Synthesis L. Kiss et al. Review

Application of Metathesis Reactions in the Synthesis and Transformations of Functionalized β-Amino Acid Derivatives

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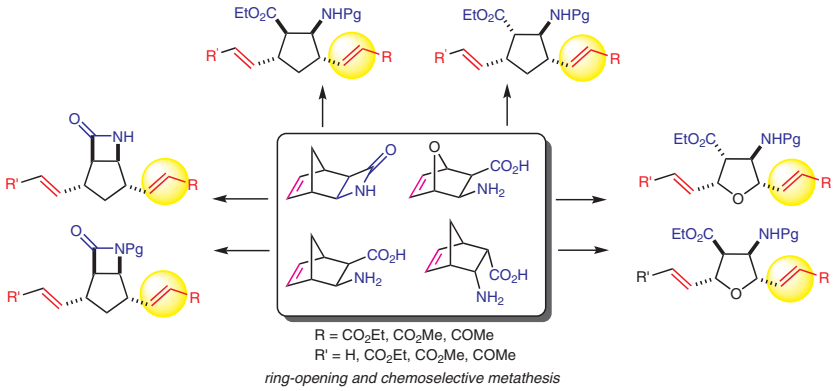

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Abstract Because of their biological relevance, cyclic β-amino acids have generated increasing interest and had significant impact in drug research over the past two decades. Their preparation and further functionalization towards new types of molecular entities have received large interest in synthetic and medicinal chemistry. Various types of metathesis reactions, such as ring-opening (ROM), ring-closing (RCM), or cross metathesis (CM) are used widely for access to either alicyclic β-amino acids or other densely functionalized derivatives of this group of compounds. This account intends to provide an insight into the most relevant synthetic routes to this class of derivatives with the application of metathesis reactions. The review focuses on the presentation of selective and stereocontrolled methodologies in view of versatility, robustness, limitations and efficiency.

Key words amino acids, heterocycles, metathesis, ring closure, stereoselectivity

1 Introduction

Because of their high biological relevance, β-amino acids occupy an important area in pharmaceutical and organic chemistry having attracted increased interest in the past two decades. These structural elements are present in many natural compounds or bioactive derivatives either in the free form or as part of more complex molecules. Some representatives such as the five-membered carbocyclic cispentacin (isolated from the culture broth of *Bacillus cereus*) or icofungipen possess strong antifungal activities. The *O*-heterocyclic compound oxetin is known as an antibiotic, while the phenyl-substituted six-membered homologue tilidin is a known analgetic (Figure 1). Moreover, new-generation peptides built from cyclic β-amino acids show well-ordered secondary structures and exhibit stability against proteases or peptidases; therefore, they are important molecules for medicinal chemistry.[1–16]

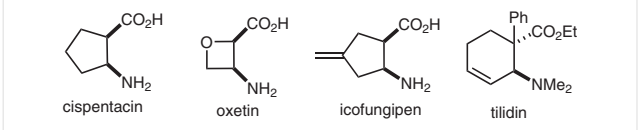


Figure 1 Some bioactive cyclic β-amino acids

Thanks to the effective development and commercial availability of well-defined Ru-based catalysts, olefin metathesis reactions have revolutionized synthetic thinking over the last three decades (Figure 2). Metathesis, accordingly, has become a powerful tool for the creation of one or more olefinic bonds in a certain molecule. By using this synthetic method, a number of natural and biologically active products have been synthesized, which were earlier challenging, difficult, or impossible to prepare. Besides their utilization at the laboratory scale, olefin metathesis has gained important industrial applications as well.[17–30]

This current account is devoted to providing an insight into the most relevant synthetic routes to various cyclic β-amino acid derivatives with the utilization of metathesis reactions. Emphasis will be on scaffolds in which the carboxylate and amino functions are extracyclic and connected to stereogenic centers ($\beta^{2,3}$-amino acids, see Figure 3). In addition, some relevant examples are also discussed in which the nitrogen atom is part of the ring system. The review focuses on the presentation of selective and stereocontrolled methodologies in view of versatility, robustness, limitations, and efficiency.

Biographical sketches

Loránd Kiss completed his Ph.D. in 2002 in the Department of Organic Chemistry at Debrecen University (Debrecen, Hungary) under the supervision of Prof. Sándor Antus. In 2003, he joined the research group of Professor Ferenc Fülöp at the Institute of Pharmaceutical Chemistry, University of Szeged (Szeged, Hungary), where he started to work in the field of cyclic β-amino acid chemistry. He followed this with postdoctoral studies in the laboratories of Prof. Norbert De Kimpe at Ghent University (Ghent, Belgium), and Prof. Santos Fustero, at the Department of Organic Chemistry, University of Valencia (Valencia, Spain). He has published 86 scientific papers in reputed journals. He is currently professor at the Institute of Pharmaceutical Chemistry, University of Szeged. His scientific interest is directed towards the selective functionalization of cyclic β-amino acids and on the synthesis of highly functionalized fluorinated building blocks.

Márton Kardos graduated as a chemist in 2011 from Debrecen University (Hungary). He has been working at the Institute of Pharmaceutical Chemistry, University of Szeged since 2013, where he started his Ph.D. under the supervision of Loránd Kiss and Ferenc Fülöp. His research topic focuses on the synthesis of variously functionalized β-amino acid derivatives across metathesis transformations.

Csaba Vass graduated as a pharmacist in 2017 from the University of Szeged (Hungary). He has been working at the Institute of Pharmaceutical Chemistry, University of Szeged since 2014. In 2017 he started his Ph.D. under the supervision of Loránd Kiss. His current research topic is directed towards the application of metathesis transformation for synthesis of variously functionalized β-amino acid scaffolds.

Ferenc Fülöp was born in Szank, Hungary in 1952. He received his M.Sc. in chemistry in 1975 and his Ph.D. in 1979 from József Attila University, Szeged, Hungary. At the beginning of his career he worked in Chinoin Pharmaceuticals, Budapest for six years. In 1991, he was appointed as a full professor at the Institute of Pharmaceutical Chemistry, University of Szeged, and has been the head of department between 1998–2017. He is a member of the Hungarian Academy of Sciences and has a wide range of research interests in synthetic organic chemistry. His recent activities have focused on the use of amino alcohols and β-amino acids in enzymatic transformations, asymmetric syntheses, foldamer construction, and flow chemistry, in view of the development of pharmacologically active compounds.

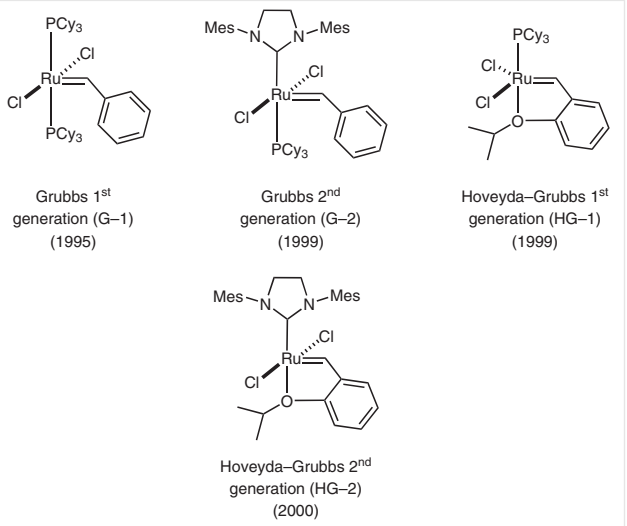


Figure 2 Some commercially available Ru-based metathesis catalysts

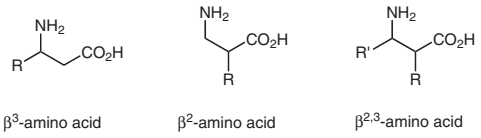


Figure 3

In the first part of this short account, the syntheses of five- and six-membered alicyclic β-amino acids are described using ring-closing metathesis (RCM) and cross metathesis (CM) protocols, followed by larger ring frameworks and condensed ring systems. In the second part, various metathesis techniques are presented to access functionalized cispentacin and transpentacin derivatives as well as some alicyclic β-amino acid scaffolds and β-lactams.

2 Synthesis and Transformation of Cyclic β-Amino Acids through Metathesis Reactions

Over the past twenty years, olefin metathesis reactions have received widespread application towards the access of various types of cyclic β-amino acids. Commercially available modern Ru-based catalysts highly facilitated the proliferation of this method since they are applicable on densely functionalized molecules leading to the formation of complex products.[31]

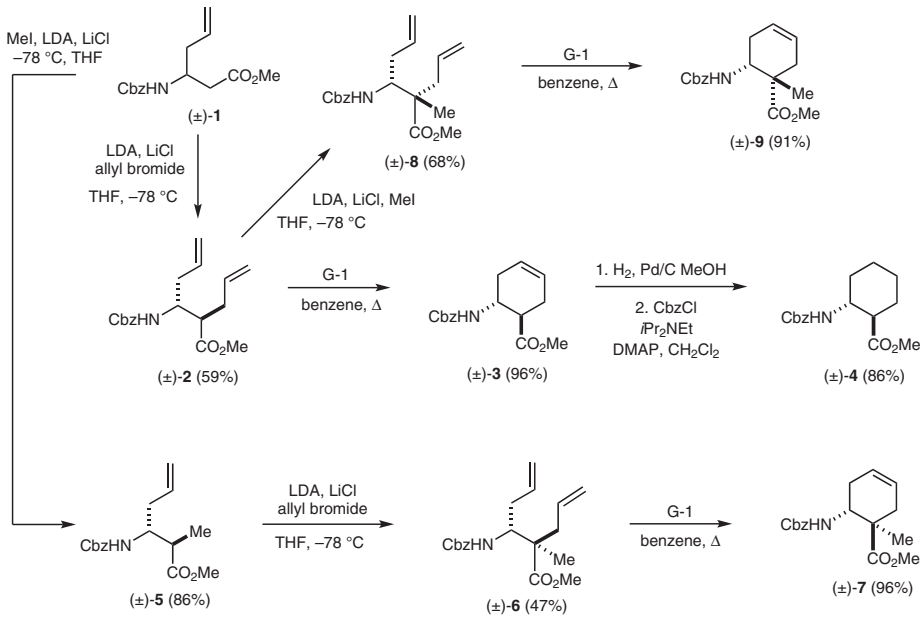
Ring-closing metathesis is a widely applied key step to build cyclic frameworks with different sizes.[32] The newly-formed olefinic bond affords great possibilities for further functionalizations, such as oxidations, aziridination, epoxidation, dihydroxylation, metal-catalyzed couplings, Diels–Alder reactions, etc. Another approach is the application of cross metathesis to form appropriate acyclic precursors for subsequent cyclizations. In most cases, metathesis protocols developed for the construction of cyclic β-amino acids are suitable for the preparation of different ring sizes. In most cases, the preparation of both five- and six-membered cycles using the same method is described; therefore, these syntheses are summarized separately from the construction of larger or condensed rings. Numerous research groups have utilized metathesis reactions toward cyclic β-amino acid derivatives and some of the major relevant developments are summarized.

