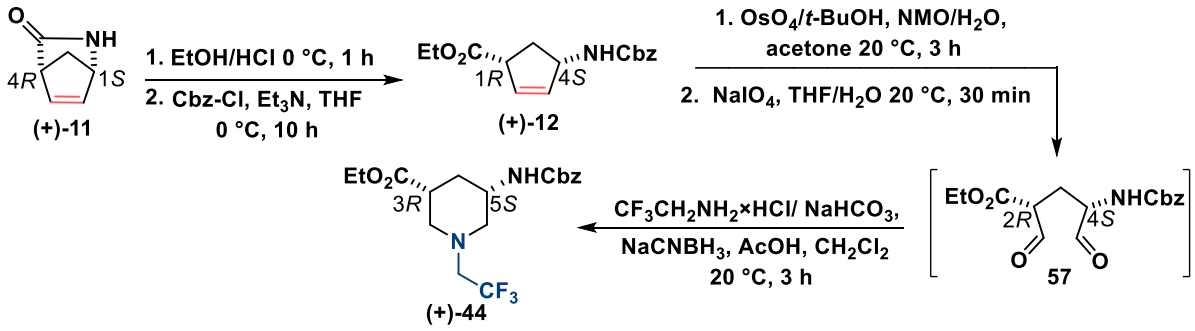
Scheme 7. Synthesis of fluorine containing piperidine derivatives **(±)-54** and **(±)-55**

Optically pure γ-lactam **(+)-11** was obtained by a literature protocol (enantioselective hydrolysis of racemic **(±)-11** catalyzed by *Candida antarctica* lipase-B, see *Scheme 8*).



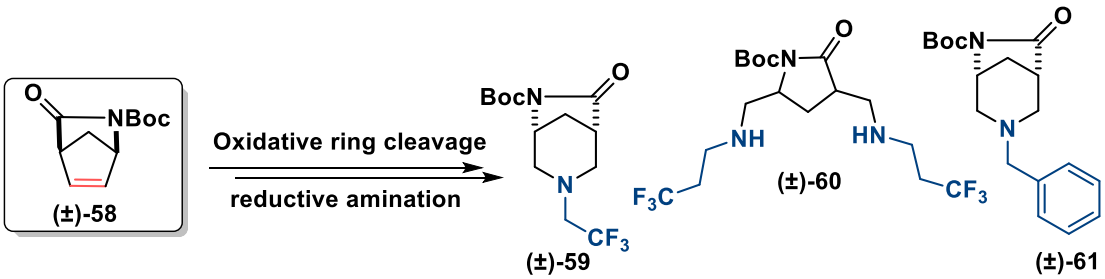
Scheme 8. Synthesis of enantiomerically pure γ-lactam **(+)-11**

Using the already established synthetic pathway, lactam **(+)-11** was transformed into enantiomerically pure fluorine-containing piperidine γ-amino ester **(+)-44** (*Scheme 9*).



Scheme 9. Synthesis of enantiomerically pure fluorine-containing γ-amino ester **(+)-44**

