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Application of Metathesis Protocols to the Stereocontrolled Synthesis of some Functionalized β-Amino Esters and Azaheterocycles

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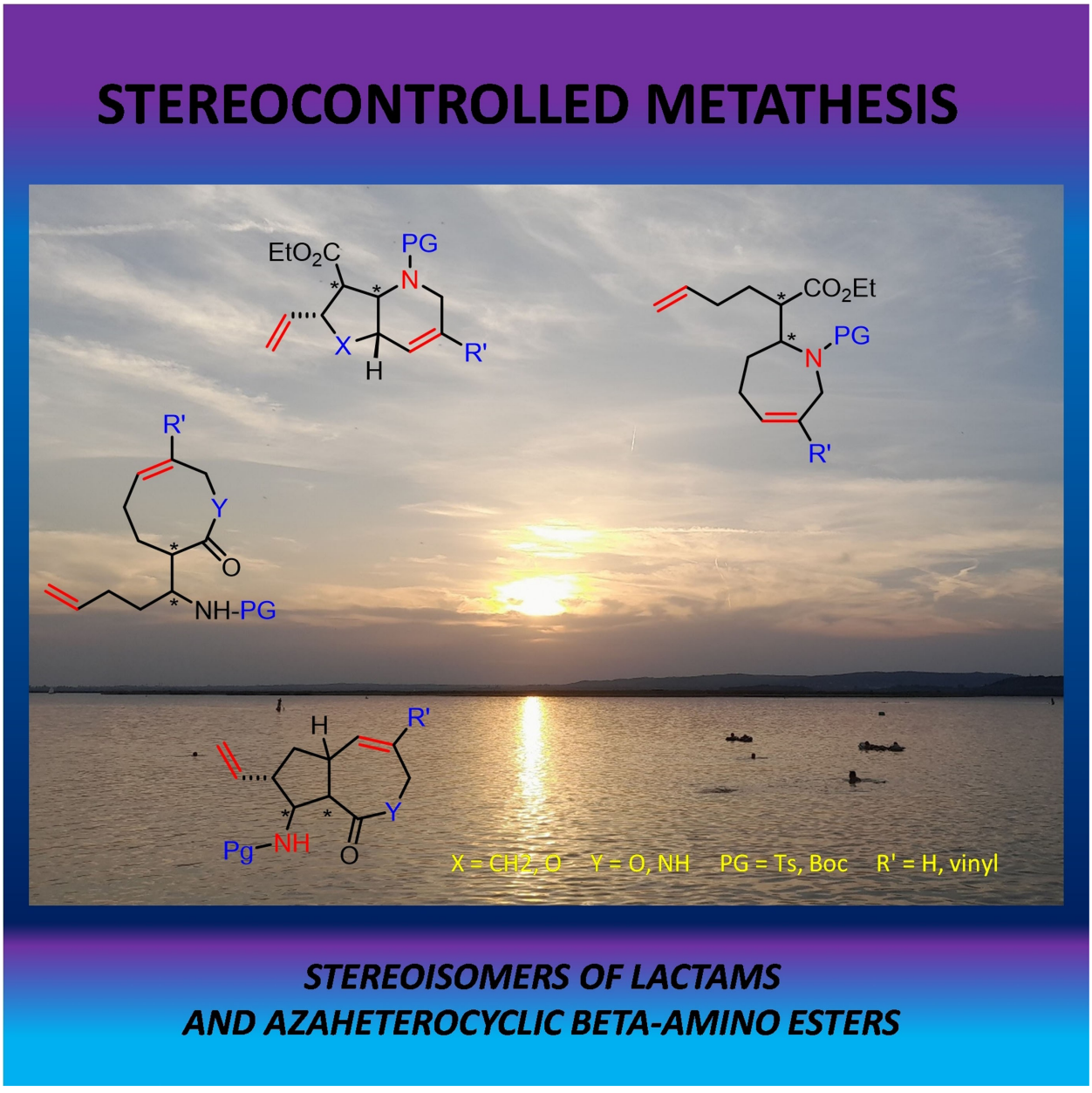

Abstract: In this account our aim was to give an insight into the application of metathesis protocols (ROM, RCM, RCEYM, CM, RRM) for the synthesis of various azaheterocyclic frameworks. Due to the high biological potential and importance in peptide chemistry and drug design of β-amino acids our intention is to give a highlight on the synthetic procedures and transformation of these class of compounds with the above-mentioned metathesis strategies with emphasis on selectivity, stereocontrol, substrate-directing effect or functional group tolerance.

