

# **Stereocontrolled and selective methods for the synthesis of densely functionalized alicyclic and heterocyclic scaffolds with multiple chiral centers**

Final report (K 119282)

During the current project our research activity was mainly directed towards:

- (a) development of selective methods for the synthesis of fluorine-containing small molecular entities
- (b) development of selective and controlled synthetic strategies to the access of highly functionalized molecules across metathesis protocol
- (c) selective synthesis of highly functionalized, orthogonally protected cyclic amino ester derivatives

## **1. Development of selective methods for the synthesis of fluorine-containing small molecular entities**

*(i) synthesis of functionalized, fluorine-containing elements through late-stage fluorinations (oxo-diF, OH-F exchange)*

Selective fluorinations were investigated by nucleophilic fluorination of various diol derivatives and diformyl-substituted cyclopentane amino esters. Studies of „late-stage” fluorinations revealed highly substrate dependent transformations with chemoselective anchimeric assistance. Various fluorohydrins, heterocycles, amino esters and amino lactones were prepared (Chem. Asian J. 2016, 11, 3376, <http://real.mtak.hu/70681/>; ChemistrySelect 2017, 2, 3049, <http://real.mtak.hu/70682/>; Beilstein J. Org. Chem. 2017, 13, 2364, <http://real.mtak.hu/70685/>). The oxidative ring cleavage of some cyclohexene amino esters and the intramolecular regioselective aldol cyclization followed by chemoselective nucleophilic fluorination of the resulted aldehyde derivatives proceeded with anchimeric and substrate effect. The „late-stage” fluorinations provided either heterocycles possessing vinyl fluoride moieties or difluorinated cyclic amino ester stereoisomers (Eur J Org Chem 2018, 3735, <http://real.mtak.hu/87161/>).

*(ii) functionalizations with diastereoselective oxirane formation/oxirane opening with fluoride*

The functionalization strategy involved the stereoselective oxirane formation through ring olefin bond epoxidation followed by nucleophilic oxirane opening with Deoxofluor or XtalFluor. The heteroring opening with fluoride in these systems was detected to be highly reagent and substrate dependent (Molecules 2016, 21, 1943, <http://real.mtak.hu/63286/>; Fluorine Notes,

2017, 4 (113), <http://real.mtak.hu/70684/>; Fluorine Notes 2018, 116 (1-2), <http://real.mtak.hu/87163/>).

(iii) selective halofluorination protocols towards highly functionalized fluorine-containing small molecules

Another strategy of fluorination was based on the halonium ion activation of the ring olefin bond of some substituted cycloalkane model compounds, followed by nucleophilic fluorinations with Deoxofluor and XtalFluor. Substrate-dependence, neighboring effect and stereochemical outcome of the transformations were deeply investigated (Beilstein J. Org. Chem. 2020, 16, 2562–2575, <http://real.mtak.hu/id/eprint/117140>).

*(iv) synthesis of fluorine-containing azaheterocycles*

A highly efficient stereocontrolled synthetic approach was developed to the access of various functionalized, fluorine containing azaheterocycles. The protocol involved OsO<sub>4</sub>-catalyzed diol formation/NaIO<sub>4</sub> mediated oxidative opening of some substituted cycloalkenes, followed by double reductive amination of the resulted dialdehydes in the presence of some fluorine-containing primary amines. Note, that the transformations proceeded with the conservation of the configuration of the chiral centers, thus the structure of the starting materials predetermines the stereochemistry of the products (Tetrahedron 2016, 72, 7526, <http://real.mtak.hu/63276/>; Synthesis 2017, 49, 1206, <http://real.mtak.hu/70683/>).

A novel synthetic strategy was developed for the creation of derivatives with tetrahydroisoquinoline skeleton. The concept was based on the transformation of various indene derivatives through olefin bond oxidative ring cleavage followed by double reductive amination of the formed dialdehydes with some aliphatic amines and fluorine-containing primary amines. the protocol might be regarded as a novel synthetic pathway to the construction of isoquinoline skeleton (Synlett 2018, 29, 2066, <http://real.mtak.hu/87162/>).

Synthesis of novel fluorine-containing azaheterocyclic amino acid derivatives has been performed, thus some unsaturated cyclic amino acids were selected as model compounds, which were converted, across oxidative ring cleavage, followed by reductive amination with fluorine-containing amines of the formed dialdehyde intermediates into the corresponding azaheterocyclic amino ester stereoisomers. The transformations proceeded with stereocontrol: the structures of the starting materials predetermined the configuration of the stereocenters in the products (Fluorine Notes 2019, 122 (1-2) <http://real.mtak.hu/103316/>). Similar synthetic strategy was applied for the stereocontrolled access to  $\gamma$ -amino esters with piperidine core. (Eur. J. Org. Chem. 2019, 2202, <http://real.mtak.hu/103317/>). The method based on oxidative ring opening/reductive amination with cyclization was extended for the stereocontrolled preparation of several fluorine-containing lactams and benzazepines as well

(Chem. Rec. 2020, 20, 120, <http://real.mtak.hu/id/eprint/98883>; J. Fluorine Chem. 2020, 232: 109466, <http://real.mtak.hu/id/eprint/105967>).

