Syntheses of functionalised β-amino acids through ring-opening/cross metathesis

PhD Thesis

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LIST OF ABBREVIATIONS

ADMET	acyclic diene metathesis polymerisation
CM	cross metathesis
CSI	*N*-chlorosulfonyl isocyanate
d.e.	diastereomeric excess
DIEA	*N,N*-diisopropylethylamine
DMAP	4-dimethylaminopyridin
DMF	dimethylformamide
d.r.	diastereomeric ratio
EDCI	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
e.r.	enantiomeric ratio
EYM	ene-yne metathesis
G1	Grubbs Catalyst 1st Generation
G2	Grubbs Catalyst 2nd Generation
HG1	Hoveyda-Grubbs Catalyst 1st Generation
HG2	Hoveyda-Grubbs Catalyst 2nd Generation
LDA	lithium diisopropylamide
LiN(TMS)$_2$	lithium bis(trimethylsilyl)amide
m-CPBA	*meta*-chloroperoxybenzoic acid
PMP	*para*-methoxyphenyl
RCM	ring-closing metathesis
ROM	ring-opening metathesis
ROMP	ring-opening metathesis polymerisation
RRM	ring-rearrangement metathesis
SHOP	shell higher olefin process
TEA	triethylamine
THF	tetrahydrofuran
TsCl	4-toluenesulfonyl chloride

1. INTRODUCTION AND AIMS

As a consequence of their high biological relevance, β-amino acids have gained an important role in medicinal and organic chemistry in the last twenty years. These structures are present in many natural compounds either in free form or as part of more complex molecules. Certain representatives such as the 5-membered carbocyclic cispentacin (isolated from the culture broth of *Bacillus cereus*) or icofungipen possess strong antifungal activities. Moreover, new generation peptides built from 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] Since the early 1990s thanks to the effective development and commercial availability of well-defined Ru-based catalysts, olefin metathesis reactions have revolutionised the synthetic thinking. Metathesis, consequently, has become a powerful tool for the creation of one or more C–C double bonds. With this new method in hand, many natural and biologically active compounds have been prepared, which were previously challenging or impossible to synthesize. Besides their utilisation at the laboratory scale, olefin metathesis has gained industrial applications as well.[17-39]

In the Institute of Pharmaceutical Chemistry at the University of Szeged, a number of synthetic methods were developed to access highly-functionalised cyclic β-amino acids.[40-63] Although the synthetic approaches presented in these studies cover a broad spectrum of chemical transformations including selective techniques, olefin metathesis reactions were not utilised. It has been realised, however, that the numerous types of metathesis transformations [ring-closing metathesis (RCM), ring-opening metathesis (ROM), ring-opening metathesis polymerisation (ROMP), acyclic diene metathesis polymerisation (ADMET), ene–yne metathesis (EYM), and cross metathesis (CM)] provide versatile protocols for the convenient preparation of diversely substituted β-amino acids and β-lactams.

The present PhD work focuses on the development of stereocontrolled synthetic methods for the preparation of novel alkenyl-functionalised β-amino acids and β-lactams through ring-opening metathesis reaction and on their subsequent functionalisation via cross metathesis taking place in highly selective manner in some cases. The ring-opening protocol is based on the high ring strain of the starting bi- or tricyclic compounds, which works as a driving force during stereocontrolled transformations. The products sometimes were prepared in optically pure form through enzymatic kinetic resolution of racemic compounds with azetidinone framework.

2. LITERATURE BACKGROUND

2.1. Background and history of metathesis reactions

Over the last 50 years, olefin metathesis has revolutionised synthetic organic chemistry and became a powerful tool to create one or more C–C double bonds under mild conditions with good functional group tolerance. This is a catalytic process in which redistribution of C–C double bonds occur mediated by a transition metal–carbene complex.[64] The word metathesis comes from the Greek μεταθεσιζ meaning transposition and has been used for this kind of reaction since 1967.[65-66] Metathesis reactions have gone through a long and difficult path to reach the present versatile form and they are not only new elements of the synthetic toolbar of organic chemistry, but changed the way chemists think about synthetic problems.[67-75]

The metathesis story started from three seemingly unrelated observations. In the late 1950s researchers at multiple companies reported the transformation of propylene to ethylene and 2-butenes in the presence of molybdenum compounds. It is interesting that in 1931 Schenider and Fröhlich reported a very similar transformation when they heated propylene at 752 °C without any catalyst, but their publication was ignored for a long time.[76-80] The next discovery was made in 1960 by a group at DuPont. They submitted norbornene to polymerisation resulting in a highly unsaturated polymer chain instead of the expected saturated one.[81] Finally, in 1964, during the attempted polymerisation of cyclopentene with tungsten and molybdenum halide catalysts, Natta et al. reported the unexpected formation of an unsaturated polymer.[82] These serendipities served a good starting point for further research.

In early times poorly-defined homogeneous and heterogeneous catalytic systems were used. These were based on transition metal compounds with strong Lewis acidic nature. Most functional groups did not tolerate these acids, which had many other drawbacks as well such as sensitivity to moisture or air. For these reasons in this time period the applicability of metathesis reaction was strongly limited.[67] The breakthrough came when Grubbs published the first well-defined Ru-based catalyst, which successfully polymerised norbornene and exhibited high stability against oxygen and water.[83] The real success for olefin metathesis comes from the wide range of transformations (RCM, ROMP, CM, ROM, EYM, and ADMET), which are feasible through this catalytic process (Fig. 1). A further useful property is that in most of the practically important cases the only side-product is a volatile olefin, which significantly facilitates purification. However, it should be taken into consideration that during metathesis reactions every starting material and possible product are in equilibrium with each other.
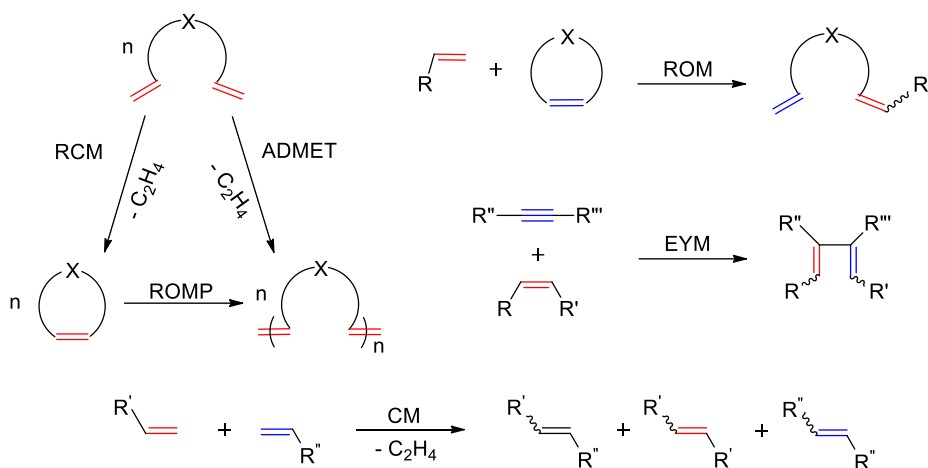
Figure 1.

2.2. Development of the olefin metathesis mechanism

Since the late 1950s researchers have been highly interested in olefin metathesis reactions because it seemed to be something mysterious, because numerous observations could not be explained on the basis of common knowledge at that time. The chemical community had to wait until 1967 for the first mechanistic proposal, which came from Bradshaw and was updated by Calderon in the following year (Fig. 2).[84-86] A four-centred pathway was assumed in which the interchange of the C–C double bonds takes place through a cyclobutane–metal complex intermediate ("pair-wise" mechanism). In 1972 Robert H. Grubbs, who had the primary role in the development of metathesis catalysts, also proposed a mechanism where the formation of the new olefin proceeds via a metallacyclopentane intermediate.[87] However, at that time the mechanism accepted today was already known published in 1971 by Yves Chauvin and his student Jean-Louis Hérisson.[64] Their theory, which is in agreement with all of experimental results, assumed the viability of a metal alkylidene (or metal carbene) complex.[88-97] In the first step it reacts with the olefin in a [2+2] cycloaddition (**A** reaction) to form the corresponding metallacyclobutane **B**. Note that [2+2] cycloadditions of alkenes are not allowed thermally, because of the symmetry rules.[98] In the following cycloreversion step, the formation of both the new C–C double bond and the new carbene complex occur by the redistribution of electrons (see **C**). The new alkylidene complex **D** can start a new catalytic cycle again with an olefin. Every step of the mechanistic pathway is reversible, resulting in an equilibrium mixture. In 2005, when the Chemistry Nobel Prize was announced, the metathesis reaction was compared in an animation to dance, where the participants (olefins) can exchange their partner only if they make a dance with the master of ceremony (catalyst) before.[99]
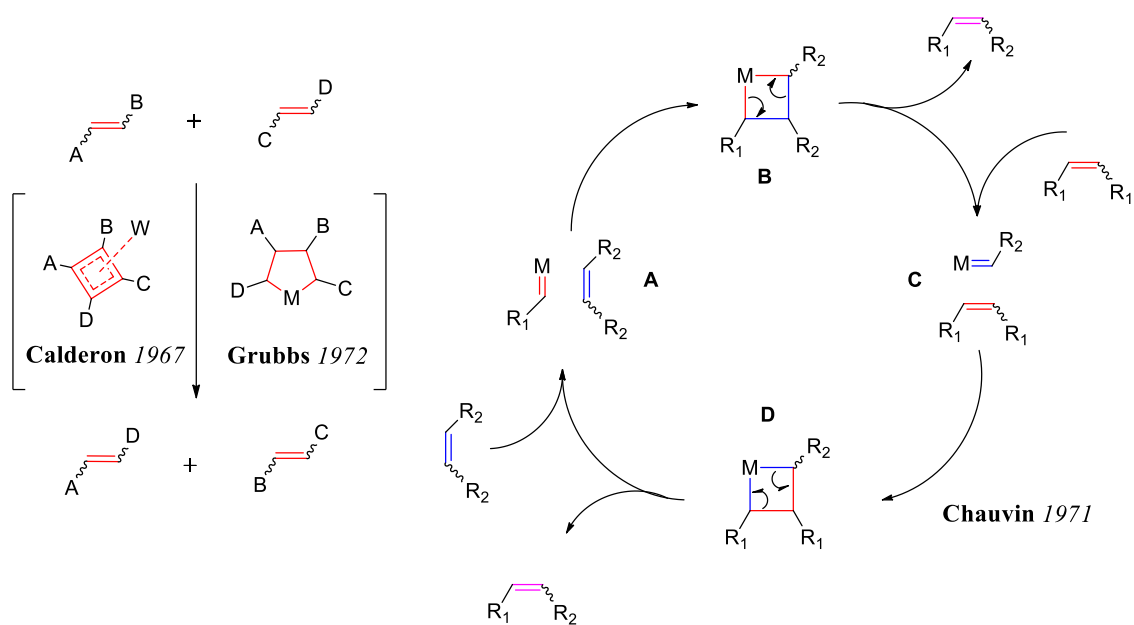
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Figure 2.

2.3. Evolution of metathesis catalysts

As it was mentioned previously, ill-defined early catalytic systems had many drawbacks which, together with the need to understand the mechanism better, made catalyst development necessary.[67] In general, metathesis catalysts today can be divided into two categories based on the central metal. Schrock catalysts possess Mo or W in the coordination centre, while the Grubbs catalysts have Ru. This section intends to deal only with the evolution of Grubbs catalysts since during our research work Ru-based catalysts were exclusively used. Thanks to easy handling and good functional group tolerance, Grubbs catalysts have gained considerable attention among organic chemists as useful tools to create one or more C–C double bonds. Their commercial availability enabled widespread utilisation, greatly contributing to the success of metathesis reactions.[100-104]

The first well-defined Ru catalyst for olefin metathesis was published in 1992 by Robert H. Grubbs (Fig. 3).[83] After some modification of the ligands, Grubbs and co-workers reported the next well-defined catalyst three years later what is now known as the first generation Grubbs catalyst.[105] These two communications have been real milestones in the metathesis history since from this time on, metathesis reactions do not need rigorous exclusion of air and moisture, making them available for practically everyone. In 1999 after an intensive study of ligand effect in metathesis reactions, a second generation catalyst was reported by Grubbs and co-workers.

They have introduced a mixed catalyst where one phosphine of the parent complex was replaced by an aryl-substituted *N*-heterocyclic carbene ligand.[106] While these catalysts possess superior activity and significantly expanded the scope of metathesis reactions, they still retained the beneficial properties of the first generation molecule.

Another significant episode during the time of catalyst development was the introduction of chelating benzylidene ligands by Hoveyda in 1999.[107] This idea has opened numerous new possibilities to the fine tuning of the catalysts through the modification of the stability of the Ru–O bond. These studies clearly showed that steric crowding around the chelating oxygen and an electron–withdrawing group on the benzylidene ring lead to the weakening of the OiP→Ru bond resulting in faster initiation.[108-112] It is worth mentioning that the detailed mechanistic pathway of the Hoveyda catalysts was a long-standing question although the release–return mechanism (boomerang effect) became a widely accepted theory.[113]
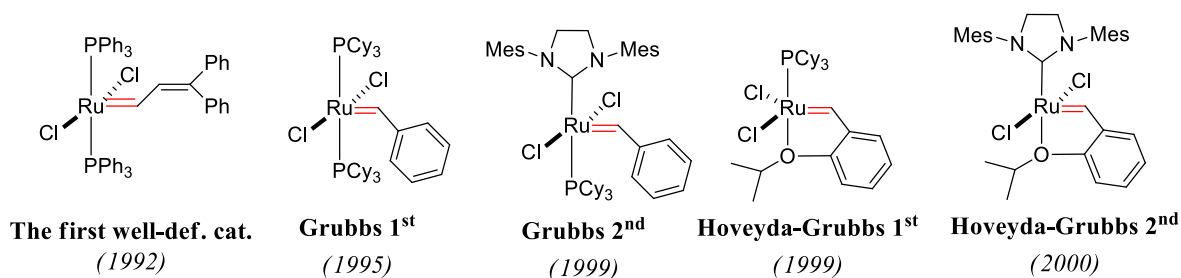

Figure 3.

2.4. Industrial applications of the metathesis reaction

Beside of research laboratories, olefin metathesis reactions appeared in different fields of industrial chemistry including the production of petrochemicals, oleochemicals, and polymers.[33-39] It is difficult to select, which should be discussed among industrial applications, because of the widespread exploitation of metathesis reactions. Nevertheless, the following processes cannot be ignored. The Phillips Triolefin Process was originally developed for the production of ethylene and 2-butene by the CM reaction of propylene. Taking advantage of the equilibrium nature of metathesis, today this reaction is utilised in the reverse direction because of the high commercial demand of propylene.[34] Almost 50 years before, an elegant process was elaborated for the manufacture of primary C_{11}–C_{15} fatty alcohols in the laboratories of Shell Development Company. The Shell Higher Olefin Process (SHOP) consists of four main parts (oligomerisation, linear hydroformylation, isomerisation, and metathesis). In the last step, olefin metathesis is responsible for the utilisation of "nonmarketable" olefins.[114]

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Last but not least, olefin metathesis has a huge impact in the field of polymer chemistry. Several strained cyclic and bicyclic olefins have been polymerised by ROMP. One of the best-known industrial products is *Telene*[R] or *Metton*[R] manufactured by the polymerisation of dicyclopentadiene.[34]

2.5. Application of metathesis for the synthesis of natural and bioactive products

Since the discovery of well-defined Ru-based catalysts, several naturally occurring and biologically active products were prepared where some metathesis reactions was utilised as a key step during the procedure.[25-31] In this field <u>R</u>ing-<u>R</u>earrangement <u>M</u>etathesis (RRM) is especially useful, because it enables the formation of highly diverse unsaturated ring systems in a tandem fashion.[115-116] This reaction has many advantages over the usual stepwise approach, such as decreasing the number of steps, and minimizing the necessary reagent, solvent, and purification. These benefits were utilised in 1999 by Granja et al. when "taxosteroid" containing the same [5,3,1] bicyclic ring system as taxol was synthesised via cascade dienyne metathesis reaction (Fig. 4).[117] RCM was applied successfully during the synthesis of the potential cancer drug epothilone *A* or the hepatitis C virus (HCV) protease inhibitor BILN 2061 to form the corresponding macrocycle.[118-119] Chemoselectivity achievable by selecting the appropriate catalyst even in the case of highly-functionalised molecules is another great advantage of metathesis reactions.[120]
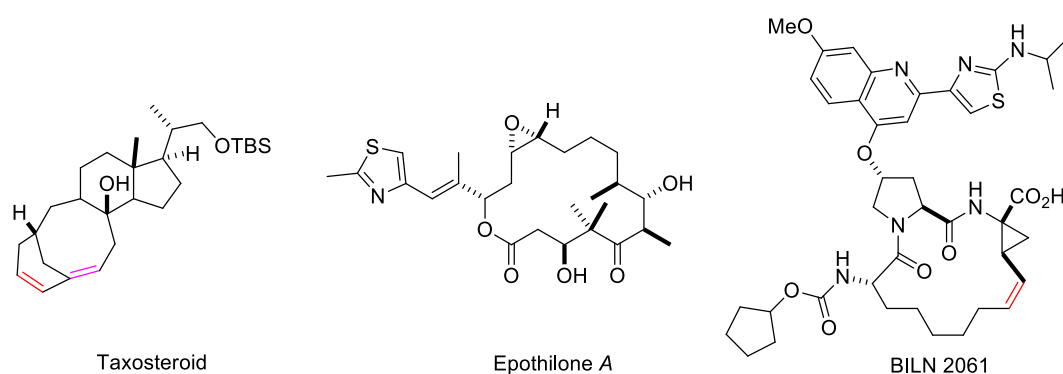

Figure 4.