Keywords: amino acids, azaheterocycles, cyclization, metathesis, stereocontrol

1. Introduction

Carbocyclic and azaheterocyclic β-amino acids exert a growing interest in pharmaceutical and medicinal chemistry. Such molecular entities can be found in a large number of natural products, bioactive compounds, and drugs.[1–19] A wide variety of methods were developed during last two decades to obtain such derivatives.[20–33] Azaheterocyclic β-amino acid derivatives were also synthesized through oxidative ring opening followed by cyclization across double reductive amination.[26,30–36]

Highly functionalized azaheterocycles (including the azaheterocyclic β-amino acid derivatives) are an interesting and highly abundant compound class in pharmaceutical and medicinal chemistry.[14–15,37–43] A number of functionalized azaheterocycles were prepared from functionalized cycloalkenes through oxidative ring opening followed by ring closing with double reductive amination.[44–47]

Olefin metathesis uses commercially available metal alkylidenes to cleave C=C bonds, then reassemble the resulting alkylidene fragments into new olefins.[48–56] A high number of metathesis processes are known, including ring-opening metathesis (ROM), ring-closing metathesis (RCM), cross-metathesis (CM), cross enyne metathesis (CEYM), ring-closing enyne metathesis (RCEYM), and ring-rearrangement metathesis (RRM).[49,51,53] The last procedure is a domino metathesis process, which consists of a ring-opening metathesis (ROM) substep followed by either a ring-closing metathesis (RCM) or a ring-closing enyne metathesis (RCEYM).[57–59] Ru-based metathesis catalysts are relatively robust and have good functional group tolerance.[50,53] Furthermore, olefin metathesis does not affect the configurations of stereogenic centers and requires only mild conditions. Thanks to their attractive characteristics and versatility, metathesis processes are being widely used in chemical industry[60–63] as well as in the synthesis of bioactive molecules and natural products.[64–68] Ring-opening metathesis and regioselective cross-metathesis was an approach to obtain various novel functionalized scaffolds from cyclic β-amino acid derivatives.[29–33]

Diversity-oriented synthesis (DOS), whose aim is the construction of valuable (structurally and chemically diverse) molecular libraries, has become an important principle during the last two decades in pharmaceutical chemistry and drug design. Three-dimensional complex scaffolds are common DOS targets, because such compounds are more promising in drug discovery.[69–81] Ring-rearrangement metathesis (RRM) is one of the methods which can easily and efficiently generate highly complex frameworks that would be difficult to synthesize by conventional common methods.[57–58]

The present account summarizes metathesis protocols to the preparation of structurally diverse molecular entities focusing on stereocontrolled synthetic routes for accessing azaheterocyclic β-amino acid derivatives, with the strategy based on ring-rearrangement metathesis of highly strained unsaturated bicyclic compounds (Scheme 1).

1.1. Importance of Cyclic β-Amino Acid Derivatives

Cyclic β-amino acids exert a wide range of biological properties, can be found in some natural products and drugs, and are promising building elements of various foldamers. As a result of this, such compounds and their synthesis was always a hot topic in pharmaceutical and medicinal chemistry.[1–19,82–88]

Figure 1 shows a number of relevant carbocyclic β-amino acid derivatives. Cispentacin (**1**), an antifungal antibiotic, was isolated from the culture broth of a *Bacillus cereus* strain.[7] One synthetic analogue, icofungipen (**2**), has similar bioactivity (but its development stopped after Phase II trials).[8] Tilidine [(±)-**3**] is a synthetic analgesic commercial drug.[7]