2.1 Synthesis of Five- and Six-Membered Cyclic β-Amino Acids by Ring-Closing Metathesis

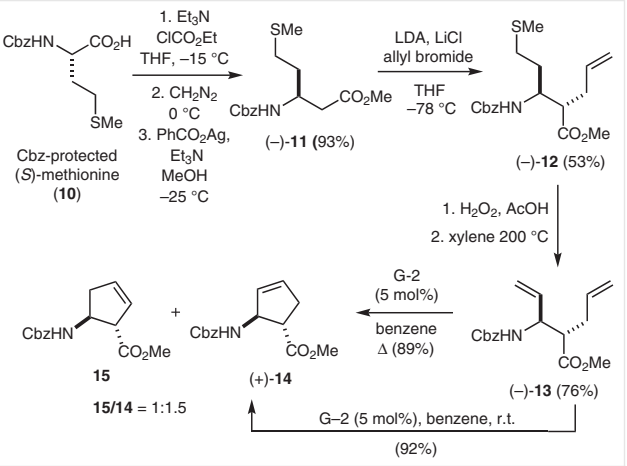
Abell and co-workers described an elegant process involving ring-closing metathesis (RCM) for the construction of cyclohexene *cis*- and *trans*-$\beta^{2,3}$-amino esters substituted or unsubstituted at the α-position (Scheme 1).[33a] Acyclic β-amino ester (±)-**1** (obtained from protected allylglycine) was transformed into diene (±)-**2** by stereoselective base-mediated allylation. This was followed by RCM in the presence of Grubbs first-generation catalyst (G-1) readily affording *trans*-$\beta^{2,3}$-amino acid derivative (±)-**3** with a cyclohexene framework. Its saturated counterpart (±)-**4** was easily accessible by hydrogenation of the olefinic bond over Pd/C.[33b]

To extend the developed approach, α-substituted cyclic β-amino acids (±)-**7** and (±)-**9** were synthesized (Scheme 1) . The relative stereochemistry of the carboxylic and amino functions depended on the sequence of alkylation. When compound (±)-**1** was first reacted with alkyl iodide and then with allyl bromide, the cyclization of resulting (±)-**6** afforded *trans* derivative (±)-**7**. However, if the alkylation sequence was reversed (allylation followed by alkylation) compound (±)-**8** was formed, which could be cyclized to *cis*-amino acid (±)-**9**. Noteworthy, the use of optically pure **1** prepared by using Evans chiral auxiliary group enables the synthesis of (–)-**3** and (–)-**4** in enantiomerically pure form.

Abell and co-workers then published an extended version of this method for the synthesis of cyclic $\beta^{2,3}$-amino acid derivatives substituted or unsubstituted at the α-position (Scheme 2).[34] This approach is suitable for access to five-, six-, and seven-membered ring systems. Starting from readily accessible optically active α-amino acid building blocks such as (*S*)-methionine or (*R*)-allylglycine, enantiomerically pure five- or six-membered cyclic $\beta^{2,3}$-amino acids could easily be synthesized. The first step of the synthetic strategy towards five-membered rings was the Arndt–Eistert carbon chain elongation of Cbz-protected (*S*)-methionine **10** to form the corresponding β-amino ester (–)-**11**, which was subsequently submitted to stereoselective allylation with allyl bromide and LDA in the presence of LiCl. The other alkenyl group, necessary for cyclization, was introduced in the next step by oxidative elimination to afford (–)-**13**.

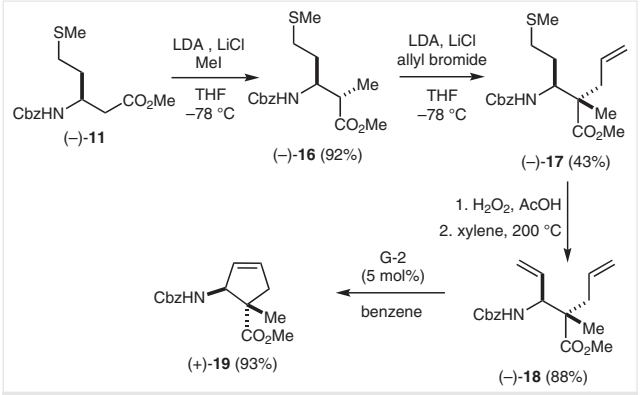


Scheme 1



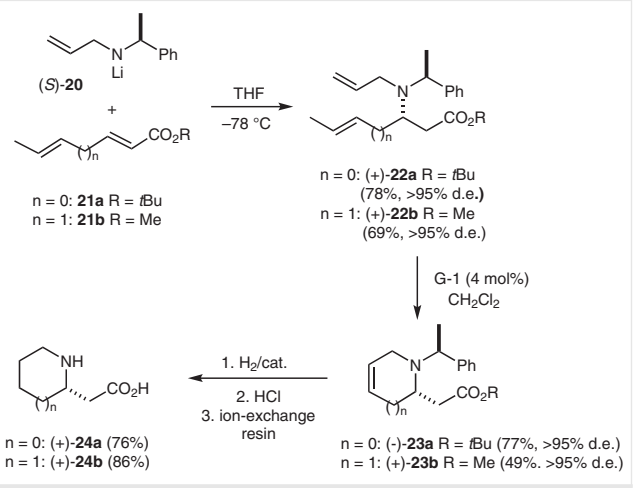
Scheme 2

Compound (–)-**13** was readily transformed to cyclopentene β[2,3]-amino ester in the presence of Grubbs second-generation catalyst (G-2). However, when the temperature was increased, both the expected ring-closure product (+)-**14** and its isomerized derivative **15** were formed in a 1.5:1 ratio. This synthetic strategy is also suitable for the preparation of α-substituted cyclic derivatives. For this purpose, compound (–)-**11** was stereoselectively alkylated by MeI, which afforded α-methyl-substituted ester (–)-**16** as a single diastereomer (Scheme 3). Diastereoselective allylation of (–)-**16** gave (–)-**17**, which was transformed by oxidative elimination to acyclic β-amino acid derivative (–)-**18** bearing two alkenyl side chains. To avoid isomerization observed before, RCM of compound (–)-**18** was conducted at room temperature with G-2 catalyst to give α-methyl-substituted cyclopentene β[2,3]-amino ester (+)-**19**.



Scheme 3

Davies and co-workers developed a versatile synthetic methodology enabling the stereoselective synthesis of five-membered cyclic β[2,3]- and β[3]-amino acids and six-membered cyclic β[3]-amino acids.[35a] First, compounds (+)-**22a**,**b** were prepared by conjugate addition of lithium (*S*)-allyl(1-phenylethyl)amide (**20**) to α,β-unsaturated esters **21a**,**b** with high diastereomeric excess (Scheme 4). Ring-closing metathesis of (+)-**22a**,**b** furnished *N*-heterocyclic β[3]-amino acid derivatives (–)-**23a** and (+)-**23b**, which were then converted into free amino acids (+)-**24a**,**b**.



Scheme 4

In order to synthesize cyclic β[2,3]-amino acids, allylation of diolefin (+)-**22a** was performed yielding an inseparable mixture of *anti* and *syn* diastereomers **25** (Scheme 5). Next, the corresponding secondary amines obtained by *N*-deallylation of compound **25** with Wilkinson catalyst were separable by column chromatography and the major (*anti*) diastereomer (–)-**26** was isolated in 77% yield with >95% d.e.

On the basis of earlier experience, the amine function was transformed into a carbamate in order to avoid chelate formation, which greatly reduces the activity of the Grubbs catalyst. Cyclization of (–)-**27** by RCM gave cyclic β[2,3]-amino acid derivative (+)-**28**, which was subsequently deprotected to afford transpentacin hydrochloride [(+)-**29**].

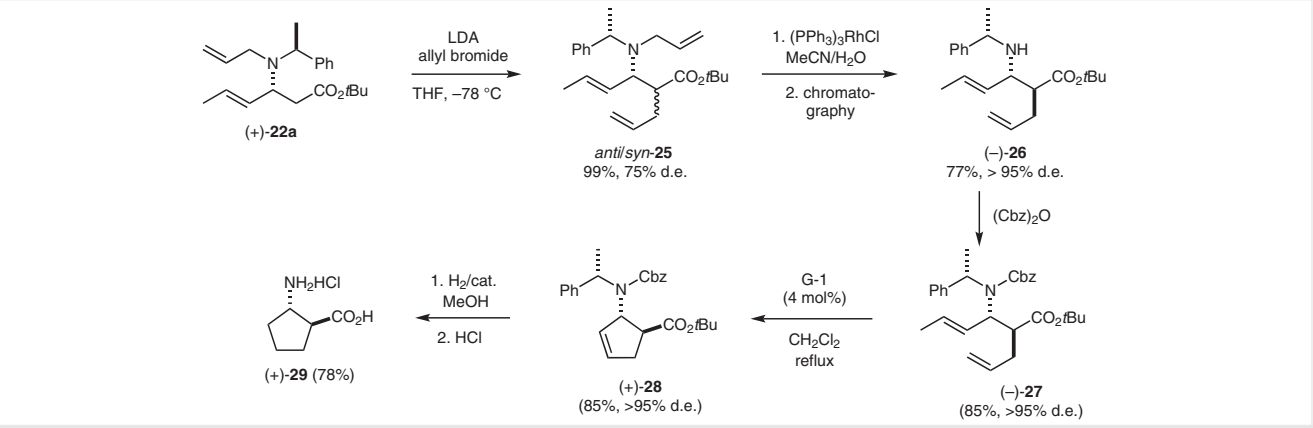
Davies and co-workers extended the above ring-closing metathesis protocol for access to various alkyl-substituted (Me, Et, Bn, *i*Pr, *t*Bu, etc.) cispentacin derivatives involving the Ireland–Claisen rearrangement of various allylic ester derivatives as the key step.[35b]

Davis and Theddu elaborated a general method for the asymmetric synthesis of cyclic *cis*-β-amino Weinreb amides, which are easily transformed in two steps to cyclic *cis*-β[2,3]-amino acid derivatives.[36] As depicted in Scheme 6, optically pure open-chain dienes (+)-**32a**,**b** were synthesized with varied alkenyl chains by the conjugate addition of unsaturated prochiral Weinreb amide **31a**,**b** (enolates generated with LDA) to chiral sulfinimine (*S*)-(+)-**30** with high d.r. (99:1). Oxidation of compounds (+)-**32a**,**b** with *m*-CPBA provided tosyl-protected derivatives (–)-**33a**,**b**. RCM of compounds (+)-**32a**,**b** and (–)-**33a**,**b** with G-2 catalyst gave the expected cyclic β-amino Weinreb amides (+)-**35a**,**b** and (+)-**34a**,**b**, respectively.