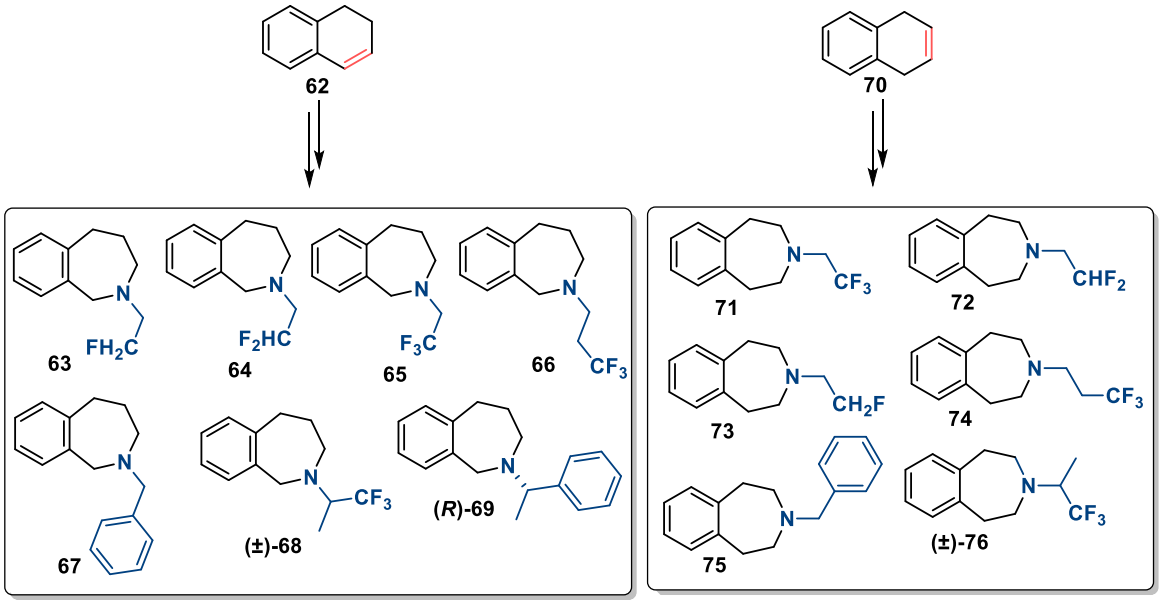
The synthetic methodology was further extended for the access of novel fluorine-containing γ-lactam derivatives. Subjecting *N*-Boc-protected Vince lactam **(±)-58** to ring cleavage followed by double reductive amination with $CF_3CH_2NH_2$, $BnNH_2$ or $CF_3CH_2CH_2NH_2$ yielded piperidine-fused γ-lactams **(±)-59, (±)-61** and monocyclic γ-lactam **(±)-60** (*Scheme 10*).



Scheme 10. Synthesis of piperidine-fused γ-lactams **(±)-59, (±)-61** and monocyclic γ-lactam **(±)-60.**

3.5 Synthesis of functionalized benzazepines through reductive amination

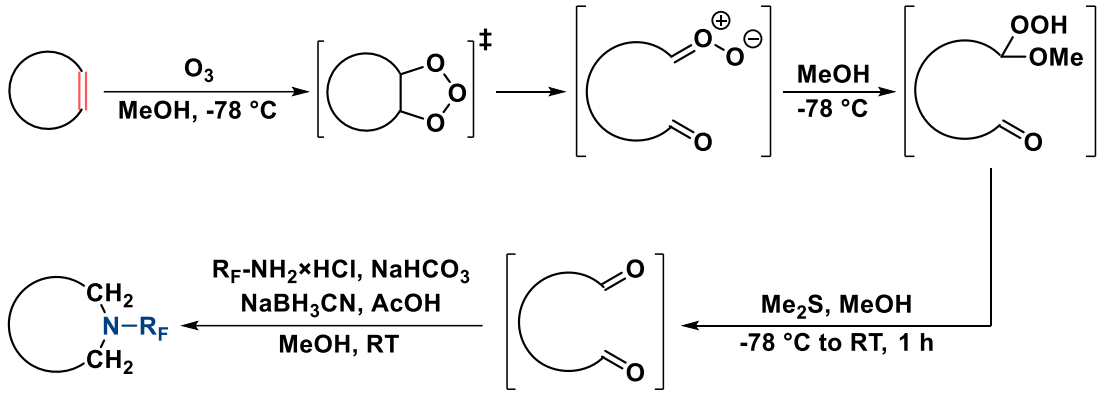
The protocol described above was extended towards the preparation of novel benzo[*c*]azepine and benzo[*d*]azepine derivatives. Oxidative ring cleavage of dihydro-naphthalenes and subsequent cyclization via double reduction amination with $BnNH_2$ or different fluorine-containing amines provided the corresponding benzazepines **63-67**, **(±)-68**, **(*R*)-69**, **71-75**, and **(±)-76** (*Scheme 11)*.



Scheme 11. Synthesis of novel fluorinated benzo[*c*]azepine and benzo[*d*]azepine derivatives.