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Santos Fustero studied chemistry at the University of Zaragoza, where he obtained his bachelor's degree in 1972. He received his Ph.D. in organic chemistry in1975 from the same university under the supervision of Profs. Barluenga and Gotor. He carried out postdoctoral studies for two years at Prof. Lehmkuhl's group at the Max-Planck-Institut für Kohlenforschung in Mülheim/Ruhr, Germany. In 1983, he became an associate professor at the University of Oviedo, and in 1990, he was promoted to a full professor at the University of Valencia. His research interests include organofluorine and medicinal chemistry, organocatalysis, heterocyclic chemistry and new reaction methodologies.

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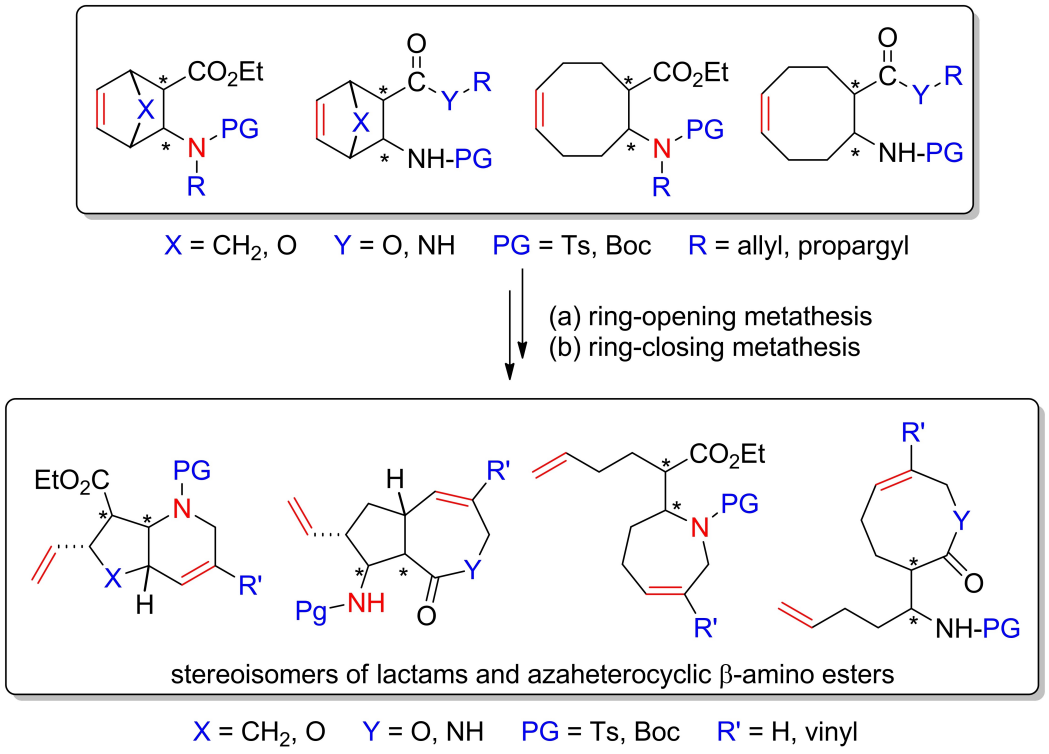


Scheme 1. Summary of the present account.