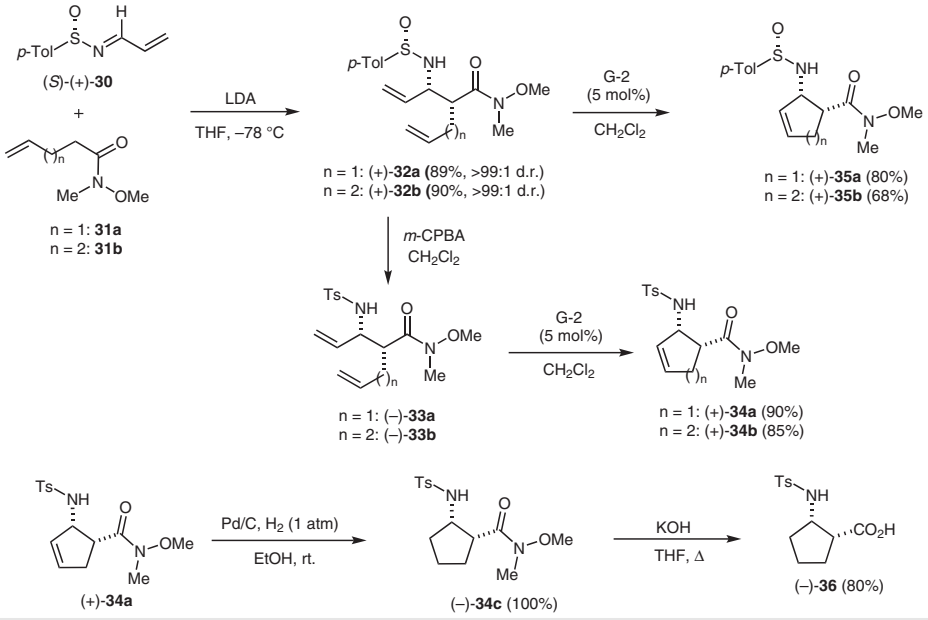
The possibility of creating the free carboxyl group was studied in details in the case of five-membered derivatives (+)-**34a** and (+)-**35a**. Both compounds decomposed during hydrolysis; however, in the case of Weinreb amide (+)-**34a**, saturation of the ring followed by hydrolysis readily afforded aminocarboxylic acid (–)-**36** (Scheme 6).

This strategy[36] was applicable to the asymmetric synthesis of seven-membered cyclic *cis*-β-amino Weinreb amides. It is worth mentioning that in addition to β-amino acids, other valuable molecules, such as ketones, aldehydes, β-keto esters, and β-ketophosphonates, are also achievable via Weinreb amides.

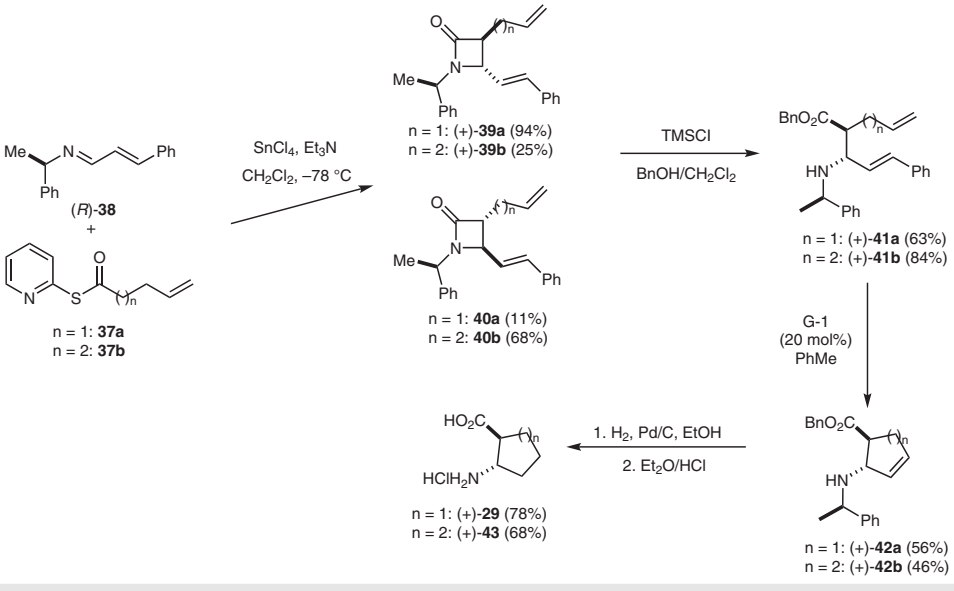
A stereoselective route towards cyclic β[2,3]-amino acids was described by Perlmutter and co-workers. The protocol involved the transformation of the bonds formed by nucleophilic addition utilizing ring closure (Scheme 7).[37] This method is frequently applied for the synthesis of hetero- and carbocyclic compounds.[38]



Scheme 5



Scheme 6



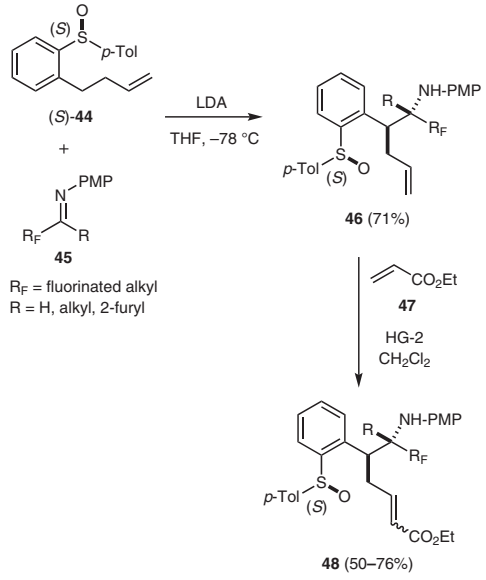
Scheme 7

The first step of the procedure is the diastereoselective condensation between *S*-pyridyl thioesters **37a**,**b** and optically pure imine (*R*)-**38** (Scheme 7). The reaction provided a mixture of diastereomers [(+)-**39** as major and **40** as minor product], which were separable by chromatography. Attempted ring closure of (+)-**39a**,**b** to form bicyclic β-lactams was unsuccessful because of ring strain. To avoid this problem, the azetidinone rings were opened to produce acyclic dienes (+)-**41a**,**b**, which easily underwent RCM with G-1 catalyst. Hydrogenation of the olefinic bond followed by hydrolysis in the presence of HCl afforded optically pure five- and six-membered saturated cyclic β-amino acid hydrochlorides (+)-**29** and (+)-**43**.

2.2 Synthesis of Five- and Six-Membered Cyclic β-Amino Acids by Cross Metathesis

Although some acyclic dienes have been successfully transformed further by RCM, only a few examples were reported in which cross metathesis (CM) was utilized to ac-

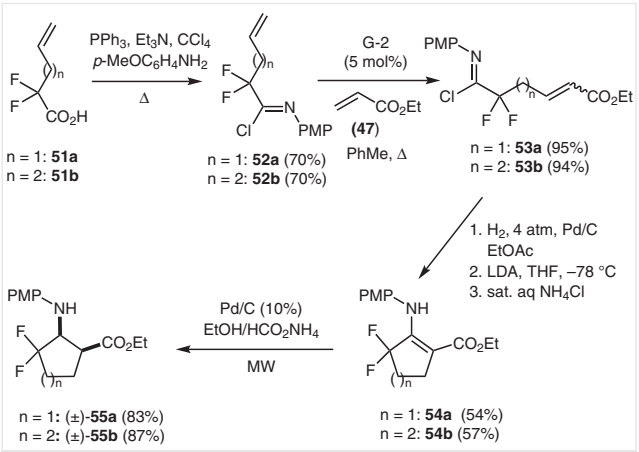
cess of cyclic β-amino acids. In these examples, metathesis played a role in the synthesis of the appropriate acyclic precursors, which were then cyclized by intramolecular addition or condensation. In one of these examples, Fustero and co-workers reported a diastereodivergent synthesis of enantiomerically pure fluorinated homoproline derivatives (cyclic β^3-amino acids) with three stereogenic centers.[39] As shown in Scheme 8, deprotonation of sulfoxide (*S*)-**44** at the benzylic carbon led to the corresponding carbanion that upon addition to fluorine-containing aldimine **45** gave amine **46** with high diastereoselectivity. Cross metathesis performed with ethyl acrylate (**47**) in the presence of Hoveyda–Grubbs second-generation catalyst (HG-2) furnished **48** as a mixture of *E*/*Z* diastereomers.