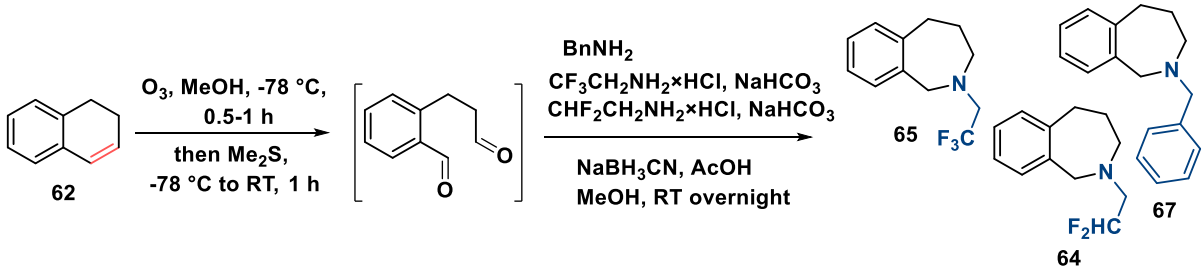
3.6 Synthesis of various N-heterocycles via ozonolysis/reductive amination

Our next aim was to improve the above designated method for the synthesis of functionalized azaheterocycles. Therefore, oxidative ring cleavage was performed in a single step by ozonolysis and workup with Me_2S. Subjected the resulting diformyl intermediate to reductive amination without isolation resulted in a telescoped synthetic pathway towards azaheterocycles (*Scheme 12*). This one-pot two-step approach is shorter and greener that the previous method, because it no longer needs toxic and expensive OsO_4, produces much less inorganic and organic wastes and involves less amount of solvents and chromatographic purification steps.



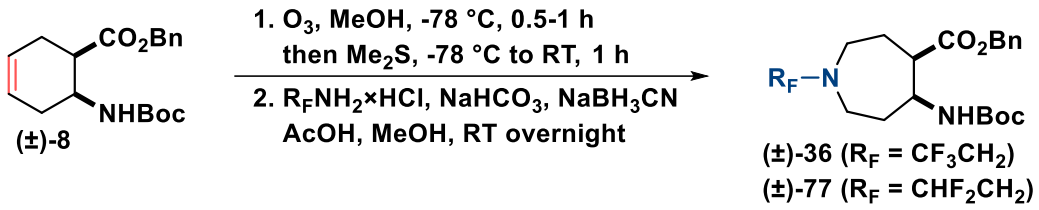
Scheme 12. The greener, improved synthetic pathway towards *N*-heterocycles

The new synthetic strategy was applied for the synthesis of various known or new *N*-heterocyclic compounds including benzo[*c*]azepines [*Scheme 13*, note that products: **64**, **65**, **67** were synthetized by the above described alternative method].



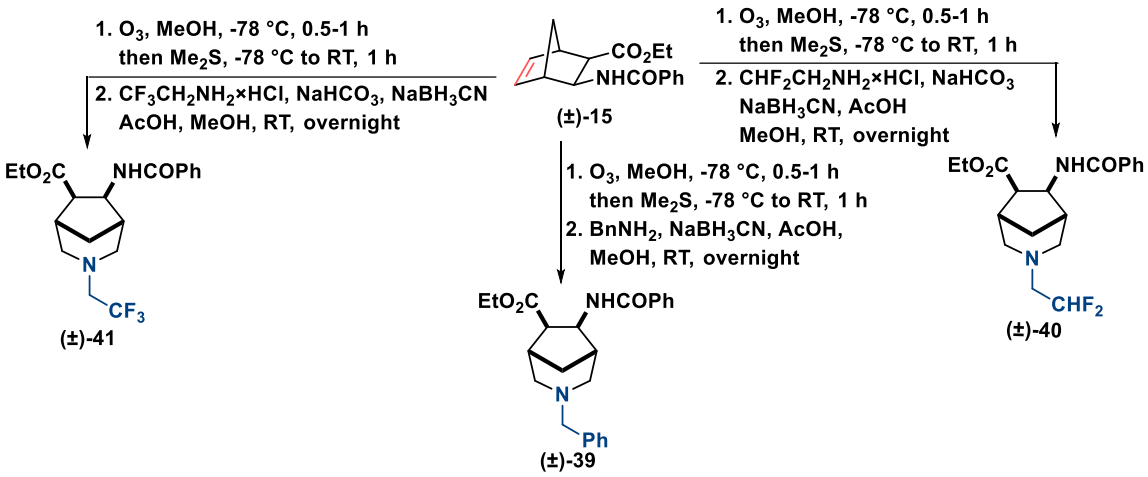
Scheme 13. Synthesis of benzo[*c*]azepines through ozonolysis/reductive amination protocol

Cyclohexene β-amino ester **(±)-8** was transformed under ozonolysis/reductive amination to monocyclic azepane β-amino esters (*Scheme 14*). Compound **(±)-36** was already known, but compound **(±)-77** is a new product.



