PhD thesis

Application of nucleophilic fluorinating reagents for the synthesis and transformations of cyclic β-amino acid derivatives

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1. Introduction and aims

Fluorination has become a highly important topic in recent decades, because incorporation of the highly electronegative F atom can greatly influence key pharmaceutical parameters like metabolism, lipophilicity and bioavailability. Thanks to their advantageous properties, fluorinated drug molecules have become common with their current ratio within newly approved drugs is about 20-25%.

Cyclic amino acids are of high importance in pharmaceutical chemistry. Conformational restrictions resulting from their cyclic nature make them promising building blocks of new bioactive peptides. Numerous natural or synthetic cyclic amino acid derivatives, including approved drugs, show relevant biological activities.

Because of the importance of fluorination, fluorinated cyclic amino acid derivatives also gained attention. However, within this compound family, fluorinated cyclic β-amino acids received less interest. As a result, synthesis of such molecules became an important research topic in the Institute of Pharmaceutical Chemistry at the University of Szeged. With the help of nucleophilic fluorinating reagents, preparation of numerous fluorinated cyclic β-amino acid derivatives was accomplished.

The present PhD work focused on the synthesis of various types of fluorinated functionalized cyclic β-amino acid derivatives. The aim of the research was to obtain such compounds through new synthetic pathways starting from selectively epoxidated or dihydroxylated cyclic β-amino acid derivatives, utilizing deoxyfluorinating reagents. High emphasis was placed on substrate dependence (including neighboring group effects), selectivity, and chemodifferentiation between functional groups.

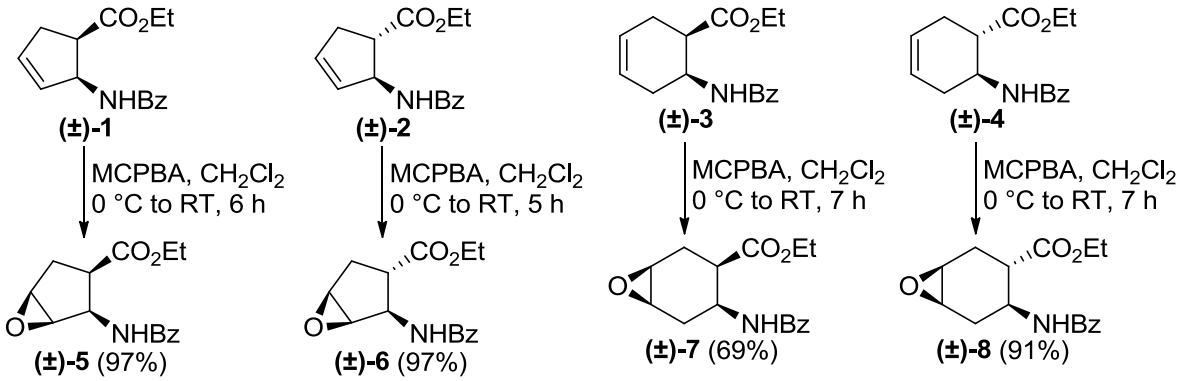
2. Methods

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

3. Results and discussion

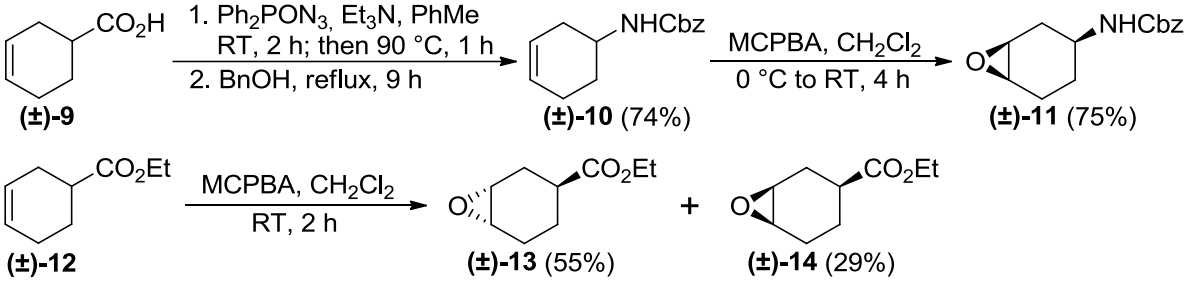
3.1.1. Synthesis of epoxy amino esters

Unsaturated cyclic β-amino esters, obtained from β-lactams, were subjected to stereoselective epoxidation to synthesize the starting epoxy β-amino esters (*Scheme 1*).



Scheme 1. Stereoselective epoxidation of β-amino esters

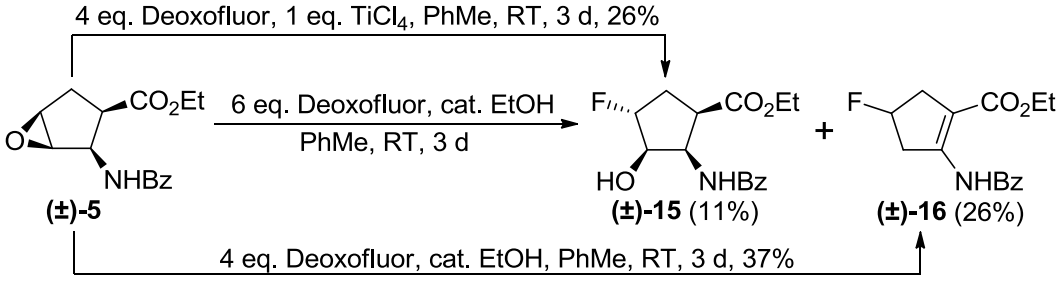
Some other oxiranes were also synthesized to study the effects of the ester and protected amine moieties individually. Epoxidation of cyclohex-3-eneamine derivative **(±)-10** (obtained from cyclohex-3-enecarboxylic acid by Curtius rearrangement) was stereoselective, while epoxidation of ethyl cyclohex-3-enecarboxylate **(±)-12** yielded a product mixture (*Scheme 2*).



