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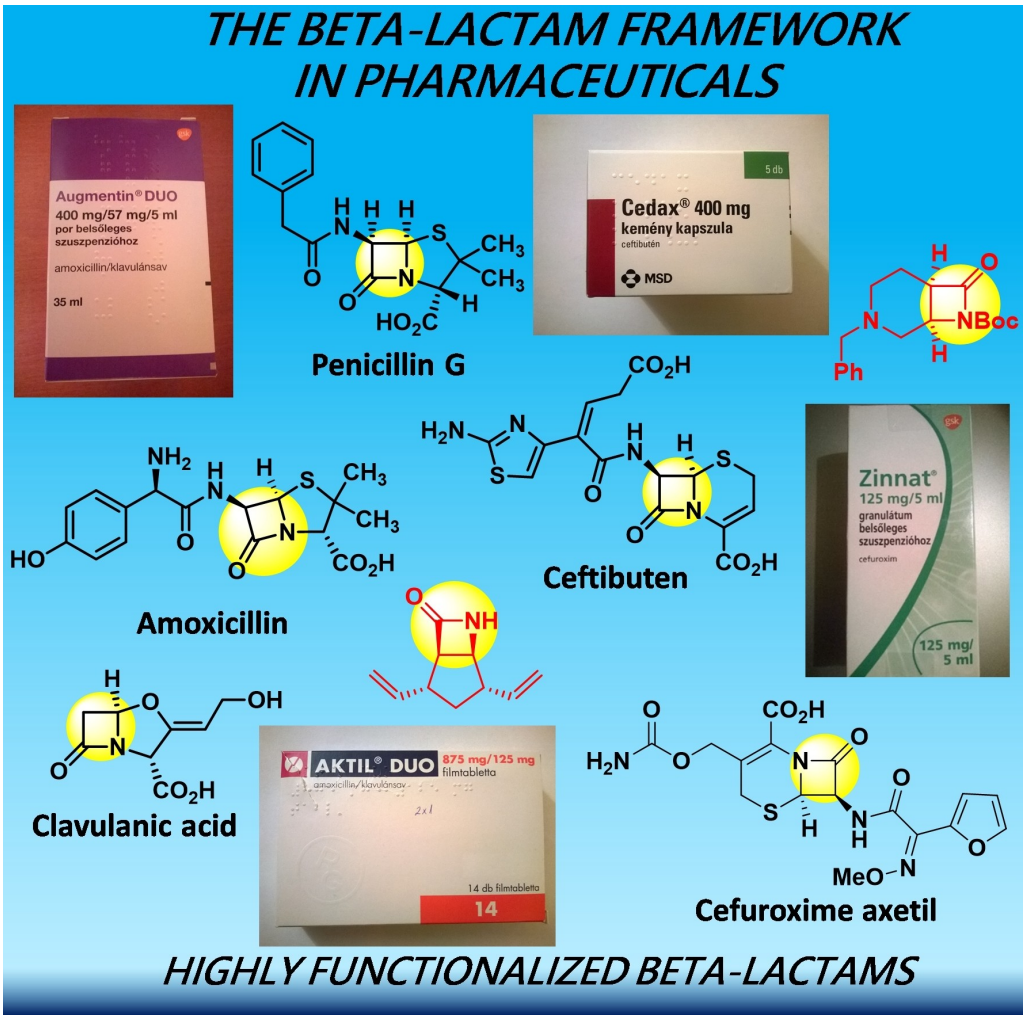
# Selective Functionalizations of Cycloalkene-Fused β-Lactams and their Transformations into Densely-Substituted Three-Dimensional Molecular Entities

Melinda Nonn[a] and Loránd Kiss*[b]



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Highly-functionalized, three-dimensional molecules have had an increasing impact in synthetic organic chemistry and pharmaceutical research over the past decades. Their syntheses and the development of novel synthetic approaches towards versatile, small molecules with chemical and structural diversity have generated great interest. We have designed various selective and stereocontrolled methodologies for the functionalization of cycloalkene-fused β-lactams with a common C–C bond, as three-dimensional, functionalized scaffolds, involving the transformation of their ring olefin bond. The synthetic methodologies developed to access various pharmacologically interesting derivatives with multiple chiral centers might be valuable protocols for the preparation of other classes of organic compounds as well.

## 1. Introduction

### 1.1. Importance of β-lactams

Highly-functionalized, three-dimensional molecules have had an increasing impact in synthetic organic chemistry and pharmaceutical research over the past decades. Their syntheses and the development of novel synthetic approaches towards versatile, small molecules with chemical and structural diversity, among them β-lactams, have generated great interest. Some terms such as "conformational restriction",[1] "escape from flatland",[2] or "scaffold hopping",[3] have also received high relevance in medicinal chemistry in the last 20 years. Densely-functionalized, three-dimensional small molecules with multiple chiral centers and high chemical diversity represent promising scaffolds in drug development. The introduction of a three-dimensional shape into a compound library, that is, transformation of a nearly planar molecule into a 3D scaffold leads to architectural complexity and increased structural diversity. Accordingly, selective and controlled synthetic approaches towards such elements containing *sp*3 hybridized carbon atoms are of relevant significance in synthetic organic and medicinal chemistry.[4]

β-Lactams are of outstanding interest in organic and medicinal chemistry due to their broad range of biological and, in particular, antibacterial properties. Various antibacterial agents possess the lactam framework in various structural forms, such as heterocycle-fused (bicyclic) azetidin-2-ones (e.g. penicillins, cephalosporins) or functionalized azetidinones (monocyclic) (e.g. amino substituted monobactams) (Figure 1).[5a–f] Some β-lactam molecular hybrids have also been described as anticancer agents.[5g]

The azetidine-2-one framework is the key component of the fluorine-containing blockbuster drug Ezetimibe, which is a well-known non-statin cholesterol-lowering drug (Figure 2).[5h,i]

The high biological relevance of β-lactams led to the design and synthesis of various classes of β-lactam-based antibiotics, and it gave rise to a number of synthetic protocols for the creation of the azetidin-2-one framework. The bacterial resistance with reducing efficacy of versatile types of β-lactam derivatives makes the synthesis of novel generation of product molecules with azetidin-2-one as structural motif a challenge in synthetic organic chemistry. Noteworthy, that besides the construction of the four-membered heterocyclic system, in view of drug design, emphasis on the construction of systems with a wide range of substitution pattern is also desirable.

Various synthetic methods, such as transition-metal catalyzed reactions, carbonylations, enolate-imine condensations, or Staudinger cycloaddition, which is known as a formal [2 + 2] cycloaddition of an imine and a ketene, are the most common approaches to fabricate β-lactam rings.[6]

### 1.2. Synthesis of cycloalkene-fused β-lactams and their synthetic relevance

Due to their significant biological and pharmacological applications,[5,7] the synthesis of β-lactams, starting from simple transformations to more complex synthetic protocols, is considered to be a hot topic in the field of organic chemistry.[6]

In the current section we summarize several preparation procedures for the synthesis of cycloalkane-fused β-lactams. Rai reported a three-component reaction method (glucose-aldehyde, amine, and 1,3-oxazolan-5-one), where iodine was used as a catalyst using ionic liquids as solvents.

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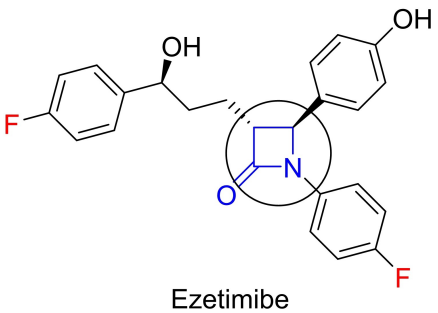

Ezetimibe

**Figure 2.** The structure of Ezetimibe, a cholesterol-lowering blockbuster drug.


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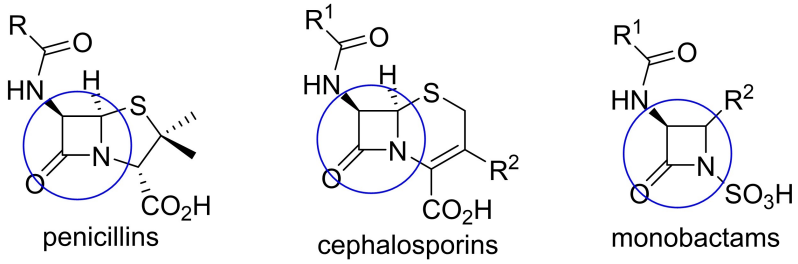


**Figure 1.** The structure of some β-lactam antibiotics.

First, a condensation between the aromatic amine (**2**) and glucose-aldehyde (**1**) was performed, where the *in situ* generated imine underwent an imine-aldol addition with 1,3-oxazolan-5-one. Then, in a subsequent diastereoselective ring-closing step, *cis*-β-lactams **4** were formed (Scheme 1).[8]

Radical cyclization is also used as a preparation method for the synthesis of β-lactams.[9] The Grainger group reported a protocol for the preparation and functionalization of β-lactams by bond formation at the C2–C3 position. First, carbamoyl dithiocarbamate **6** was prepared as a precursor for the radical initiation step, then generation of carbamoyl radical **7** was performed upon light irradiation inducing the homolytic cleavage of the C–S bond. Intramolecular cyclization of the alkene moiety of compound **7** is the last step of the procedure delivering β-lactam **10** (Scheme 2). Functionalization of the prepared β-lactam has also been performed by this group.[9]

1,2-Dipolar cycloaddition of chlorosulfonyl isocyanate (CSI) to different cycloalkenes or dienes is a well-known and efficient route for the synthesis of cycloalkane-fused β-lactams.[10] The general reaction of CSI addition to cyclic dienes is shown on Scheme 3. Fülöp and co-workers applied and extended this method and a number of β-lactams fused with cycloalkenes of various ring sizes (compounds **12**) have been synthesized starting from different dienes **11** (Scheme 3).[11,22,28,29]

The 1,2-dipolar cycloaddition of CSI to the dienes (**11a–e**) proceeds in a regioselective manner and in accord with literature investigations, in each case, only a single product (**12a–e**) is detected. The stepwise, 1,2-dipolar cycloaddition produces, in the transition state, an allyl-type stabilized carbonium ion. Although not detailed, DFT calculations at the level of B3LYP/6-31+g(d,p) also supported the observed regioselectivity.[12] Thanks to the presence of the C=C double bond in the prepared β-lactam derivatives, products **12a–e** give many opportunities for further chemical transformations. Last, but not least, ring opening of the β-lactam moiety also provides possibilities for the preparation of β-amino acid or amino ester derivatives.