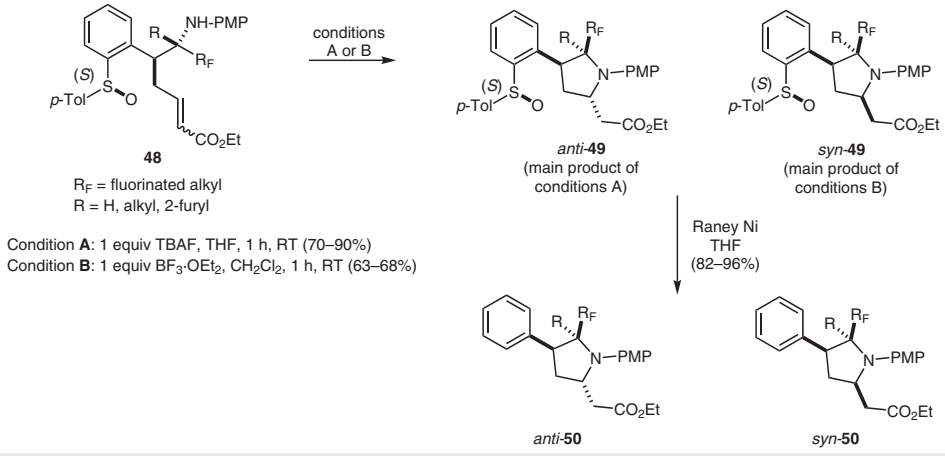
Scheme 8

Cyclization of **48** through intramolecular aza-Michael reaction can result in two epimers of **49** with relative *syn* or *anti* arrangement of the fluorinated alkyl group and the ester moiety. The diastereoselectivity was found to depend on the reaction conditions: base-mediated cyclization provided the *anti* epimer as the main product, while treatment with $BF_3{\cdot}OEt_2$ afforded mostly the *syn* epimer. The change in stereoselectivity was due to the formation of a chelate ring involving the ester carbonyl, the sulfoxide and the nitrogen atom (Scheme 9). Removal of the chiral auxiliary was performed in the final step using Raney Ni catalyst in THF giving homoproline derivatives **50**.

Fustero and co-workers also described an interesting synthetic example. They successfully performed racemic and asymmetric syntheses of difluorinated five- and six-membered *cis* cyclic $\beta^{2,3}$-amino acid derivatives through CM (Scheme 10; for the synthesis of seven-membered rings, see Section 2.3).[40] In the first step, imidoyl chlorides **52a**,**b** were synthesized from the corresponding 2,2-difluorinated carboxylic acids **51a**,**b**. Cross-coupling reaction between imidoyl chlorides and ethyl acrylate (**47**) afforded the expected open-chain compounds **53a**,**b**.



Scheme 10



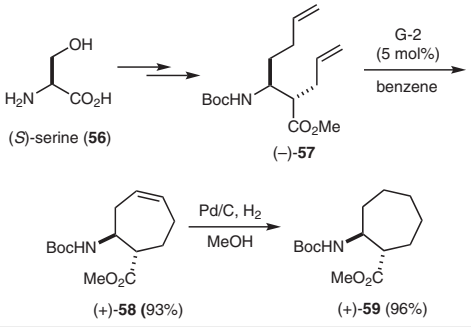
Scheme 9

This is a remarkable achievement as the first reported case of using the G-2 catalyst in the reaction of imidoyl chlorides. Chemoselective hydrogenation of the olefinic bond and subsequent Dieckmann condensation in the presence of LDA at –78 °C resulted in the formation of cyclic enamino compounds **54a**,**b**. In the final step, chemo- and stereoselective reduction was accomplished to give final products (±)-**55a**,**b** with *cis* configuration. The method was extended to the preparation of enantiomerically pure compounds. For this purpose, (+)-8-phenylmenthol acrylate was coupled with imidoyl chloride **52a** to afford the optically pure analogue of compound **53a**, which was further transformed similar to the racemic counterpart (**53a**).

2.3 Synthesis of β-Amino Acids with Larger Ring Systems by Ring-Closing Metathesis

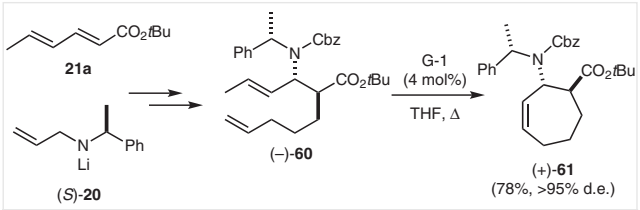
Construction of larger ring systems has challenged synthetic chemists for a long time; however, several techniques are available in the synthetic toolbar today.[41] RCM opened up new possibilities for access to ring sizes from medium rings to macrocycles, because low substrate concentrations prefer ring closure over polymerization even in the case of these challenging ring systems.[32] Among various compounds, β-amino acid derivatives were also prepared in this manner.

The method developed by Abell and co-workers, where five- and six-membered cyclic $\beta^{2,3}$-amino esters were synthesized from easily accessible α-amino acid building blocks, was further extended to construct seven-membered rings (Scheme 11).[34] Acyclic precursor (–)-**57**, prepared from (*S*)-serine (**56**) in multiple steps similar to (–)-**13** (Section 2.1, Scheme 2), was cyclized by G-2 catalyst then hydrogenated on Pd/C to furnish target compound (+)-**59**.



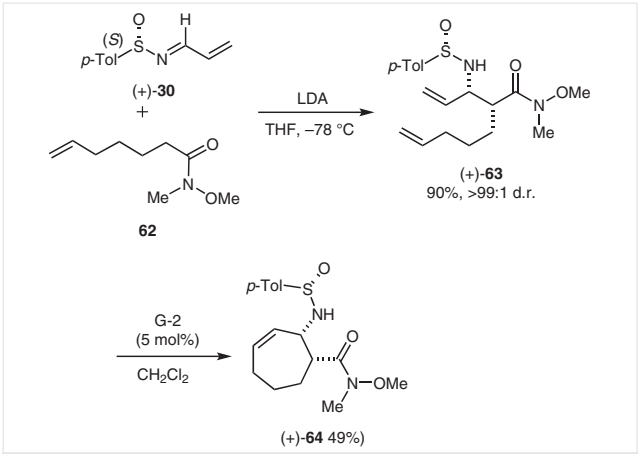
Scheme 11

Diastereoselective conjugate addition of lithium (*S*)-*N*-allyl-*N*-α-methylbenzylamide (**20**) to α,β-unsaturated ester **21a** described by Davies and co-workers (Section 2.1, Scheme 4) is also applicable for the creation of larger ring systems.[35] As presented in Scheme 12, compound (–)-**60**, synthesized similar to (–)-**27**, was treated with G-1 catalyst to yield seven-membered unsaturated cyclic amino ester (+)-**61**.



Scheme 12

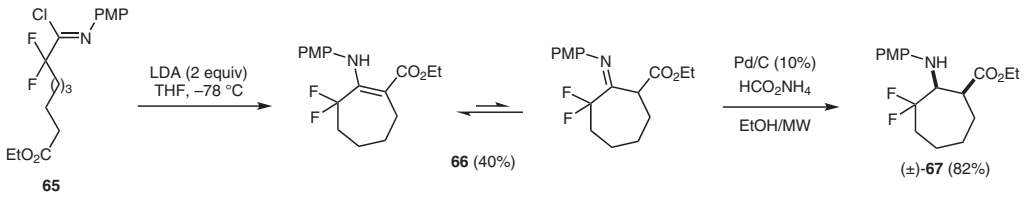
Davis and Theddu successfully applied their approach (Section 2.1, Scheme 6) for the preparation of a seven-membered ring by submitting prochiral Weinreb amide **62** to conjugate addition with acrolein-derived sulfinimine (*S*)-(+)-**30**.[36] Precursor (+)-**63** thus formed was readily cyclized with G-2 catalyst to seven-membered cyclic β-amino acid derivative (+)-**64** (Scheme 13).



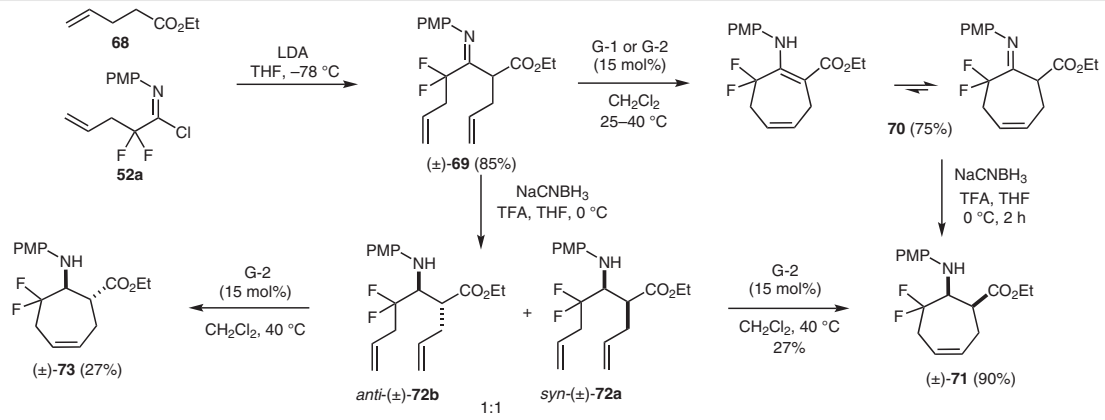
Scheme 13

The synthetic route developed by Fustero and co-workers, where imidoyl chlorides obtained through CM and subsequent reduction (Section 2.2, Scheme 10) were submitted to Dieckmann condensation, is also suitable to form a seven-membered ring system.[40] As shown in Scheme 14, cyclization of **65**, in this case, resulted in compound **66** as a tautomeric mixture with a 3:2 ratio. In the final step, chemo- and stereoselective reduction provided fluorinated *cis*-2-aminocycloheptanecarboxylic acid derivative (±)-**67**.