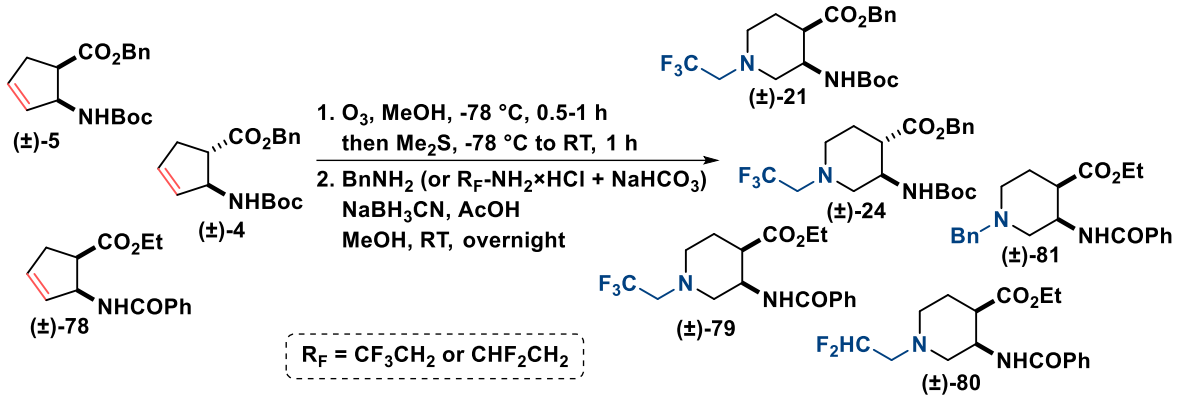
Scheme 14. Synthesis of protected azepane β-amino esters

Methylene bridged azepane β-amino esters were also synthesized with ozonolysis/reductive amination of norbornene β-amino esters **(±)-15** [*Scheme 15*, note that products: **(±)-39**, **(±)-40**, **(±)-41** were synthetized previously by the dihydroxylation/diol cleavage/reductive amination method].



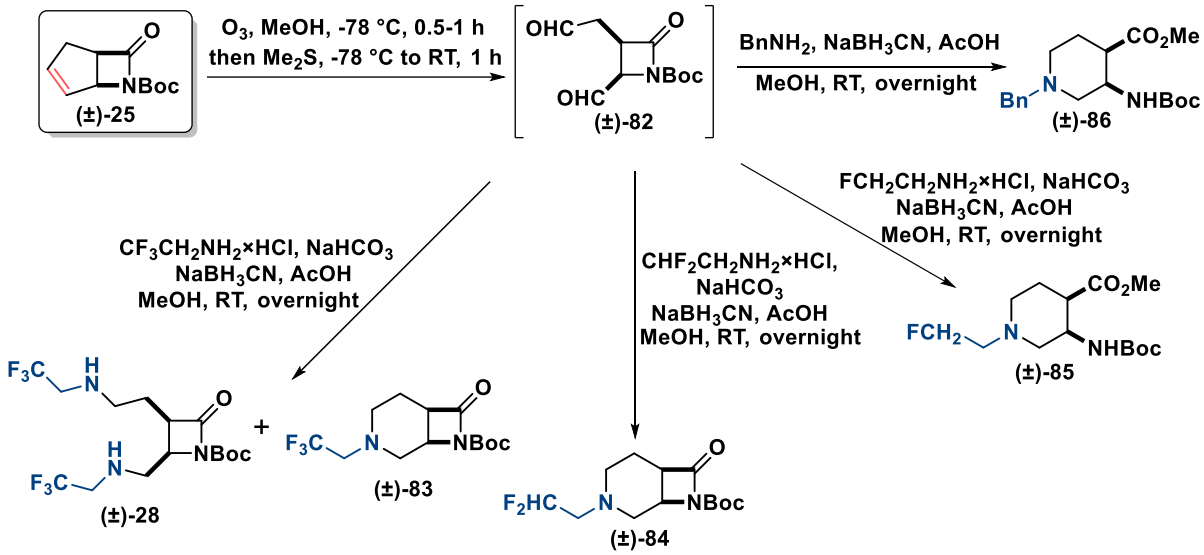
Scheme 15. Synthesis of methylene bridged azepane β-amino esters