### 1.3. Synthetic access to optically pure cycloalkene-fused β-lactams

The Dailler group published a $Pd^0$-catalyzed method for the preparation of β-lactam derivatives (**15** and **16**). The protocol involving the $Pd^0$-catalyzed C($sp^3$)-H activation gives the possibility to prepare enantiomerically pure β-lactams by using chiral ligand **14** (Scheme 4).[13]

Enantiopure α,β-unsaturated lactams were synthesized by Aydin and co-workers from a readily available chloroalkene nitrile (**17**) and (*S*)-methylbenzylamine via substitution reaction. Diastereomer products **18** and **19** (formed in a 1:1 ratio) were separated by crystallization and subsequent acidic hydrolysis of the nitrile groups furnished the corresponding **20** and **23** amides. These provided novel lactams (**21**, **22**, **24**, and **25**)

Loránd Kiss completed his Ph.D. in 2002 in the Department of Organic Chemistry, Debrecen University (Debrecen, Hungary) under the supervision of Prof. Sándor Antus. In 2003, he joined the research group of Prof. Ferenc Fülöp at the Institute of Pharmaceutical Chemistry, University of Szeged (Szeged, Hungary), where he started working in chemistry of cyclic β-amino acid chemistry. He followed postdoctoral research in the laboratories of Prof. Norbert De Kimpe at Ghent University (Ghent, Belgium), and Prof. Santos Fustero, University of Valencia. He is currently director of the Institute of Organic Chemistry, Research Center for Natural Sciences (Budapest) and head of the Stereochemistry Research Group in the same institute. His scientific interest is directed towards the selective functionalization of non-natural amino acid derivatives, the functionalization strategies for beta-lactams, and on the synthesis of highly functionalized fluorinated small molecular entities.

Melinda Nonn received her PhD degree at the Institute of Pharmaceutical Chemistry, University of Szeged (Hungary) under the supervision of Prof. Ferenc Fülöp in 2013. Since 2022 she has been working at the Institute of Materials and Environmental Chemistry, Research Center for Natural Sciences (Budapest). Her research interest includes synthesis of highly functionalized amino acid derivatives and beta-lactams, development of asymmetric synthetic methods toward the preparation of this class of derivatives and organofluorine chemistry.


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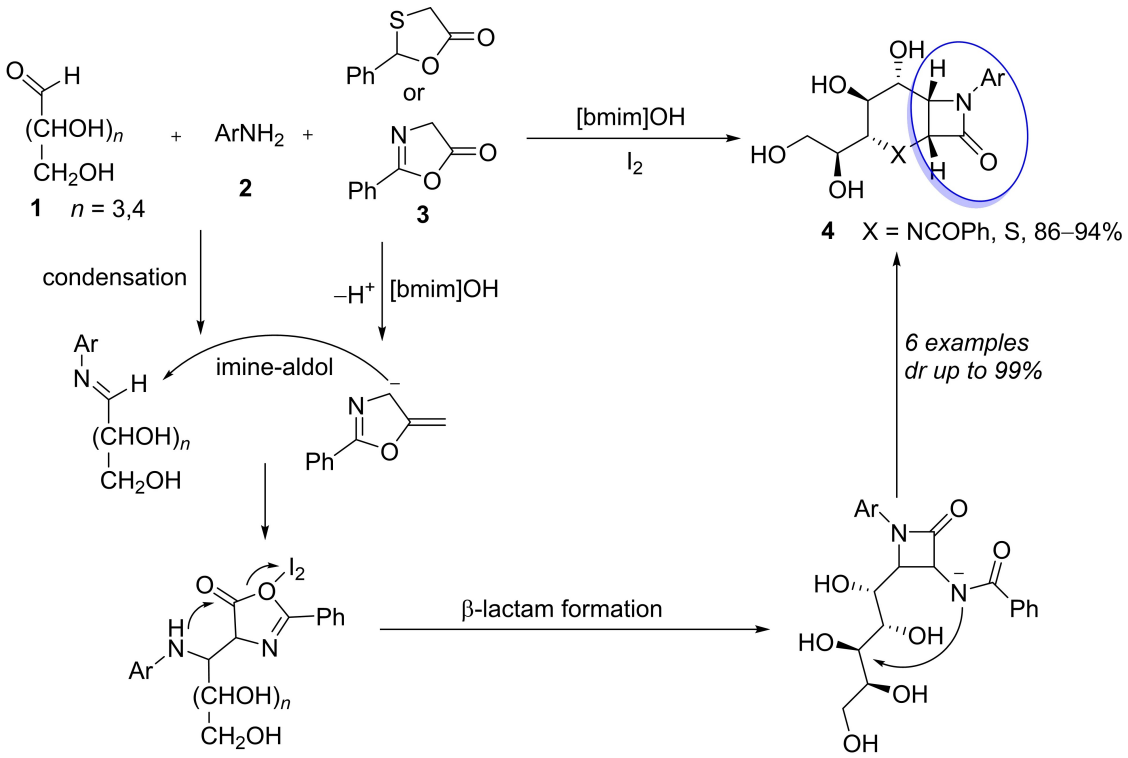
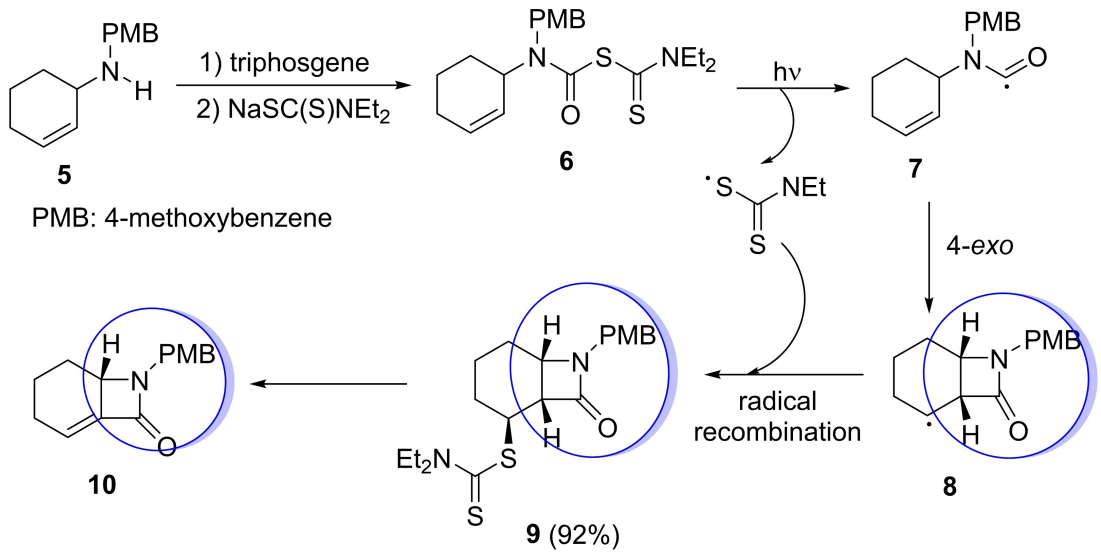



**Scheme 1.** Synthesis of β-lactam **4** from monosaccharide **1**.




**Scheme 2.** Synthesis of β-lactam **10** from cyclic amine **5** via radical cyclization.

through DDC assisted carbonyl group activation and then hydrogenation (Scheme 5).[14]

The synthesis of tricyclic β-lactam enantiomers was developed through a three-component Ugi reaction in water or under solvent-free conditions (Scheme 6).

According to a possible mechanistic interpretation, in the first step a condensation reaction takes place between the enantiomerically pure amino acid (**26**) and aldehydes **27a–c**. Then the resulting Schiff-base is transformed to the seven-membered ring intermediate leading to the corresponding β-lactam diastereomers **29** and **30** via ring-contraction. Because of steric effects, compound **29** was the major product in all cases. The detected diastereomeric ratios (**29**/**30**) were found in a range of 67:33 up to 100:0, and the diastereomers were separated by column chromatography.[15]