2.6. General rules for cyclisation through metathesis reaction

Thanks to the well-defined Ru-based Grubbs catalysts, RCM reactions evolved into a very popular and widely used method for the construction of simple or more complex ring systems from the corresponding diene. The literature became enormous and excellent studies were published over the last two decades. A further feature that increases the value of this process is that not only carbocyclic compounds but also their heterocyclic counterparts can be prepared (Fig. 5). Basically, two factors determine the equilibrium and, therefore, the outcome of the RCM: entropy and enthalpy. Removal of the formed volatile ethylene, which can be accelerated with increasing the temperature, results in entropic gain, which facilitates both ring-closing and polymerisation of the diene. In order to prefer cyclisation over polymerisation, the use of low concentrations is a commonly applied technique. On the other hand, enthalpy also plays a crucial role during ring formation. Creation of thermodynamically stable 5- or 6-membered cyclic compounds is usually readily accomplished with RCM protocol. Problems, however, arise when larger or strained ring systems are desired. Finally, it is worthwhile to mention that selection of both the appropriate catalyst and its quantity are of pivotal importance. Unfortunately, a universally applicable catalyst, which outperforms all others in all cases, does not exist, and the amount of the catalyst used strongly influences the outcome of the reaction.[121-126]
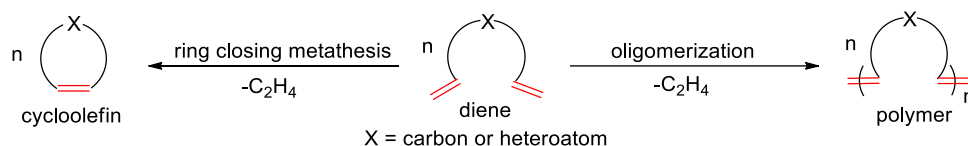

Figure 5.

2.7. Synthesis and transformations of cyclic β-amino acids through metathesis reaction

Over the last two decades, olefin metathesis reactions have gained widespread application towards the access of cyclic β-amino acid. Modern Ru-based catalysts greatly facilitated the proliferation of this method, since they are applicable on densely-functionalised molecules leading to the formation of complex products.[67] Ring-closing metathesis is a frequently applied key step to construct cyclic frameworks with different sizes.[124] The formed C–C double bond affords great possibilities for further functionalisation such as epoxidation, dihydroxylation, or Diels–Alder reactions. This pathway requires furnishing the acyclic compounds with alkenyl groups to enable cyclisation. A less common approach is application of cross metathesis to form

appropriate acyclic precursors for subsequent cyclisation. In most cases, protocols developed for the construction of cyclic β-amino acids are suitable for the preparation of different ring sizes. Publications usually describe preparation of both 5- and 6-membered cycles using the same method; therefore, these syntheses were summarised separately from the construction of larger or condensed rings. Numerous research groups utilised metathesis reaction toward cyclic β-amino acids and some of the major developments are summarised below.

2.8. Synthesis of 5- and 6-membered cyclic β-amino acids by ring-closing metathesis (RCM)

Abell and Gardiner have elaborated an elegant process by RCM for the construction of 6-membered cyclic *cis* and *trans* β^{2,3}-amino esters substituted or unsubstituted at the α-position (Scheme 1).[127] First, acyclic β-amino ester (±)-**1** (obtained from protected allyl-glycine) was transformed into diene (±)-**2** by stereoselective allylation. This was followed by RCM in the presence of Grubbs 1st generation catalyst (G1) smoothly affording *trans* cyclohexene β^{2,3}-amino acid derivative (±)-**3** with cyclohexene skeleton. Saturated derivative (±)-**4** was easily accessible with the reduction of the C–C double bond by hydrogenation on Pd/C.
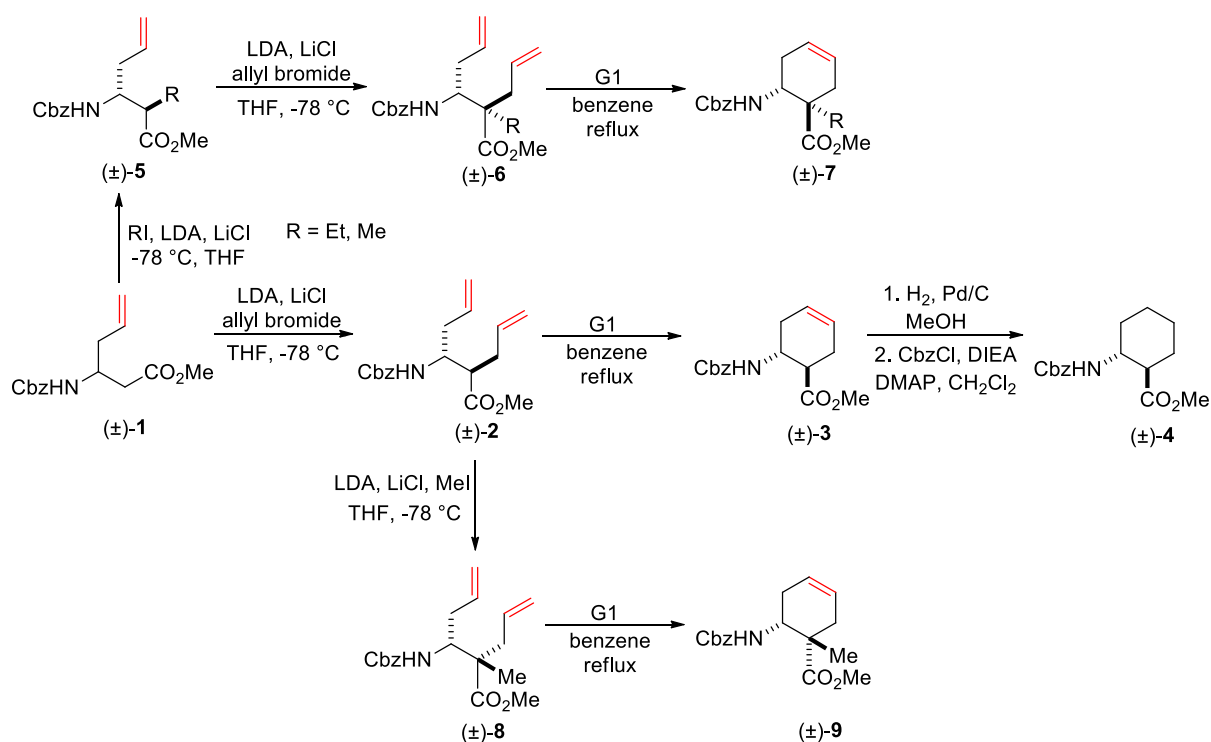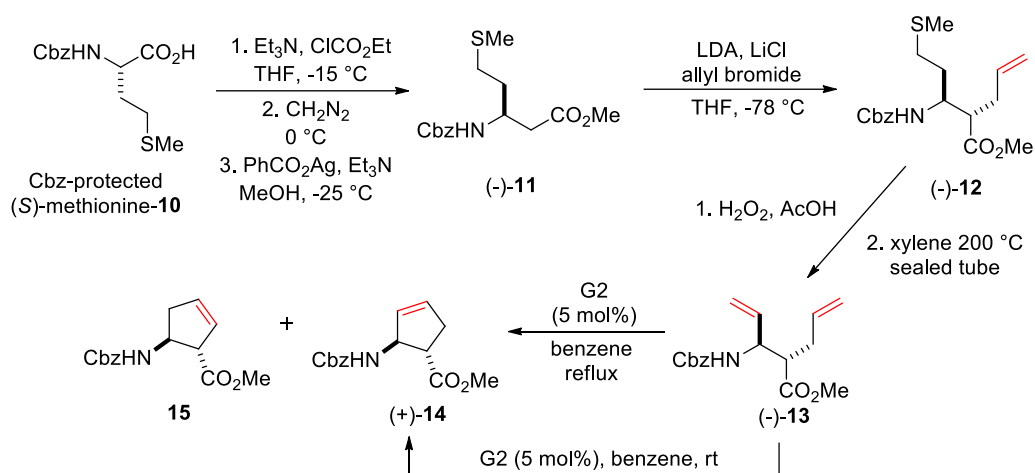

Scheme 1.

To extend the former approach, α-substituted cyclic β-amino acids (±)-**7** and (±)-**9** were synthesised (Scheme 1). The relative stereochemistry of the carboxylic and the amino functions

depended on the sequence of alkylation. When compound (±)-**1** was first reacted with alkyl iodide and then with allyl bromide, the cyclisation of resulting (±)-**6** afforded *trans* derivative (±)-**7**. However, if the alkylation sequence was changed (allylation followed by alkylation) compound (±)-**8** was formed, which can be cyclised to *cis* amino acid (±)-**9**. Noteworthy that the use of optically pure **1** prepared using Evans chiral auxiliary group enables the synthesis of (-)-**3** and (-)-**4** in enantiopure form.

The same group published an extended version of the above method for the synthesis of cyclic $\beta^{2,3}$-amino acid derivatives substituted or unsubstituted at the α-position (Scheme 2).[128] This approach is suitable for the preparation of 5-, 6- and 7-membered ring systems. From readily accessible optically active α-amino acid building blocks such as (*S*)-methionine or (*R*)-allyl glycine, enantiopure 5- or 6-membered cyclic $\beta^{2,3}$-amino acids can easily be prepared. The first step of the synthetic strategy towards 5-membered rings was an Arndt–Eistert carbon chain elongation of Cbz-protected (*S*)-methionine-**10** to form the corresponding β-amino acid (-)-**11**, which was subsequently submitted to stereoselective allylation with allyl bromide and LDA in the presence of LiCl. The other alkenyl group, necessary for the cyclisation [product (-)-**13**], was formed in the next step by oxidative elimination.
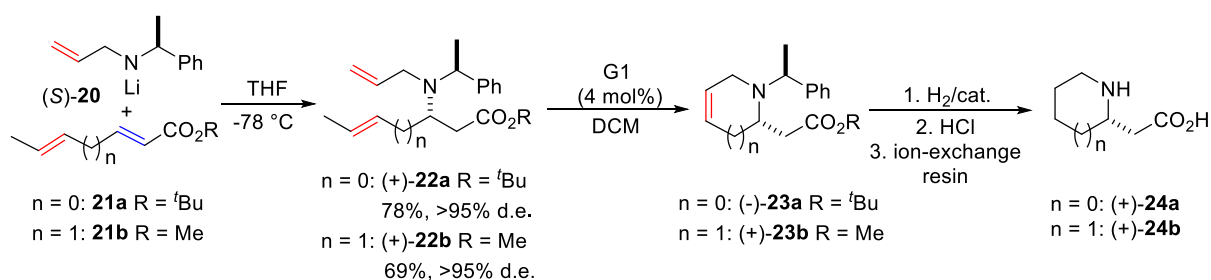

Scheme 2.

Compound (-)-**13** was readily transformed to 5-membered cyclic $\beta^{2,3}$-amino acid in the presence of Grubbs 2nd catalyst (G2) with excellent yield. However, if the temperature was increased both the expected ring-closure product (+)-**14** and its isomerised derivative **15** were formed in a 1.5:1 ratio. As it was mentioned above, this synthetic strategy is suitable for the preparation of α-substituted cyclic derivatives. For this purpose, compound (-)-**11** was stereoselectively alkylated by MeI, which gave the α-methyl substituted ester as a single diastereomer (-)-**16** (Scheme 3).

Diasteroselective allylation of compound (-)-**16** gave product (-)-**17**, which was transformed by oxidative elimination to acyclic β-amino acid derivatives (-)-**18** with two alkenyl side-chains.
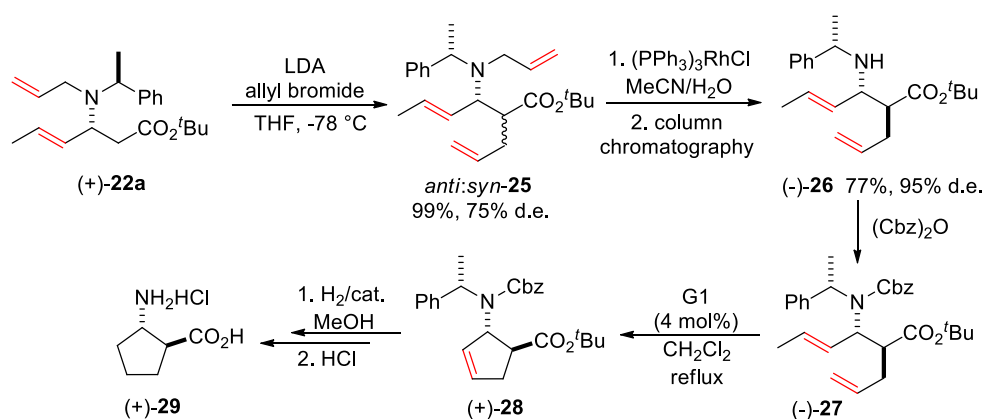

Scheme 3.
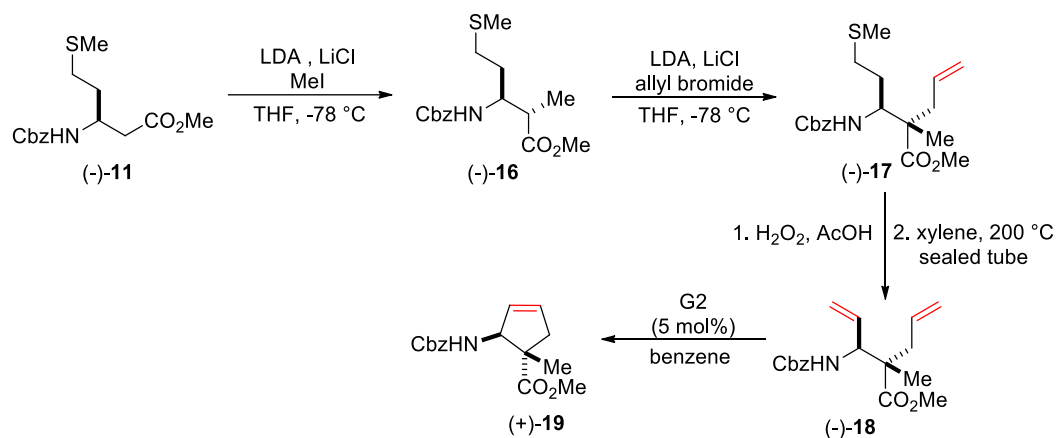
To avoid isomerisation experienced before, RCM of compound (-)-**18** was executed at room temperature with G2 catalyst to afford unsaturated 5-membered α-methyl substituted cyclic β^{2,3}-amino ester (+)-**19**. The authors also improved their method towards enantiopure 6-membered cyclic β-amino esters by finding an alternative route to prepare starting compound **1**. Asymmetric synthesis was used to prepare Cbz-protected (*R*)-allyl glycine, which was submitted to Arndt–Eistert homologation resulting in optically pure (+)-**1**. Following the steps of Scheme 1 led to (-)-**3** and (-)-**4**.

Chippindale and co-workers developed a versatile method enabling the stereoselective synthesis of 5-membered cyclic β^{2,3}- and β^3-amino acids and 6-membered cyclic β^3-amino acids.[129] First, compounds (+)-**22a,b** were synthesised by conjugate addition of lithium (*S*)-allyl(1-phenylethyl)amide **20** to α,β-unstaurated esters **21a,b** with high d.e. (Scheme 4). RCM reaction of (+)-**22a,b** resulted in *N*-heterocyclic β^3-amino acid derivatives (-)-**23a** and (+)-**23b**, which were transformed into free amino acids (+)-**24a,b**.
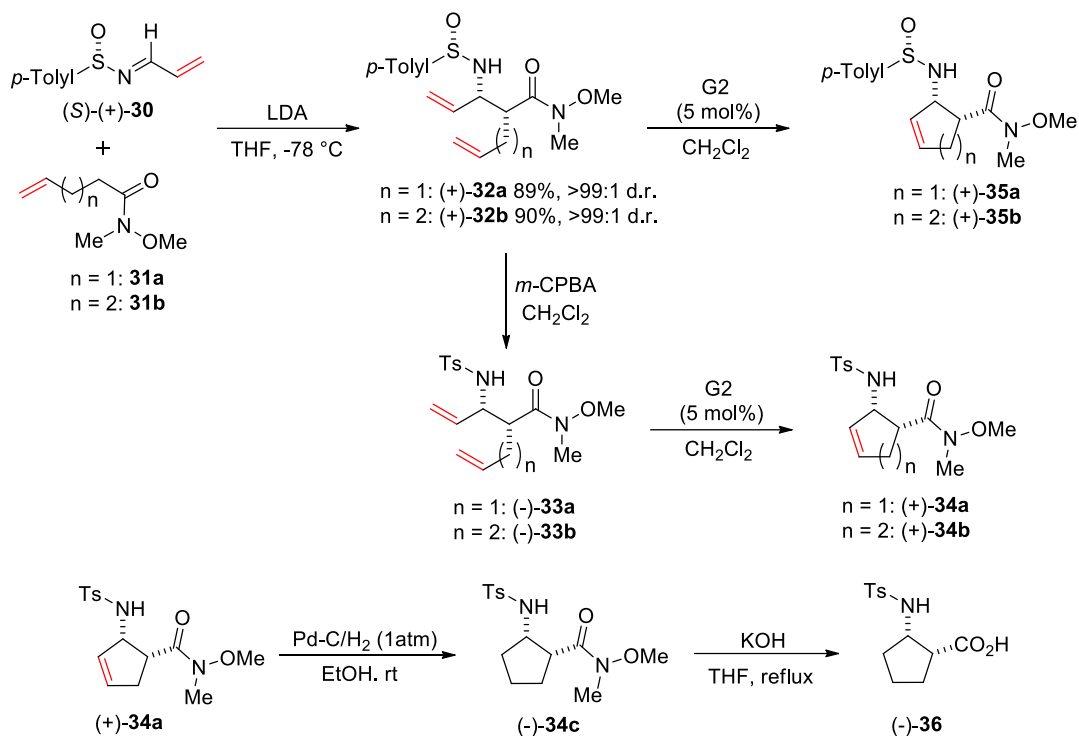

Scheme 4.