Fustero and co-workers also published a study where seven-membered cycles such as compounds (±)-**71** and (±)-**73** were synthesized exclusively through RCM (Scheme 15).[42] In this approach, fluorinated imidoyl chloride **52a** synthesized earlier (Section 2.2, Scheme 10) was subjected to condensation with the enolate of ethyl pent-4-enoate (**68**) to give β-imino ester (±)-**69**. Next, cyclization was performed with both first- and second-generation Grubbs cat-



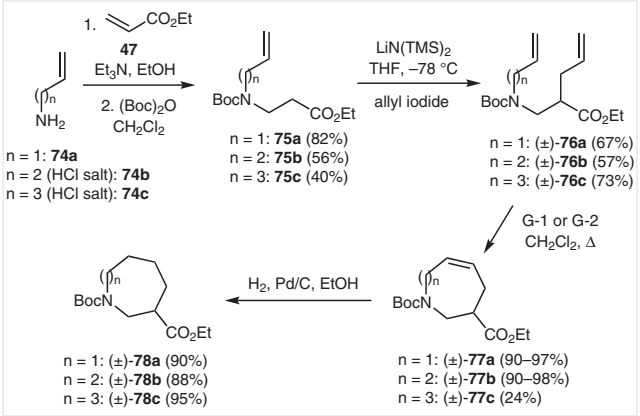
Scheme 14



Scheme 15

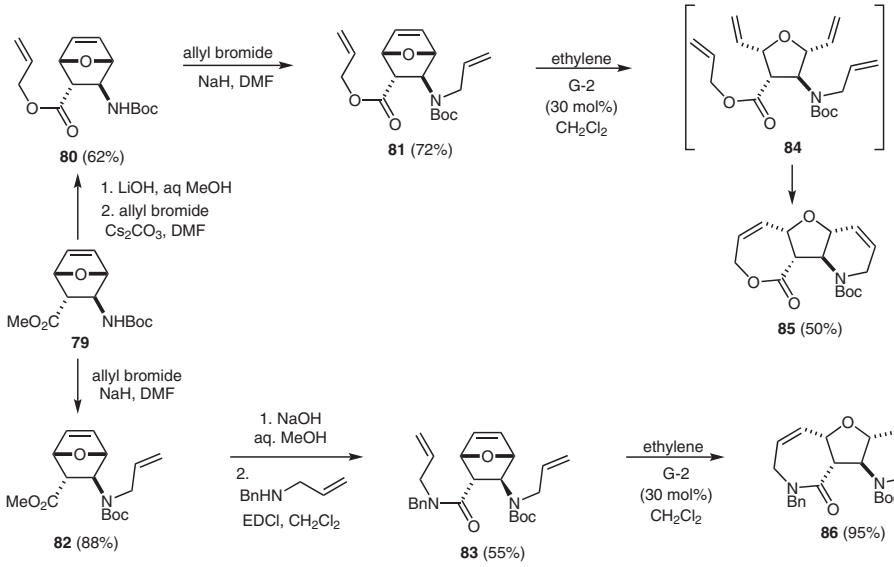
alysts with the latter affording a better result. The resulting tautomeric mixture **70** with the dominating imino form was reduced with $NaCNBH_3$ in a diastereoselective manner to furnish fluorinated *cis*-β-amino acid derivative (±)-**71** with cycloheptene ring as the sole product. Furthermore, the synthesis of *trans* derivative (±)-**73** could also be achieved. Thus, reduction of (±)-**69** with $NaCNBH_3$ gave a 1:1 mixture of *syn* and *anti* diastereomeric acyclic β-amino esters (±)-**72a** and (±)-**72b** and this mixture afforded the cyclized compounds in the final RCM steps.

Ohkubo and co-workers elaborated a general procedure for the synthesis of larger 7-, 8-, and nine-membered cyclic β²-amino acid derivatives utilizing RCM (Scheme 16).[43a] The acyclic diene derivatives were prepared in three consecutive steps from readily available aliphatic amines in which the alkenyl chain length predetermined ring sizes during cyclization. β-Amino ester moieties were formed by conjugate addition of amines **74a–c** to ethyl acrylate (**47**). Subsequent *N*-Boc-protection followed by allylation at the α-position resulted in the corresponding (±)-**76a–c** precursors. In the case of (±)-**76a** and (±)-**76b**, cyclization smoothly afforded the desired seven- and eight-membered cycloalkene derivatives (±)-**77a** and (±)-**77b**, respectively. However, during the cyclization of (±)-**76c**, because of olefin bond isomerization in the starting material, (±)-**77c** and (±)-**77b** were formed in a 4:1 ratio. Saturated cyclic β²-amino acid derivatives (±)-**78a–c** were prepared by reduction of the ring olefinic bonds. By slightly modifying the synthetic route discussed above, the authors were also able to synthesize *N*-Boc-protected seven- and eight-membered cyclic β²-amino acids in enantiomerically pure form.



Scheme 16

Peptidomimetics incorporating seven-membered cyclic β-amino acids in their structure, in which the nitrogen atom is part of the ring system were synthesized by ring-closing metathesis of some diolefinated acyclic α- or β-amino acid derivatives.[43b]



Scheme 17

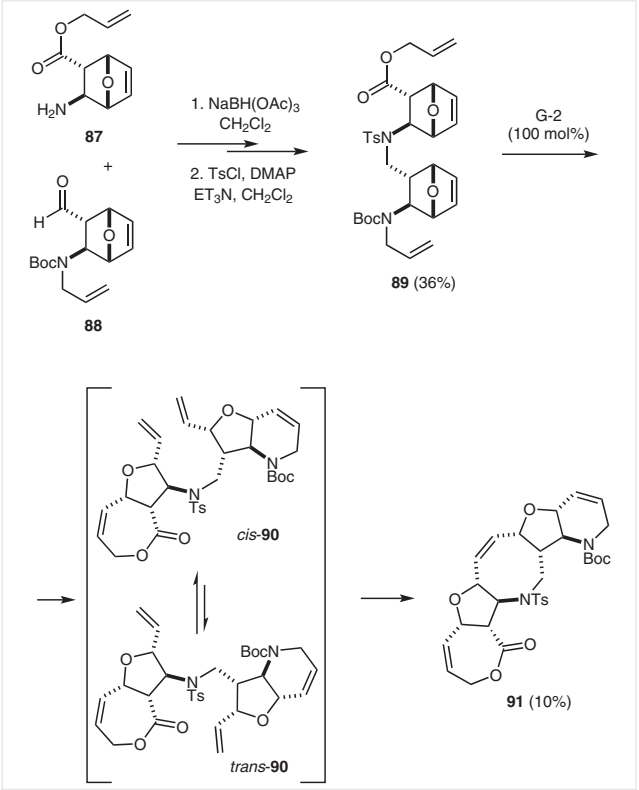
2.4 Synthesis of β-Amino Acids with Condensed Ring Systems by Ring-Rearrangement Metathesis

The usefulness of domino and tandem metathesis reactions in the synthesis of β-amino acid derivatives with condensed ring is described in this short section. These transformations allow the rapid synthesis of carbo- or heterocyclic ring systems fused in varied fashions through the rearrangement of the olefin bonds. A frequently used sequence in these cases is the intramolecular ring-opening/ring-closing protocol. Because of their high ring strain, bridged bicyclic frameworks (e.g., norbornene and oxanorbornene) provide a great possibility to access condensed five- or six-membered carbo- or heterocyclic systems.[44]

Winkler and co-workers utilized the benefits of the oxanorbornene framework for the syntheses of novel tri- and pentaheterocyclic ring systems via tandem metathesis.[45] Metathesis substrates were prepared from bicyclic oxanorbornene amino ester **79** by changing the methyl ester to an allyl ester (compound **80**) followed by *N*-allylation to give **81**. Alternatively, amino ester **79** underwent *N*-allylation to **82** and subsequent creation of an *N*-allylamide moiety **83** (Scheme 17).

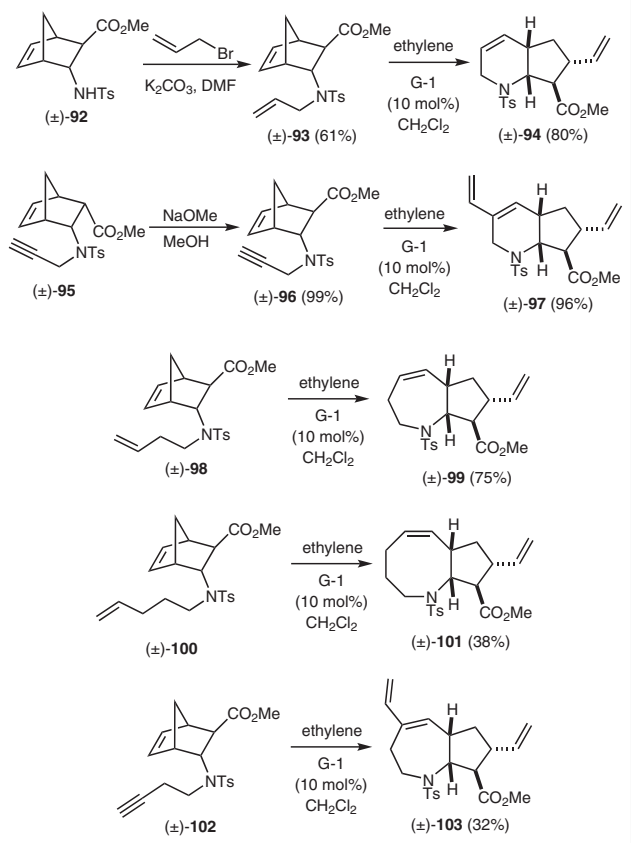
Ring-opening metathesis of the strained oxabicyclo ring of **81** provided reactive intermediate **84** with four terminal olefinic functions. It reacted immediately through RCM to form condensed tricyclic β-amino acid derivative **85**. Analogous tandem metathesis of precursor **83** gave derivative **86**, a lactam analogue of compound **85**.

Amino ester derivative **87** in reaction with **88** led to metathesis precursor **89** through reductive amination of aldehyde **88** with *O*-allylated amino ester **87** followed by *N*-tosylation. An important role of the tosyl group is to influence the rotational equilibrium of **90** ensuring the presence of the *cis* rotamer needed for the RCM step (Scheme 18).



Scheme 18

Nadany and Mckendrick applied a similar strategy towards constrained bicyclic β-amino acid derivatives. In these cases, however, only a single ring closure occurred (Scheme 19).[46a] To avoid the chelate formation with participation of the catalyst involving the carbonyl oxygen and the nitrogen atom, *trans*-*N*-tosylated β-amino esters were utilized as starting compounds in all cases. Thus, amino ester (±)-**92** was reacted with allyl bromide to produce metathesis substrate (±)-**93**. Next, ring rearrangement metathesis (RRM) of *trans* β-amino ester (±)-**93** in the presence of ethylene and G-1 catalyst smoothly afforded the desired nitrogen-containing condensed heterocycle (±)-**94** in a tandem fashion. Domino metathesis reaction of alkyne derivative (±)-**96** and homologous (±)-**98**, (±)-**100**, and (±)-**102** allows the formation, respectively, of 5,6-fused (±)-**97**, 5,7-fused (±)-**99** and (±)-**103**, as well as 5,8-fused bicyclic β-amino esters (±)-**101**.