Numerous enzymatic protocols have been reported for the preparation of enantiomerically pure β-lactams.[16] In an article published in 2004, the synthesis of β-lactams **12a–c** and **32** as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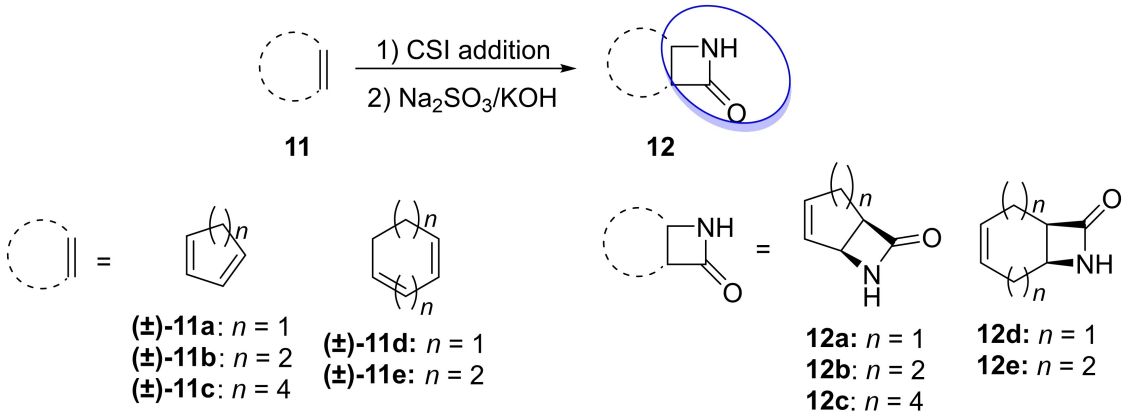
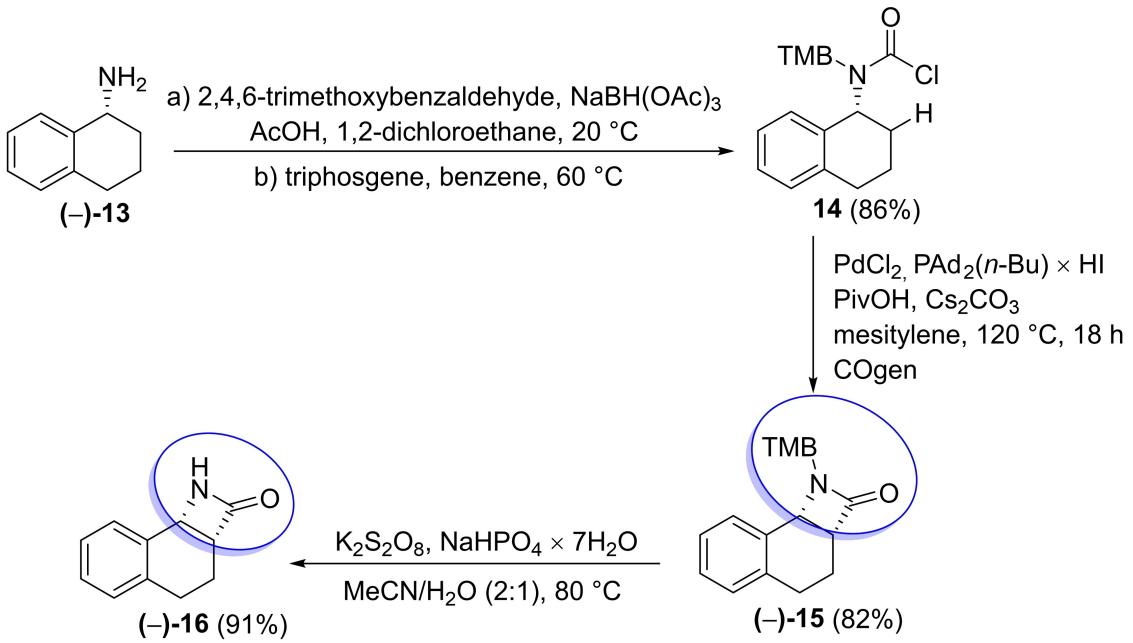



**Scheme 3.** General procedure for the synthesis of cycloalkane-fused β-lactams **12a–e**.




**Scheme 4.** Synthesis of enantiomerically pure β-lactam **16** (COgen: methylfluorene-9-carbonyl chloride).

well as β-amino acids **31a,b** and **33a,b** was described in enantiomerically pure form simultaneously, starting from the unsaturated racemic β-lactams (**12a,b,c** and **32**; see Scheme 3 for their synthesis). *Lipolase* was used as an enzyme catalyst for the enantioselective ring opening of racemic β-lactams **12a,b,c** and **32** (Scheme 7).[17]

Reactions were carried out with 1 equiv of water in the presence of *Lipolase* (lipase B from Candida Antarctica) in $i$Pr$_2$O at 70 °C. The enantiomeric excesses of the products are excellent (ee 95–99%) at 50–51% conversion. The gram-scale resolution of racemic β-lactams (**12a,b,c** and **32**) was also accomplished.

As mentioned in a previous section (section 1.2), 1,2-dipolar cycloaddition of CSI to different cycloalkenes (**35**) is a convenient approach to get cycloalkane-fused β-lactams (**36**). Treatment of enantiomerically pure alkenes **35** (using the same reaction conditions as for the racemic derivatives, see Scheme 3) under CSI addition conditions allows the synthesis of fused β-lactams **36** with ee values >99%. Then subsequent lactam ring-opening leads to various types of enantiomeric alicyclic β-amino acids (Scheme 8).[18]

## 2. Functionalization of cycloalkene-fused β-lactams across the ring olefin bond

Cycloalkene-fused β-lactams are important starting materials in organic chemistry for the preparation of highly substituted alicyclic derivatives (e.g. β-amino acids, β-amino esters, β-amino ketones or γ-amino alcohols). Thanks to the presence of the C=C double bond in the molecule several chemical transformations can be feasible, such as oxidative cleavage of the double bond, ring-opening- and cross-metathesis, epoxidation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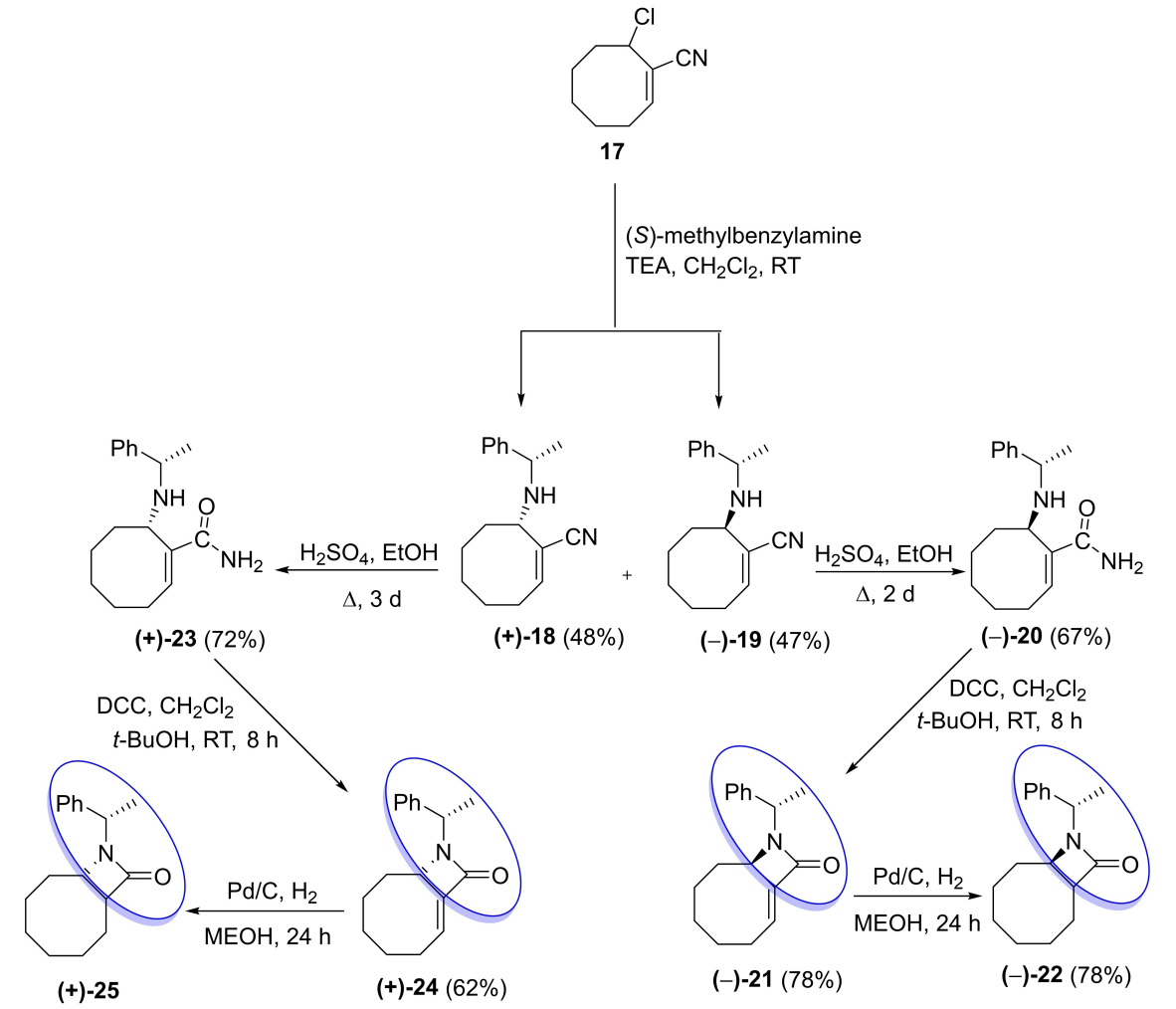
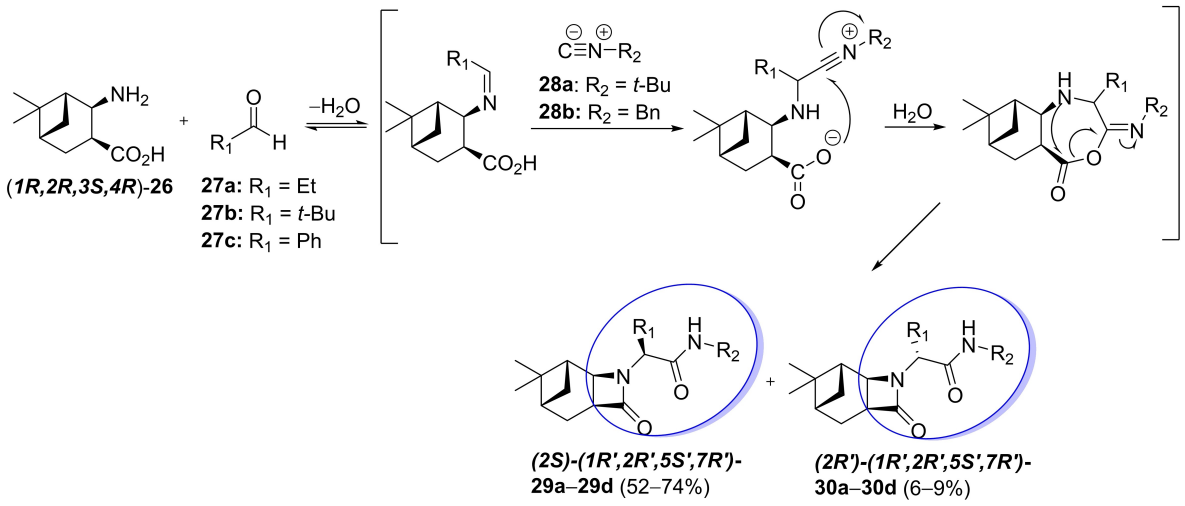