In order to synthesize cyclic $\beta^{2,3}$-amino acids, allylation of intermediate (+)-**22a** was performed affording an inseparable mixture of *anti* and *syn* diastereomers **25** (Scheme 5). However, the related secondary amines obtained through *N*-deallylation of compound **25** with Wilkinson catalyst were separable by column chromatography and the major (*anti*) diastereomer (-)-**26** was isolated with >95% d.e. and in 77% yield. Based on earlier experience, the amine function was transformed to carbamate in order to avoid chelate formation, which greatly reduces the activity of the Grubbs catalyst. Cyclisation of (-)-**27** by RCM led to cyclic $\beta^{2,3}$-amino acid derivative (+)-**28**, which was subsequently deprotected to afford transpentacin (+)-**29**.

Scheme 5.

Davis and Theddu elaborated a general methodology for the asymmetric synthesis of cyclic *cis*-β-amino Weinreb amides, which are easily convertible in two steps to cyclic *cis* $\beta^{2,3}$-amino acid derivatives.[130] As depicted in Scheme 6, optically pure acyclic dienes (+)-**32a,b** were synthesised with varied alkenyl chains by the conjugate addition of unsaturated prochiral Weinreb amide **31a,b** (enolates generated by LDA) to chiral sulfinimine (*S*)-(+)-**30** with high >99:1 d.r. Oxidation of compounds (+)-**32a,b** at sulfur resulted in tosyl-protected compounds (-)-**33a,b**. RCM of compounds (+)-**32a,b** and (-)-**33a,b** with G2 catalyst gave the expected cyclic β-amino Weinreb amides (+)-**34a,b** and (+)-**35a,b**, respectively. The possibility of liberating the carboxyl group was studied in details in the case of 5-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 smoothly afforded aminocarboxylic acid (-)-**36**.

Scheme 6.

The strategy discussed above in detail is applicable for the asymmetric synthesis of 7-membered cyclic *cis*-β-amino Weinreb amides too. It is worth mentioning that in addition to β-amino acids, several valuable molecules are achievable via Weinreb amides, such as ketones, aldehydes, β-ketoesters, and β-ketophosponates.

A stereoselective route towards cyclic $\beta^{2,3}$-amino acids was developed by Perlmutter et al. in which the bonds formed by nucleophilic addition (A_N) were transformed by ring closure (RC) (NARC protocol).[131] This is a frequently applied method for the synthesis of hetero- and carbocyclic compounds.[132] A key step of the procedure is the diastereoselective condensation between pyridyl thioesters **37a,b** and optically pure imine (*R*)-**38** (Scheme 7). The reaction provided a mixture of diastereomers [(+)-**39** is the major and **40** the minor product], which were readily separable by flash chromatography. Attempted ring closure of (+)-**39a,b** to form bicyclic β-lactams were unsuccessful because of the evolving ring strain. To avoid this synthetic problem the 4-membered heterocyclic rings were opened to get acyclic dienes (+)-**41a,b**, which easily underwent RCM with G1 catalyst. Hydrogenation of the double bond then hydrolysis with HCl afforded optically pure 5- and 6-membered saturated cyclic β-amino acid hydrochlorides (+)-**29** and (+)-**43**.
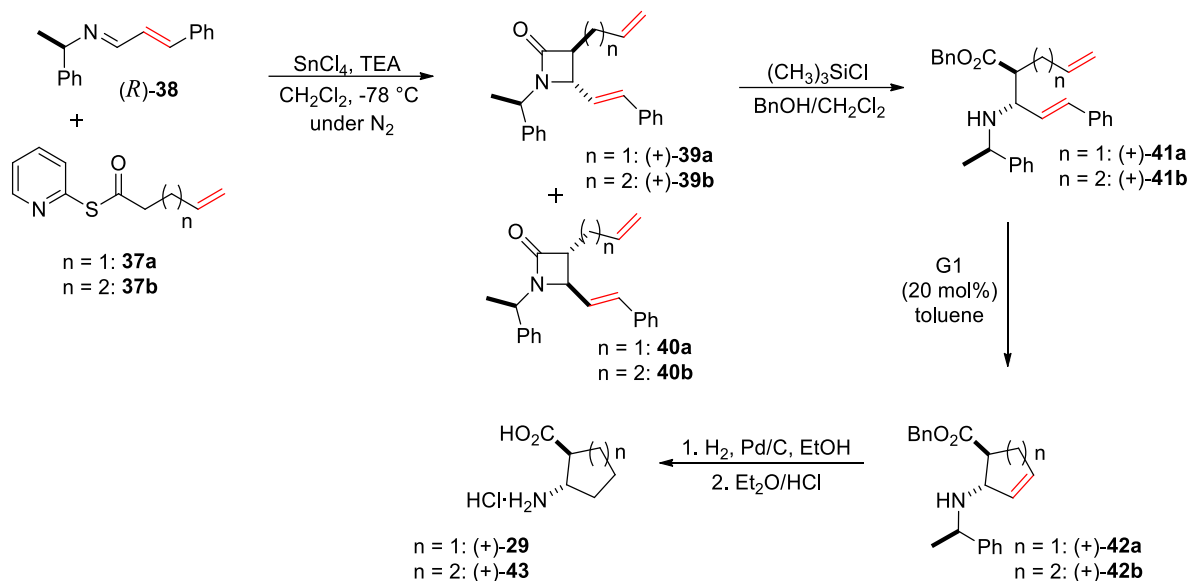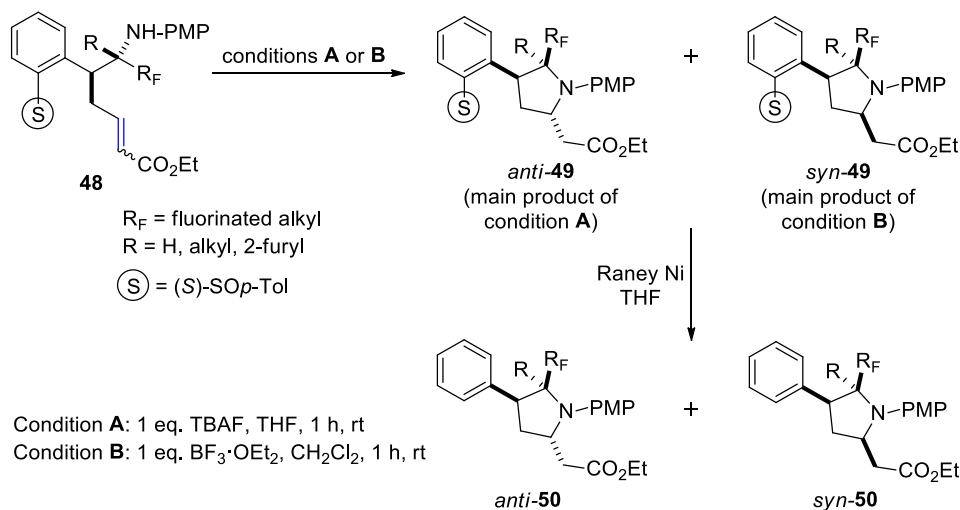
Scheme 7.

2.9. Synthesis of 5- and 6-membered cyclic β-amino acids by cross metathesis (CM)

While several open-chain dienes have been successfully transformed by RCM, only a few examples were reported where CM was utilised toward cyclic β-amino acids. In these cases, the role of metathesis was the preparation of appropriate acyclic precursors, which were cyclised by intramolecular addition or condensation. In one of these examples, Fustero and co-workers recently reported a diastereodivergent synthesis of enantiomerically pure fluorinated homoproline derivatives (cyclic β^3-amino acids) with three chiral centers.[133] As shown in Scheme 8, deprotonation of sulfoxide (*S*)-**44** at the benzylic position led to the corresponding carbanion. Addition of the latter to fluorine-containing aldimine **45** yielded amine **46** with high diastereoselectivities. Cross metathesis performed with ethyl acrylate **47** in the presence of Hoveyda-Grubbs 2nd catalyst (HG2) gave **48** as a mixture of *E/Z* diastereomers. Cyclisation *via* intramolecular *aza*-Michael reaction can result in two epimers of **49** with relative *syn* or *anti* arrangement of the fluorinated alkyl group and the CH_2CO_2Et moiety.
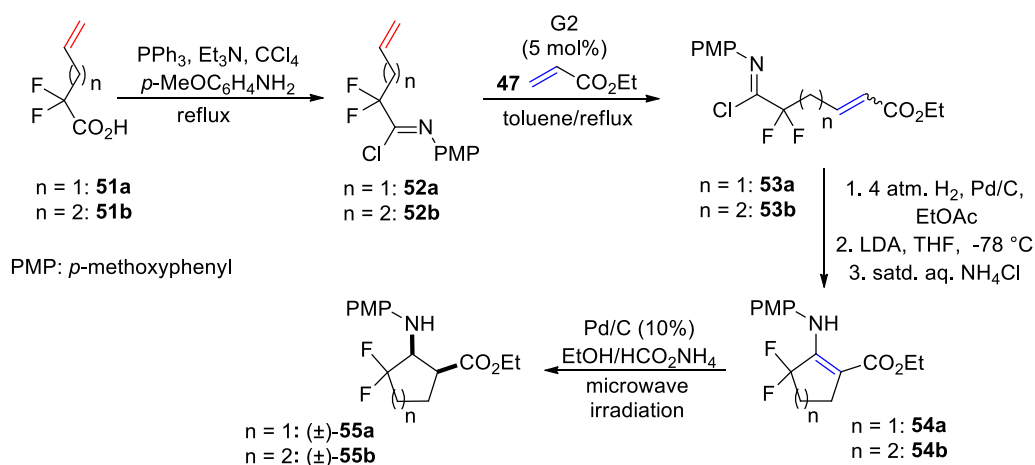

Scheme 8.

13
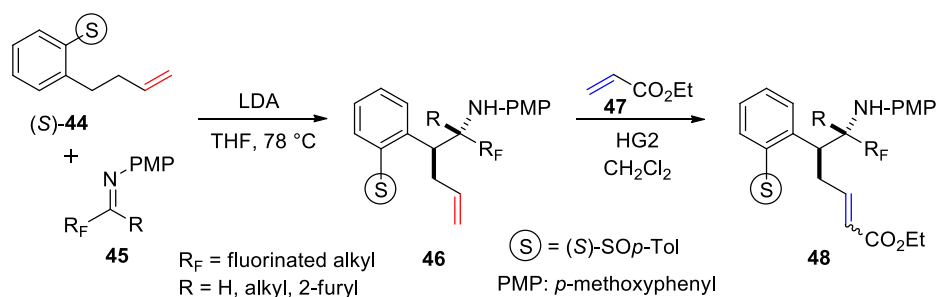
Diasteroselectivity depended on the reaction conditions: base-promoted cyclisation gave the *anti* epimer as the main product, while treatment with Lewis acidic $BF_3 \cdot OEt_2$ afforded mostly the *syn* epimer because of the formation of a chelate ring involving the ester carbonyl, the sulfoxide and the nitrogen atom (Scheme 9). Removal of the chiral auxiliary was achieved in the final step using Raney Ni catalyst in THF to give homoproline derivatives **50**.

Scheme 9.

The second example was also elaborated by the same research group. They successfully conducted racemic and asymmetric syntheses of difluorinated 5-, 6-, and 7-membered (see later) *cis* cyclic $\beta^{2,3}$-amino acids through CM (Scheme 10).[134] In the first step, imidoyl chlorides **52a,b** were prepared from the corresponding 2,2-difluorinated carboxylic acids **51a,b**. Cross-coupling reaction between these imidoyl chlorides and ethyl acrylate **47** gave the expected acyclic compounds **53a,b**. This is a remarkable achievement as the first reported case of using the G2 catalyst in the reaction of imidoyl chlorides.
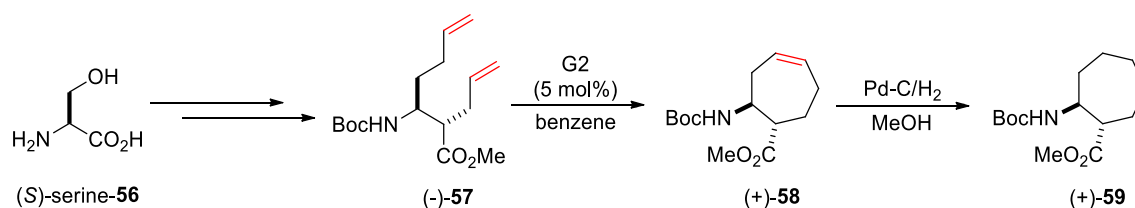

Scheme 10.

Chemoselective hydrogenation of the C–C double bond and subsequent Dieckmann condensation with LDA at -78 °C resulted in the formation of cyclic enamino compounds **54a**,**b**. After several experiments, chemo- and stereoselective reduction was accomplished to furnish the final product (±)-**55a,b** with *cis* configuration. In the final step 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 similarly to the racemic counterpart (**53a**).

2.10. Synthesis of β-amino acids with larger ring system by ring-closing metathesis (RCM)

Construction of larger rings has challenged organic chemists for a long time; however, several techniques are available in the synthetic toolbar today.[135] RCM opened up new possibilities for the syntheses of medium rings to macrocycles, because low substrate concentrations prefer ring closing over polymerisation even in the case of these challenging ring systems.[124] Among several compounds, β-amino acid derivatives were also prepared in this manner. Of the methods described in Sections 2.8 and 2.9, four strategies were applicable for the construction of larger ring systems.

The method developed by Gardiner and co-workers, where 5- and 6-membered cyclic β^{2,3}-amino esters were prepared from easily accessible α-amino acids building blocks, was extended to create 7-membered rings (Scheme 11).[128] Acyclic precursor (-)-**57**, synthesised from (*S*)-serine-**56** in multiple steps similar to (-)-**13**, was cyclised by G2 catalyst then hydrogenated on Pd-carbon to give the target compound (+)-**59**.
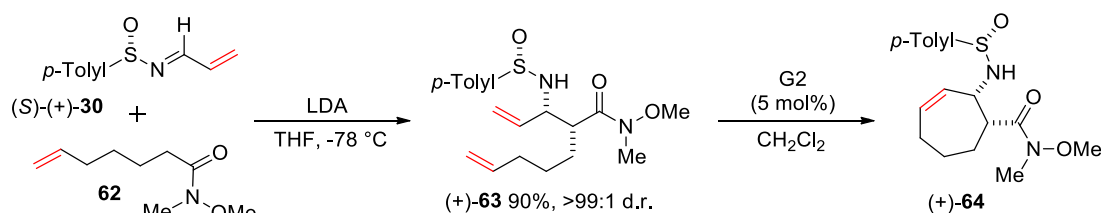

Scheme 11.

Diastereoselective conjugate addition of lithium (*S*)-*N*-allyl-*N*-α-methylbenzylamide **20** to α,β-unsaturated ester **21a** developed by Chippindale and co-workers is also applicable for the preparation of larger ring.[129] As depicted in Scheme 12 compound (-)-**60**, which was synthesised in a similar fashion to (-)-**27** (see section 2.8 for the detailed pathway), was treated with G1 catalyst to afford 7-membered unsaturated cyclic molecule (+)-**61**.
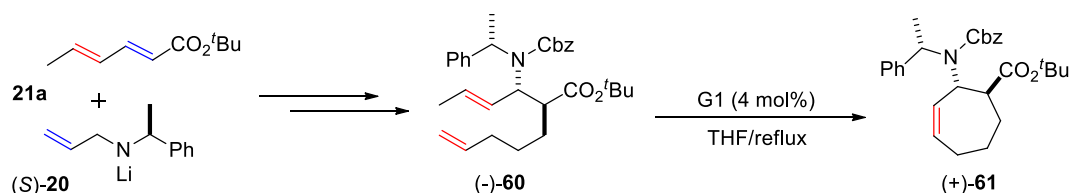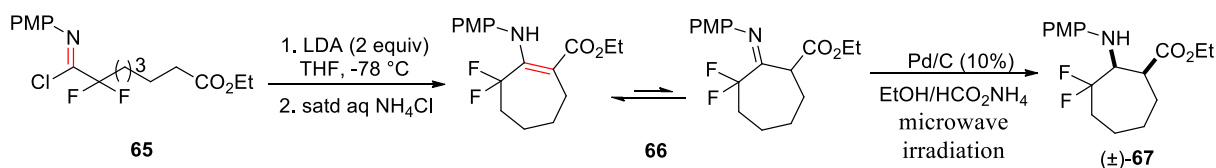
Scheme 12.