Scheme 19

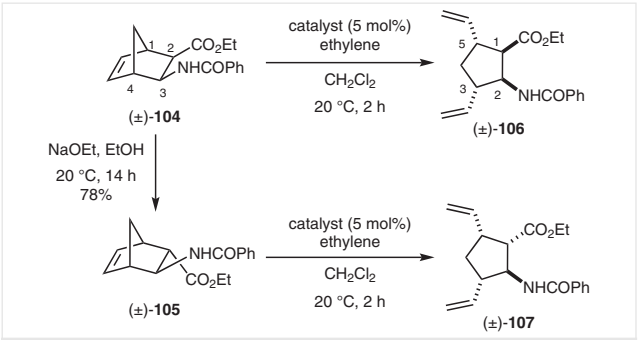
Various *N*-allylated oxanorbornene β-amino acids were also converted by ring-opening or ring-rearrangement metathesis techniques into bicyclic amino acid frameworks.[46b,c]

2.5 Stereocontrolled One-Step Synthesis of Functionalized Cispentacin and Transpentacin Derivatives

2.5.1 Stereocontrolled Synthesis of Functionalized Cispentacin and Transpentacin Derivatives through Ring-Opening Metathesis of Norbornene β-Amino Acid Derivatives

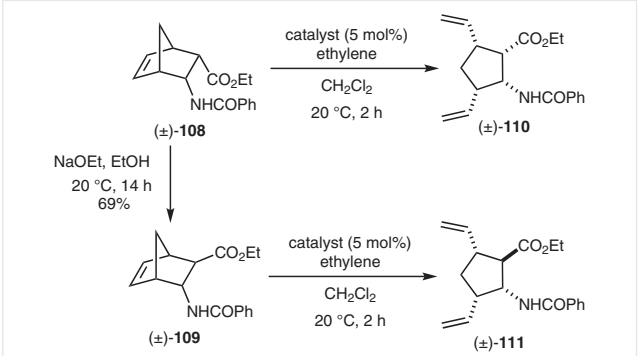
Cispentacin and its derivatives and various highly substituted cyclic amino acids are considered to be valuable bioactive small compounds as well as important building elements in the synthesis of various antimicrobial peptides.[1–16] Therefore, a logical concept was to extend metathesis towards this class of compounds. The synthesis of difunctionalized cispentacin and transpentacin derivatives was based on ROM reactions of constrained unsaturated bi- and tricyclic ring systems driven by the release of their high ring strain. For this purpose, some norbornene β-amino ester isomers were excellent precursors.

Thus norbornene β-amino ester stereoisomers as four bicyclic metathesis substrates [(±)-**104**, (±)-**105**, (±)-**108**, and (±)-**109**] were selected as stating materials and their ring-opening metathesis reaction was investigated toward the preparation of diolefinated cispentacin derivatives. Racemic 3,5-divinylated amino ester stereoisomers (±)-**106**, (±)-**107**, (±)-**110**, and (±)-**111** differing in the relative configuration of the C-1 and/or C-2 atom, were found to be readily accessible through ROM of the corresponding starting bicyclic compounds in the presence of ethylene and various Ru-based metathesis catalysts (Scheme 20 and Scheme 21).[47]



Scheme 20

Ring-opening metathesis reactions were systematically performed in anhydrous CH_2Cl_2 with ethylene in the presence of metathesis catalysts (G-1, G-2, HG-1, or HG-2). In the case of di-*exo*- and di-*endo*-β-amino ester substrates (±)-**104** and (±)-**108**, a general correlation between yields and the used catalyst was not found, although HG-2, in both cases, was slightly more effective than the other catalysts. However, the yields in the case of *endo*-*exo* (±)-**105** and *exo*-*endo* (±)-**109** derivatives found with first-generation catalysts were more than twice as high as those by sec-



Scheme 21

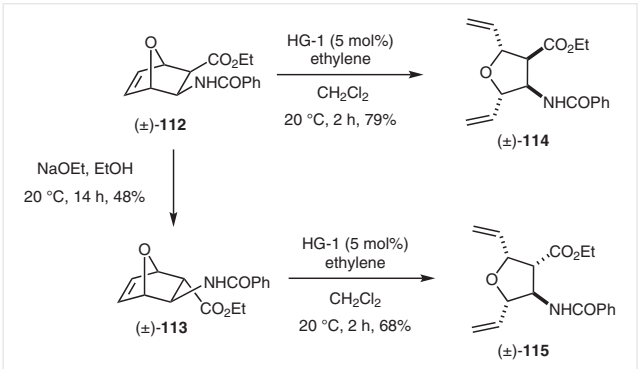
ond-generation ones (Schemes 20 and 21, Table 1). Furthermore, these two compounds afforded the best yields as well (80% and 68%). Lower yields found with di-*exo* and di-*endo* derivatives (±)-**104** and (±)-**108** may be explained by chelation with the catalyst. The *cis* arrangement of the amide and ester groups in these substrates enables their simultaneous coordination to the Ru center, which highly reduces the efficiency of the catalyst. It is worth mentioning that the bicyclic starting materials possess four asymmetric centers, and since these stereogenic centers are unaffected during the transformations, the chiral information is transferred to the final products.

Table 1 Isolated Yields for (±)-**106**, (±)-**107**, (±)-**110**, and (±)-**111** in ROM Reactions with Various Catalysts

Substrate	Product	Catalyst G-1	G-2	HG-1	HG-2
di-*exo* (±)-**104**	(±)-**106**	37%	33%	38%	41%
endo-*exo* (±)-**105**	(±)-**107**	46%	20%	80%	28%
di-*endo* (±)-**108**	(±)-**110**	6%	26%	29%	31%
exo-*endo* (±)-**109**	(±)-**111**	68%	29%	45%	16%

The synthetic approach discussed above was extended to the preparation of optically pure target substances (+)-**106** and (–)-**107**. Optically pure norbornene β-lactam prepared by lipolase-catalyzed enantioselective enzymatic ring opening of the corresponding racemic azetidinone, followed by ethanolysis, benzoylation, and ROM afforded the desired enantiopure divinylated substances.[47]

As a consequence of the relevance of oxygen-containing cyclic β-amino acids (e.g., oxetin),[1,2] the stereocontrolled one-step method described above was extended toward divinylated tetrahydrofuran β-amino esters as depicted in Scheme 22.[47]



Scheme 22

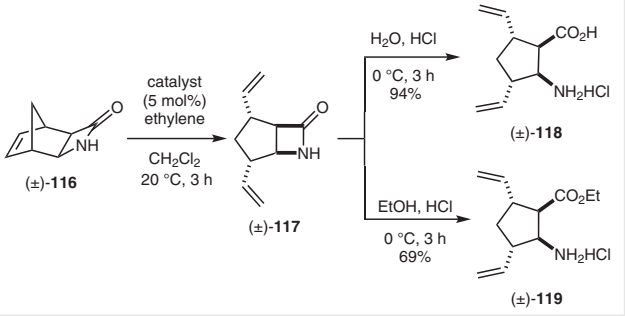
The synthesis of (±)-**114** and (±)-**115** was accomplished in good yields from the corresponding bicyclic starting materials (±)-**112** and (±)-**113** in ROM reaction with conservation of the configuration of the four stereogenic centers (Scheme 22).

2.5.2 Stereocontrolled Synthesis of Functionalized Azetidinones and β-Amino Acid Derivatives from Condensed Ring β-Lactams by Ring-Opening Metathesis

Some functionalized β-lactams and β-amino acid derivatives were also synthesized through metathesis reactions. The driving force of these transformations is the formation of thermodynamically more stable scaffolds that have lower ring strain than the bi- or tricyclic starting materials.

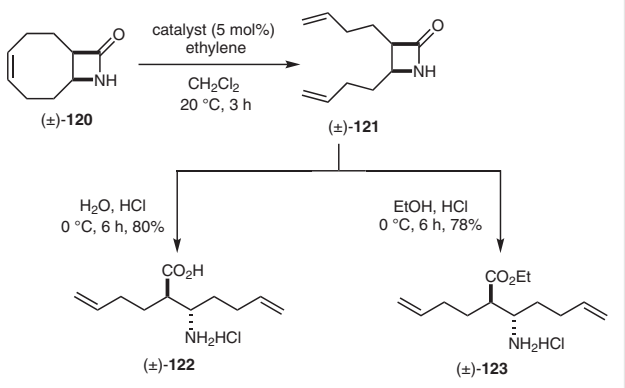
During these processes, epimerization was not observed: the stereochemistry of the starting β-lactams was conserved and it determined the configuration of the chiral centers in the final products. Di-*exo*-β-lactam (±)-**116** was subjected to ROM reaction in the presence of various first- and second-generation Ru-based catalysts (G-1, G-2, HG-1, and HG-2) with ethylene in CH_2Cl_2 at 20 °C. Divinyl-substituted β-lactam (±)-**117** was formed in high yields with first-generation catalysts, while second-generation catalysts preferred the formation of polymeric materials. Racemic cispentacin derivatives (±)-**118** and (±)-**119** containing valuable C–C double bonds were accessed through opening of the heterocyclic ring. Thus, β-lactam (±)-**117** was sub-

jected to hydrolysis or ethanolysis in a stereocontrolled fashion to give the corresponding cyclopentane β[2,3]-amino acid (±)-**118** or β[2,3]-amino ester (±)-**119** as hydrochloride salts in good to high yields [(±)-**117** G-1: 80%; G-2: 5%; HG-1: 70%; and HG-2: 10%] (Scheme 23).[48]



Scheme 23

This ring-opening metathesis strategy was extended to the stereocontrolled synthesis of functionalized β-lactams with a terminal olefin moiety. Racemic monocyclic azetidinone (±)-**121** with terminal alkenyl functions was accessed through ring-opening metathesis. G-1 and HG-1 catalysts performed well in the ring-opening reaction, while G-2 and HG-2 were too reactive inducing mainly polymerization (Scheme 24, Table 2). Finally, treatment of compound (±)-**121** with HCl/H_2O at 0 °C gave the corresponding open-chain β-amino acid (±)-**122** with the carboxyl and amine functions in *anti* arrangement. Ethanolysis gave open-chain β-amino ester (±)-**123** with the same stereochemistry.