Scheme 2. Synthesis of monofunctional bicyclic oxiranes

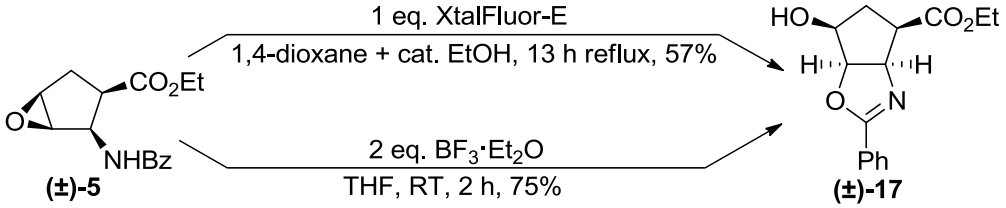
3.1.2. Fluorination reactions

Reactions of oxirane **(±)-5** were studied first. Initially, a catalytic amount of EtOH was added to the reaction mixtures to produce some HF, which can facilitate the ring-opening through electrophilic activation of the epoxide ring. Reaction with 6 eq. Deoxofluor in anhydrous PhMe resulted in both fluorohydrin **(±)-15** and unsaturated fluorine-containing product **(±)-16**, while 4 eq. reagent produced only compound **(±)-16**. Other agents for electrophilic activation were also tested and in the presence of $TiCl_4$ fluorohydrin **(±)-15** was obtained (*Scheme 3*).



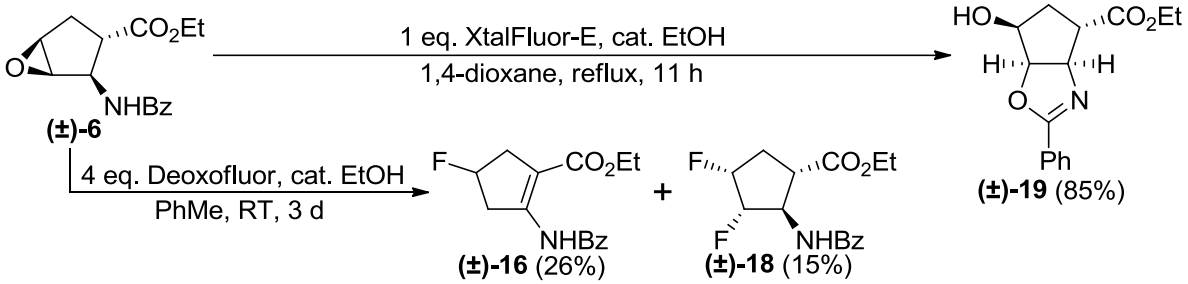
Scheme 3. Reactions of epoxide **(±)-5** with Deoxofluor

During our experiments with Deoxofluor–Lewis acid systems, the reaction of **(±)-5** with only $BF_3 \cdot OEt_2$ was tested too, resulting in heterocycle **(±)-17** thanks to participation of the protected amino group. Use of XtalFluor-E gave similar results (*Scheme 4*).



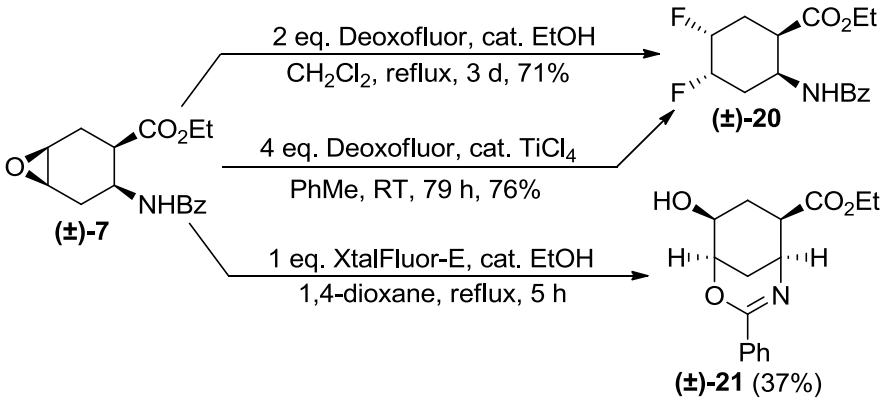
Scheme 4. Reactions of epoxide **(±)-5** with XtalFluor-E and $BF_3 \cdot OEt_2$

Reaction of epoxide **(±)-6** with Deoxofluor in the presence of catalytic amount of EtOH gave both unsaturated derivative **(±)-16** and difluorinated product **(±)-18**. Reaction with XtalFluor-E yielded heterocyclic derivative **(±)-19** (*Scheme 5*).



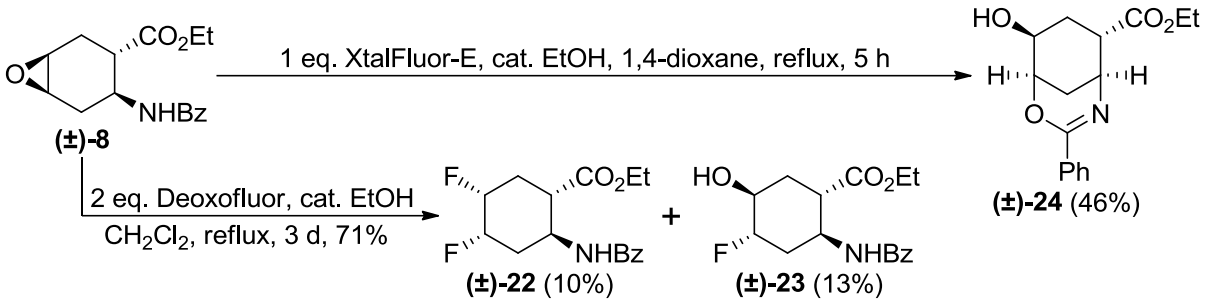
Scheme 5. Fluorinations of epoxide **(±)-6**

Reaction of epoxide **(±)-7** with Deoxofluor in the presence of EtOH was the most effective in refluxing CH_2Cl_2, where difluorinated product **(±)-20** was obtained in 71% yield. The use of $TiCl_4$ instead of EtOH improved the yield to 76%. Treatment of epoxide **(±)-7** with XtalFluor-E furnished cyclized product **(±)-21** (*Scheme 6*).