**Scheme 5.** Synthesis of enantiopure α,β-unsaturated lactams (–)-**21**, (–)-**22**, (+)-**24**, and (+)-**25**.




**Scheme 6.** Synthesis of tricyclic β-lactams **28** and **29** trough Ugi reaction.

followed by oxirane opening, as well as aziridination then opening of the aziridine ring. In addition, functionalized cyclic β-amino acids can also be prepared by the ring opening of the azetidinone ring (Scheme 9).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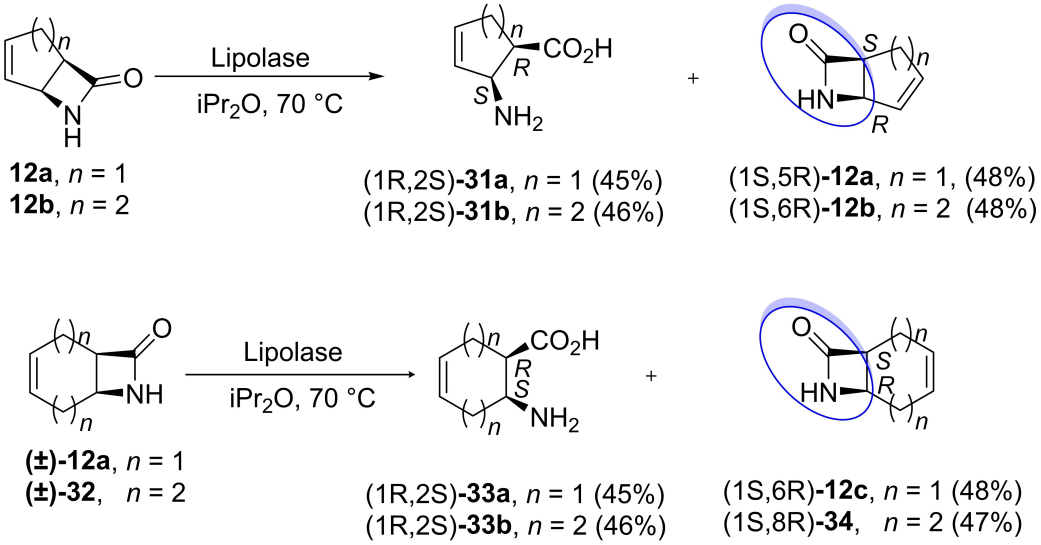
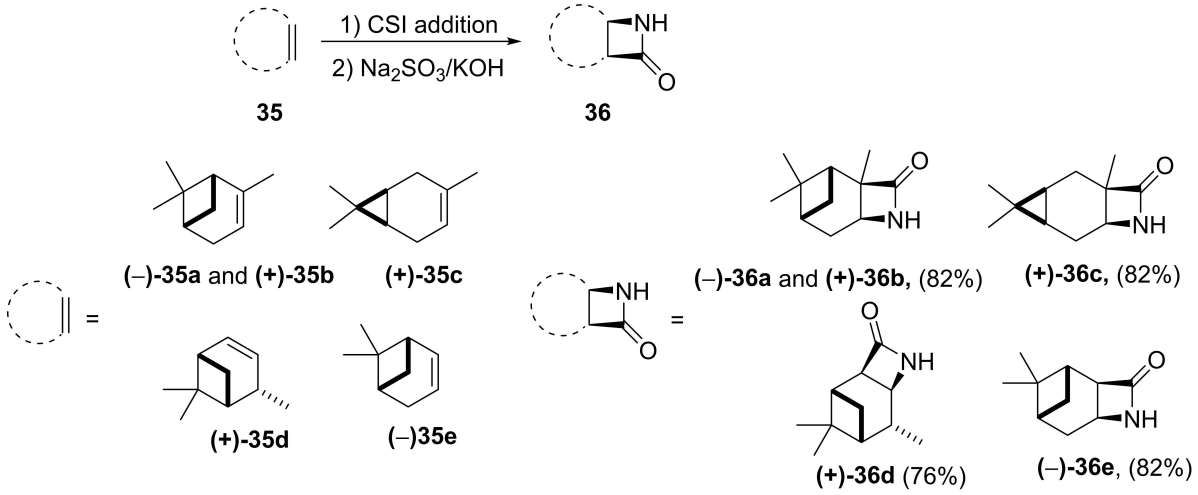
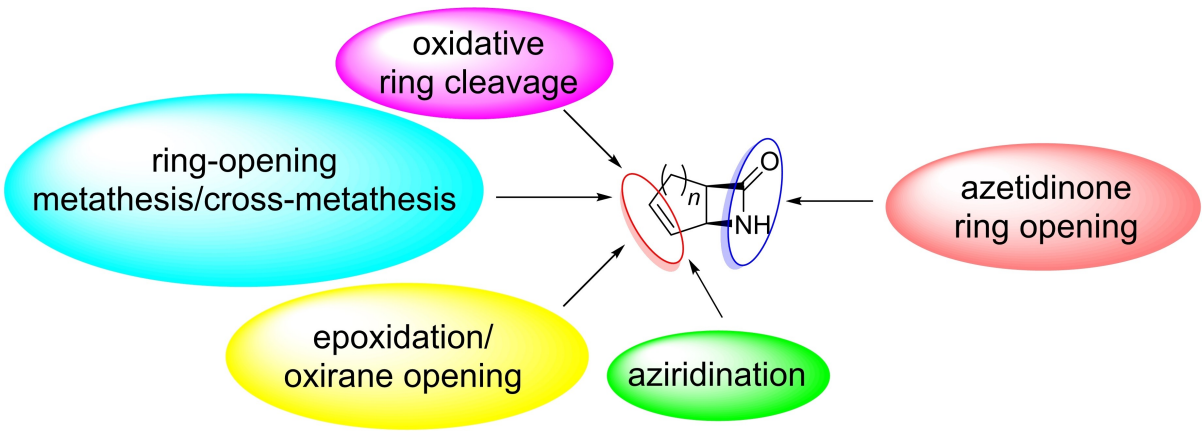



**Scheme 7.** Enantioselective hydrolysis of β-lactams **12a,b,c** and **32**.




**Scheme 8.** Synthesis of optically pure β-lactams **36a–e**.




**Scheme 9.** Diversity of cycloalkane-fused β-lactams. Possible reactions of cycloalkene-fused β-lactams involving the C=C double bond.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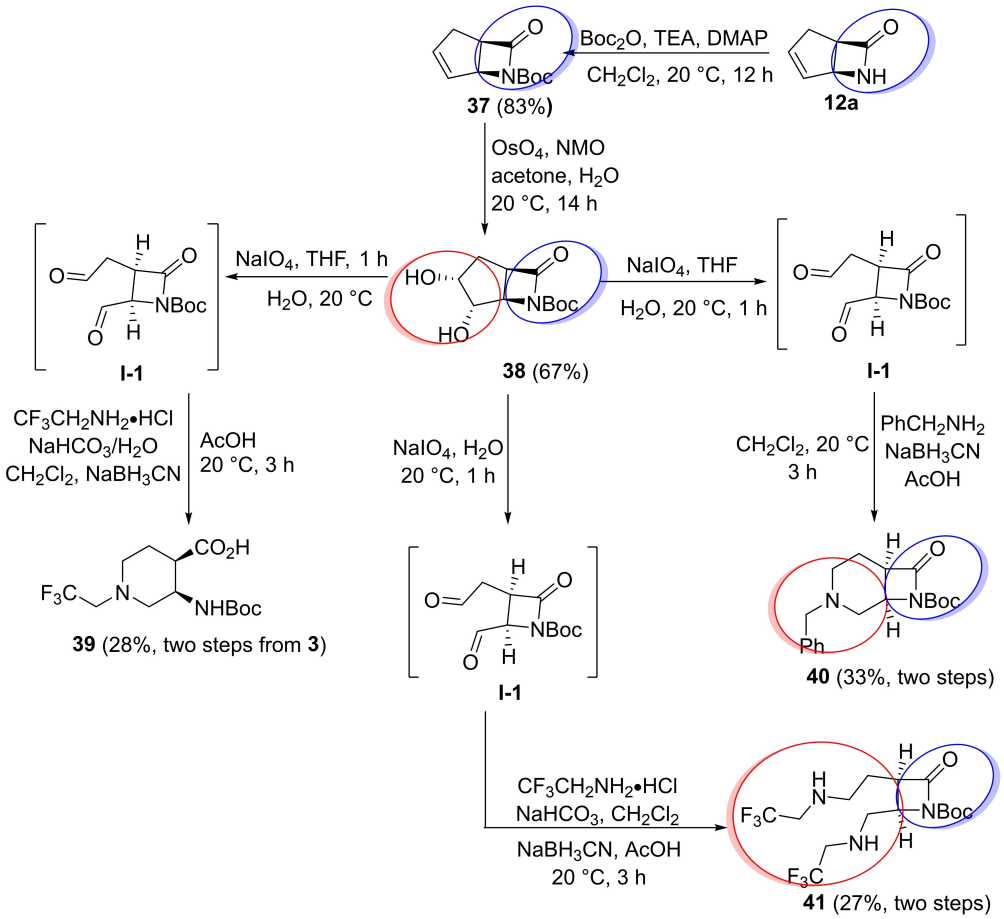
The functionalization opportunities due to the presence of the C=C bond in the cycloalkene-fused β-lactams were explored and various transformations were performed in recent years. Some relevant examples of these methods are collected and summarized in the current review.