The described strategy towards the synthesis of some novel fluorine-containing small azaheterocycles has been further improved. The oxidative ring opening of substituted cycloalkene model derivatives was efficiently performed under ozonolysis, providing the corresponding dialdehydes. Thus, the highly toxic OsO<sub>4</sub>, as well as the utilization of NaIO<sub>4</sub> and of the large amount of solvent and silica gel could be avoided, the number of reaction steps could be reduced accordingly. The reductive amination with fluorine-containing amines of the formed diformyl intermediates through ozonolysis gave, by stereocontrol, the corresponding saturated azaheterocyclic compounds (Ouchakour L, Nonn M, Remete AM, Kiss L: *Eur J Org Chem* 2021, 3874, <http://real.mtak.hu/133706/>; Nonn M, Kara D, Ouchakour L, Forró E, Haukka M, Kiss L: *Synthesis* 2021, 53, 1163, <http://real.mtak.hu/133702/>).

## **2. Development of selective and controlled synthetic strategies to the access of highly functionalized molecules across metathesis protocol**

Another direction of our research was the functionalization of versatile small molecules under metathesis reaction protocols (ring-opening, ring-closing and cross metathesis). The ring-opening metathesis (ROM) of various highly substituted unsaturated cyclic systems was investigated by taking into consideration the character of the catalyst, the stereochemistry of the starting model derivatives and the ring size of the substrate as well as the functional group tolerance. The ROM protocols furnished various divinyl-substituted, highly functionalized interesting scaffolds, such as isoxazolines, lactams or lactones with different framework (*Eur. J. Org. Chem.* 2017, 1894, <http://real.mtak.hu/63280/>; *Beilstein J. Org. Chem.* 2018, 14, 2698, <http://real.mtak.hu/87160/>). Various three-dimensional small molecules were synthesized by “flat molecule functionalization” through diversity-oriented synthesis protocol by the selection of some readily available, commercial starting model compounds: cyclodienes with different ring size, which in turn were functionalized by selective nitrile-oxide cycloaddition, followed by ring-opening metathesis to give novel alkenylated scaffolds (*ChemistrySelect* 2019, 4, 2886, <http://real.mtak.hu/103319/>).

The chemical behavior, the reactivity of various functionalized, unsaturated strained systems (lactams, amino esters) were investigated under ring-opening metathesis. The reactions afforded under stereocontrol, across ring-opening metathesis, versatile polifunctionalized, alkenylated alicycles with multiple chiral centers (amino esters, lactams etc). The chemodifferentiation of the olefin bonds in various substrates were also studied under the cross-metathesis protocol (*Eur. J. Org. Chem.* 2019, 5285, <http://real.mtak.hu/98876/>). The above synthetic strategies based on ring opening metathesis/cross-metathesis (ROM/CM)

were further extended by investigating the catalyst and substrate scope. A new generation of various functionalized small molecules were synthesized accordingly. The behavior of various divinyl-substituted scaffolds, in view of the chemodiscrimination of the olefin bonds under CM conditions was studied ("Fluorine notes" 2019, Vol. 6(127), <http://real.mtak.hu/id/eprint/105334>; Chem Rec, 2020, 20, 1129, <http://real.mtak.hu/id/eprint/117141>).

A new stereocontrolled access route has been developed towards the synthesis of novel azaheterocycles by starting from norbornene amino acid derivatives. The transformations involved simultaneous ROM/intramolecular RCM of some strained N-allylated or propargylated amino esters. Some three-dimensional, fluorine-containing small molecules were also synthesized through metathesis synthesis protocol. Selected starting model compounds obtained from some readily available cycloienes, which in turn were functionalized by selective cycloaddition (providing lactams and isoxazolines), followed by ring-opening metathesis and cross metathesis with fluorine-containing alkenes (Benke Z, Nonn M, Remete AM, Fustero S, Kiss L: *Beilstein J. Org. Chem.* 2021, 17, 2051, <http://real.mtak.hu/133708/>; Benke Z, Nonn M, Remete AM, Fustero S, Kiss L: *Synlett* 2021, 32, 1911, <http://real.mtak.hu/133707/>; Benke Z, Remete AM, Semghouli A, Kiss L: *Asian J Org Chem* 2021, 10, 1184, <http://real.mtak.hu/133705/>).

### **3. Selective synthesis of highly functionalized, orthogonally protected cyclic amino ester derivatives**

Versatile, orthogonally protected cyclic beta- and gamma-amino esters, as useful monomers for peptide synthesis, have been accessed. The molecular entities, such as stereo- and regiosimers of various diamino esters were prepared by stereo- and regiocontrolled synthetic procedures based on oxirane formation/oxirane opening may be regarded as interesting molecular scaffolds with multiple stereocenters which possess a second N-atom, available for protonation, incorporated in their structure (*Synthetic Commun* 2020, 50, 1199, <http://real.mtak.hu/id/eprint/111831>; *Helv. Chim. Acta* 2020, 103, e2000090, <http://real.mtak.hu/id/eprint/111832>).