Next, we investigated the preparation of some β-amino acids, β-amino esters and β-lactams with a piperidine ring. Thus, synthesis of piperidine β-amino esters were accomplished from readily accessible cyclopentene β-amino esters **(±)-4, (±)-5** and **(±)-78** (*Scheme 16*). Note that **(±)-81** is a new product, while compounds **(±)-21**, **(±)-24**, **(±)-79** and **(±)-80** were synthetized previously by the dihydroxylation/diol cleavage/reductive amination method. The reactions proceeded with stereocontrol: *cis* starting materials provided the corresponding *cis* amino esters, while the *trans* starting compounds gave the desired piperidines with the functional groups in *trans* relative positions.



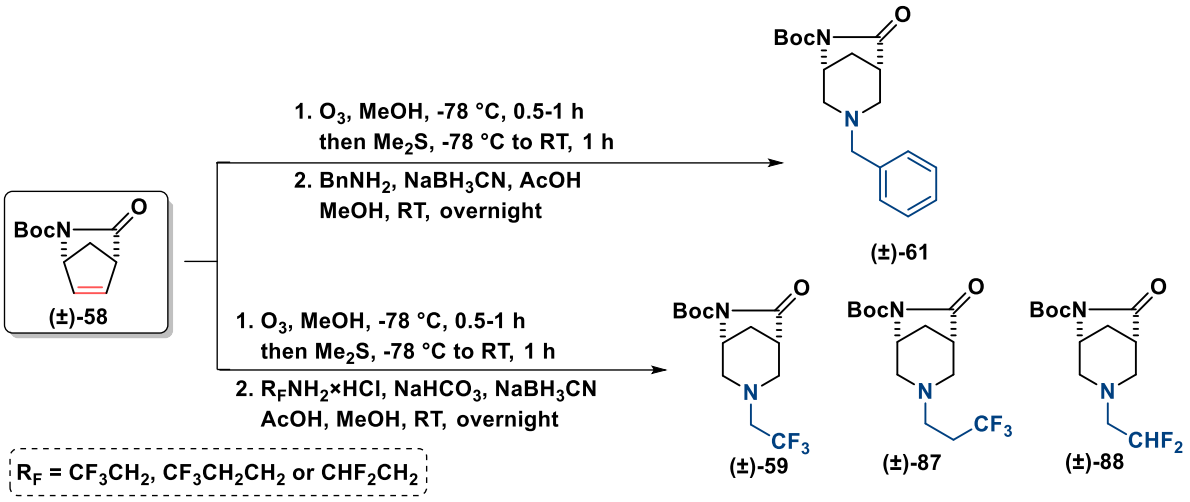
Scheme 16. Synthesis of piperidine β-amino esters.

The ozonolysis/reductive amination method was generally more versatile and it usually provided better yields. However, during transformation of *N*-Boc protected β-lactam **(±)-25**, the expected piperidine-fused β-lactams were obtained only with $CF_3CH_2NH_2$ and $CHF_2CH_2NH_2$ [**(±)-83** and **(±)-84**] (and in the former case, monocyclic diamino lactam **(±)-28** was also formed). With $BnNH_2$ and $FCH_2CH_2NH_2$, reductive amination was accompanied with lactam methanolysis and new β-amino methyl esters **(±)-85** and **(±)-86** were formed.