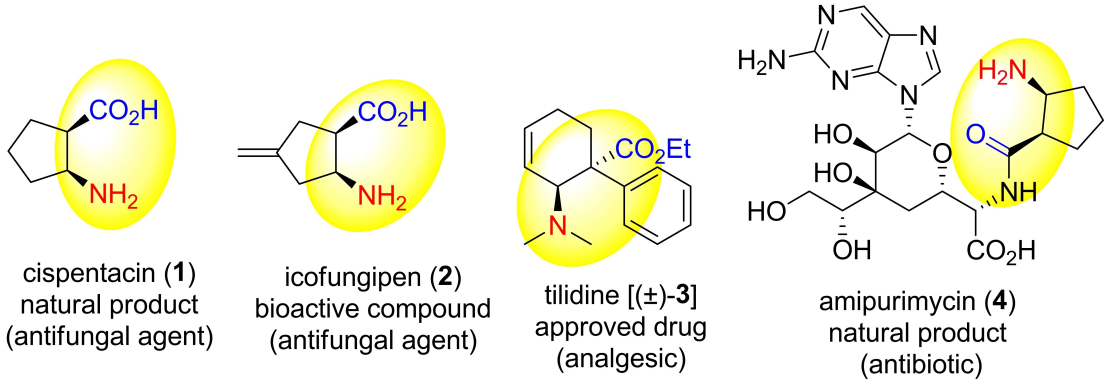


Figure 1. Alicyclic β-amino acids in natural products, bioactive derivatives and drugs.

Amipurimycin (**4**) is a peptidyl nucleoside antibiotic which was isolated from *Streptomyces novoguineensis*, and contains a cispentacin unit.[9]

Several important azaheterocyclic β-amino acid derivatives are depicted on Figure 2. Avacopan (**5**), a complement 5a receptor antagonist, is used in the treatment of an autoimmune disease (anti-neutrophil cytoplasmic autoantibody-associated vasculitis).[18] Elarofiban (**6**) is a platelet aggregation inhibitor (a glycoprotein IIb/IIIa antagonist) whose development stopped after Phase II trials.[10] Dexmethylphenidate (**7**) stimulates the central nervous system, and it is used in the treatment of attention deficit hyperactivity disorder (ADHD).[11] Cucurbitin (**8**) is a natural product that is found in seeds of *Cucurbita* species and possesses activity against *Schistosoma japonicum* (a parasitic worm).[19]

Figure 3 depicts some relevant oxacyclic β-amino acid derivatives. Oxetin (**9**) is an antibiotic which was isolated from the fermentation broth of a *Streptomyces* species.[82] Compounds **10–12** are nucleoside analogue antibiotics. Blasticidin S (**10**) was isolated from *Streptomyces griseochromogenes*,

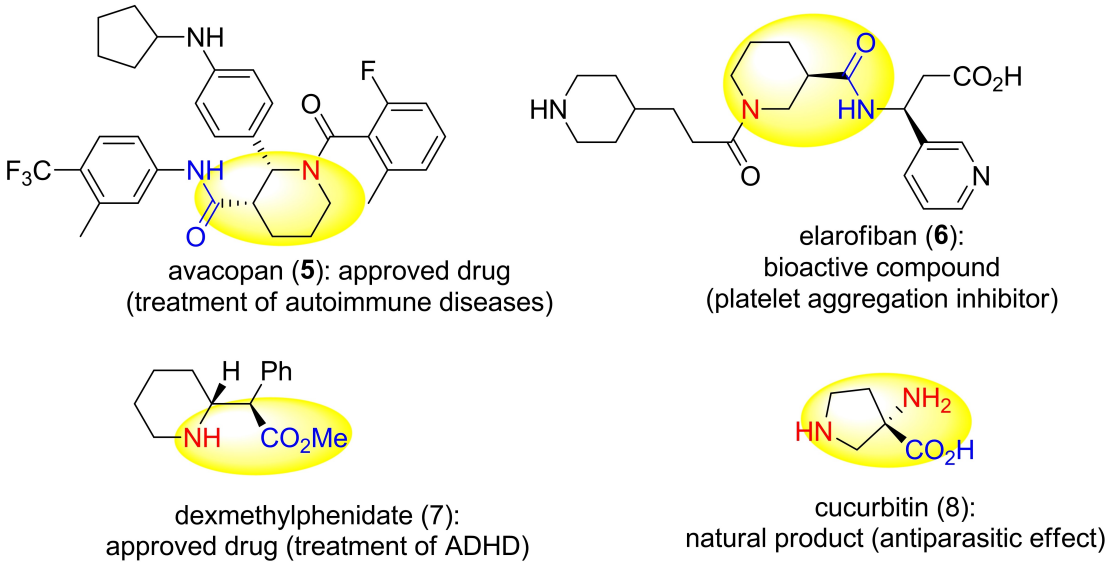


Figure 2. Azaheterocyclic β-amino acid element containing molecules in natural products, bioactive compounds and drugs.