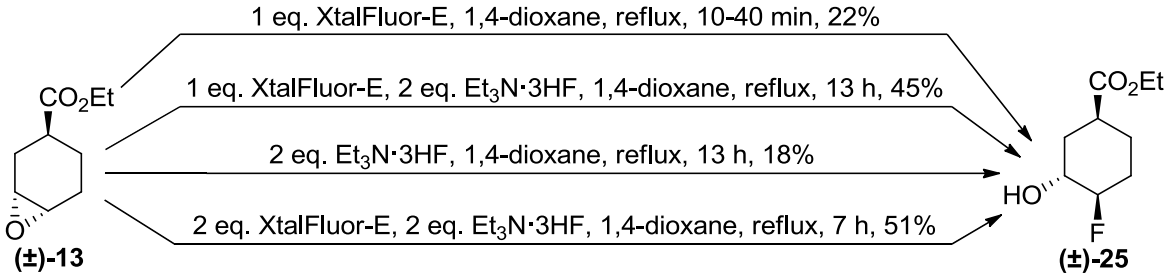
Scheme 6. Reactions of epoxide **(±)-7** with nucleophilic fluorinating reagents

From compound **(±)-8**, in the presence of EtOH, products **(±)-22** and **(±)-23** were obtained in low yields with Deoxofluor. Reaction with XtalFluor-E gave cyclized **(±)-24** (*Scheme 7*).



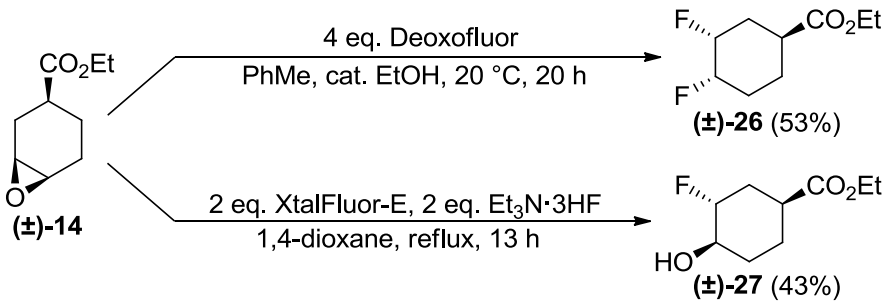
Scheme 7. Reactions of epoxide **(±)-8** with nucleophilic fluorinating reagents

The reaction of *trans*-epoxycyclohexanecarboxylate **(±)-13** with Deoxofluor did not give any identifiable products. When various amounts of XtalFluor-E and $Et_3N{\cdot}3HF$ were applied, fluorohydrin **(±)-25** was isolated in 22-51% yield from the reaction mixture (*Scheme 8*).

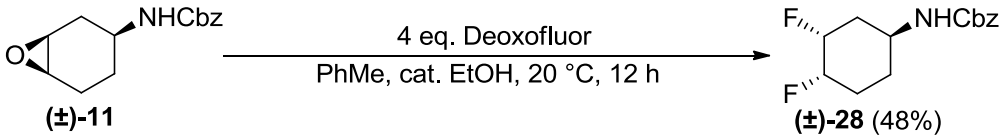


Scheme 8. Selective ring opening of epoxide **(±)-13** with nucleophilic fluorinating reagents

In contrast with its *trans* isomer, reaction of *cis*-epoxycyclohexanecarboxylate **(±)-14** with Deoxofluor yielded difluorinated derivative **(±)-26**. With XtalFluor-E and $Et_3N{\cdot}3HF$, oxirane **(±)-14** reacted similarly to its *trans* isomer (*Scheme 9*). From epoxyaminocyclohexane derivative **(±)-11** difluorinated compound **(±)-28** was obtained with Deoxofluor (*Scheme 10*).



Scheme 9. Ring opening of epoxide **(±)-14** with nucleophilic fluorinating reagents