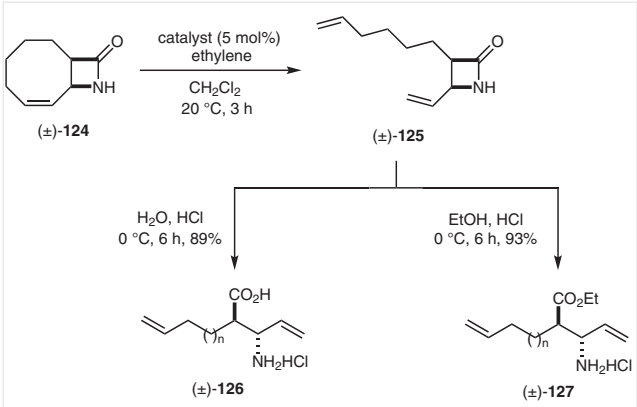


Scheme 24

Bicyclic β-lactam (±)-**124** derived from cycloocta-1,3-diene is a regioisomer of compound (±)-**120** (Scheme 25, Table 2). During the ring-opening protocol, first-generation catalysts proved to be beneficial again, although ring-opening product (±)-**125** was also isolated in modest but acceptable yields in the presence of catalysts G-2 and HG-2 in this case.

Table 2 Isolated Yields for (±)-**121** and (±)-**125** in ROM Reactions with Various Catalysts

Substrate	Product	Catalyst G-1	G-2	HG-1	HG-2
(±)-**120**	(±)-**121**	75%	7%	74%	17%
(±)-**124**	(±)-**125**	60%	25%	67%	26%

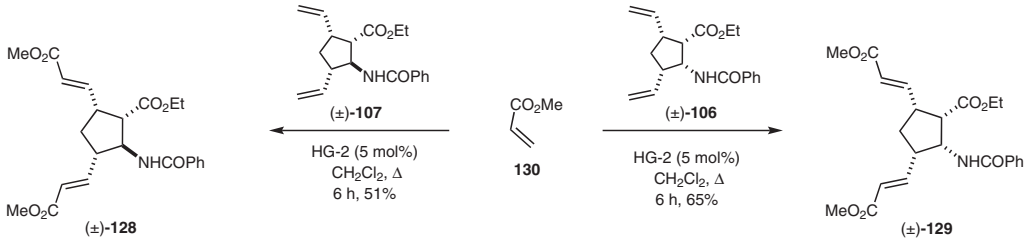


Scheme 25

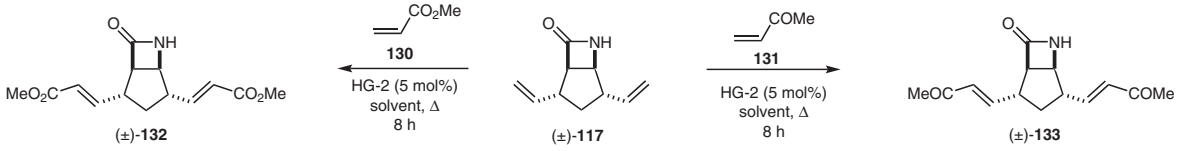
Acyclic β-amino acid (±)-**126** and β-amino ester (±)-**127** possessing olefinic bonds were prepared by azetidinone ring opening mediated by H_2O or EtOH under protic conditions furnishing the expected products with *anti* arrangement of the carboxyl and amino hydrochloride groups, as depicted in Scheme 25.

2.5.3 Carbon–Carbon Double Bond Functionalization of β-Amino Acid Derivatives and β-Lactams with α,β-Unsaturated Carbonyl Compounds through Cross Metathesis

Cross metathesis is a widely used method for the functionalization of olefinic bonds even in various complex structures. The reaction can proceed in a chemoselective manner and it is, in general, *E*-selective.[49] The functionalization of terminal alkene moieties of the corresponding β-lactams or β-amino acid derivatives could be achieved with CM reaction. For this purpose, α,β-unsaturated carbonyl compounds were used as electron-deficient olefins in the presence of HG-2 catalyst. Thus, divinylated transpentacin (±)-**107** was reacted with methyl acrylate (**130**) in the pres-



Scheme 26



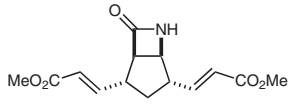
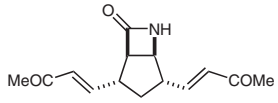
Scheme 27

ence of HG-2 catalyst in CH_2Cl_2 at reflux temperature to give dicoupled product (±)-**128** (Scheme 26). All-*cis*-divinylated β-amino ester (±)-**106** was submitted to cross metathesis with methyl acrylate (**130**) in the presence of HG-2 catalyst. Both cispentacin derivatives (±)-**128** and (±)-**129** with three ester functions were obtained without epimerization of the stereogenic centers. The CM reaction proceeded under stereocontrol with *E* selectivity, that is the configuration of the newly created olefinic bonds in (±)-**128** and (±)-**129** also have *E* geometry.[47]

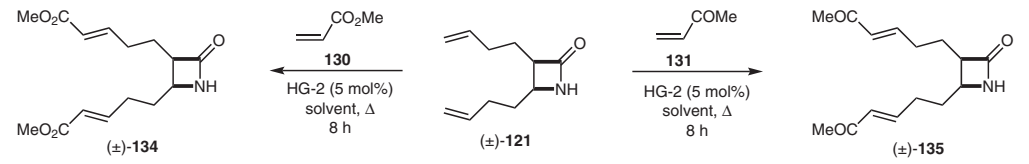
The cross-metathesis reaction was expanded to the coupling reaction to β-lactams. In addition to methyl acrylate (**130**), the terminal alkene moieties were also transformed with methyl vinyl ketone (**131**). Bicyclic β-lactam (±)-**117** was submitted to coupling reactions with α,β-unsaturated carbonyl compounds **130** and **131** in the presence of HG-2 catalyst. Cross-metathesis products (±)-**132** and (±)-**133** with *E* geometry were isolated in modest to good yields in both CH_2Cl_2 and toluene (Scheme 27, Table 3).[48]

The CM reaction could be expanded to monocyclic unsaturated β-lactam derivatives. Ring-opening product (±)-**121** was coupled with methyl acrylate (**130**) and methyl vinyl ketone (**131**) in the presence of HG-2 catalyst leading to the expected products (±)-**134** and (±)-**135** with *E* geometry (Scheme 28, Table 4).

Table 3 Isolated Yields for (±)-**132** and (±)-**133** in CM Reactions with HG-2 Catalyst in Different Solvents

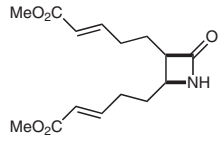
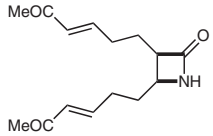
Product	Solvent	
	CH_2Cl_2	PhMe
 (±)-**132**	53%	18%
 (±)-**133**	88%	63%

β-Lactam derivative (±)-**125** (a regioisomer of (±)-**121**) underwent cross-metathesis reactions with electron-deficient olefins **130** and **131** yielding β-lactam diester (±)-**136** and its ketone counterpart (±)-**137** (Scheme 29, Table 5).[48]



Scheme 28

Table 4 Isolated Yields for (±)-**134** and (±)-**135** in CM Reactions with HG-2 Catalyst in Different Solvents

Product	Solvent CH_2Cl_2
 (±)-**134**	68%
 (±)-**135**	48%

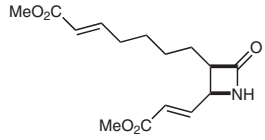
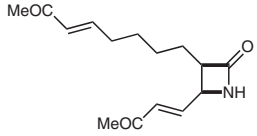
Product	Solvent CH_2Cl_2	PhMe
 (±)-**136**	63%	73%
 (±)-**137**	70%	56%

Table 5 Isolated Yields for (±)-**136** and (±)-**137** in CM Reactions with HG-2 Catalyst in Various Solvents

2.5.4 Synthesis of Functionalized β-Amino Acid Derivatives and β-Lactams through Chemoselective Cross Metathesis

Since the outcome of these transformations is often catalyst dependent, chemoselectivity observed in the field of metathesis reactions (RCM, CM) can originate from multiple factors, including the choice of catalyst. Steric or electronic deactivation of one of the olefinic bonds is also capable of inducing chemoselectivity.[50] On the other hand, several studies reported plausible hydrogen bond interaction in the pre-assembly phase between the catalyst halogen ligand and the substrate hydrogen atom, which favors the selective transformation of a certain olefinic bond.[51–53]

It was also described that the metallacyclobutane intermediate can be stabilized by the interaction of the metal center with nearby donor groups of the substrate, hindering further transformation of the involved olefinic bond.[54]

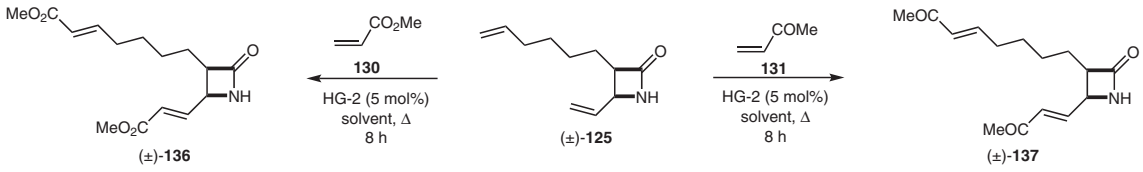
Reactions of some divinylated β-amino esters and β-lactams (derived from ROM reactions) with methyl vinyl ketone or acrylate esters in the presence of various metathesis catalysts furnished monocoupled products in a chemoselective manner.

Bicyclic lactam (±)-**117** was submitted to coupling reactions with methyl vinyl ketone (**131**) or acrylic esters **47** and **130** in the presence of commercially available G-1, G-2, HG-1, and HG-2 catalysts. However, coupling products (±)-**138** and (±)-**139a**,**b** were detected only in the presence of second-generation catalysts. Monocoupled products, involving the α,β-unsaturated carbonyl part located near to the amide nitrogen atom, were isolated only in moderate yields (Scheme 30).