Davis and Theddu successfully applied their approach (detailed in Scheme 6) for the preparation of a 7-membered ring by subjecting prochiral Weinreb amide **62** to conjugate addition with acrolein-derived sulfinimine (*S*)-(+)-**30**.[130] Precursor (+)-**63** thus formed was easily cyclised with G2 catalyst to 7-membered cyclic β-amino acid derivative (+)-**64** (Scheme 13).
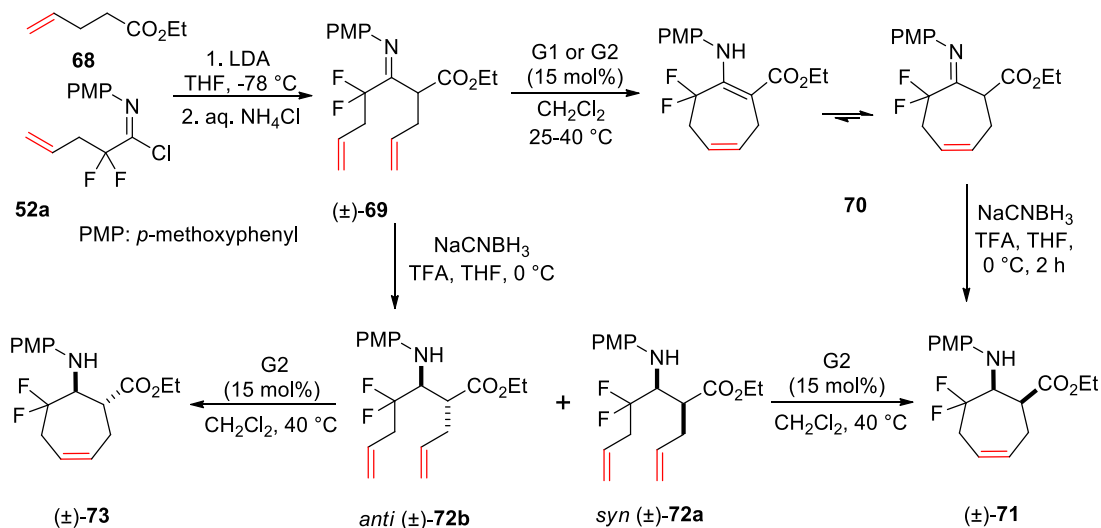

Scheme 13.

The method developed by Fustero and co-workers synthetize, where imidoyl chlorides obtained through CM and subsequent reduction were subjected to Dieckmann condensation, is also capable of furnishing a 7-membered ring system.[134] As shown in Scheme 14, cyclisation 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 afforded fluorinated *cis*-2-aminocycloheptane carboxylic acid derivative (±)-**67**.
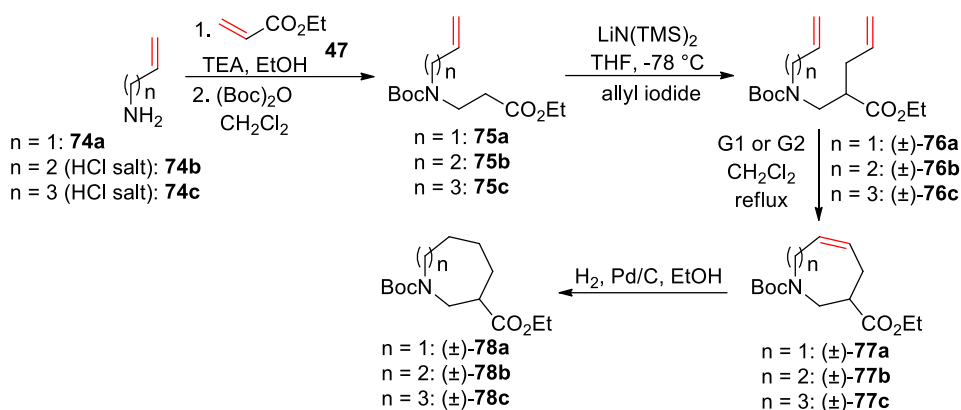

Scheme 14.

In 2003, the Fustero's group published a study where 7-membered cycles such as compounds (±)-**71** and (±)-**73** were synthesised exclusively through RCM (Scheme 15).[136] In this approach fluorinated imidoyl chloride **52a** prepared earlier (see Scheme 10) was submitted to condensation with enolate of 4-pentenoic acid ethyl ester **68** to yield β-imino ester (±)-**69**. Next, cyclisation was executed with both first- and second-generation Grubbs catalysts where the latter afforded a better performance. The resulting tautomeric mixture **70**, in which the imino

form dominated, was reduced with NaCNBH$_3$ in a diastereoselective fashion to afford fluorinated *cis* β-amino acid derivative (±)-**71** with 7-membered ring as the sole product. Furthermore, the synthesis of *trans* derivative (±)-**73** could also be accomplished. Namely, reduction of (±)-**69** with NaCNBH$_3$ gave a 1:1 mixture of *syn* and *anti* diastereomeric open-chain β-amino esters (±)-**72a** and (±)-**72b**, and this mixture gave the desired compound through RCM.

Scheme 15.

For the preparation of β-turn mimetics, Ohkubo and co-workers developed a general procedure towards the exclusive synthesis of larger 7-, 8-, and 9-membered cyclic β^2-amino acid derivatives via RCM (Scheme 16).[137] The acyclic dienes were prepared in three consecutive steps from readily available aliphatic amines where the alkenyl chain length predetermined ring sizes during cyclisation. β-Amino ester skeletons were formed by conjugate addition of amines **74a-c** to ethyl acrylate **47**. Subsequent *N*-protection followed by allylation at the α-position resulted in the corresponding precursors (±)-**76a-c**. In the case of (±)-**76a** and (±)-**76b**, cyclisation smoothly afforded the desired 7- and 8-membered cycloalkene derivatives (±)-**77a** and (±)-**77b**, respectively. During the cyclisation of (±)-**76c**, because of olefin bond isomerisation of the starting material, (±)-**77c** and (±)-**77b** were formed together in a 4:1 ratio. Saturated cyclic β^2-amino acid derivatives (±)-**78a-c** were synthesised by reduction of the C–C double bonds. By slightly modifying the synthetic route discussed above, the authors were also able to prepare *N*-Boc protected 7- and 8-membered cyclic β^2-amino acids in enantiopure form.
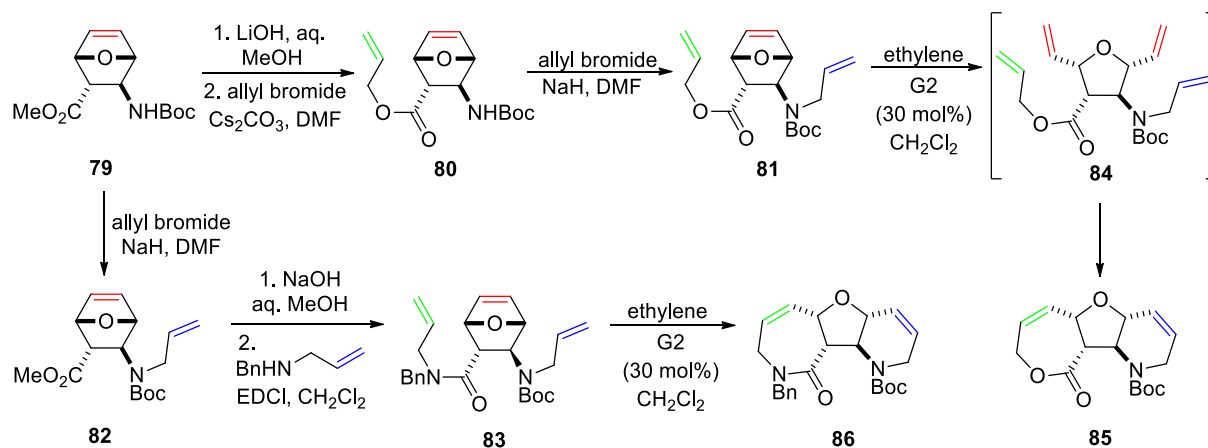
Scheme 16.

## 2.11. Synthesis of β-amino acids with condensed ring systems by ring-rearrangement metathesis (RRM)

In the following short section, the usefulness of domino and tandem metathesis reactions in the synthesis of β-amino acid derivatives with condensed ring will be exemplified. These transformations allow the rapid and safe syntheses of highly diverse fused carbo- or heterocyclic ring systems through the rearrangement of the C–C double bonds. A frequently applied sequence in these cases is the intramolecular ring-opening/ring-closing protocol. Thanks to their high ring strain, bridged bicyclic frameworks such as norbornene and oxanorbornene provide a great possibility toward condensed 5- or 6-membered carbo- or heterocyclic systems. [115-116]

Winkler et al. utilised the benefits of the oxanorbornene framework for the syntheses of novel tri- and pentaheterocyclic ring systems via tandem metathesis.[138] First, metathesis substrates were prepared from bicyclic oxanorbornene amino ester **79** by changing the methyl ester to allyl ester **80** followed by *N*-allylation to give **81** or *N*-allylation to **82** and subsequent creation of an *N*-allylamide moiety (product **83**, Scheme 17). Ring-opening metathesis of the strained oxabicyclo ring of **81** afforded reactive intermediate **84** with four terminal alkene functions. It immediately reacted further by RCM to form condensed tricyclic β-amino acid derivative **85**. Analogous tandem metathesis of precursor **83** gave compound **86** a lactam analogue of **85**.
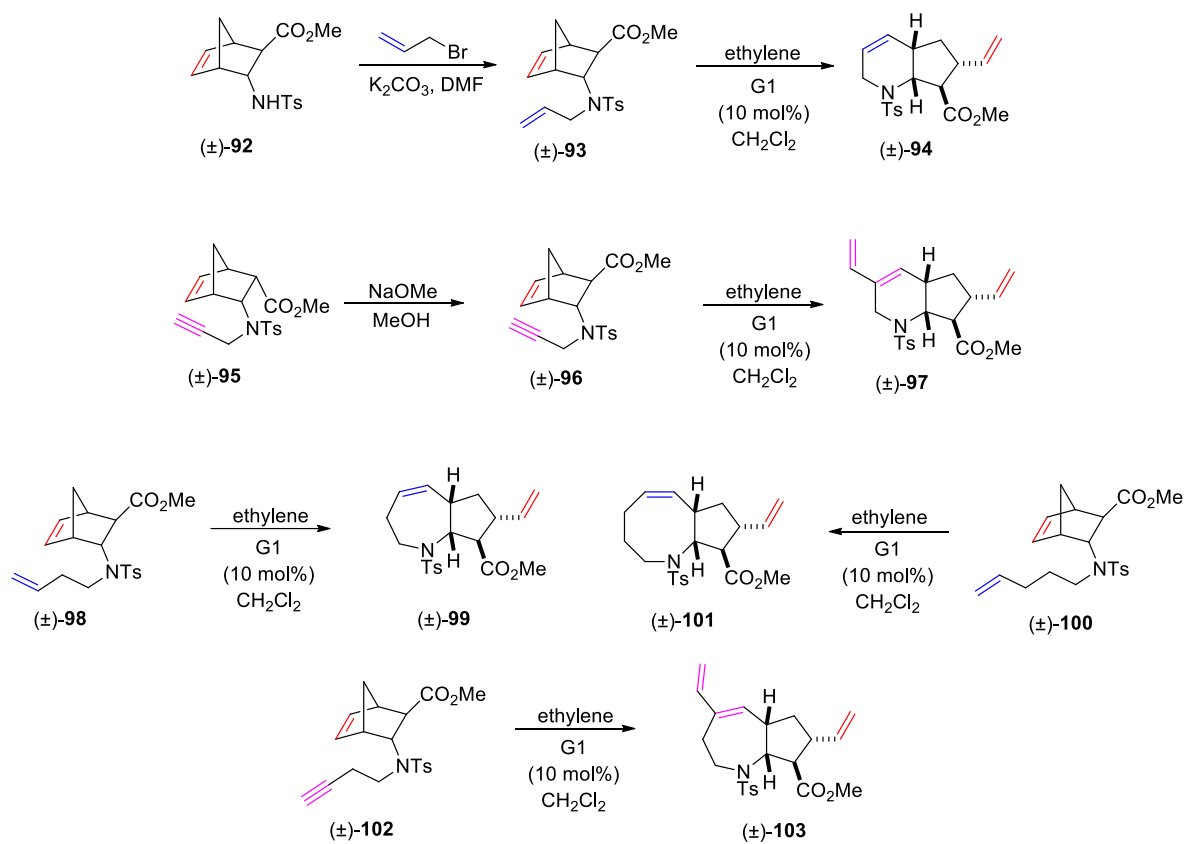
Scheme 17.

Pentacyclic product **91** can be synthesised in a similar fashion, although it requires a very high catalyst loading during the ROM/RCM step (Scheme 18). In this case, metathesis precursor **89** was prepared by reductive amination of aldehyde **88** with *O*-allylated amino ester **87** prepared previously 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.
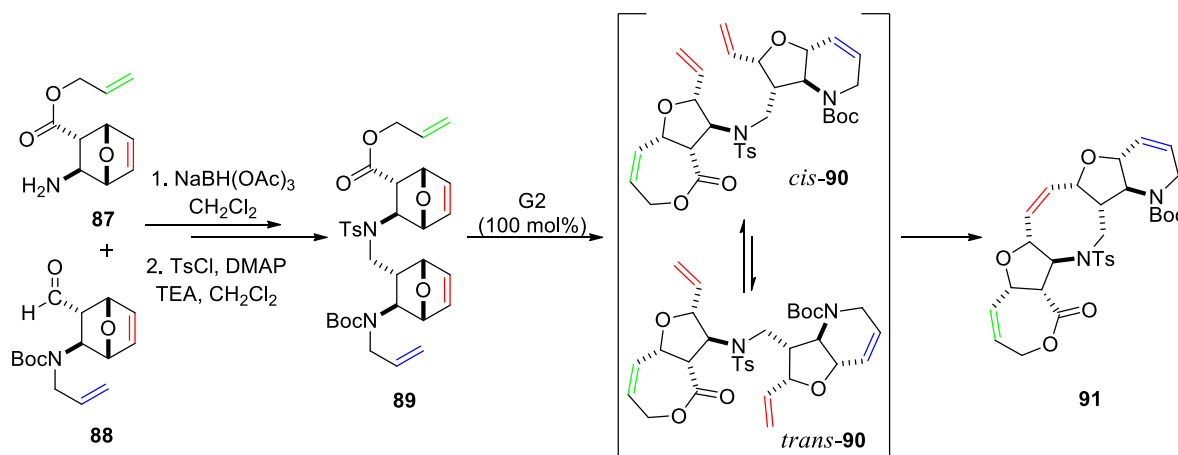
Scheme 18.

Nadany and Mckendrick applied a similar pathway towards constrained bicyclic β-amino acid derivatives. However, in these cases, only a single ring closure occurred (Scheme 19).[139] To avoid the chelate formation with participation of the catalyst, carbonyl oxygen and the nitrogen atom, *trans N*-tosylated β-amino esters were utilised as starting materials in all cases. First, compound (±)-**92** was reacted with allyl bromide to produce metathesis substrate (±)-**93**. Next, RRM of *trans* β-amino ester (±)-**93** in the presence of ethylene and G1 catalyst readily afforded the desired nitrogen-containing condensed heterocycle (±)-**94** in tandem fashion.

Domino metathesis reaction of the previously prepared homologous (±)-**96**, (±)-**98**, (±)-**100**, and (±)-**102** allows the formation, respectively, of 5,6-fused (±)-**97**, 5,7-fused (±)-**99**, and (±)-**103**, and 5,8-fused bicyclic β-amino acid esters (±)-**101**.
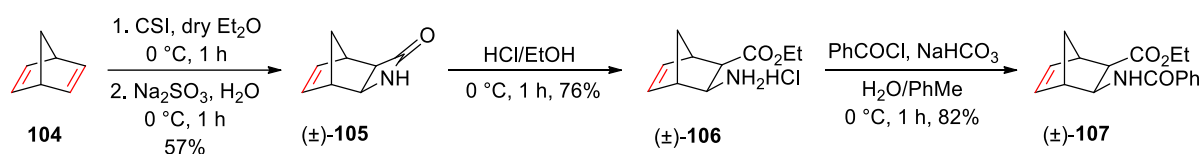

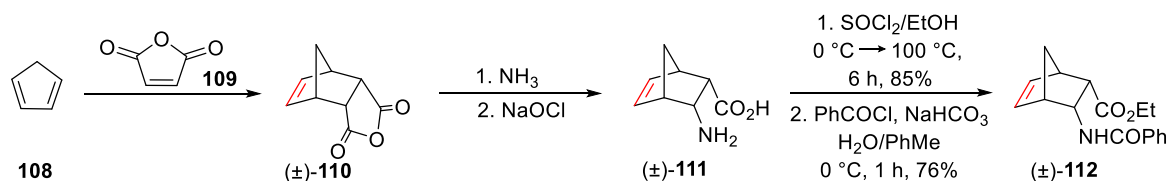**Scheme 19.**

3. RESULTS AND DISCUSSION

3.1. Stereocontrolled one-step synthesis of difunctionalised cispentacin and transpentacin derivatives through ring-opening metathesis (ROM) of norbornene β-amino acids

Our synthetic strategy towards difunctionalised cispentacin and transpentacin derivatives was based on the ROM reactions of constrained unsaturated bi- and tricyclic ring systems driven by the release of their high ring strain. For this purpose, norbornene β-amino esters were excellent candidates. In order to increase the number of achievable cispentacin stereoisomers, some stereoisomeric bicyclic precursors were synthesised. In the first step metathesis substrate compound (±)-**107** was prepared by the well-known pathway from readily available starting materials. The synthetic strategy started with the stereoselective addition of chlorosulfonyl isocyanate (CSI) to norbornadiene **104** in dry Et$_2$O followed by chlorosulfonamide hydrolysis with Na$_2$SO$_3$ resulting exclusively in *exo*-lactam (±)-**105** as depicted in Scheme 20.[140]
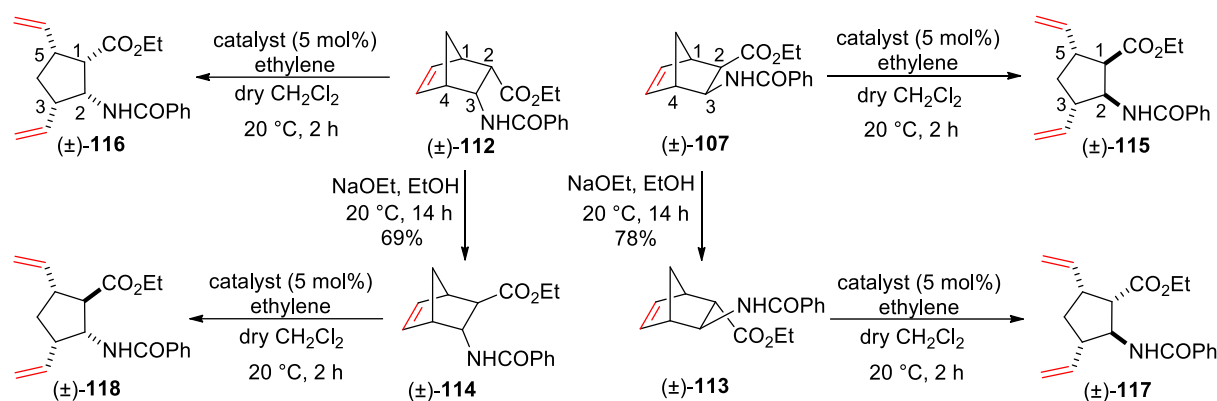

Scheme 20.