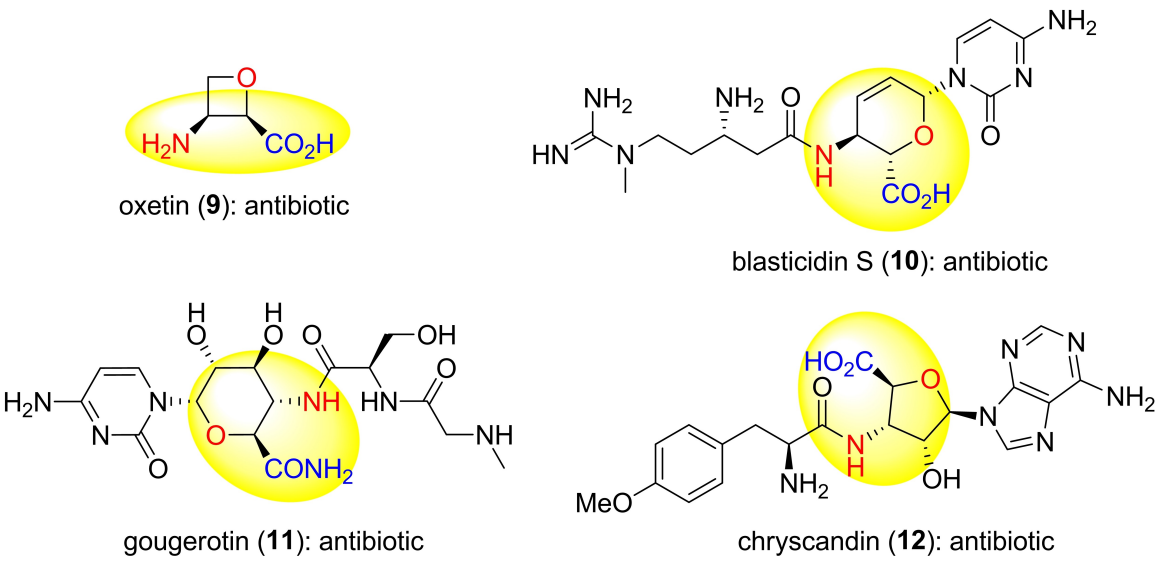


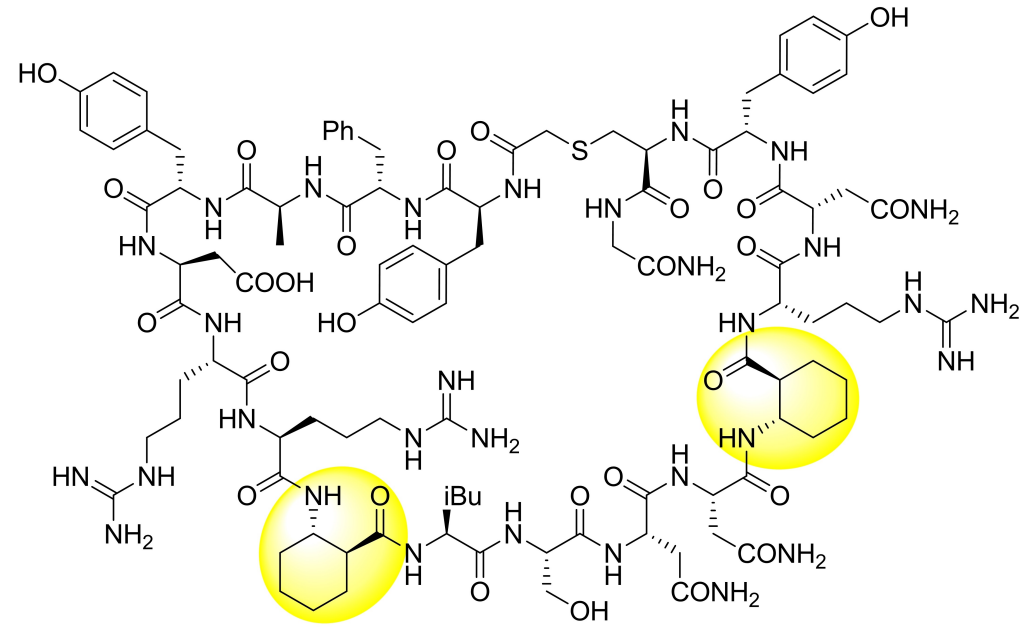
Figure 3. Oxacyclic β-amino acids in some natural products.