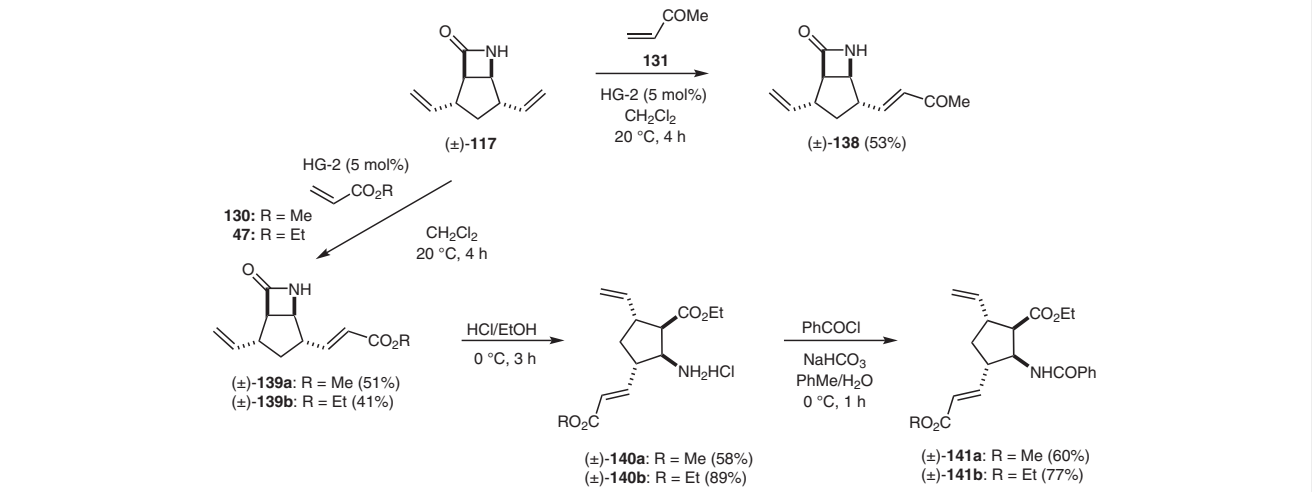
Monocoupled β-lactams (±)-**139a**,**b** were considered to be suitable precursors for stereocontrolled access to different cispentacin derivatives with olefinic bond via opening the heterocyclic ring. Thus, monocoupled cispentacin esters (±)-**140a**,**b** were synthesized from the corresponding β-lactams (±)-**139a**,**b** by ethanolysis. The amino function was protected by benzoylation to access novel monocoupled cyclic β-amino esters (±)-**141a**,**b** (Scheme 30).[55]

Although less known in metal-catalyzed processes, it was assumed that hydrogen bonding interaction between the halogen atom of the Ru–alkylidene complex and the amide N–H function as hydrogen bonding donor function could force the olefin bond closer to the amide nitrogen atom to participate in the coupling reaction.[51–53] This leads to the mono-metathesised product before further CM reaction could take place.

Metathesis substrate (±)-**142**, which cannot function as a hydrogen donor, was submitted to CM reaction with ethyl acrylate (**47**) in the presence of HG-2 catalyst. Since the directing effect was excluded in this case, the coupling reac-

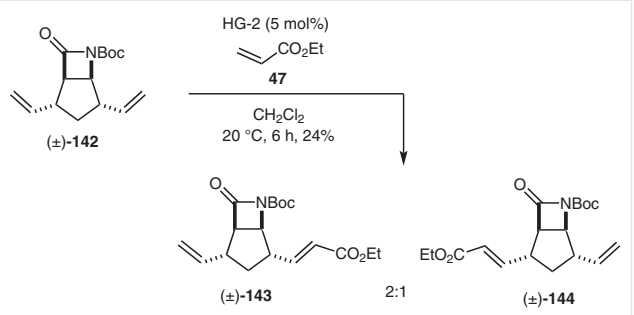


Scheme 29



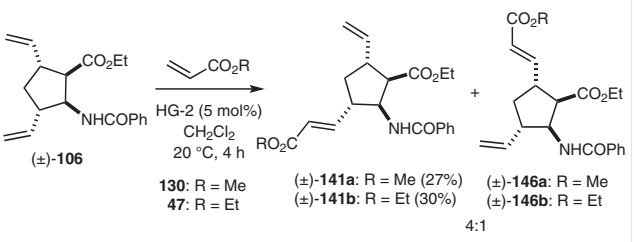
Scheme 30

tion was not selective and afforded a mixture of the two mono-metathesised isomers (±)-**143** and (±)-**144** in a ratio close to 2:1 (Scheme 31).



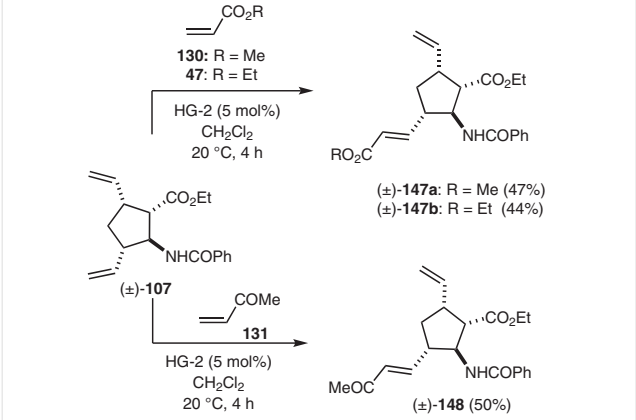
Scheme 31

Divinyl-substituted cispentacin (±)-**106** was submitted to CM reactions with acrylic esters **47** and **130** (Scheme 32) . However, these cross-metathesis reactions of compound (±)-**106** in view of monocoupled products were not completely selective: a mixture of two regioisomers (±)-**141** and (±)-**146** was formed in a 4:1 ratio through a partial hydrogen bonding directing effect.



Scheme 32

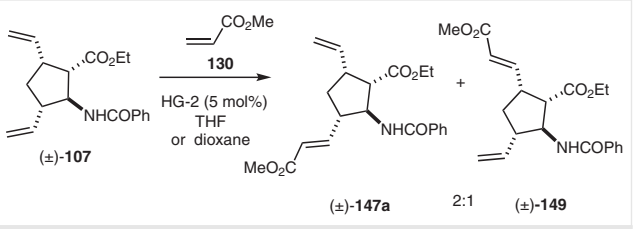
The chemical properties of diolefinated transpentacin (±)-**107** in chemoselective CM reactions were also investigated. Accordingly, compound (±)-**107** was subjected to cross-coupling with acrylic esters **47** and **130** or methyl vinyl ketone (**131**) at room temperature in CH_2Cl_2 with HG-2 catalyst to afford the corresponding mono-metathesised products (±)-**147a**,**b** and (±)-**148** (Scheme 33). In contrast to divinylated cispentacin (±)-**106**, the CM reaction in these cases resulted in single monocoupled isomers.



Scheme 33

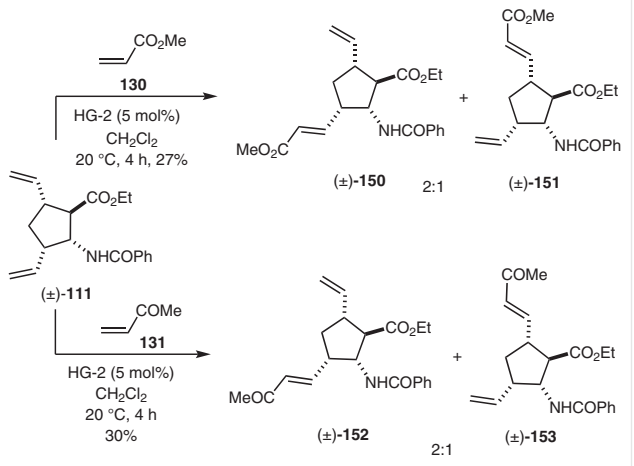
The results of the NH–NBoc change found previously suggested that the reason of the observed chemoselectivity in CM reactions is a hydrogen bond between the chlorine atom of the catalyst and the N–H moiety of the substrates. To disrupt this hydrogen bonding, CM reaction between compound (±)-**107** and methyl acrylate (**130**), which previously afforded only a single isomer in CH_2Cl_2, was performed in three additional solvents (THF, dioxane, and toluene). The solvents capable of participating in hydrogen bonding with the substrate (dioxane, THF) compete with

the catalyst providing a mixture of regioisomers (±)-**147a** and (±)-**149** (in ca. 2:1 ratio). In contrast, reactions in solvents not being able to form a hydrogen bond (CH_2Cl_2 and toluene) clearly gave only a single product (Scheme 33 and Scheme 34).



Scheme 34

However, when another diolefinated transpentacin stereoisomer, namely (±)-**111** was submitted to CM reaction with α,β-unsaturated carbonyl compounds **130** and **131**, inseparable mixtures of regioisomers (±)-**150**/(±)-**151** and (±)-**152**/(±)-**153**, respectively, were isolated. In both cases, isomeric ratios of about 2:1 were measured (Scheme 35).



Scheme 35

These results clearly suggested that, in addition to the hydrogen bonding effect, chemoselectivity may originate from steric effects. It is also highly probable, that coordination of ruthenium to the carbonyl oxygen creating a stable six-membered chelate ring stabilizes the metallacyclobutane intermediate and hinders further transformations.

3 Conclusions and Outlook

In summary, the current account is devoted to highlight synthetic methods through the application of ring-closing/ring-opening or cross-metathesis protocols for the access of varied, highly functionalized β-amino acid derivatives. Thus, the synthesized olefinated alicyclic or acyclic β-amino acid building blocks possess multiple stereogenic centers and high chemical diversity. The olefinated β-amino acids, achievable through the transformation of their C–C double bond, may be interesting precursors for the access of other novel classes of compounds. The applied metathesis protocols were summarized with emphasis on stereocontrol, efficiency, scalability, or/and robustness. The metathesis techniques and strategies discussed herein might be of high interest for the preparation of various other valuable densely functionalized olefinated derivatives. Because of the presence of the olefinic bond in their structure, the alkenylated molecular entities as three-dimensional scaffolds might have high synthetic relevance as well. Some of them may also function as building blocks for the synthesis of novel β-peptides and they may be considered interesting scaffolds for further pharmaceutical investigations.

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