### 2.1. Functionalizations through the oxidative cleavage/ozonolysis of ring olefin bond

A stereocontrolled synthetic method was elaborated for the preparation of conformationally restricted β-lactam and β-amino acid derivatives with a piperidine or azepane core. The synthetic protocol was based on the oxidative ring cleavage of dihydroxylated β-lactam derivative **37**, followed by ring closing with double reductive amination, which furnished some azaheterocyclic β-lactam derivatives (**39**, **40**, and **41**) (Scheme 10). The dihydroxylated β-lactam **38** was prepared diastereoselectively by using $OsO_4$ as the oxidizing agent in the presence of *N*-morpholine-*N*-oxide (NMO). Then oxidative ring cleavage of vicinal diol with $NaIO_4$ as the oxidizing agent was performed. The formed dialdehyde **I-1** was immediately reacted with various amines (fluorinated amine and benzylamine). The oxidative ring cleavage/reductive ring closing step was found to be dependent on reaction conditions. When dihydroxylated compound **38** was reacted with $NaIO_4$ (oxidative ring opening step), followed by treatment with trifluoroethylamine HCl salt and $NaCNBH_3$, cyclization into piperidine derivatives **40** took place.[19a]

A new, sustainable, one-pot strategy for the synthesis of piperidine derivatives described above (see Scheme 10) was reported recently. The synthetic strategy was not a simple task to carry out. The work-up was tedious and the storage of the dialdehyde intermediates was very difficult, because of their instability. In a simpler approach, the toxic reagents such as $OsO_4$, NMO, and $NaIO_4$ were not used. Furthermore, only small quantities of the organic solvents were applied, and the number of steps could be reduced. The procedure was based on the oxidation of the C=C double bond into the corresponding dialdehydes by ozonolysis (Scheme 11).[20]

In a previous work,[19a] the dihydroxylation/diol cleavage/reductive amination protocol of the *N*-Boc-protected β-lactam (**37**) showed low reactivity under the conditions used (Scheme 10). In contrast, applying the ozonolysis/reductive amination procedure the reaction was more successful. The reaction was carried out at low temperature (−78 °C) in MeOH. First, the 1,3-dipolar cycloaddition between ozone and the alkene occurs. After reduction of the ozonide, the methanolic dialdehyde solution could be used immediately in the reductive amination procedure. In this process the chromatographic




**Scheme 10.** Functionalization of cyclic β-lactam **37** through ring olefin bond oxidative cleavage.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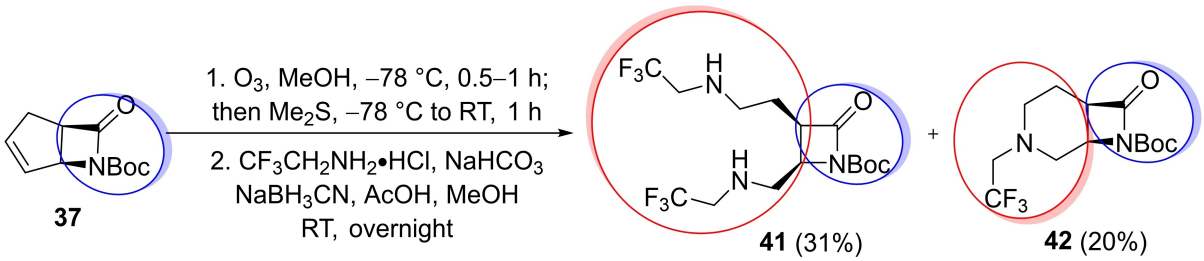



**Scheme 11.** Functionalization of cyclic β-lactam **37** through ozonolysis/double reductive amination.

purification was only necessary in the final step.[20] The ozonolysis/reductive amination method was performed with 2,2,2-trifluoroethylamine (Scheme 11). In contrast with the earlier work,[19] this reaction gave only two products: the known monocyclic diamino lactam **41** and piperidine-fused lactam **42** (Scheme 11). The products were separated by column chromatography.[20]

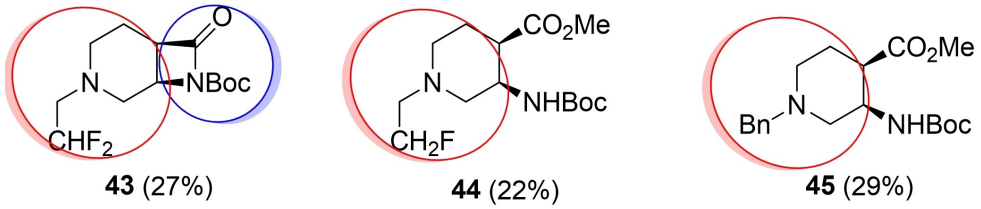
The reaction was extended with the use of other amines as well. The reaction protocol was identical with the method described in Scheme 11. When using 2,2-difluoroethylamine only the desired piperidine-fused lactam **43** was formed. In contrast, the reaction with 2-fluoroethylamine and benzylamine, owing to reductive cyclization and lactam methanolysis, β-amino methyl esters **44** and **45** were detected and isolated (Scheme 12).[20]

### 2.2. Functionalizations across ring-opening metathesis/cross-metathesis

Metathesis is a very useful and efficient method for the transformation of C=C double bonds and it is effective for the preparation of highly functionalized structures. Various sophisticated molecular scaffolds could be prepared by means of these types of procedures (ring-opening, ring-closing, cross-metathesis or ring rearrangement metathesis).[21]

A stereocontrolled metathesis strategy was applied for the preparation of functionalized β-lactams and $\beta^{2,3}$-amino acid derivatives without epimerization. The method was based on the transformation of the ring C=C double bond of cycloalkene-fused azetidinones by ring-opening metathesis applying various Ru-based catalysts (Figure 3, Scheme 13).[22]

β-Lactam **47** derived from norbornadiene was reacted with ethylene under ring-opening metathesis conditions in the presence of commercially available ruthenium-based catalysts [Grubbs-1 (G-1), Grubbs-2 (G-2), Hoveyda–Grubbs-1 (HG-1), and Hoveyda-Grubbs-2 (HG-2)] forming divinyl-substituted bicyclic β-lactam **48**. Further transformation of compound **48** was performed under the conditions of cross-metathesis, using HG-2 as the catalyst. Note that only this catalyst proved to be suitable for this transformation. Treatment of 3-butenone (an α,β-unsaturated ketone) and methyl acrylate (an α,β-unsaturated ester) in $CH_2Cl_2$ resulted in the formation of the desired products **49** and **50** isolated from low to good yields




**Scheme 12.** Synthesis of cyclic β-lactam **43** and amino esters **44** and **45** through ozonolysis/double reductive amination protocol.

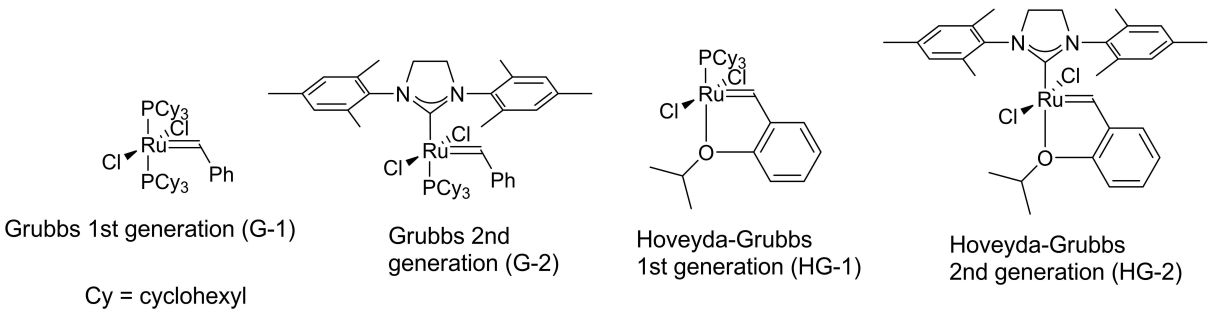



**Figure 3.** Structures of used Ru-based catalysts and their abbreviations.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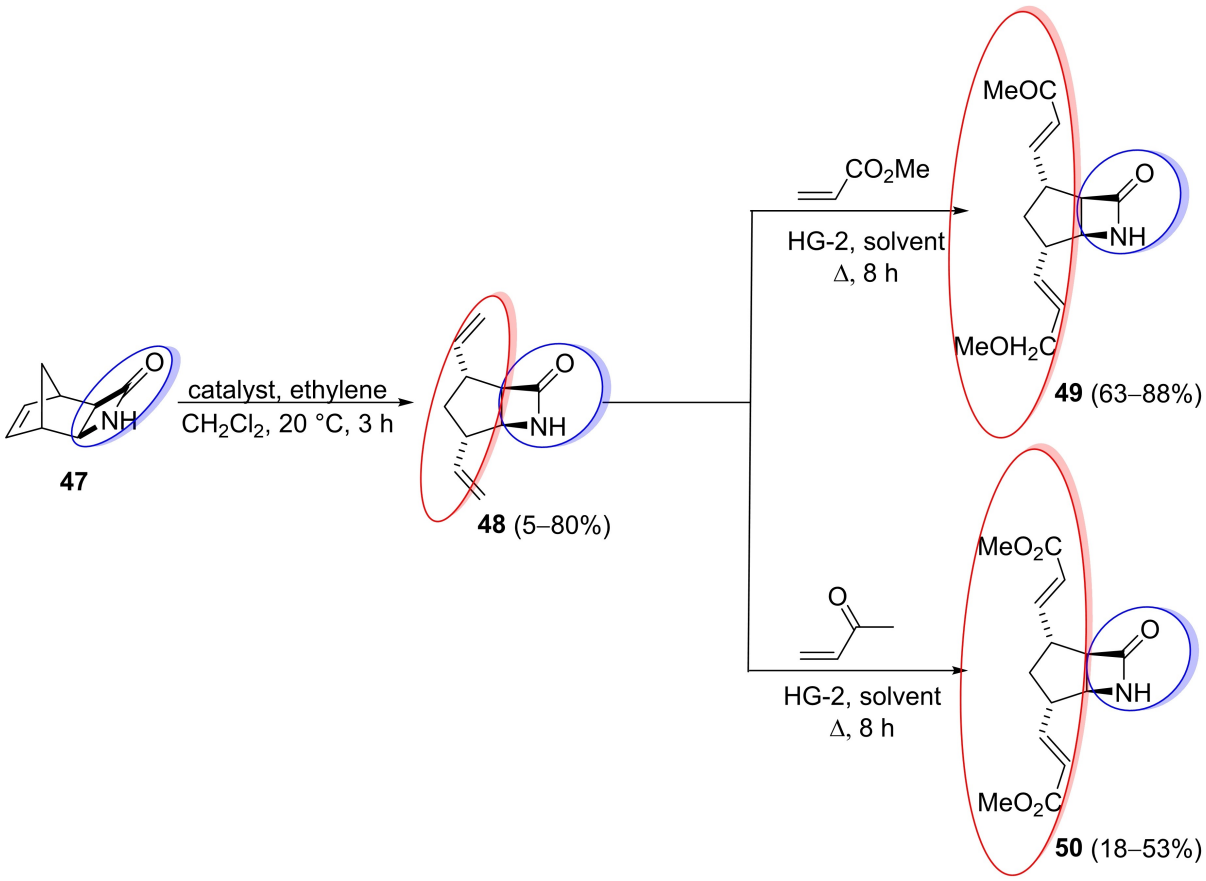
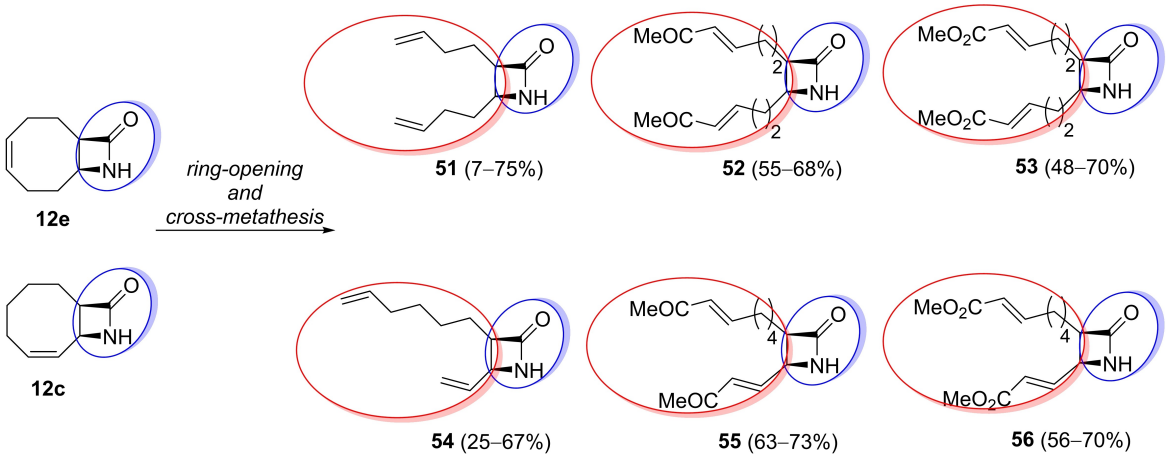