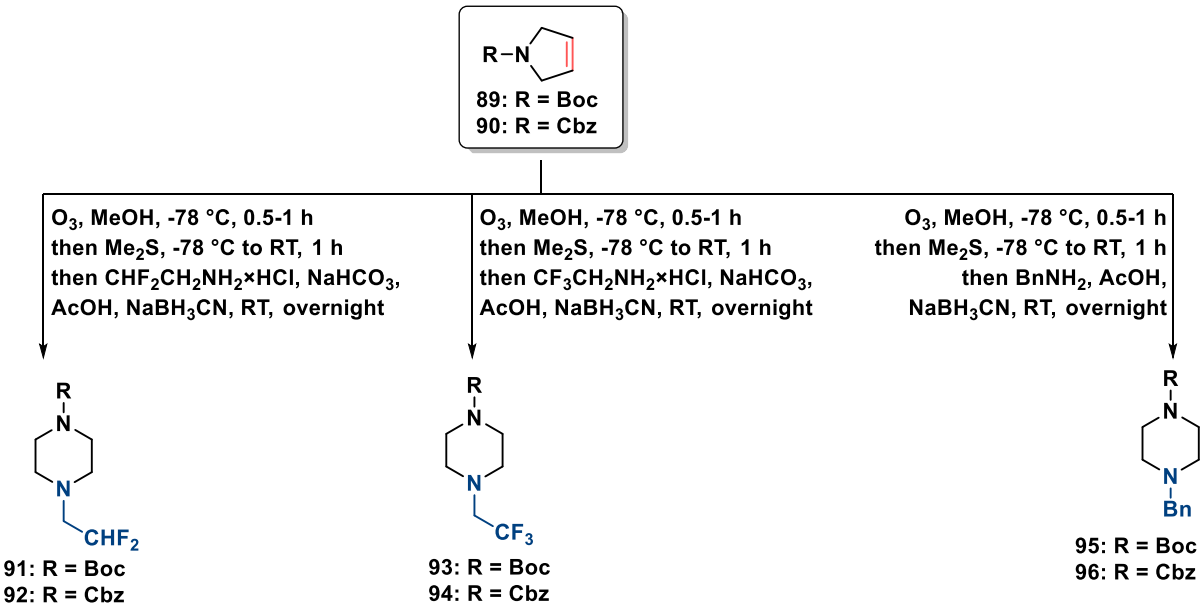
Scheme 17. Ozonolysis/reductive amination of β-lactam **(±)-25**

Piperidine-fused γ-lactams, were synthesized from *N*-Boc-protected Vince lactam **(±)-58** by ozonolysis/reductive amination procedure (*Scheme 18*). Compounds **(±)-59** and **(±)-61** were already known, while substances **(±)-87** and **(±)-88** are new products.



Scheme 18. Synthesis of azabicyclic γ-lactams with a piperidine ring

The synthetic strategy was extended for the synthesis of other *N*-heterocyclic compounds too. *N*-protected 3-pyrroline derivatives **89** and **90** were subjected to ozonolysis/reductive amination. The reactions were successful both with benzylamine and fluorinated amines, and led to the expected piperazine derivatives **91-96** (*Scheme 19*).



Scheme 19. Synthesis of piperazines via ozonolysis/reductive amination

PUBLICATION LIST

Papers related to the thesis:

I. **L. Ouchakour,** R. A. Ábrahámi, E. Forró, M. Haukka, F. Fülöp, L. Kiss:
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Eur. J. Org Chem. **2019**, 2202-2211. IF: 2.882

II. **L. Ouchakour,** M. Nonn, L. Kiss:
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Fluorine Notes **2019**, *122*, 1-2.

III. **L. Ouchakour,** M. Nonn, M. D'hooghe, L. Kiss:
A de novo synthetic method to the access of *N*-substituted benzazepines
J. Fluorine Chem. **2020**, *232*, 109466. IF: 2.055

IV. M. Nonn, D. Kara, **L. Ouchakour,** E. Forró, M. Haukka, L. Kiss:
Diversity-Oriented Stereocontrolled Synthesis of Some Piperidine and Azepane-Based Fluorine-Containing β-Amino Acid Derivatives
Synthesis **2021**, *53*, 1163-1173. IF 2.675

Other publications:

V. L. Kiss, **L. Ouchakour,** R. A. Ábrahámi, M. Nonn:
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Chem. Rec. **2020**, *20*, 120-141. IF: 6.163

Conference lectures:

VI. **L. Ouchakour,** R. A. Ábrahámi, M. Nonn, L. Kiss:
Fluortartalmú piperidinvázas γ-aminosavszármazékok sztereokontrollált szintézisei
XXIV. Nemzetközi Vegyészkonferencia
Szovátafürdő, Romania, 24-27 October, 2018, oral presentation

VII. **L. Ouchakour,** F. Fülöp, L. Kiss:
Stereocontrolled synthesis of novel fluorine-containing azaheterocycles
MTA Alkaloid- és Flavonoidkémiai Munkabizottság Ülése
Mátrafüred, Hungary, 11-12 Apr, 2019, oral presentation