In the next step, the 4-membered heterocycle was opened by HCl/EtOH and subsequent benzoyl protection of the amino group gave the corresponding unsaturated bicyclic target compound (±)-**107**.[55] *diendo*-Norbornene β-amino ester (±)-**112** was achievable in a slightly different route as shown in Scheme 21. First, *endo*-anhydride (±)-**110** was prepared via Diels–Alder reaction between cyclopentadiene **108** and maleic anhydride **109**. Next, ring-opening reaction of the heterocycle with NH$_3$ followed by Hoffmann degradation smoothly afforded bicyclic β-amino acid (±)-**111**.[139] Finally, the carboxyl function was esterified with SOCl$_2$/EtOH and subsequent benzoylation gave desired metathesis substrate *diendo*-norbornene β-amino ester (±)-**112**.[56]

Scheme 21.

Next, epimerised derivatives of (±)-**107** and (±)-**112** were prepared by their treatment with NaOEt in EtOH. The reaction afforded the so-called *endo-exo* (±)-**113** and *exo-endo* (±)-**114** compounds in which the ester and the amide group are *trans* to each other. With the four bicyclic metathesis substrates in hand [(±)-**107**, (±)-**112**, (±)-**113**, and (±)-**114**], their ring-opening metathesis reaction was studied toward the preparation of functionalised cispentacin derivatives. It was found that racemic 3,5-divinylated amino ester stereoisomers (±)-**115**, (±)-**116**, (±)-**117**, and (±)-**118**, which differ in the relative configuration of the C-1 and/or C-2 atom, were readily accessible through ROM of the corresponding starting bicyclic compounds in the presence of ethylene and metathesis catalyst (Scheme 22).
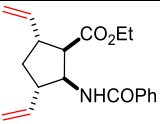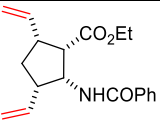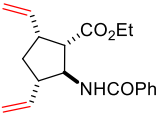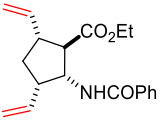

Scheme 22.

Metathesis reactions were performed systematically in anhydrous CH_2Cl_2 with ethylene under argon atmosphere in the presence of a metathesis catalysts (G1, G2, HG1, or HG2) for 2 h. In the case of *diexo-* and *diendo*-β-amino ester metathesis substrates (±)-**107** and (±)-**112**, clear general correlation between the yield and the used catalyst was not found, although HG2, in both cases, was slightly more effective than the other catalysts. Notably, however, yields in the case of *endo-exo* (±)-**113** and *exo-endo* (±)-**114** derivatives found with first generation catalysts were more than two times higher than those by second generation ones (see Table 1). The best yields (80% and 68%) were achieved also with *endo-exo* (±)-**113** and *exo-endo* (±)-**114** compounds. Lower yields found with *diexo* and *diendo* derivatives (±)-**107** and (±)-**112** may be explained by chelation of the catalyst. Specifically, the *cis* arrangement of the amide and ester groups in these substrates enable their simultaneous coordination to the Ru centre, which greatly reduces the efficiency of the catalyst. It is worth mentioning that the bicyclic starting materials have four asymmetric centres, and since these atoms are unaffected during the transformation, the chiral information is transferred to the final products. Notably, compound (±)-**115** was synthesised earlier from the same starting material (±)-**107** on another synthetic route by our research group in a 30% overall yield.[55]

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The present method not only afforded significantly higher yields and saved a number of steps, but avoided the use of highly toxic chemicals such as OsO_4. Moreover, *all-cis* divinylated amino ester (±)-**116** could not be synthesised by the previously mentioned method because of base-induced epimerisation.[56]

Table 1. Isolated yields for (±)-**115**, (±)-**116**, (±)-**117**, and (±)-**118** in ROM reactions with various catalysts.

Catalyst / Products	G1	G2	HG1	HG2	Catalyst / Products	G1	G2	HG1	HG2
(±)-**115**	37%	33%	38%	41%	(±)-**116**	6%	26%	29%	31%
(±)-**117**	46%	20%	80%	28%	(±)-**118**	68%	29%	45%	16%

A possible pathway for 3,5-divinylated final products is depicted in Figure 6. Because of the high concentration of ethylene, the first step of the mechanism is the formation of reactive methylidene complex **Ru-I** from the so-called pre-catalyst (HG2) by ligand exchange (metathesis reaction). In the next step, [2+2] cycloaddition occurs between norbornene β-amino acid derivatives and newly formed carbene **Ru-I** affording the corresponding metallacyclobutane **Ru-II** condensed with the bicyclic skeleton. Opening of the strained tricyclic framework takes place in the cycloreversion step by redistribution of the electrons forming new alkylidene complex **Ru-III**. Finally, another cycloaddition reaction of newly formed cyclic 5-membered Ru-containing β-amino ester **Ru-III** with ethylene takes place followed by cycloreversion resulting in the desired ring-opened product. The original Ru-methylidene complex **Ru-I** is reformed in this step and it can start the catalytic cycle again.

Formation of Ru-containing methylidene complex

Hoveyda-Grubbs 2nd pre-catalyst

1-isopropoxy-2-vinylbenzene
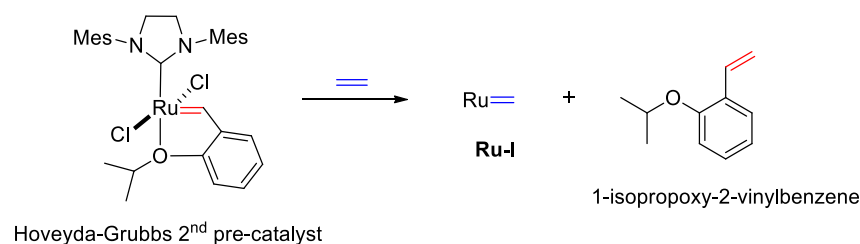
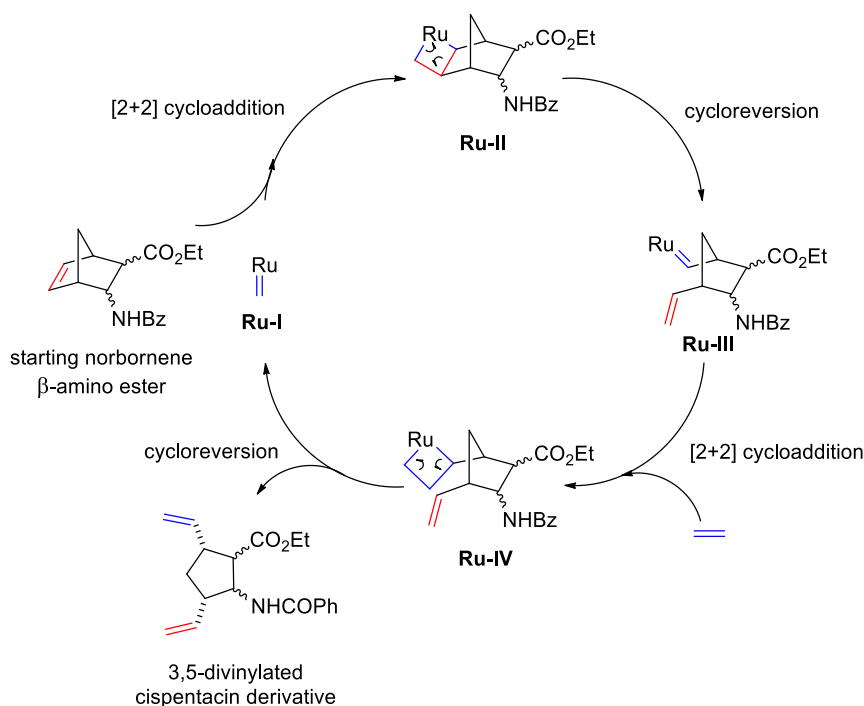Catalytic cycle of norbornene β-amino acid derivative

Figure 6.

The above detailed synthetic approach was extended to the preparation of optically pure target substances (+)-**115** and (-)-**117** (Scheme 23). First, optically active β-lactam (+)-**105** was prepared by lipolase-catalysed enantioselective enzymatic ring-opening of racemic azetidinone (±)-**105**.[141] Next, metathesis precursor (+)-**107** was synthesised in an enantiomer-enriched form via ethanolysis followed by benzoylation. Similar to the racemates, compound (+)-**107** was submitted to epimerisation by NaOEt in EtOH to afford *endo-exo*-β-amino ester derivative (-)-**113** in good yield. Finally, ROM reactions with HG1 catalyst with ethylene under argon atmosphere were executed to obtain divinylated cispentacin and transpentacin compounds (+)-**115** and (-)-**117**. The *e.r.* of optically active esters (+)-**115** and (-)-**117** were determined by chiral HPLC analysis and found to be 95:5 in both cases.
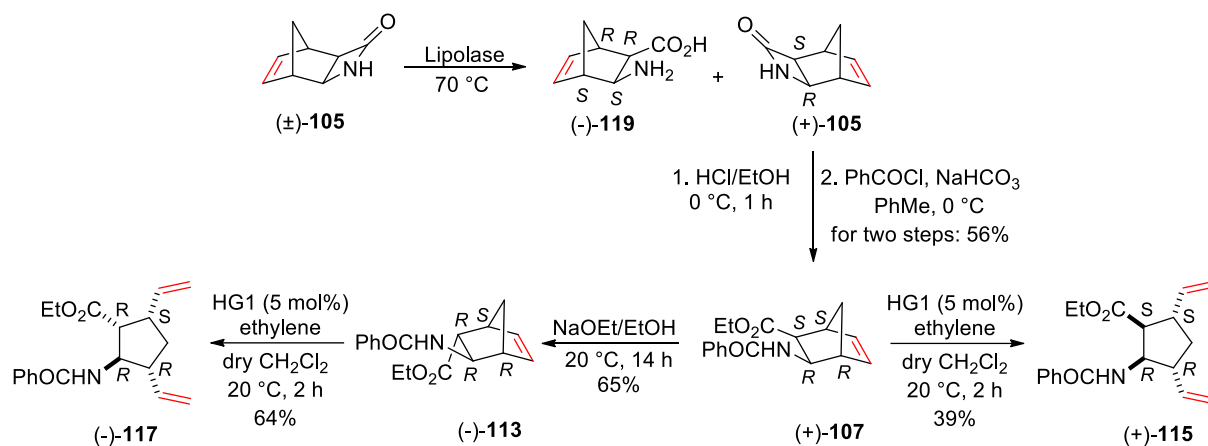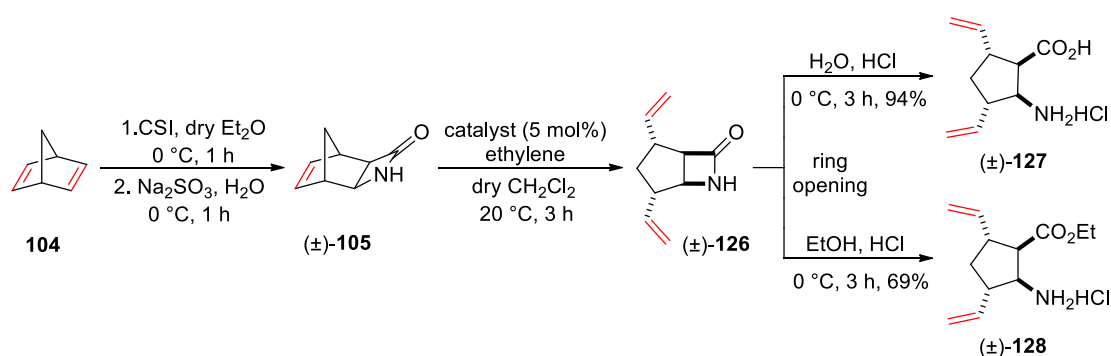
Scheme 23.

In view of the relevance of oxygen-containing cyclic β-amino acids, the stereocontrolled one-step method applied earlier was extended toward divinylated tetrahydrofuran β-amino esters as depicted in Scheme 24.[2] Thus, oxanorbornene amino ester (±)-**122** was prepared in two steps from the corresponding *diexo*-β-amino acid hydrochloride salt (±)-**120** similar to compound (±)-**112**. Epimerisation of (±)-**122** with NaOEt in EtOH at 20 °C gave *endo-exo* derivative (±)-**123** in moderate yield. The synthesis of novel divinylated tetrahydrofuran β-amino esters (±)-**124** and (±)-**125** was achieved in good yields from the corresponding bicyclic starting materials (±)-**122** and (±)-**123** in ROM reaction with the conservation of the four stereogenic centres. The metathesis reactions were performed in dry CH₂Cl₂ under ethylene and argon atmosphere in the presence of HG1 catalyst (Scheme 24).

Scheme 24.

25
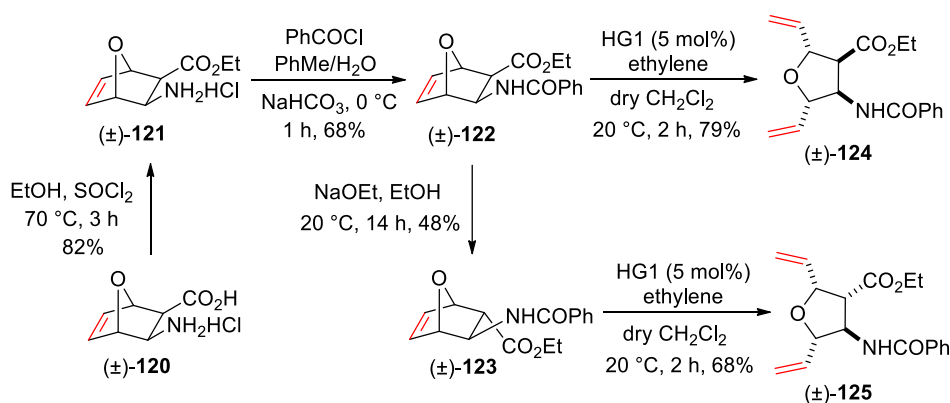
3.2. Stereocontrolled one-step synthesis of difunctionalised azetidinones and β-amino acid derivatives from condensed ring β-lactams by ring-opening metathesis (ROM)

Novel functionalised azetidin-2-ones and β-amino acid derivatives were synthesised according to our earlier strategy. The driving force of these reactions is the formation of thermodynamically more stable molecules, which have lower ring strain than the bi- or tricyclic starting materials.[115-116] During these ring-opening processes mediated by Ru–alkylidene complexes, epimerisation was not observed, that is the stereochemistry of the starting β-lactams was conserved and determined the configuration of the chiral centres in the end-products. In the first step, tricyclic β-lactam (±)-**105** was synthesised by the well-known method, via the addition of CSI to norbornadiene **104** in dry Et$_2$O at 0 °C, followed by chlorosulfonamide hydrolysis with Na$_2$SO$_3$ (Scheme 25).[2]

Scheme 25. Syntheses of divinylated cispentacin derivatives (±)-**127** and (±)-**128**. Yields of (±)-**126** G1: 80%; G2: 5%; HG1: 70%; and HG2: 10%.

Resulting *diexo*-β-lactam (±)-**105** was subjected to ROM reaction in the presence of various commercially available first and second generation Ru-based catalysts (G1, G2, HG1, and HG2) with ethylene under argon atmosphere with stirring in dry CH$_2$Cl$_2$ at 20 °C. Divinyl-substituted β-lactam (±)-**126** was formed in high yields with the first generation catalysts, while second generation catalysts preferred the formation of polymeric products. In the final step, racemic cispentacin derivatives (±)-**127** and (±)-**128** containing valuable olefinic bonds were accessed through opening of the 4-membered heterocycle. Thus, norbornadiene-derived β-lactam (±)-**126** was subjected to hydrolysis or ethanolysis in a stereocontrolled fashion to afford the corresponding cyclic 5-membered β^{2,3}-amino acid (±)-**127** or β^{2,3}-amino ester (±)-**128** as hydrochloride salts in good to excellent yields (Scheme 25).