**Scheme 13.** Functionalization of β-lactam **47** across ring-opening metathesis (ROM)/cross-metathesis (CM),

(Scheme 13). The metathesis protocols (ring-opening and cross-metathesis) described above were extended to bicyclic β-lactams **12c,e**. Likewise, the reaction conditions shown in Scheme 13 allowed the synthesis of the desired, functionalized β-lactam derivatives (**51**–**56**) (Scheme 14).[22]

Then the prepared β-lactam derivatives (**48**–**50** and **51**–**56**) were transformed to the corresponding $\beta^{2,3}$ amino acids via lactam ring-opening reaction in aqueous or ethanolic solution of HCl. These azetidinones containing multiple C=C double bonds, which are difficult to access by alternative routes, may be applicable for further functionalizations.[22]

An interesting investigation regarding the selectivity of cross metathesis was presented in the framework of the synthesis of new mono- and difunctionalized azetidin-2-ones




**Scheme 14.** Functionalization of β-lactam **12c,e** across ring-opening metathesis/cross-metathesis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through stereocontrolled ring-opening metathesis reactions with ethylene, using different Ru-based catalysts (G-1, G-2, HG-1, HG-2). Besides dimetathesis products, monocoupled β-lactams were also formed and the chemical behavior of the C=C double bonds involved in these transformations was investigated (Scheme 15).[23]

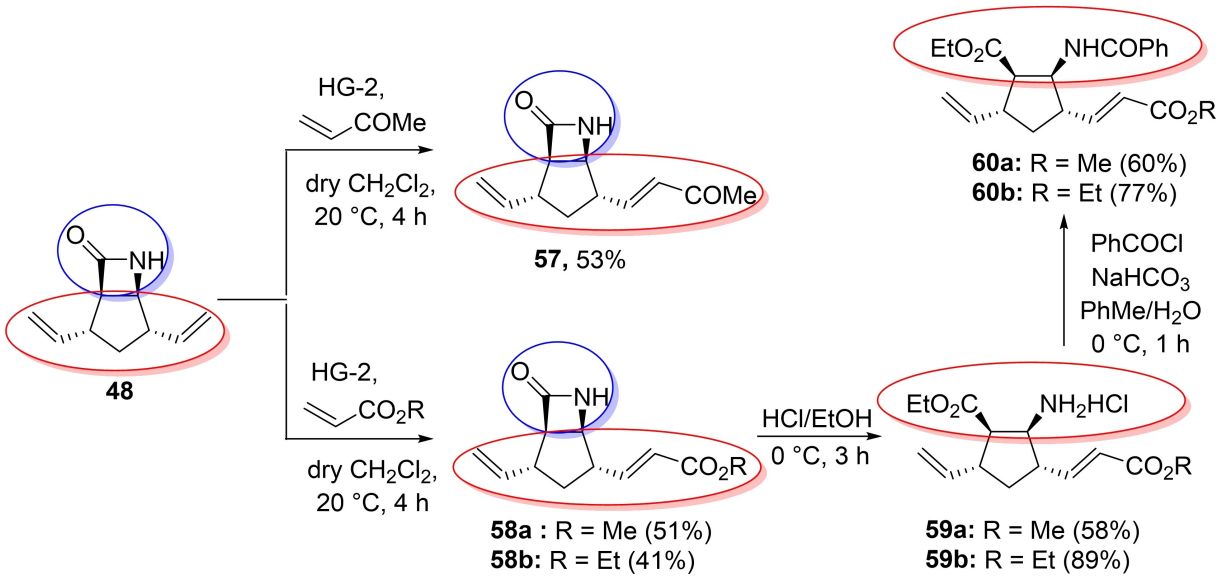
Selectivity of the cross-metathesis reaction of divinyl-substituted azetidinone **48** derived from lactam **47** was studied (see Scheme 13). During the optimization of the reaction, cross-metathesis products (**57** and **58a,b**) were detected only in the presence of catalyst HG-2 in moderate yields. The selectivity of the cross-metathesis reactions was explained by stereochemical factors (chelate-ring, stability) and hydrogen-bonding directing effect. Specifically, because of the hydrogen bonding interaction between the chlorine atom of the catalyst and the amide N–H group as a hydrogen-bond donor group, the distance between the N–H group and the C=C double bond becomes shorter, thereby facilitating the coupling reaction. By opening the lactam ring of compounds **58a,b** followed by benzoylation of **59a,b**, functionalized cispentacin derivatives (**60a,b**) were prepared (Scheme 15).[23]

According to the above-mentioned hypothesis it was interesting to investigate the hydrogen-bond directing effect. *N*-Boc-protected β-lactam **61** was used as a starting model derivative in the cross-metathesis reaction (Scheme 16). In this case starting material **61** cannot function as a hydrogen-bond donor and there is no directing effect. Consequently, a mixture of isomers **63** and **64** was detected (Scheme 16). Unfortunately, separation of the two products failed, but the NMR spectra of the crude reaction mixture indicated the exclusive presence of the two products. These experimental results supported the above-mentioned hypothesis.[23]

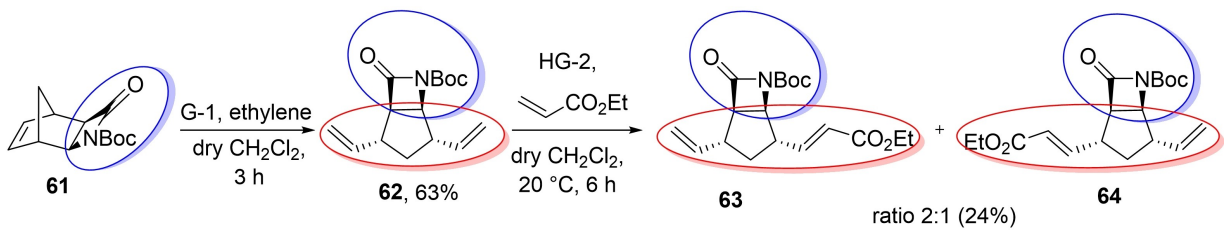
Stereocontrolled synthesis of fluorine-containing β-lactam derivatives through cross-metathesis was readily achieved. The ring opening reaction of substrate **12e** and **65** with ethylene in the presence of G-1 catalyst furnished products **51** and **66** (Scheme 17). Then these were subjected to cross-metathesis with 1,1,2,3,3,3-hexafluoropropyl ether in the presence of HG-2 to afford fluorinated β-lactams **67** and **68** (Scheme 17).

β-Lactam derivatives **12c** and **69** were reacted with ethylene under ring-opening metathesis conditions similar to the reaction of compounds **12e** and **65**. By functionalization of product **54** with allyl 1,1,2,3,3,3-hexafluoropropyl ether in the presence of catalyst HG-2, only a single dicoupled product (**72a**) was detected and isolated. Cross-metathesis reactions of compound **70** with allyl 1,1,2,3,3,3-hexafluoropropyl ether resulted in not only dicoupled product **72b**, but the formation of monocoupled product **71b** was also observed (Scheme 18).