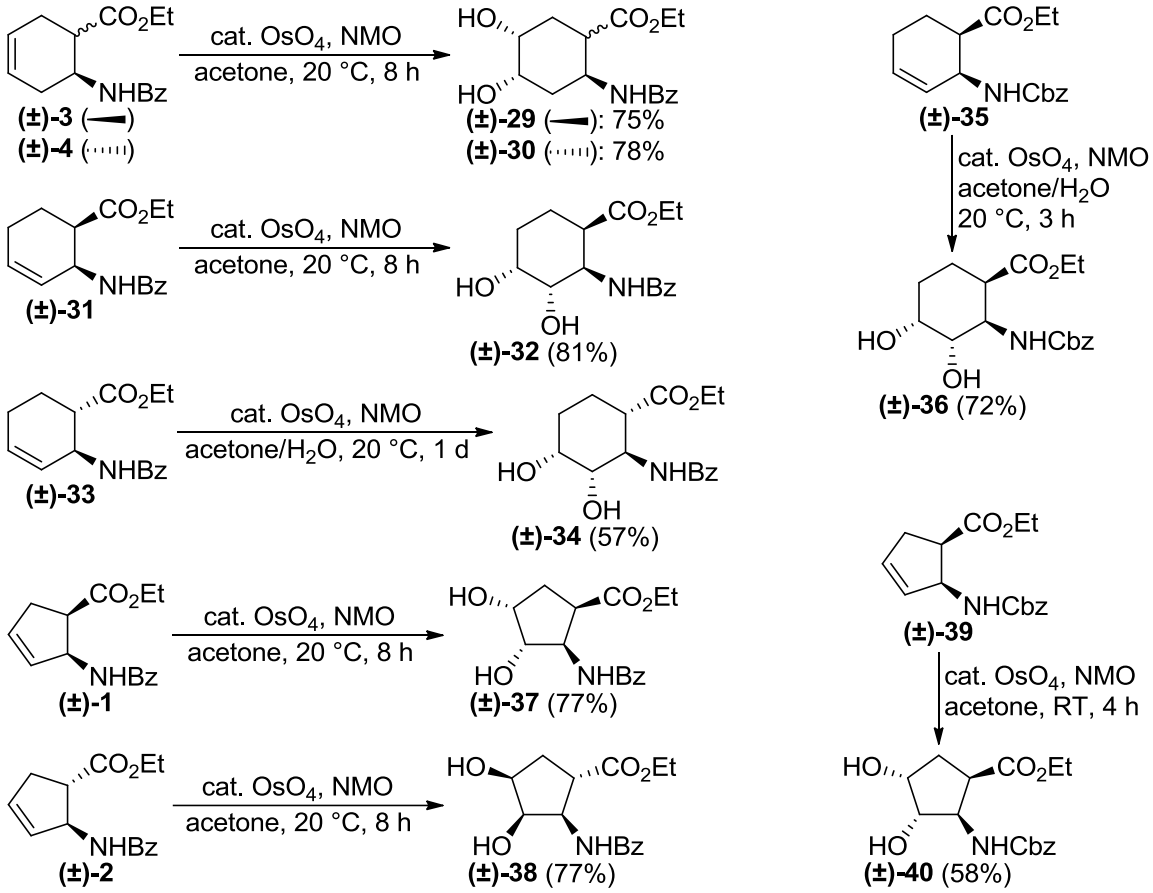


Scheme 10. Ring opening of epoxide **(±)-11** with Deoxofluor

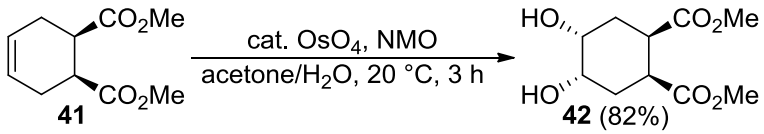
3.2. Chemoselective substrate-directed fluorinations of functionalized diol derivatives

3.2.1. Synthesis of diols

Starting diols were synthesized by *cis*-dihydroxylation of unsaturated β-amino esters and diester **41** with catalytic amount of OsO_4 in the presence of *N*-methylmorpholine-*N*-oxide or NMO (*Scheme 11 and 12*).



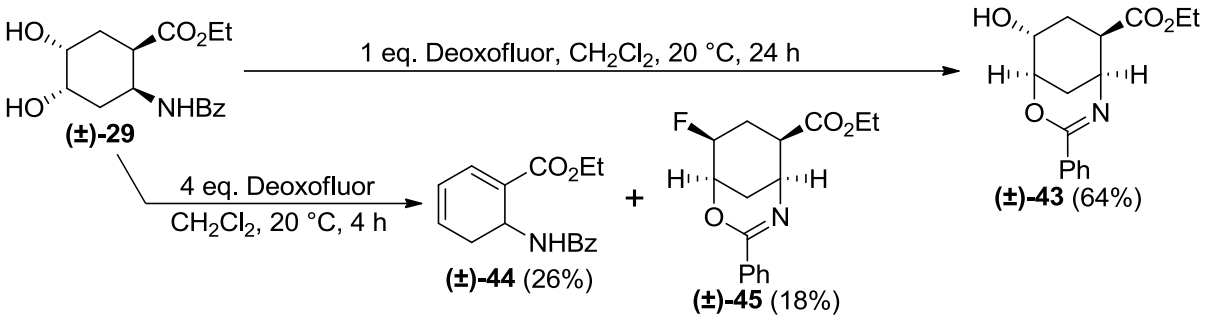
Scheme 11. Synthesis of dihydroxylated cycloalkane β-amino acid derivatives



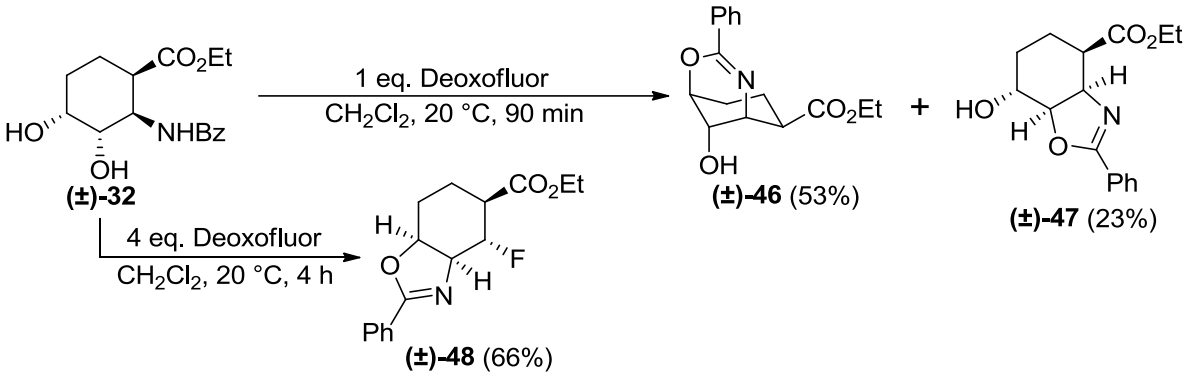
Scheme 12. Synthesis of dihydroxylated diester **42**

3.2.2. Fluorination reactions

1 eq. Deoxofluor transformed diol **(±)-29** into cyclized product **(±)-43**. The use of 4 eq. Deoxofluor resulted in unsaturated β-amino ester **(±)-44** and fluorinated oxazine **(±)-45** (*Scheme 13*). Reaction of β-amino acid derivative **(±)-32** with 1 eq. reagent yielded two cyclized products: **(±)-46** with a six-membered heterocycle and **(±)-47** with a five-membered one. With excess Deoxofluor, fluorinated amino acid derivative **(±)-48** was obtained with the nitrogen atom in γ position to CO_2Et (*Scheme 14*).