The above ring-opening metathesis protocol was extended to the stereocontrolled syntheses of monocyclic β-lactams with terminal olefin moiety. The synthesis was started with the preparation of the corresponding bicyclic azetidinone framework (±)-**130** in two steps from readily available starting materials. 1,5-Cyclooctadiene **129** was reacted with CSI in dry CH_2Cl_2 at 0 °C, then hydrolysis with Na_2SO_3 gave 1,5-cyclooctadiene-derived β-lactam (±)-**130** (Scheme 26).
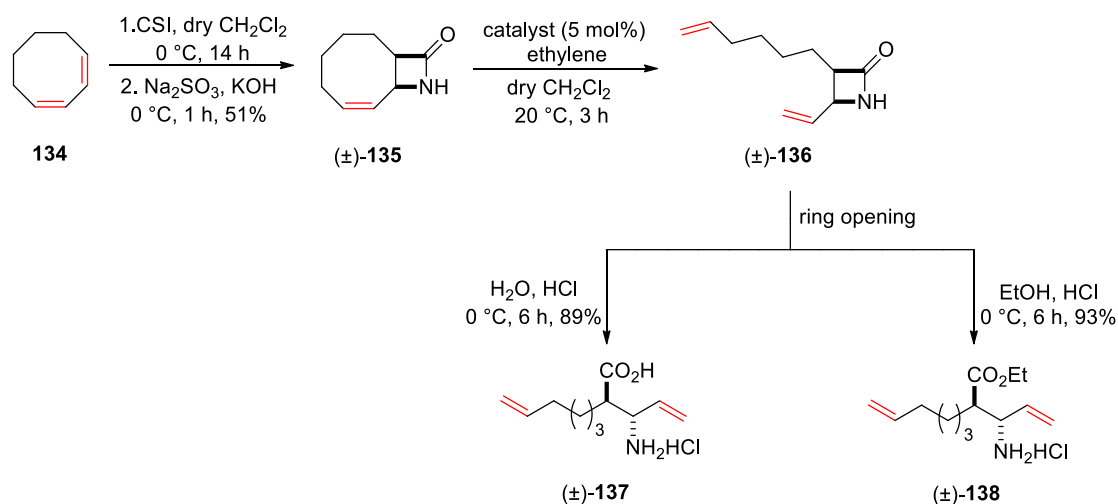

Scheme 26.
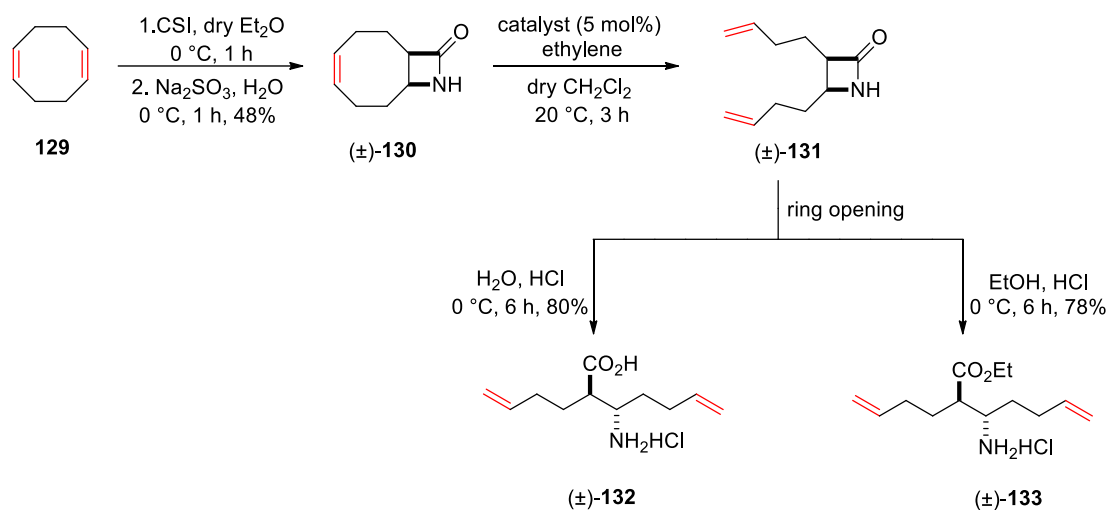
Racemic monocyclic azetidinone (±)-**131** with alkenyl moieties at the end of the alkyl chains was accessed through metathesis in dry CH_2Cl_2 at 20 °C. We have tested again first and second generation Ru-based catalysts (see Table 2) with results strikingly similar to those found with norbornene β-lactam (±)-**105**. G1 and HG1 catalysts performed well in the ring-opening reaction, while G2 and HG2 was too reactive inducing mainly polymerisation resulting in low yields of (±)-**131**. Finally, treatment of compound (±)-**131** with HCl/H_2O at 0 °C gave the corresponding open-chain β-amino acid (±)-**132** with the carboxyl and amine functions in *anti* arrangement. Ethanolysis, in turn, gave open chain β-amino ester (±)-**133** with the same stereochemistry in a yield of 78%.

Table 2. Isolated yields for (±)-**131** and (±)-**136** in ROM reactions with various catalysts.

Catalyst Product	G1	G2	HG1	HG2	Catalyst Product	G1	G2	HG1	HG2
(±)-**131**	75%	7%	74%	17%	(±)-**136**	60%	25%	67%	26%

Following our strategy, after the successful ROM in the case of compound (±)-**130**, it seemed a logical step to prepare 1,3-cyclooctadiene-derived bicyclic β-lactam (±)-**135** a regioisomer of compound (±)-**130** (Scheme 27). For this purpose, 1,3-cyclooctadiene **134** was reacted with CSI using the well-known pathway to afford the desired metathesis substrate (±)-**135** with high ring strain. During the ring-opening protocol, first generation catalysts proved to be beneficial again, although ring-opening product (±)-**136** was also isolated in modest but acceptable yields in the presence of G2 and HG2 in this case (see Table 2).
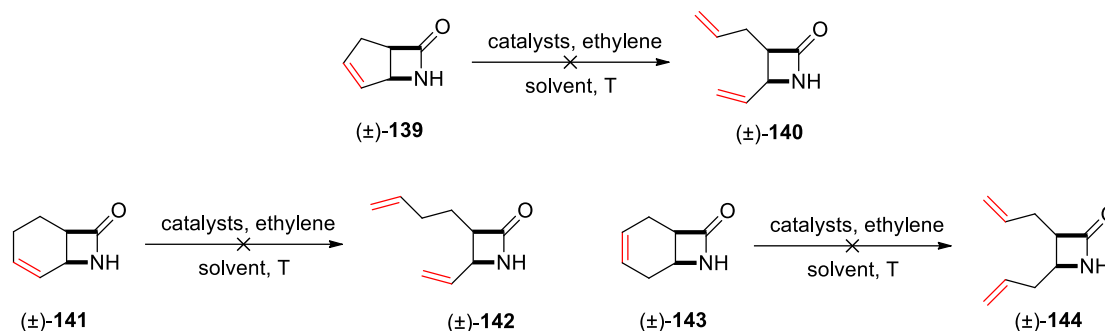

Scheme 27.

In the final step, open chain β-amino acid (±)-**137** and β-amino ester (±)-**138** bearing valuable olefinic bonds were prepared. 4-Membered heterocycle (±)-**136** was opened by H_2O or EtOH under protic conditions and gave the expected products in excellent yields in both cases. Similar to previous experiences, when compound (±)-**136** underwent hydrolysis or ethanolysis, configuration of the two asymmetric centres left unaffected and afforded *anti* arrangement for the carboxyl and amino hydrochloride groups, as depicted in Scheme 27.

However, besides successful ring-opening metathesis reactions, we have encountered difficulties in some cases (Scheme 28). Attempted ring-opening transformations of cyclopentadiene- or cyclohexadiene-derived β-lactams (±)-**139**, (±)-**141**, and (±)-**143**, which have less ring strain, did not furnish the corresponding monocyclic products (±)-**140**, (±)-**142**, and (±)-**144**. Unfortunately, all metathesis reactions performed in a variety of solvents (CH_2Cl_2, toluene) at room temperature or under reflux with all catalysts (G1, G2, HG1, and HG2) failed and only the starting materials were detected by TLC monitoring. This may be accounted for by the shift of the ring-opening/ring-closing equilibrium towards recyclisation under metathesis conditions.

Obviously ring-closing reactions of (±)-**126**, (±)-**131**, and (±)-**136** are less favoured because of evolving ring strain. Furthermore, the distance between the newly formed terminal alkene moieties further reduces the possibility for the ring closing reaction in the case of cyclooctadiene-derived compounds (±)-**131** and (±)-**136**.[124]
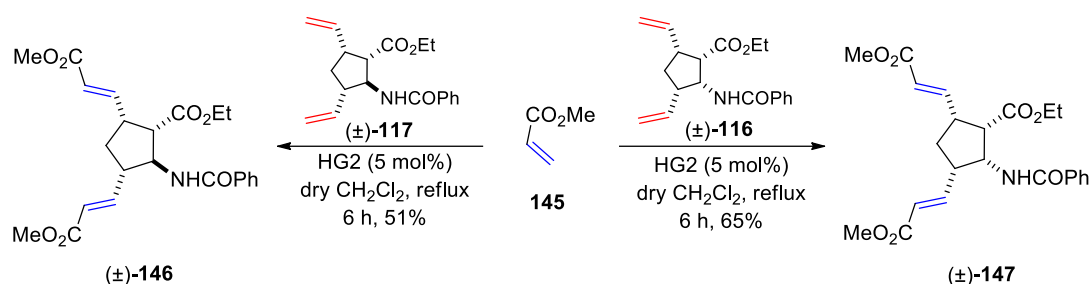

Scheme 28.

3.3. Carbon–carbon double bond functionalisation of β-amino acid derivatives and β-lactams with α,β-unsaturated carbonyl compounds through cross metathesis (CM)

Cross metathesis is a widely applied method for the functionalisation of C–C double bonds even in more complex frameworks.[142] The reaction can proceed in a chemoselective manner and it is usually *E*-selective.[120] Because of the advantages of metathesis transformations, we planned the functionalisation of terminal alkene moieties of the corresponding β-lactams or β-amino acid derivatives synthesised previously through cross metathesis reactions. For this purpose, α,β-unsaturated carbonyl compounds were used as electron-deficient olefins in the presence of HG2 catalyst. According to the literature, this is an effective cross metathesis protocol.[142] The two terminal C–C double bonds on the ring-opened products were coupled with methyl acrylate **145** and methyl vinyl ketone **148**.

First, divinylated transpentacin (±)-**117** (derived from *diexo*-norbornane β-amino ester (±)-**107** by epimerisation followed by ROM) was reacted with methyl acrylate **145** in the presence of HG2 catalyst in dry CH$_2$Cl$_2$ at reflux temperature. After the chromatographic separation from the undesired polymeric material, dicoupled product (±)-**146** was isolated in 51% yield (Scheme 29). Importantly, cross metathesis reactions were performed with both first generation Grubbs catalysts, but the desired target compound formed only in trace amounts (monitored by TLC).

After the successful cross-coupling reaction of compound (±)-**117**, *all-cis* divinylated β-amino ester (±)-**116** was subjected to cross metathesis with methyl acrylate **145** in the presence of HG2 catalyst. Cispentacin derivative (±)-**147** with three ester functions was accessed analogously to (±)-**146** in good yield, without epimerisation of the stereogenic centres. It is important to note that compound (±)-**147** was identical to the material prepared earlier on a different synthetic pathway. It may be concluded that the CM reaction proceeded under stereocontroll with *E* selectivity, that is the configuration of the newly created C–C double bonds in (±)-**146** and (±)-**147** also have *E* geometry.[56]
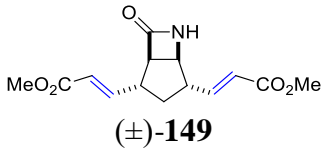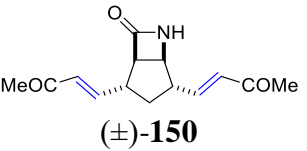

Scheme 29.

Since cross metathesis reactions worked well in the case of cispentacin derivatives (±)-**116** and (±)-**117**, we expanded the scope of the coupling reaction to β-lactams. Besides of methyl acrylate **145**, the terminal alkene moieties were transformed with methyl vinyl ketone **148** as well in these cases. First, bicyclic β-lactam (±)-**126** (derived from *exo*-lactam (±)-**105** by ROM) was subjected to coupling reactions with α,β-unsaturated carbonyl compounds **145** and **148** in the presence of HG2 catalyst (Scheme 30). In both cases, after chromatographic purification, cross metathesis products (±)-**149** and (±)-**150** with *E* geometry (high *J* values, in accordance with earlier literature data) were isolated in moderate to good yields. Cross metathesis reactions were performed in anhydrous solvents such as CH_2Cl_2 or toluene with the former giving higher yields in both cases (see Table 3).
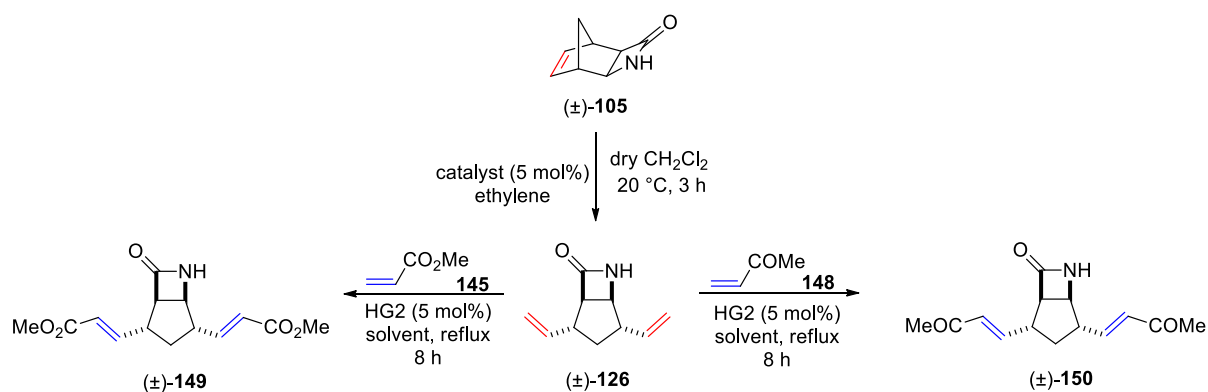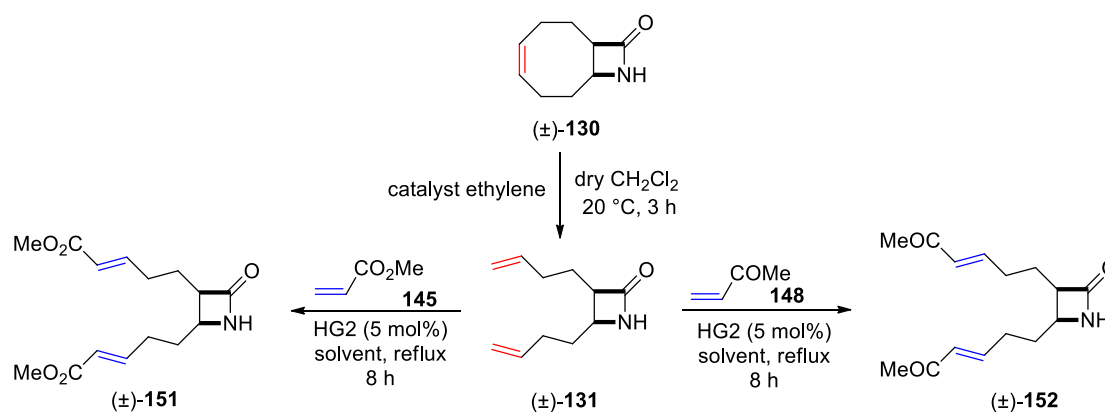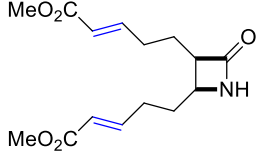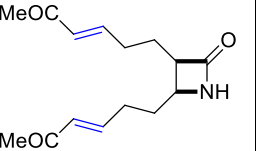

Scheme 30.

30

Table 3. Isolated yields for (±)-**149** and (±)-**150** in CM reactions with HG2 catalyst in different solvents.

Solvent	CH₂Cl₂	toluene	Solvent	CH₂Cl₂	toluene
Product			Product		
(±)-**149**	53%	18%	(±)-**150**	88%	63%

The well-established cross metathesis protocol for the synthesis of highly-functionalised bicyclic β-lactams was expanded to monocyclic unsaturated β-lactam derivatives. Ring-opening product (±)-**131** prepared previously was coupled with methyl acrylate **145** and methyl vinyl ketone **148** analogously to bicyclic β-lactam (±)-**126** in the presence of HG2 catalyst as depicted in Scheme 31. Coupling reactions smoothly afforded the expected final products (±)-**151** and (±)-**152** with *E* geometry in good yields (see Table 4) similar to the formation of products (±)-**149** and (±)-**150** synthesised previously.

Scheme 31.

Table 4. Isolated yields for (±)-**151** and (±)-**152** in CM reactions with HG2 catalyst in different solvents.