The selectivity of cross-metathesis was explained as follows. i) Chelation of the metallacycle intermediate with carbonyl




**Scheme 15.** Chemodifferentiation of the olefin bonds trough cross-metathesis reactions.




**Scheme 16.** Cross-metathesis reaction of compound **61**.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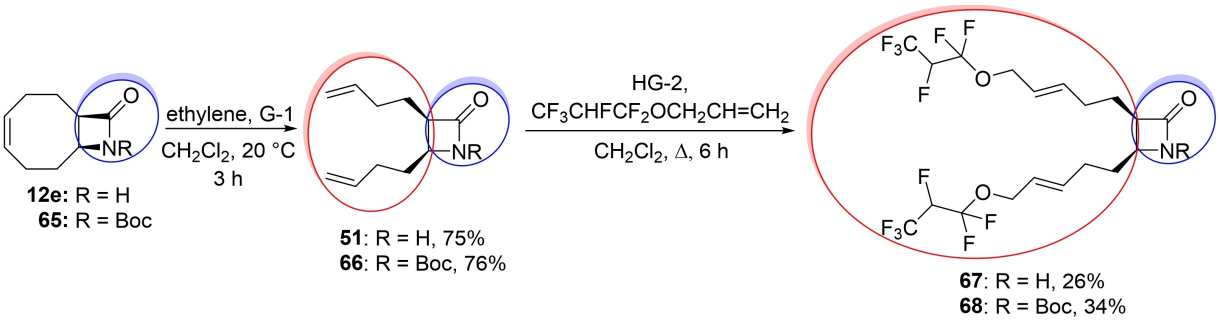
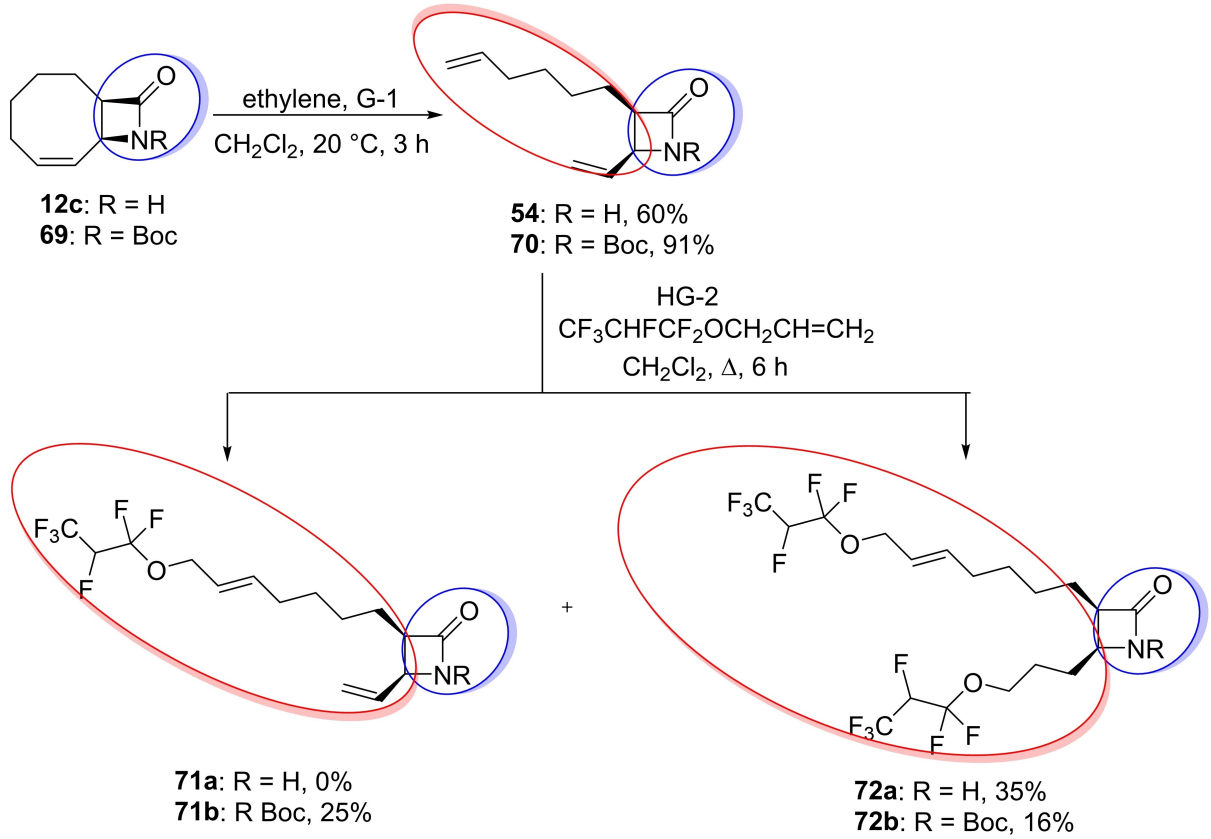



**Scheme 17.** Functionalization of β-lactam **12e** and **65** via cross-metathesis with fluorinated alkene.




**Scheme 18.** Functionalization of β-lactams **12c** and **69** via cross-metathesis with fluorinated alkene.

oxygens hinders further reactions by stabilizing the metallacycle. ii) Reactivity of the C=C double bond decreases, since the vinyl group attached directly to the lactam ring of **70** may form a six-membered chelate ring with the oxo group of Boc. iii) Finally, there is a steric hindrance between the vinyl group and the other alkene chain in the molecule and, accordingly, the possibility of the reaction with the Ru-alkylidene catalyst decreases (Figure 4, see structures **T1**, **T2** and **T3**).[24]

Lactams **73a,b** were also investigated in metathesis reactions (ROM and CM). Cross metathesis reaction of **48** and **62** with allyl 1,1,2,3,3,3-hexafluoropropyl ether appeared to be temperature-dependent. At higher temperature (under reflux conditions) the corresponding dicoupled products **74a,b** were formed. At room temperature, in turn, a mixture of two monocoupled derivatives **75a,b** and **76a,b** in a ratio of 1.5:1 was isolated. Unfortunately, separation of the products failed (Scheme 19).[25]

### 2.3. Functionalizations through aziridination/aziridine ring opening

Functionalization of a C=C double bond with aziridination is a very effective and useful technique in organic and medicinal chemistry in view of the creation of varied moieties by nucleophilic opening of the three-membered *N*-heterocycle including *N*-containing functional groups (amides, amines, etc).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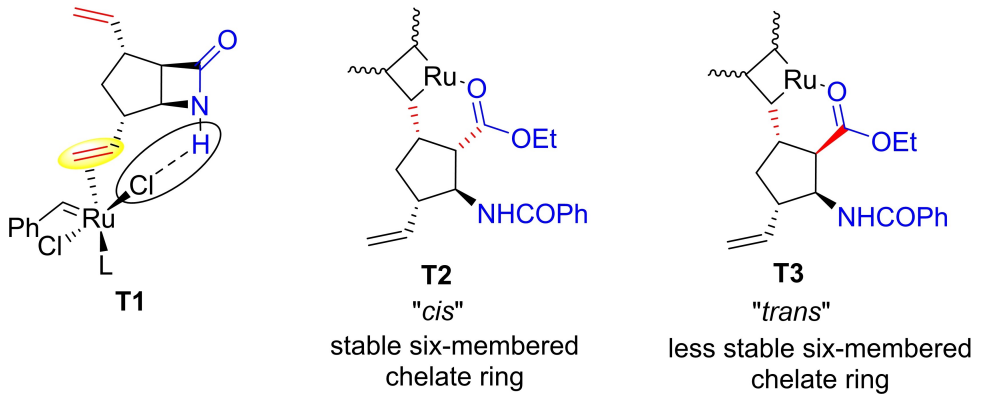
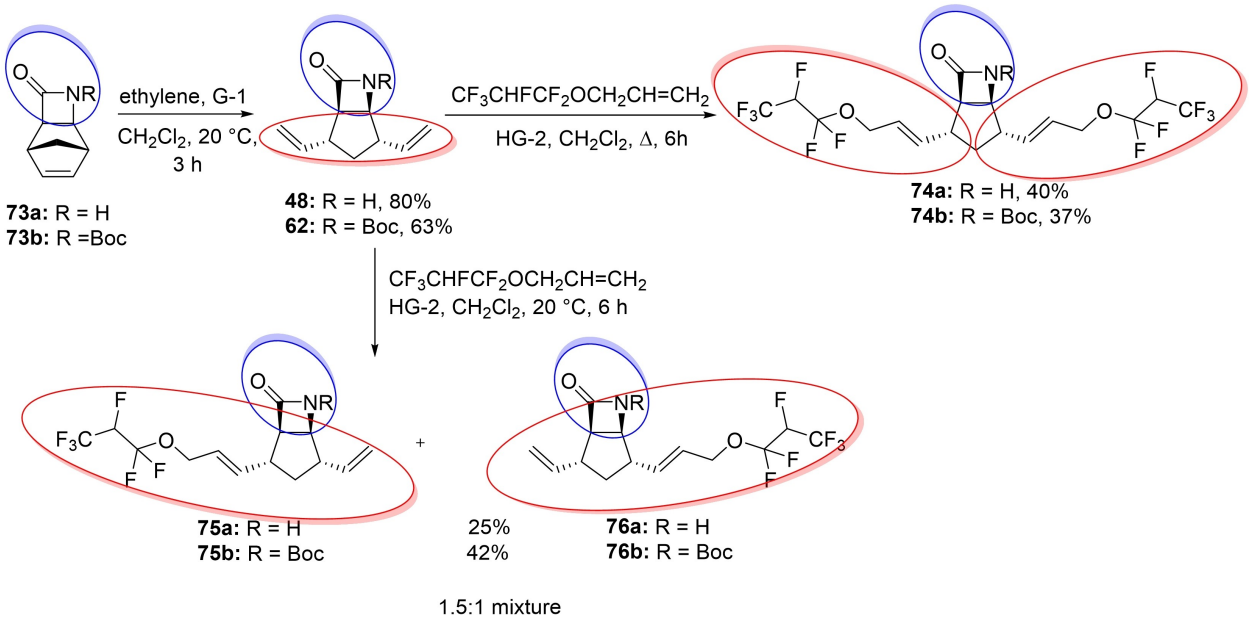



**Figure 4.** Hydrogen-bonding and chelate ring formation.

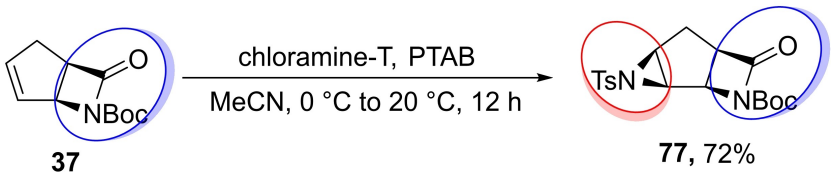



**Scheme 19.** Functionalization of β-lactam **73 a,b** via cross-metathesis with fluorinated alkene.

Furthermore, the aziridine ring is present in a number of natural products and alkaloids.[26]