gougerotin (**11**) was isolated from *Streptomyces gougerotii*, while chryscandin (**12**) is produced by a *Chrysosporium pannorum* strain.[7,83,84]

Cyclic β-amino acids are also utilized as building blocks for the synthesis of peptides and foldamers (non-natural oligomers which fold into a well-defined conformation in solution). A number of peptides which incorporate cyclic β-amino acids exhibit interesting biological activities (Figure 4).[85–88]

1.2. Olefin Bond Functionalization of Some Cycloalkene β-Amino Acid Derivatives through Metathesis Reactions

As a consequence of the high relevance of cyclic β-amino acid derivatives, transformation and preparation of such compounds was a highlighted topic, and many synthetic routes were developed.[20–36] In this chapter, after a brief introduction to olefin metathesis, those synthetic pathways will be discussed whose key steps were ring-opening and cross-metathesis.[29–33]



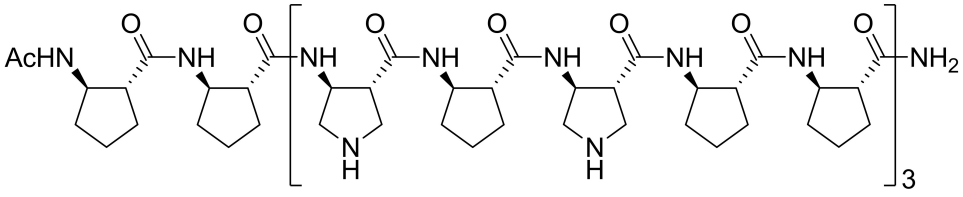


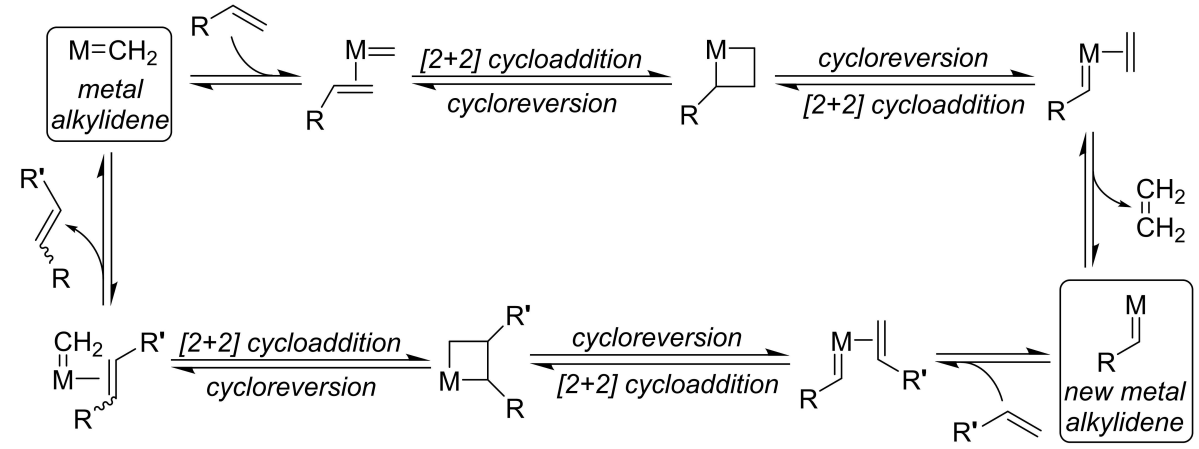
Figure 4. Bioactive foldamers containing cyclic β-amino acids.