Solvent	CH₂Cl₂	toluene	Solvent	CH₂Cl₂	toluene
Product			Product		
(±)-**151**	68%	55%	(±)-**152**	48%	70%

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Finally, β-lactam derivative (±)-**136** [a regioisomer of (±)-**131**] underwent cross metathesis reactions with the previously used electron-deficient olefins **145** and **148**. Coupling reactions were carried out in dry toluene or CH$_2$Cl$_2$ at reflux temperature in the presence of HG2 catalyst (Scheme 32). Di-ester β-lactam (±)-**153** was isolated in 73% yield when the reaction was performed in toluene, while in the case of its ketone counterpart (±)-**154** the use of CH$_2$Cl$_2$ as solvent resulted in higher yield (see Table 5).
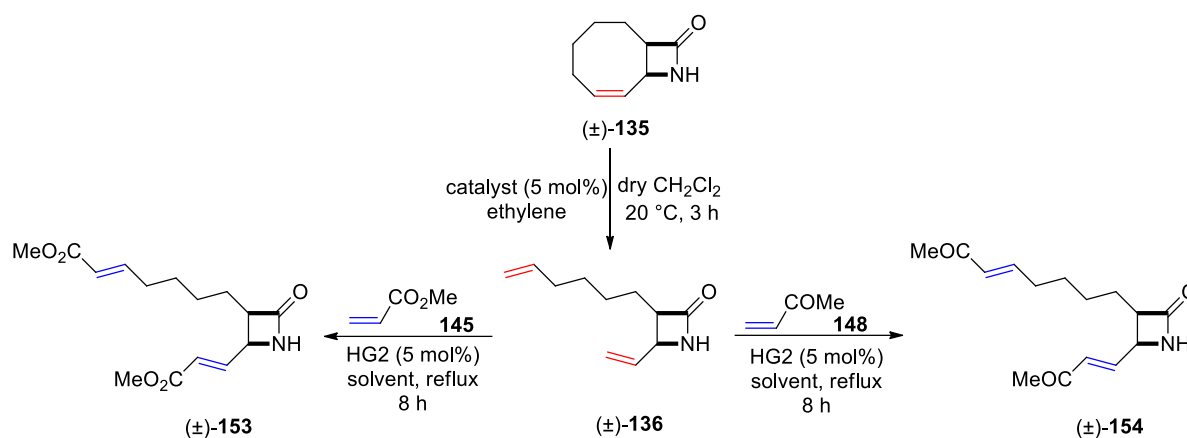
Scheme 32.

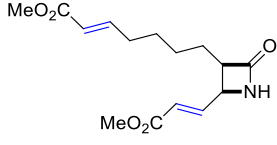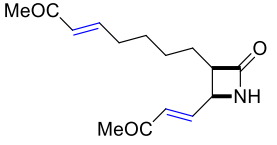**Table 5**. Isolated yields for (±)-**153** and (±)-**154** in CM reactions with HG2 catalyst in various solvents.

Solvent	CH$_2$Cl$_2$	toluene	Solvent	CH$_2$Cl$_2$	toluene
Product			Product		
(±)-**153**	63%	73%	(±)-**154**	70%	56%

However, it is important to note, that product selectivity during CM reactions is not always predictable, because it is often complicated to determine, which olefin reacts selectively. To solve this problem, Chatterjee et al. compiled a table containing different types of olefins with the appropriate catalysts.[142] With this new approach in hand, high selectivity is achievable by using the appropriate reagents during the coupling reactions. In their studies the olefins were categorised in four (+1) types based i) on the susceptibility of the starting materials to form homodimers via CM and ii) on the ability of the coupled product toward secondary metathesis reactions. The first group includes olefins, which are able to undergo rapid homodimerisation and the product homodimers possess the same reactivity towards subsequent metathesis reactions as their parent olefins.

Type II group consists of olefins, which homodimerise slowly and their homodimers are sparingly consumed in secondary coupling reactions. Type III olefins lack the ability to form homodimers but are still able to perform CM reactions with Type I or Type II olefins. Type IV alkenes cannot react in CM reactions and they have no effect on the catalyst activity. Finally, the +1 category consists of alkenes, which inhibit catalyst activity.

The study determines that selective CM reaction can be achieved by selecting the appropriate olefins from different types without using large stoichiometric excess of one compound. In our case, the reagents (α,β-unsaturated carbonyl compounds) are categorised as Type II olefins, while the substrates in the case of cispentacin and transpentacin derivatives [(±)-**115**, (±)-**116**, (±)-**117**, and (±)-**118**] belong to Type III based on our experimental results (homodimer product was not formed but reacted selectively with Type II olefins). Monocyclic unsaturated β-lactam (±)-**131** (terminal olefin) is categorised as Type I alkene. In contrast, the classification is not straightforward for (±)-**136** because of the different alkenyl moieties: the molecule contains both a terminal alkene part and a tertiary allylic position. Despite complications arising from the classification, CM products were isolated in all cases with moderate to good yields (Table 3, 4, 5 and Scheme 29). However, it is worthwhile to mention that, large stoichiometric excess of acrylate or ketone were used in the coupling reaction, which in itself increases selectivity.

A possible mechanism for the 3,5-dicoupled cispentacin derivative is depicted in Figure 7. Because of the high concentration of methyl acrylate **145** in the first step, Ru-containing complex **Ru-V** was formed by ligand exchange (metathesis reaction) with pre-catalyst HG2. Next, [2+2] cycloaddition occurs between the newly-formed carbene **Ru-V** and 3,5-divinylated cispentacin derivatives, which leads to the corresponding metallacyclobutane intermediate **Ru-VI**. Formation of the monocoupled product and the Ru-containing methylidene complex **Ru-I** by redistribution of the electrons take place in the cycloreversion step. The other vinyl group on the monocoupled 5-membered cyclic β-amino ester can be functionalised again with a further methyl acrylate **145** (in carbene form **Ru-V**) via metathesis reaction. First, cycloaddition occurs between newly formed mono-metathesised β-amino ester and **Ru-V** affording the corresponding metallacyclobutane **Ru-VII**. Formation of the desired dicoupled product takes place in the cycloreversion step by redistribution of the electrons. Finally, the reaction of the newly-formed Ru-based methylidene complex **Ru-I** with methyl acrylate **145** reproduces Ru-alkylidene **Ru-V** which starts the catalytic cycle from the beginning.

Formation of **Ru-V** complex

Hoveyda-Grubbs 2nd pre-catalyst

Ru-V

1-isopropoxy-2-vinylbenzene
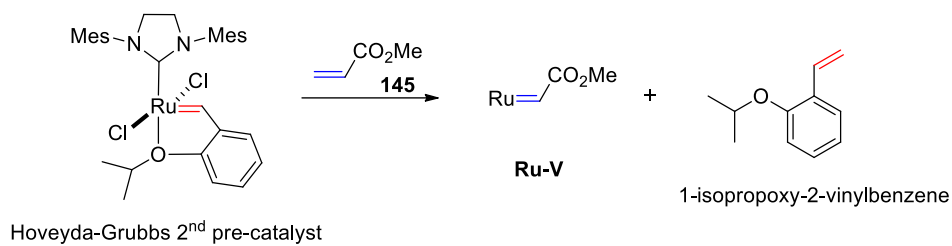
Catalityc cycle of 3,5-divinylated cispentacin derivative

[2+2] cycloaddition

Ru-VI

cycloreversion

Ru-I

starting 3,5-divinylated
cispentacin derivative

Ru-V

monocoupled
cispentacin derivative

cycloreversion

Ru-I

145

[2+2] cycloaddition
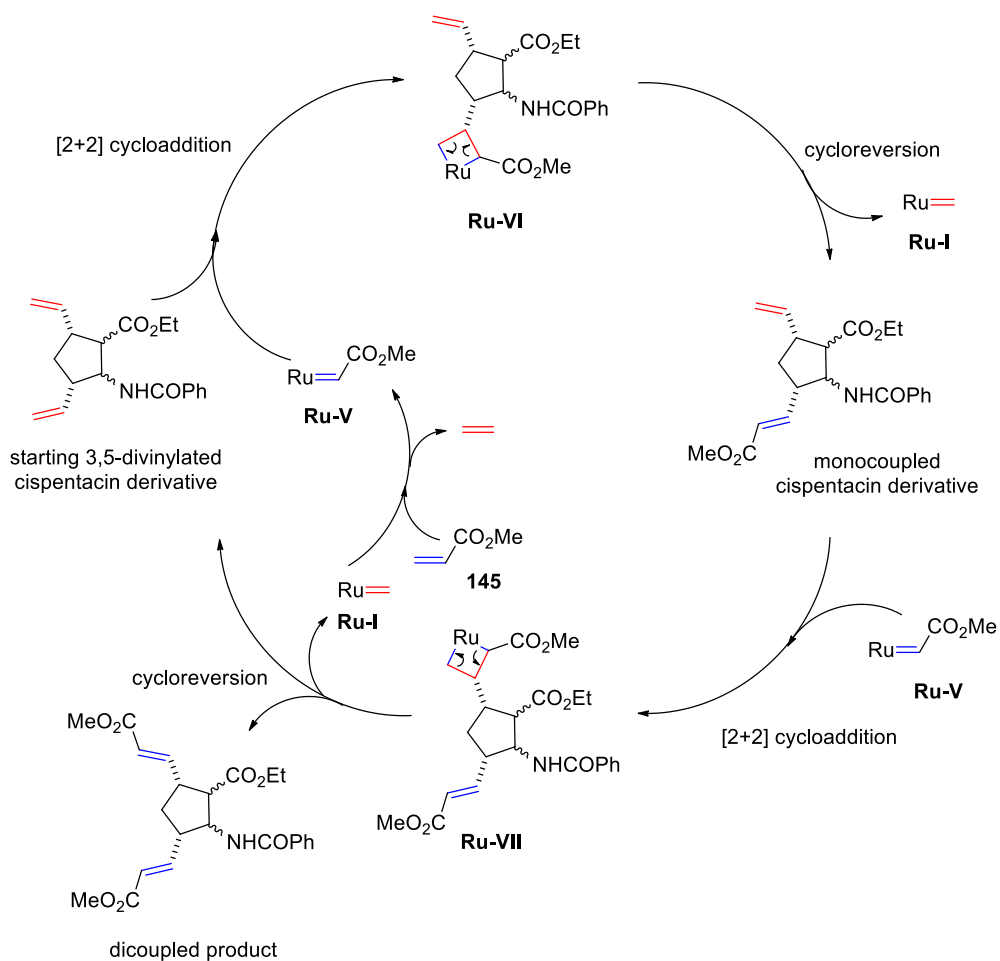
Ru-V

Ru-VII

dicoupled product

Figure 7.

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3.4. Syntheses of functionalised β-amino acid derivatives and β-lactams through chemoselective cross metathesis (CM)

Chemoselectivity was observed in the field of metathesis reactions (RCM, CM, and EYM) in several cases. It can originate from multiple factors, including the choice of catalyst, since the outcome of these reactions is often catalyst dependent. Steric or electronic deactivation of one of the C–C double bonds is also capable of inducing chemoselectivity.[120] Furthermore, 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 C–C double bond.[143-145] It was also reported that the metallacyclobutane intermediate can be stabilised by interaction of the metal centre with nearby donor groups of the substrate, hindering further transformation of the involved C–C double bond.[146]

During our experimental investigation we realised that under appropriately selected reaction conditions, chemodiscrimination of the olefinic bonds in cross metathesis reactions is achievable. Reactions of some divinylated β-amino esters and a divinylated β-lactam (derived from ROM reactions) with methyl vinyl ketone or acrylate esters in the presence of various metathesis catalysts afforded monocoupled products in a chemoselective manner. The aim of this section is the presentation of these reactions and to explain the reasons behind their chemoselectivity.

We have started our experiments with the investigation of cross metathesis reaction of divinyl-substituted azetidinone (±)-**126** derived from norbornene β-lactam (±)-**105** by ROM reaction (Scheme 33). This bicyclic lactam was subjected to coupling reactions with methyl vinyl ketone **148** or acrylic esters **47** and **145** in the presence of commercially available G1, G2, HG1, and HG2 catalysts. However, coupling products (±)-**155** and (±)-**156a,b** were detected (by TLC monitoring) only in the presence of second generation catalysts. After trying several experimental conditions, the best yields were achieved by using 5 mol% HG2 catalyst in dry CH$_2$Cl$_2$ for 4 h. Monocoupled products, involving the α,β-unsaturated carbonyl part located near to the amide *N*-atom, were isolated in moderate yields (see Table 6). It is important to note that our attempts to increase the yields of the mono-metathesised products failed because of various side reactions, such as polymerisation and formation of dicoupled products.
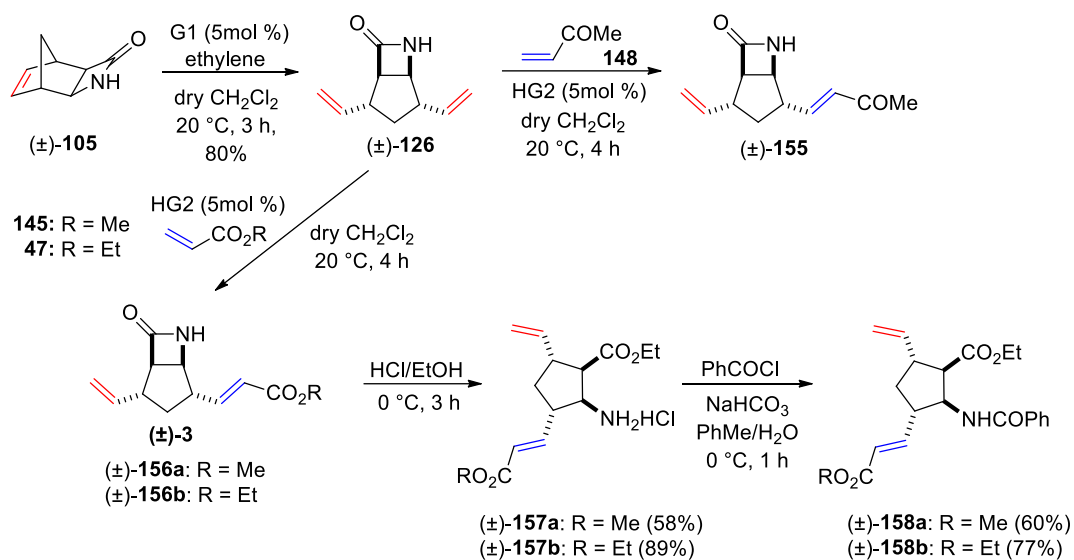
Scheme 33.

Table 6. Isolated yields for (±)-**155** and (±)-**156a**,**b** in selective CM reactions with HG2 catalyst.

Catalyst	HG2	Catalyst	HG2	Catalyst	HG2
Product		Product		Product	
	53%		**51%**		**41%**
(±)-**155**		(±)-**156a**		(±)-**156b**	

Monocoupled β-lactams (±)-**156a**,**b** were considered to be suitable precursors for stereocontorolled access to different cispentacin derivatives with C–C double bond via opening of the heterocyclic ring. Thus, monocoupled cispentacin ester hydrochlorides (±)-**157a**,**b** were synthesised from the corresponding β-lactams (±)-**156a**,**b** by ethanolysis. Importantly, transesterification did not take place in the case of (±)-**156a**. Finally, the amino function was protected by benzoylation to access novel monocoupled cyclic β-amino esters (±)-**158a**,**b** (Scheme 33). Unfortunately, attempted ring-opening of compound (±)-**155** by HCl/EtOH resulted in polymerisation.

Although less known in metal-catalysed processes, we assumed in our first approach that hydrogen bonding interaction between the halogen atom of the Ru-alkylidene complex and the amide N–H moiety as hydrogen bonding donor function could force the olefin bond closer to the amide *N*-atom to participate in the coupling reaction (Fig. 8).[143-145] This leads to the mono-metathesised product before further CM reaction could occur.
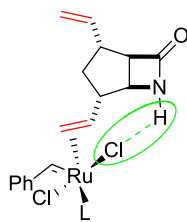
Figure 8.

In further studies, we were interested in the hydrogen bonding directing effect. To verify our hypothesis, *N*-Boc-protected divinylated β-lactam (±)-**160** was prepared by ROM reaction with G1 catalyst under ethylene atmosphere from the corresponding tricyclic compound (±)-**159** (Scheme 34). The resulting metathesis substrate (±)-**160**, which cannot function as a hydrogen donor, was subjected to CM reaction with ethyl acrylate **47** in the presence of HG2 catalyst. According to our expectation, when the directing effect was excluded, the coupling reaction was not selective and afforded a mixture of the two mono-metathesised isomers (±)-**161** and (±)-**162** in a ratio close to 2:1 determined by the NMR analysis of the crude mixture. Unfortunately, our attempts to separate and isolate these two monocoupled β-lactams failed.
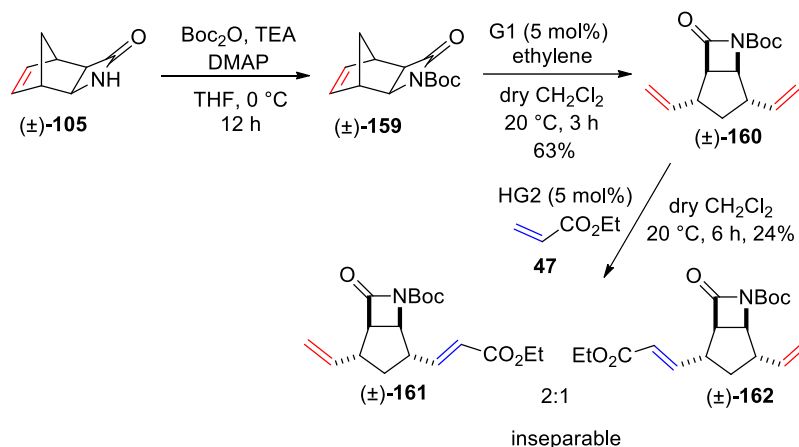
Scheme 34.