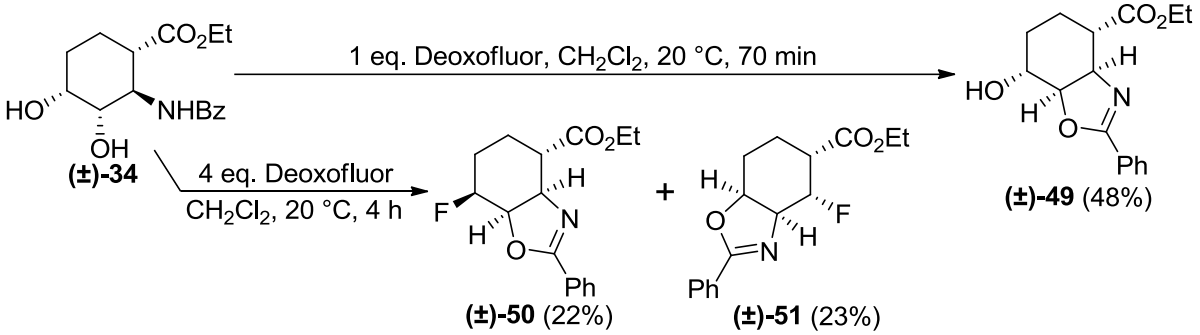


Scheme 13. Fluorination of 4,5-dihydroxy-2-aminocyclohexanecarboxylate **(±)-29**



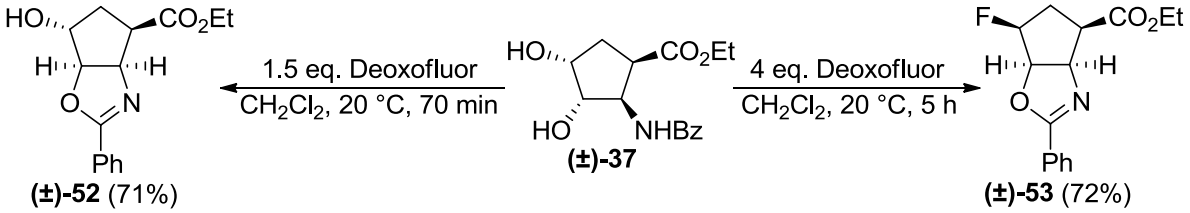
Scheme 14. Reaction of dihydroxylated β-amino acid derivative **(±)-32** with Deoxofluor

When C-1 epimeric diol **(±)-34** was subjected to 1 eq. Deoxofluor, **(±)-49** the only single cyclized product was obtained, epimer of **(±)-47**. This indicates that the OH group at C-3 is more reactive. The use of 4 eq. reagent resulted in two fluorine-containing heterocyclic products (*Scheme 15*). Compound **(±)-51** has the nitrogen atom in γ position to CO_2Et.



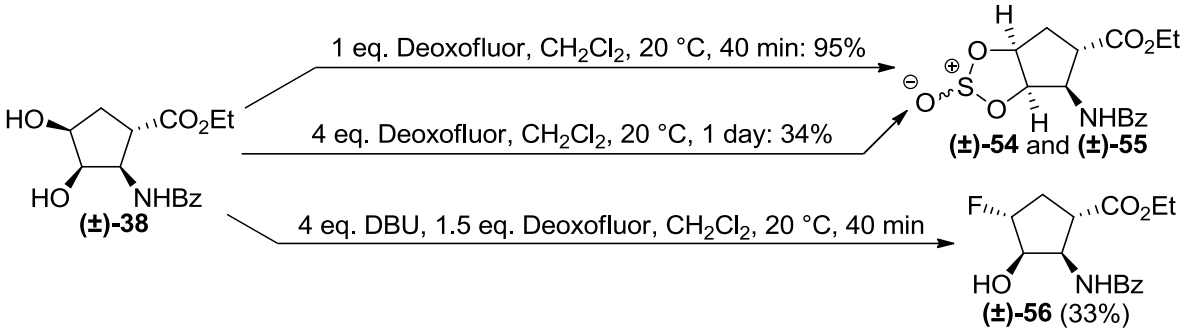
Scheme 15. Reactions of diol **(±)-34** with Deoxofluor

With 1.5 eq. Deoxofluor, diol **(±)-37** was transformed into cyclized product **(±)-52**. The use of excess reagent produced fluorinated oxazoline **(±)-53** (*Scheme 16*).



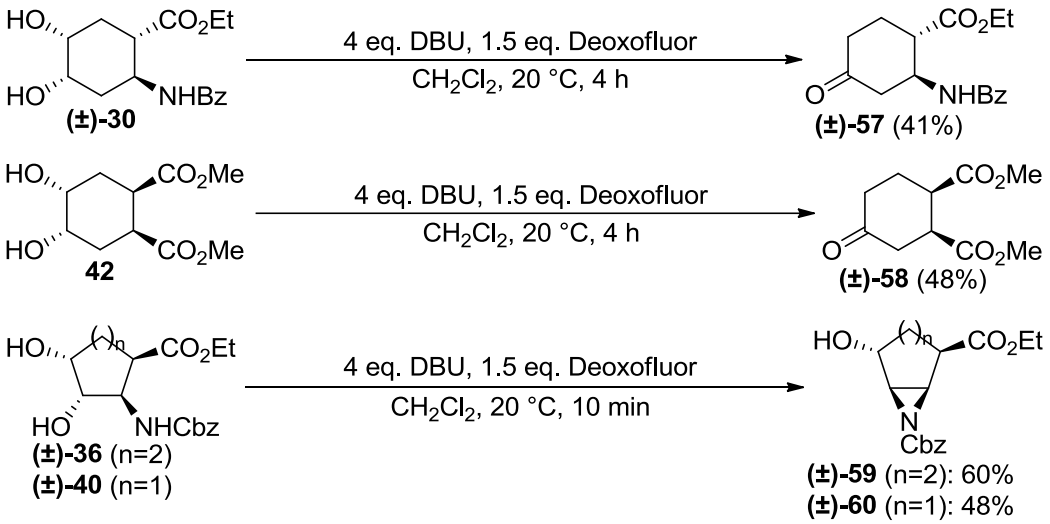
Scheme 16. Fluorinations of diol **(±)-37**

Reaction of diol **(±)-38** with Deoxofluor resulted in a diastereomeric mixture of cyclic sulfites. In order to avoid cyclic sulfite formation, deoxyfluorination was attempted in the presence of DBU, resulting in fluorohydrin **(±)-56** (*Scheme 17*).