1.2.1. A Brief Overview to Olefin Metathesis

Over the past two decades, olefin metathesis became increasingly important and widely used in synthetic organic chemistry.[60–68] The accepted mechanism for the olefin metathesis was proposed by Chauvin in 1971 (Scheme 2).[48] The process starts with a [2 + 2] cycloaddition between the metal alkylidene and an olefin, then the formed metallacyclobutane intermediate undergoes cycloreversion. The resulting new metal-alkylidene then repeat the previous process with another olefin. Note that metathesis processes are generally reversible, and the alkylidene fragments of the starting compounds are reassembled in a more or less statistical fashion.[48–53]

The properties of the metal alkylidene catalyst are very important. The first well-defined homogenous catalysts appeared in the late 1970s (after the mechanistic proposal of Chauvin), and underwent enormous development since then.[50–56] Currently, two types of metathesis catalysts are commonly used, which have somewhat complementary properties. The molybdenum-based Schrock catalysts are highly active, but (like the majority of other metathesis catalysts) they are sensitive to moisture or air, and incompatible with many functional groups (however, they tolerate amines and phosphines which are incompatible with ruthenium-based catalysts).[50,51,53] In contrast, the ruthenium-based Grubbs and Hoveyda-Grubbs catalysts are easy to handle (because they are reasonably oxygen and moisture resistant), have good functional tolerance, and somewhat lower activity.[50,51,53] In addition, ruthenium-based catalysts are easily accessible, which contributed crucially to the current importance of olefin metathesis processes. Figure 5 shows structures of the most commonly used Ru-based catalysts.[53]

Several types of metathesis reactions have been developed, such as ring-opening metathesis (ROM), ring-opening metathesis polymerization (ROMP), ring-closing metathesis (RCM), acyclic diene metathesis polymerization (ADMET),



Scheme 2. Olefin metathesis mechanism proposed by Chauvin in 1971.