After successful chemoselective coupling of (±)-**126**, we have expanded the scope of the metathesis substrates for these reactions. β-Amino esters with 5-membered ring were used as our next starting compounds. First, divinyl-substitued cispentacin (±)-**115** (prepared by our ROM method) was submitted to CM reactions with acrylic esters **47** and **145** (Scheme 35). However, contrary to our previous experimental results, these cross metathesis reactions of compound (±)-**115** in view of monocoupled products were not completely selective. As determined by ^{1}H-NMR analysis, a mixture of two regioisomers (±)-**158** and (±)-**163** was formed in a 4:1 ratio through a partial hydrogen bonding directing effect.
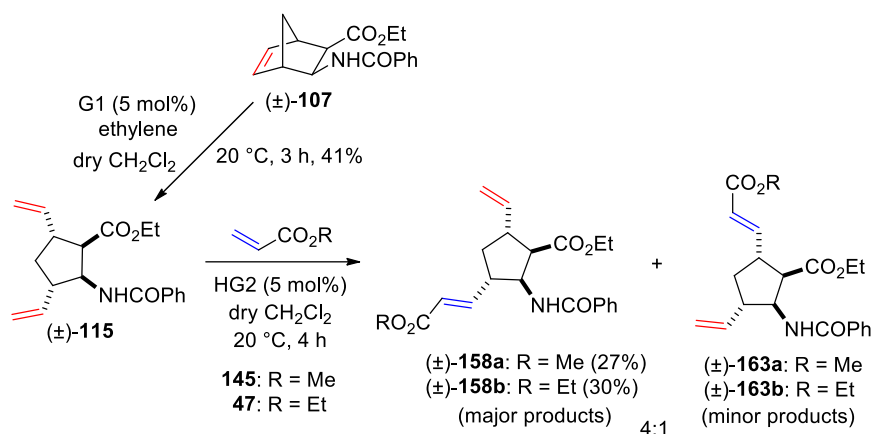
Scheme 35.

After several failed attempts to separate the two regioisomers by column chromatography, the major products (±)-**158a,b** where the α,β-unsaturated ester part is located near to the amide *N*-atom could be successfully isolated by crystallisation from hexane/EtOAc. Their NMR data were completely identical with the final products shown in Scheme 33 thereby proving unambiguously their structure. Because of the limitations of crystallisation and metathesis side reactions such as the formation of dicoupled products or polymerised material, chemoselective coupling resulted in moderate but acceptable yields.

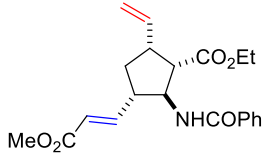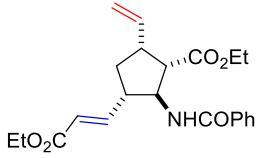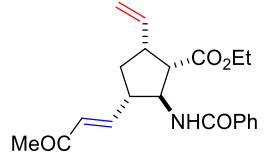After the unexpected experimental results (two isomers instead of one), we next investigated the chemical properties of diolefinated transpentacin (±)-**117** in chemoselective CM reactions. For this purpose, divinylated amino ester (±)-**117**, where the protected amino group and the ester moiety are in *trans* relationship, was prepared by the usual ROM protocol (Scheme 36).
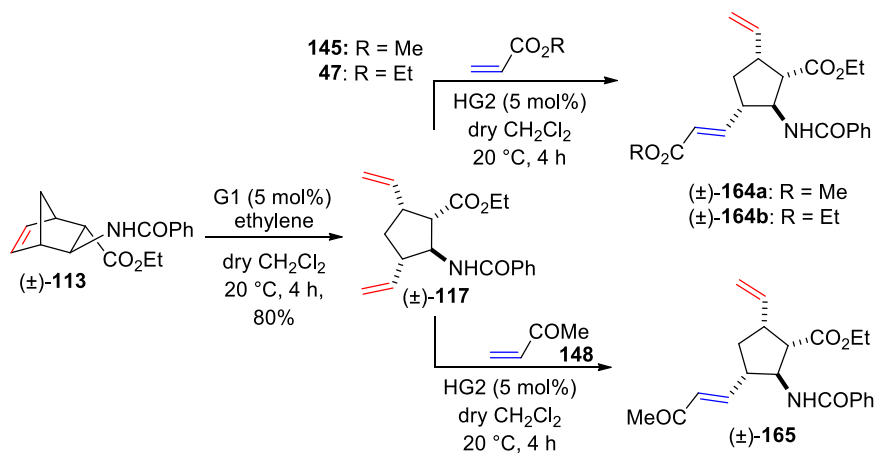
Scheme 36.

Accordingly, compound (±)-**117** was submitted to cross-coupling with acrylic esters **47** and **145** or methyl vinyl ketone **148** at room temperature in dry CH_2Cl_2 with HG2 catalyst to afford the corresponding mono-metathesised products (±)-**164a,b** and (±)-**165** in medium yields (see Table 7). In contrast with divinylated cispentacin (±)-**115** [and at the same time similarly to divinylated β-lactam (±)-**126**], the CM reaction in these cases resulted in single monocoupled isomers. The structure of **164a** was also determined by X-ray crystallography (Fig. 9).

Table 7. Isolated yields for (±)-**164a,b** and (±)-**165** in selective CM reactions with HG2 catalyst.

Catalyst	HG2	Catalyst	HG2	Catalyst	HG2
Product		Product		Product	
(±)-**164a**	47%	(±)-**164b**	44%	(±)-**165**	50%

Figure 9. X-ray structure of compound **164a**

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 further support this theory, we tried to disrupt this hydrogen bonding, which should decrease the selectivity. To achieve this goal, CM reaction between compound (±)-**117** and methyl acrylate **145**, which previously afforded only a single isomer in CH_2Cl_2, was performed in three additional solvents (THF, dioxane, and toluene). The results were in complete agreement with our expectation and showed that solvents capable of participating in hydrogen bonding with the substrate (dioxane, THF) compete with the catalyst providing a mixture of regioisomers (±)-**164a** and (±)-**166** (approximately 2:1 ratio,

determined by NMR analysis of the crude product). In contrast, solvents not being able to form a hydrogen bond (CH_2Cl_2 and toluene) clearly gave only a single product (Schemes 36 and 37).
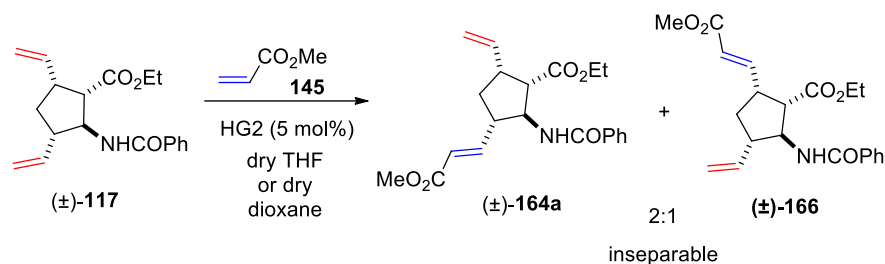
Scheme 37.

However, when another diolefinated transpentacin stereoisomer, namely (±)-**118** (derived from *diendo*-norbornene β-amino ester (±)-**112** by epimerisation and subsequent ROM) was submitted to CM reaction with α,β-unsaturated carbonyl compounds **145** and **148**, inseparable mixtures of regioisomers (±)-**167**/(±)-**168** and (±)-**169**/(±)-**170**, respectively, were formed. Regioisomeric ratios, determined by NMR analysis of the crude products, were nearly 2:1 in both cases (Scheme 38).
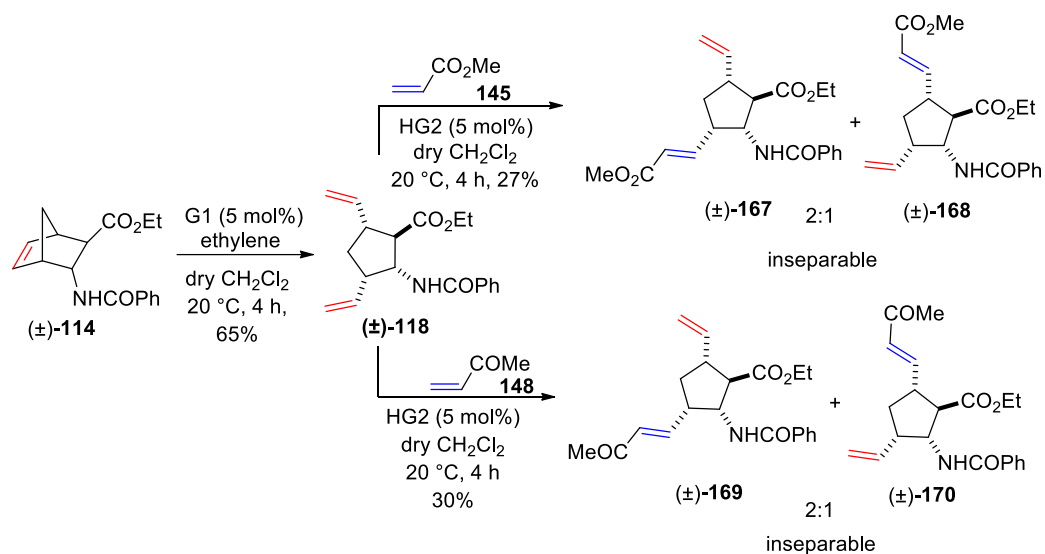
Scheme 38.

These results clearly suggested that in addition to the hydrogen bonding effect, other factors also influence the outcome of the coupling reactions. Chemoselectivity may originate from steric effects. It is also highly probable, that coordination of ruthenium to the carbonyl oxygen, which creates a stable 6-membered chelate ring (**T1**), stabilizes the metallacyclobutane and hinders further transformations. In the case of **T2** and **T3** structures, in which the vinyl side-chain and the ester function are *trans* to each other, formation of the chelate ring is less favored and, therefore, the cross metathesis reaction is not selective (Fig. 10).
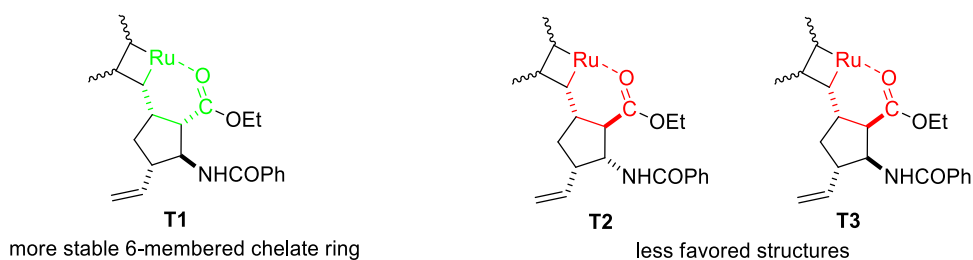
Figure 10. Chelate ring stability in the case of transpentacin derivatives (±)-**117**, (±)-**118**, and (±)-**115**.

Because of the importance of oxygen-containing heterocyclic β-amino acids (such as oxetin) we extended the scope of the chemoselective transformations with CM reactions to the synthesis of monocoupled *O*-heterocyclic counterparts. For this reason, diolefinated amino ester (±)-**124**, in which the ester and the protected amino group are in a *cis* arrangement, was prepared by ROM reaction from the corresponding bicyclic starting material (±)-**122**. Cross metathesis reaction was performed between acrylate ester **47** and compound (±)-**124** in the presence of HG2 catalyst. Similar to its carbocyclic counterpart (±)-**115**, it afforded an inseparable mixture of (±)-**171** and (±)-**172** in nearly 2:1 ratio (Scheme 39).
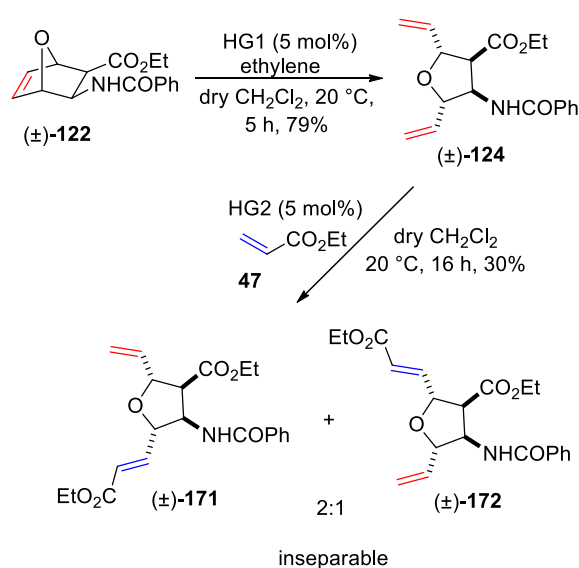
Scheme 39.

Finally, it seemed to be logical to prepare the *trans* isomer of oxygen-containing heterocyclic (±)-**125** and subject it to CM reaction with ethyl acrylate **47** in the presence of HG2 catalyst (Scheme 40). For this purpose, oxanorbornene amino ester (±)-**122** was epimerised with NaOEt in EtOH at 20 °C in moderate yield to afford metathesis substrate (±)-**123**, which then underwent ROM reaction. According to our expectation (and confirming the chelate theory in these cases), the CM reaction led to single monocoupled product (±)-**173** analogously to *trans* amino ester (±)-**117**.
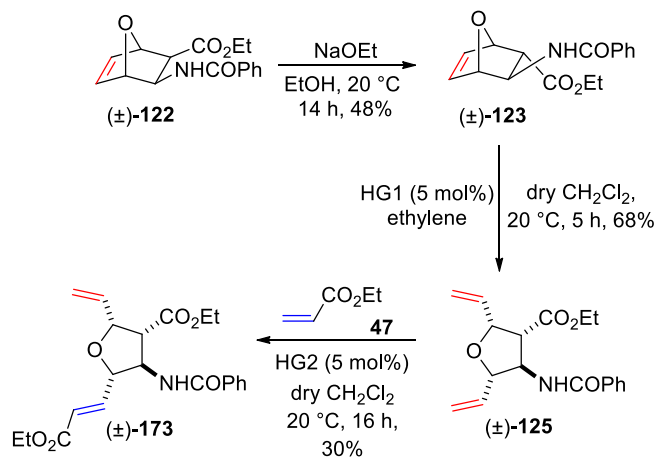
Scheme 40.

4. SUMMARY

- An efficient, stereocontrolled one-step protocol has been developed for the syntheses of divinylated cispentacins **115**, **116**, **117**, and **118** as well as oxacispentacin **124** and **125** stereoisomers with multiple chiral centres from *diexo*-norbornene **107** and *diendo*-norbornene **112** or oxanorbornene β-amino acid derivatives **122** by ROM reaction (Schemes 22 and 24).

- During ROM reactions, the stereocentres of the starting materials were unaffected allowing the transfer of chiral information to the final products. ROM reactions were executed in the presence of commercially available Ru-based first and second generation Grubbs and Hoveyda-Grubbs catalysts (G1, G2, HG1, and HG2) with ethylene under argon atmosphere.

- In the case of cispentacin derivatives **115** and **116**, clear correlation between yields, the used catalysts and the structure of starting materials **107** and **112** was not observed, although HG2 catalyst was slightly more effective than the others. However, when the carboxyl and the amino function were in *trans* arrangement in starting materials **113** and **114**, first generation catalysts G1 and HG1 gave yields more than two times higher. Lower yields found with *diexo* **107** and *diendo* **112** derivatives may be explained by chelation of the catalyst.

- The well-established one-step synthetic protocol was also applied for the access of optically pure divinylated cispentacin derivatives (+)-**115** and (-)-**117** from an enantiomerically enriched *diexo*-norbornene β-lactam (+)-**105** obtained by enzymatic kinetic resolution of racemic azetidinone **105** (Scheme 23).

- The stereocontrolled ring-opening method was applied to the preparation of a divinylated bicyclic β-lactam **126** and monocyclic β-lactams **131** and **136** with terminal alkene functions. The ROM reactions in all cases [β-lactams and (oxa)norbornene β-amino acid derivatives] were largely facilitated by the high ring strain of the unsaturated starting materials, which is released during these transformations.

- Functionalised β-lactams **126**, **131**, and **136** were suitable precursors for stereocontrolled access of divinylated cispentacins or open-chain β-amino acid derivatives with *anti* arrangement of the carboxyl and amino moieties. Thus, these valuable olefinated β-amino acids **127**, **132**, and **137** or esters **128**, **133**, and **138** were prepared through the opening of the 4-membered heterocyclic ring by aqueous or ethanolic solution of HCl (Schemes 25, 26, and 27).

- Ring-opened products containing the valuable olefin bond were further functionalised with α,β-unsaturated carbonyl compounds (methyl acrylate **145** or methyl vinyl ketone **148**) through CM reaction (Schemes 29, 30, 31, and 32). The coupling reactions were executed in the presence of HG2 catalyst affording dicoupled azetidinones **149**, **150**, **151**, **152**, **153** and **154** as well as dicoupled β-amino acid derivatives **146** and **147** with *E* geometry with moderate to good yields (see Tables 3, 4, and 5).

- In the final section, olefin chemodifferentiation of divinylated products **115**, **117**, **118**, **124**, **125**, **126**, and **160** (derived from ROM) through CM reactions was presented. With a simple modification of reaction conditions, valuable monocoupled azetidinones **155** and **156a**,**b**, cispentacin **158a**,**b**, **164a**,**b**, and **165** as well as oxacispentacin derivatives **173** were the main products instead of previously described disubstituted products (Schemes 33, 35, 36, and 40).

- The selectivity in the case of bicyclic β-lactam **126** originates from the hydrogen bond between the catalyst chlorine atom and the N–H moiety, which was confirmed by NH–NBoc exchange (Figure 8 and Scheme 34). However, in the case of 5-membered cyclic β-amino acid derivatives **115**, **117**, and **118**, selectivity was determined by multiple factors (Schemes 35, 36, 37, and 38).

- Besides of secondary interactions, chelate ring stability also proved to be responsible for chemodifferentiation (Figure 10). This resulted in a single mono-metathesised product in the cases of transpentacin **117** and its oxa-analogue **125**. In contrast, a mixture of regioisomers were formed when cispentacin **115**, its oxa-analogue **124** and transpentacin **118** were used as starting material (Schemes 35, 36, 38, 39, and 40). The structure of **164a** was also certified by X-ray crystallography (Figure 9).

5. ACKNOWLEDGEMENTS

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ANNEX