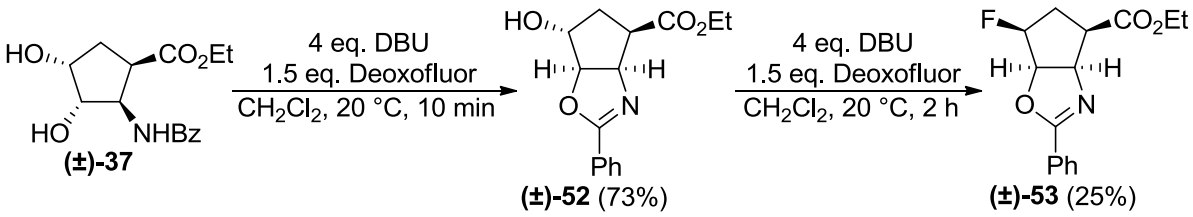
Scheme 17. Reactions of diol **(±)-38** with Deoxofluor in the absence or presence of DBU

When subjected to Deoxofluor and DBU, compounds **(±)-30** and **42** were dehydrated to oxo compounds **(±)-57** and **(±)-58**. Similar treatment of *N*-Cbz-protected β-amino esters **(±)-36** and **(±)-40** resulted in aziridines **(±)-59** and **(±)-60** (*Scheme 18*).



Scheme 18. Reactions of diols **(±)-30**, **(±)-36**, **(±)-40** and **42** with Deoxofluor and DBU

In the presence of DBU, reaction of dihydroxy-β-amino ester **(±)-37** with Deoxofluor produced oxazoline **(±)-52** more quickly and somewhat more efficiently. Fluorination of isolated **(±)-52** in the presence of DBU produced fluorinated derivative **(±)-53** (*Scheme 19*).

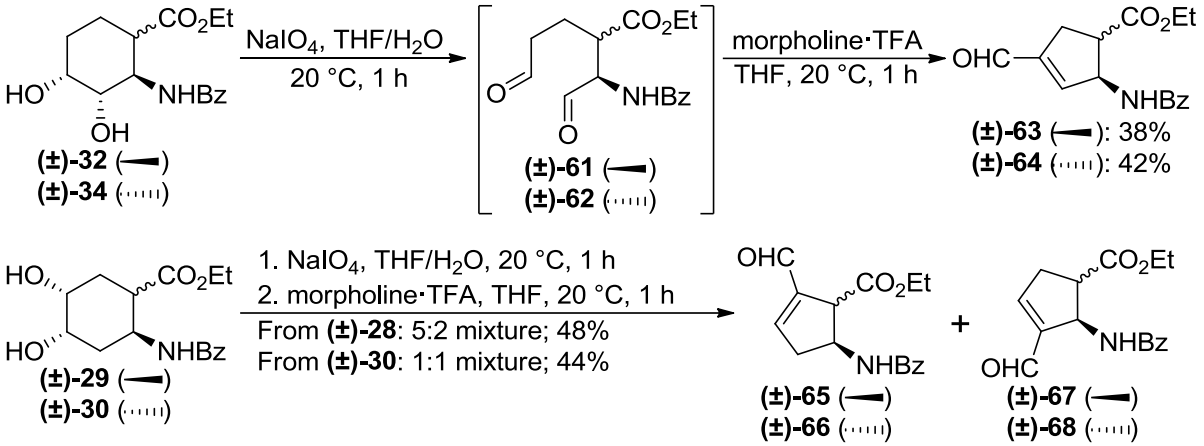


Scheme 19. Reaction of dihydroxy-β-amino ester **(±)-37** with Deoxofluor and DBU

3.3. Transformation of functionalized diol derivatives through ring opening/ring contraction and substrate-dependent fluorinations

3.3.1. Synthesis of formyl-substituted cyclic β-amino esters

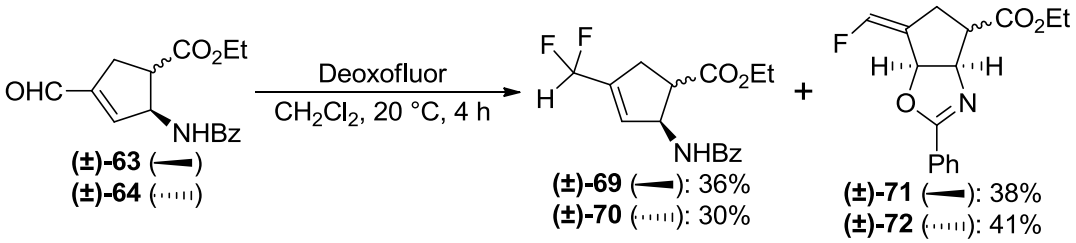
Oxidative ring opening of 3,4-dihydroxy-β-amino esters **(±)-32** and **(±)-34** with periodate, followed by aldol reaction of the obtained dialdehydes produced unsaturated aldehydes **(±)-63** and **(±)-64** as single products. Analogous transformation 4,5-dihydroxy-β-amino esters **(±)-29** and **(±)-30** resulted in mixtures of unsaturated aldehydes (*Scheme 20*).



Scheme 20. Ring opening/ring contraction of diols **(±)-29**, **(±)-30**, **(±)-32** and **(±)-34**

3.3.2. Fluorination reactions

Reactions of aldehydes **(±)-63** and **(±)-64** with DAST or Deoxofluor yielded two products: the expected CHF_2-containing derivatives and fluorovinyl-containing compounds (*Scheme 21*).