The aziridination of bicyclic β-lactam **37** was accomplished in a diastereoselective manner. The functionalization reaction was based on the transformation of the C=C double bond with chloramine-T in the presence of PTAB (phenyltrimethylammonium tribromide) used in catalytic amount. Due to steric factors, the attack of the bromonium ion (from PTAB) occurs from the opposite side of the lactam ring, whereas the attack of the chloramine-T takes place selectively from the opposite side of the non-classical bromonium ion intermediate. As a result, only a single product (compound **77**) was detected and isolated in good yield with the azetidinone and the aziridine ring having a *cis* relative arrangement (Scheme 20).[27]

The synthesis of highly functionalized cyclic β-amino acid derivatives was achieved through the ring opening of aziridine-fused lactam derivative **77**. Various nucleophiles were used in order to perform the opening of the three-membered nitrogen




**Scheme 20.** Functionalization of bicyclic β-lactam **37** with aziridination,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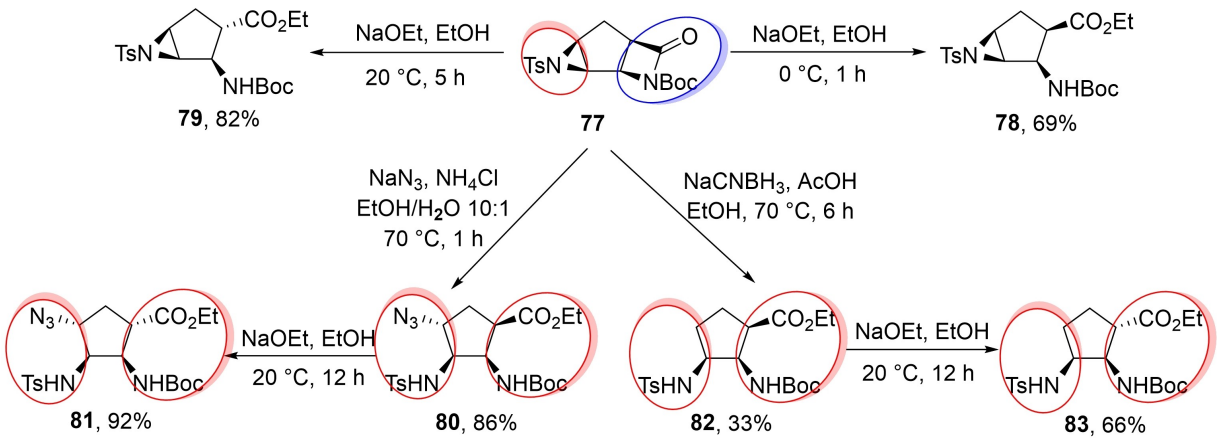
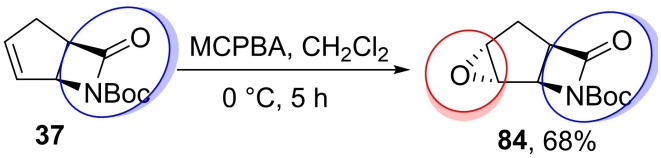



**Scheme 21.** Ring opening reaction of aziridine-fused cyclic β-lactam **77** with nucleophiles.

ring. Namely, either an azide or a hydride was applied for the opening of the aziridine ring, thus forming multifunctionalized alicyclic derivatives **80**–**83** (Scheme 21).[27]

### 2.4. Functionalizations through oxirane formation/oxirane ring opening

Functionalization of the C=C double bond with epoxidation was also performed. The epoxidation reaction was performed in the presence of *m*-chloroperbenzoic acid (MCPBA) and resulted in oxirane derivative **84** as a single product in a total diastereoselective manner. In the product molecule the azetidinone and the oxirane rings are in a *trans* relative steric arrangement (Scheme 22).[28]

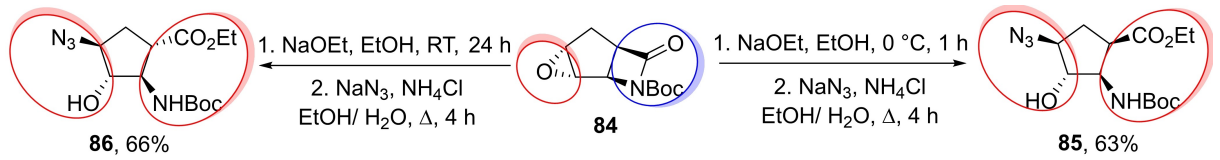



**Scheme 22.** Functionalization of β-lactam **37** with epoxidation.

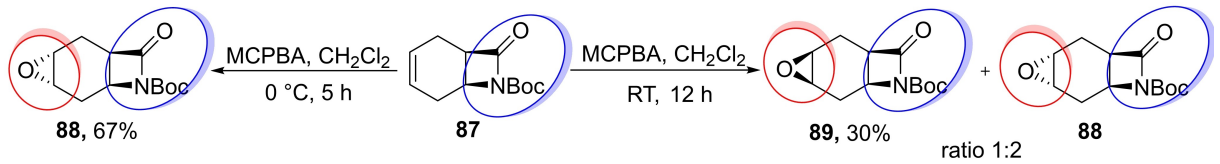
The epoxidation strategy was efficiently extended for the preparation of highly functionalized cyclic β-amino acid derivatives containing multiple stereogenic centers. Thus, the prepared oxirane-containing cyclic β-lactam **84** was transformed by lactam ring opening and then oxirane ring opening with azide nucleophile led to the corresponding highly functionalized scaffolds **85** and **86** (Scheme 23).[28]

Analogously, the above-mentioned epoxidation protocol was extended for cyclohexene-fused β-lactam **87** (Scheme 24). When the reaction was performed at 0 °C, only product **88** was formed because of the presence of the bulky Boc group. Interestingly, when the reaction was performed at room temperature, a mixture of *trans*- and *cis*-epoxide **88** and **89** were formed (Scheme 24).[29]

The epoxidation/oxirane opening strategy allowed the preparation of hydroxylated β-amino acid derivatives. Accordingly, the prepared β-lactam **88** containing the oxirane ring was first treated with $NaBH_4$ in EtOH and hydroxylated product **90** was isolated. In order to prepare the other regioisomer of **90**, the lactam ring-opening of compound **88** with NaOEt was




**Scheme 23.** Ring opening reactions of epoxy-fused cyclic β-lactam **84**.




**Scheme 24.** Epoxidation of compound **87**.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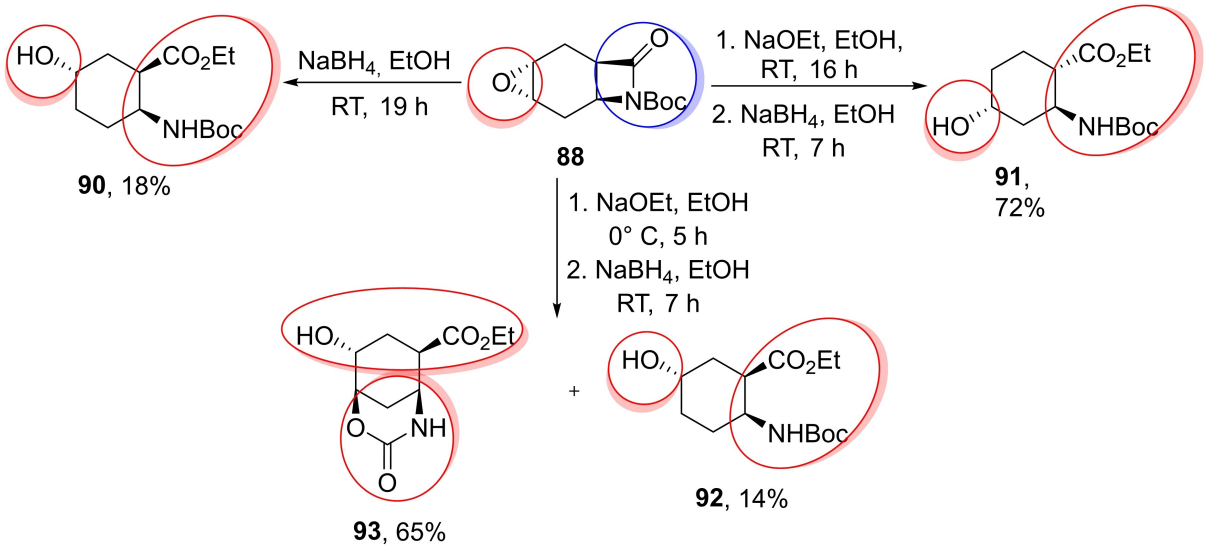


**Scheme 25.** Regioselective oxirane ring opening of **88** with $NaBH_4$.

assayed. The reaction led to the isomerization at C-1 and then subsequent oxirane ring opening with $NaBH_4$ gave hydroxylated cyclic β-amino acid derivative **91** (Scheme 25). To avoid the isomerization reaction at C-1 the lactam ring-opening reaction was performed at 0 °C in the presence of NaOEt followed by treatment with $NaBH_4$. This approach resulted in the formation of hydroxylated amino acid derivative **92**. The main product in this reaction was oxazinone derivative **93**, whose formation involves the attack of the carbonyl oxygen at C-4 of the oxirane ring.[29]

## 3. Summary and Outlook

The β-lactam ring system, as a key element of numerous antibiotics, antibacterial or anticancer agents, is unequivocally of high relevance in medicinal chemistry and pharmaceutical design, whose importance is continuously expanding in recent years. Moreover, because of the increasing importance in drug design of three-dimensional small molecules containing $sp^3$ carbon atoms, functionalized cycloalkane-fused β-lactams might raise high interest in medicinal chemistry and in pharmaceutical applications. Therefore, the synthesis of such type of subclass of β-lactams might be of high utility in organic chemistry. The synthetic methodologies presented in the current account in view of the access of various highly-substituted compounds, across olefin bond functionalization of some cycloalkene-fused β-lactams, gave rise to interesting molecular entities, whose further application might be of interest among synthetic organic and medicinal chemists. Among the stereo- and regiocontrolled synthetic methods, economically acceptable, safe, simple, and scalable processes, leading to highly functionalized β-lactam derivatives as three-dimensional structures, might receive importance and applicability in preparative organic chemistry as well as in the pharmaceutical industry.

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## Conflict of Interests

The authors declare no conflict of interest.

**Keywords:** cycloalkenes · functionalization · lactam · selectivity · stereochemistry

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