#### **Other review publications related to the project**

1. Fülöp F, Forró E, Kiss L, Szakonyi Z, Szatmári I, Ötvös S:  
Kutatások az SZTE Gyógyszerkémiai Intézetében  
*Magyar Kém. Lapja* 2017, LXXII, 10, 306

2. Nonn M, Remete AM, Fülöp F, Kiss L:

Recent advances in the transformations of cycloalkane-fused oxiranes and aziridines

Tetrahedron 2017, 73, 5461

<http://real.mtak.hu/63283/>

3. Kiss L, Mándity IM, Fülöp F:

Highly functionalized cyclic  $\beta$ -amino acid moieties as promising scaffolds in peptide research and drug design

Amino Acids 2017, 49, 1441

<http://real.mtak.hu/63281/>

4. Kiss L, Fülöp F:

Selective Synthesis of Fluorine-Containing Cyclic  $\beta$ -Amino Acid Scaffolds

*The Chem. Rec.* 2018, 266

<http://real.mtak.hu/87166/>

5. Remete AM, Nonn M, Fustero S, Fülöp F, Kiss L:

Synthesis of fluorinated amino acid derivatives through late-stage deoxyfluorinations

*Tetrahedron* 2018, 74, 6367

<http://real.mtak.hu/87164/>

6. Kiss L, Kardos M, Vass C, Fülöp F:

Application of Metathesis Reactions in the Synthesis and Transformations of Functionalized  $\beta$ -Amino Acid Derivatives

*Synthesis* 2018, 50, 3571

<http://real.mtak.hu/87165/>

7. Kiss L, Remete AM:

Synthesis of fluorine-containing molecular entities through fluoride ring opening of oxiranes and aziridines

*Eur. J. Org. Chem.* 2019, 5574

<http://real.mtak.hu/103323/>

8. Kiss L:

Fluorozások az SZTE Gyógyszerkémiai Intézetében: játék a molekulákkal és a reagensekkel

*Magy. Kém. Lap.* 2019, 106

<http://real.mtak.hu/103320/>

9. Kiss L, Remete AM, Volk B:  
Comprehensive Heterocyclic Chemistry IV 2019, K 119282,  
<http://real.mtak.hu/id/eprint/106524>

10. Han J, Remete AM, Dobson LS, Kiss L, Izawa K, Moriwaki H, Soloshonok VA, O'Hagan D:  
*J Fluorine Chem* 2020, 239, 109639  
<http://real.mtak.hu/id/eprint/117138>

11. Mei H, Remete AM, Zou Y, Moriwaki H, Fustero S, Kiss L, Soloshonok VA, Han J:  
*Chin. Chem. Lett.* 2020, 31, 2401  
<http://real.mtak.hu/id/eprint/117139>

12. Benke Z. Remete AM, Kiss L:  
Funkcionalizált aliciklusok diverzitás orientált szintézise dipoláros cikloaddíciót követő metatézis reakciókkal.  
*Magy. Kém. Foly.* 2021, 127 (2), 89  
<http://real.mtak.hu/133709/>

13. Han J, Kiss L,\* Mei H, Remete AM, Ponikvar-Svet M, Sedgwick DM, Roman R, Fustero S, Moriwaki H, Soloshonok VA:  
*Chem Rev* 2021, 121, 4678  
<http://real.mtak.hu/id/eprint/128853>

**Other related or collaborative publications:**

14. Forró E, Kiss L, Árva, J, Fülöp F:  
Efficient Enzymatic Routes for the Synthesis of New Eight-membered Cyclic beta-Amino Acid and beta-Lactam Enantiomers  
*Molecules* 2018, 22, 2221

15. Kiss L:  
A de novo Synthetic Route to 1,2,3,4-Tetrahydroisoquinoline Derivatives  
*Synform* 2018, DOI: 10.1055/s-0037-1609801

16. Remete AM, Kiss L:  
Alicyclic  $\beta$ - and  $\gamma$ -Amino Acids: Useful Scaffolds for the Stereocontrolled Access to Amino Acid-Based Carbocyclic Nucleoside Analogs

Molecules 2019, 24, 161

<http://real.mtak.hu/103318/>

17. Harnisch H, Ilisz I, Fülöp F, Szakonyi Z, Kiss L, Péter A, Scriba GKE:

Cyclodextrin-mediated capillary electrophoresis enantioseparation of dansylated beta-amino acids with bicyclo[2.2.2]octane, bicyclo[3.1.1]heptane and cyclopenta[d][1,2]oxazole core structures

Electrophoresis 2019, 40, 1931

<http://real.mtak.hu/103322/>

18. Szabó E, Koványi-Lax G, Szénási G, Dancsó A, Kiss L, Kormány R, Simig G, Németh G, Volk B:

A novel tool for structure assignment of hydroxylated metabolites of (aryl)piperazinylbutyl oxindole derivatives based on relative HPLC retention times

J. Pharm. Biomed. Anal. 2019, 170, 102

<http://real.mtak.hu/103321/>

19. Remete AM, Nonn M, Semghouli A, Sillanpää R, Kiss L:

“Fluorine notes” 2021, Vol. 1(134)

<http://real.mtak.hu/133703/>