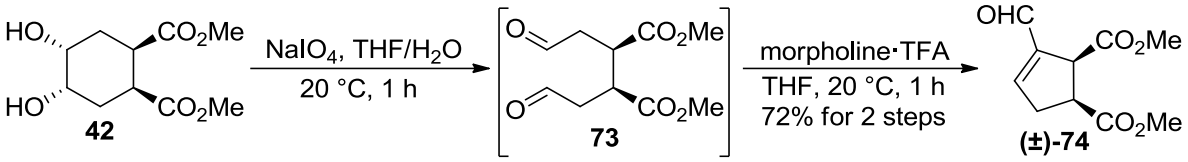


Scheme 21. Fluorinations of aldehydes **(±)-63** and **(±)-64**

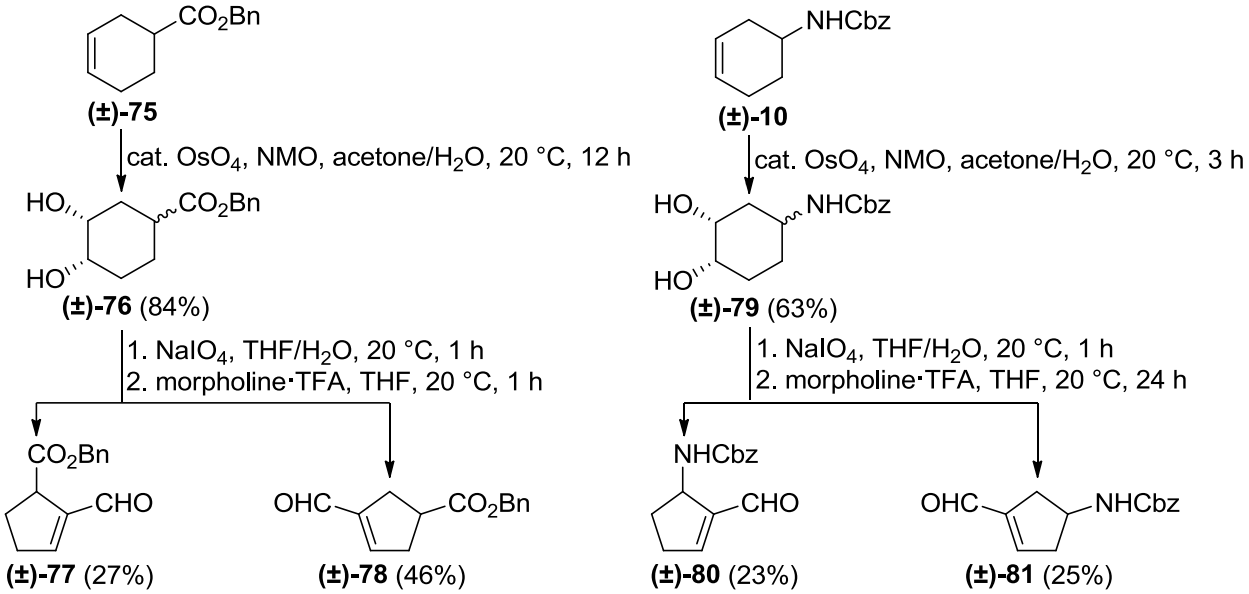
3.3.3. Extension of the method

We aimed to extend this strategy to other functionalized cyclohexanediols with special emphasis on the fluorination conditions. Symmetric diol **42** provided a single unsaturated aldehyde (*Scheme 22*). In contrast, transformation of diastereomeric mixtures **(±)-76** and **(±)-79** (obtained by dihydroxylation of ester **(±)-75** and *N*-Cbz-protected amine **(±)-10**, respectively) resulted in two aldehydes (*Scheme 23*). To further extend our strategy, bicyclic aldehyde **(±)-84** was synthesized from *N*-benzyl-*cis*-tetrahydrophthalimide **82** by stereoselective dihydroxylation,

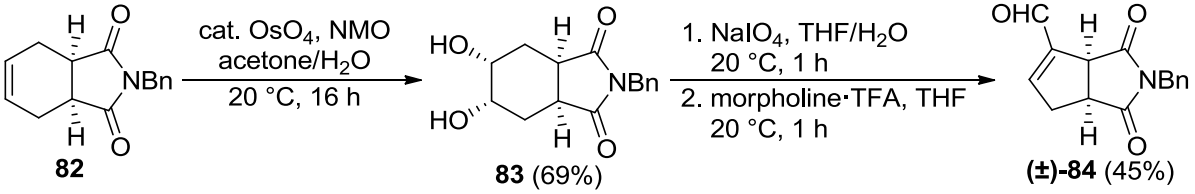
oxidative ring opening and intramolecular aldol reaction (*Scheme 24*). Fluorinations of these aldehydes produced the desired CHF_2-containing products (*Scheme 25*).



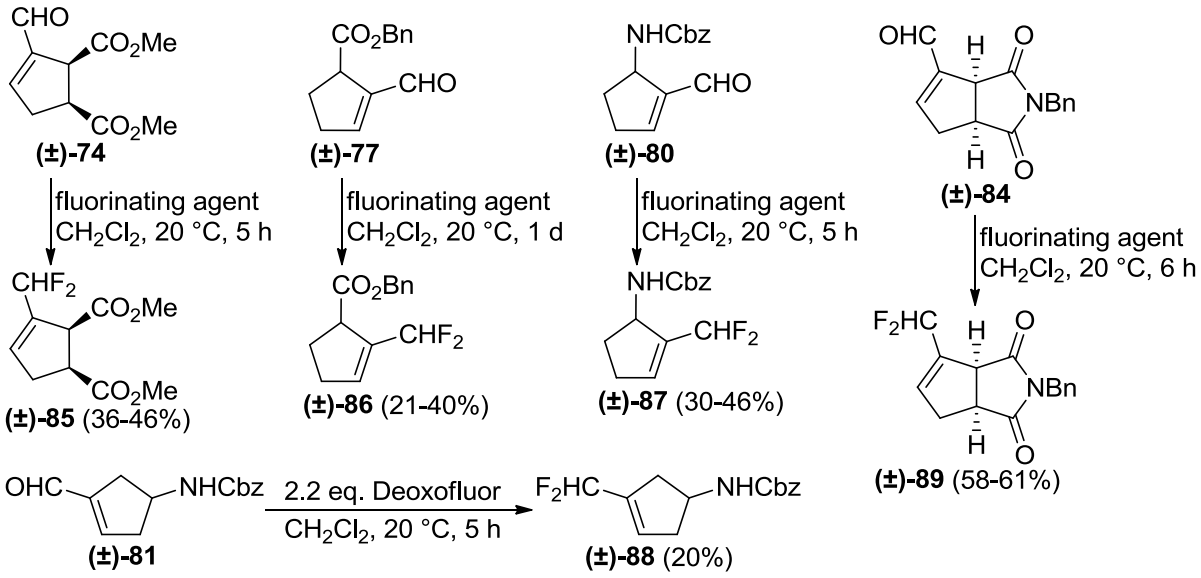
Scheme 22. Transformation of diol **42** into unsaturated aldehyde **(±)-74**



Scheme 23. Synthesis of unsaturated aldehydes from monofunctionalized cycloalkenes



Scheme 24. Synthesis of bicyclic unsaturated aldehyde **(±)-84**



Scheme 25. Reactions of unsaturated aldehydes with nucleophilic fluorinating reagents

List of publications and lectures

Full papers related to the thesis:

I. **Remete, A. M.**; Nonn, M.; Fustero, S.; Fülöp, F.; Kiss, L.:
A Stereocontrolled Protocol to Highly Functionalized Fluorinated Scaffolds through a Fluoride Opening of Oxiranes
Molecules **2016**, *21*, 1493 **IF: 2.861**

II. **Remete, A. M.**:
Új, fluortartalmú funkcionalizált ciklusos β-aminosavszármazékok szintézise
Magyar Kémikusok Lapja, 2017/2, 41

III. **Remete, A. M.**; Fülöp, F.; Kiss, L.:
Fluorination of some functionalized cycloalkenes through epoxidation and oxirane opening with Deoxofluor or XtalFluor-E
Fluorine Notes, Volume #4 (113), July - August **2017**

IV. **Remete, A. M.**; Nonn, M.; Fustero, S.; Haukka, M.; Fülöp, F.; Kiss, L.:
Fluorination of some highly functionalized cycloalkanes: chemoselectivity and substrate dependence
Beilstein J. Org. Chem. **2017**, *13*, 2364 **IF: 2.330**

V. **Remete, A. M.**; Nonn, M.; Fustero, S.; Haukka, M.; Fülöp, F.; Kiss, L.:
Fluorine-Containing Functionalized Cyclopentene Scaffolds Through Ring Contraction and Deoxofluorination of Various Substituted Cyclohexenes
Eur. J. Org. Chem. **2018**, 3735 **IF: 2.882***

Other publications:

VI. Kiss, L.; **Remete, A. M.**; Nonn, M.; Fustero, S.; Sillanpää, R.; Fülöp, F.:
Substrate-dependent fluorinations of highly functionalized cycloalkanes
Tetrahedron **2016**, *72*, 781 **IF: 2.651**

VII. Nonn, M.; **Remete, A. M.**; Fülöp, F.; Kiss, L.:
Recent advances in the transformations of cycloalkane-fused oxiranes and aziridines
Tetrahedron **2017**, *73*, 5461 **IF: 2.377**

VIII. **Remete, A. M.**; Nonn, M.; Fustero, S.; Fülöp, F.; Kiss, L.:
Synthesis of fluorinated amino acid derivatives through late-stage deoxyfluorinations
Tetrahedron **2018**, *74*, 6367 **IF: 2.377***

***2017 impact factor

Scientific lectures related to the thesis:

I. Kiss, L.; **Remete, A. M.**; Nonn, M.; Fustero, S.; Fülöp, F.:
Synthesis of Fluorinated β-Amino Acid Scaffolds Through Fluoride Opening of Cycloalkane-Fused Oxiranes or Aziridines
Bremen FluorineDays 2016
Bremen, Germany, 7-3 July, 2016, Abstr.: P06, poster presentation

II. **Remete, A. M.**; Kiss, L.; Nonn, M.; Fustero, S.; Fülöp, F.:
An Insight Into the Substrate Dependent Chemoselective Fluorination of Highly Functionalized Cycloalkanes

17th Blue Danube Symposium on Heterocyclic Chemistry
Linz, Austria, 30 Aug – 2 Sep, 2017, Abstr.: PO57, poster presentation

III. **Remete, A. M.**; Kiss, L., Nonn, M.; Fustero, S.; Fülöp, F.:
Fluortartalmú ciklusos építőelemek szintézisei fluoriddal történő aziridin és oxirán nyitással
MTA Heterociklusos és Elemorganikus Kémiai Munkabizottság Ülése
Balatonszemes, Hungary, 18-20 May, 2016, oral presentation

IV. **Remete, A. M.**; Fülöp, F.; Kiss, L.:
Funkcionalizált cikloalkánok fluorozásai: kemoszelektivitás és szubsztrátfüggés
MTA Heterociklusos és Elemorganikus Kémiai Munkabizottság Ülése
Balatonszemes, Hungary, 15-17 May, 2017, oral presentation

V. **Remete, A. M.**; Nonn, M.; Fülöp, F.; Kiss, L.:
Fluortartalmú funkcionalizált aliciklusos illetve heterociklusos építőelemek szelektív szintézisei
MTA Alkaloid- és Flavonoidkémiai Munkabizottság Ülése
Mátrafüred, Hungary, 12-13 Apr, 2018, oral presentation

VI. **Remete, A. M.**; Nonn, M.; Fülöp, F.; Kiss, L.:
Funkcionalizált, fluortartalmú aliciklusos építőelemek szubsztrátfüggő és szelektív szintézisei
MTA Heterociklusos és Elemorganikus Kémiai Munkabizottság Ülése
Balatonszemes, Hungary, 6-8 June, 2018, oral presentation

VII. **Remete, A. M.**; Fülöp, F.; Kiss, L.:
„Late-stage" nukleofil fluorozások háromdimenziós, funkcionalizált molekulák körében
Gyógyszerkémiai és Gyógyszertechnológiai Szimpózium '18
Szeged, Hungary, 6-7 September, 2018, oral presentation

Other scientific lectures:

VIII. **Remete, A. M.**; Kiss, L.; Nonn, M.; Wölfling, J.; Fülöp, F.:
Fluorinations of Highly Functionalized Alicyclic Beta-Amino Acids
ICOS-20
Budapest, Hungary, 29 June – 4 July, 2014, Abstr.: P-94, poster presentation

IX. **Remete, A. M.**; Kiss, L.:
Fluortartalmú ciklusos β-aminosavszármazékok szintézise
XXXVI. Kémiai Előadói Napok
Szeged, Hungary, 28-30 Oct, 2013, Abstr.: p. 349, oral presentation

X. **Remete, A. M.**; Kiss, L.; Wölfling, J.:
Új, fluortartalmú funkcionalizált ciklusos β-aminosavszármazékok szintézisei
XXXVII. Kémiai Előadói Napok
Szeged, Hungary, 3-5 Nov, 2014, Abstr.: p. 156, oral presentation

XI. **Remete, A. M.**; Kiss, L., Nonn, M.; Fülöp, F.:
Multifunkciós gyűrűs aminosav-származékok szerkezetfüggő fluorozása
MTA Heterociklusos és Elemorganikus Kémiai Munkabizottság Ülése
Balatonszemes, Hungary, 27-29 May, 2015, oral presentation