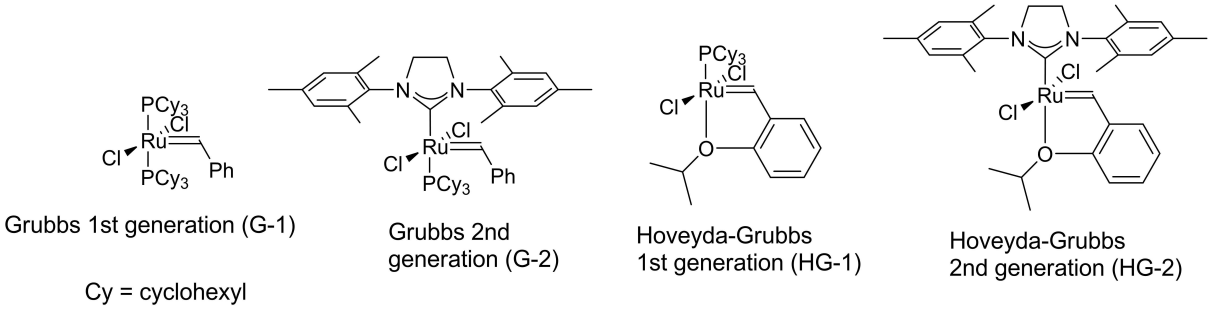


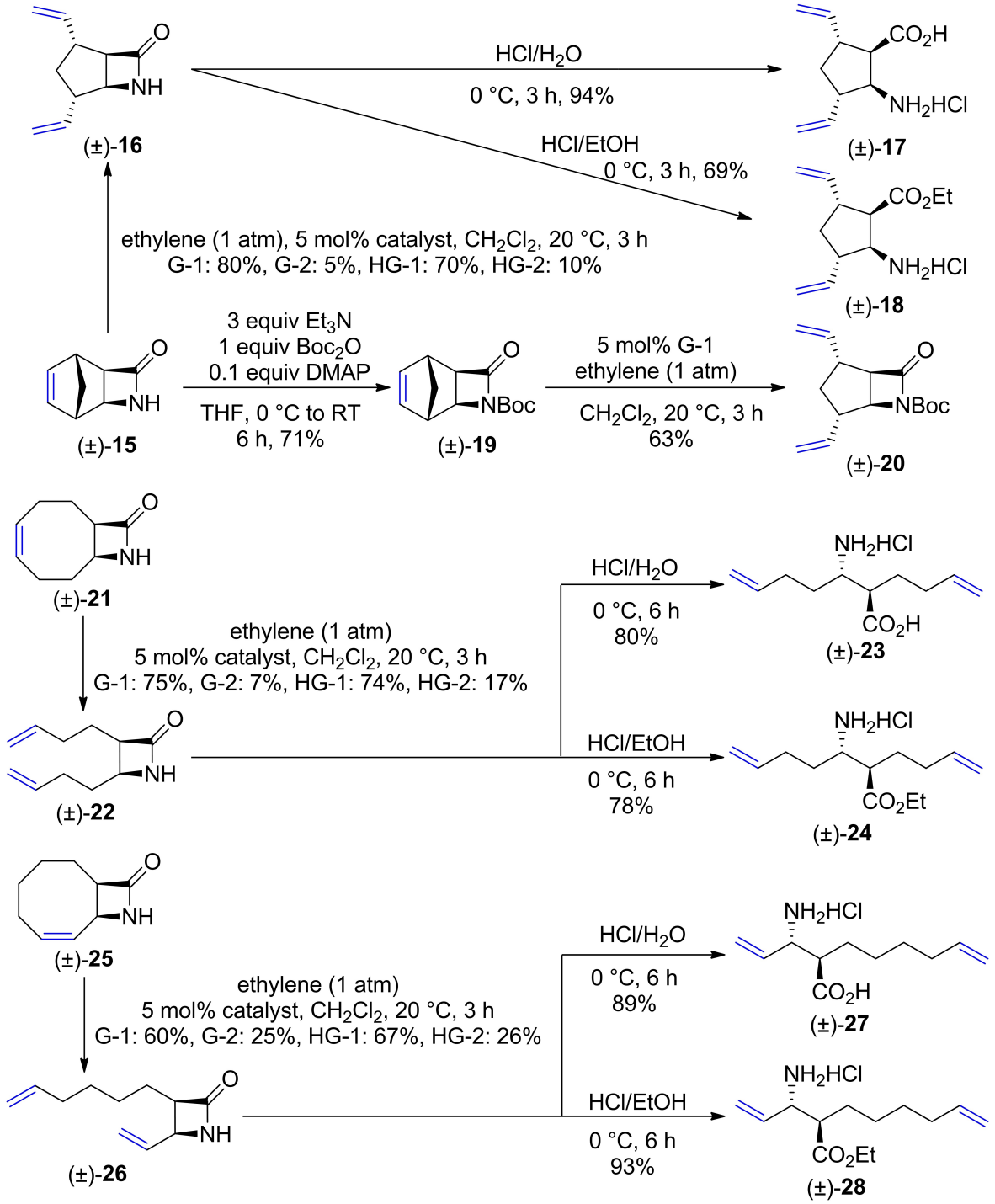
Figure 5. Structures of the most commonly used Ru-based catalysts and their abbreviations.

cross-metathesis (CM), cross enyne metathesis (CEYM), ring-closing enyne metathesis (RCEYM), and ring-rearrangement metathesis (RRM).[49–53,57] All of these transformations are stereocontrolled: the metathesis process only affects sp^2 carbons of olefin bonds, sp^3 carbons (including stereocenters) are untouched. Notably, although all metathesis reactions are reversible, the position of the equilibrium is highly affected by the reaction conditions and the stabilities of the olefins.[51,53] Nowadays, olefin metathesis reactions are commonly used in the synthesis of a wide variety of complex bioactive molecules and natural products.[58–59,64–68] Besides research laboratories, this process appeared in different fields of chemical industry such as the production of petrochemicals, oleochemicals and polymers.[60–63]

1.2.2. Olefin Bond Functionalization through Ring-Opening Metathesis

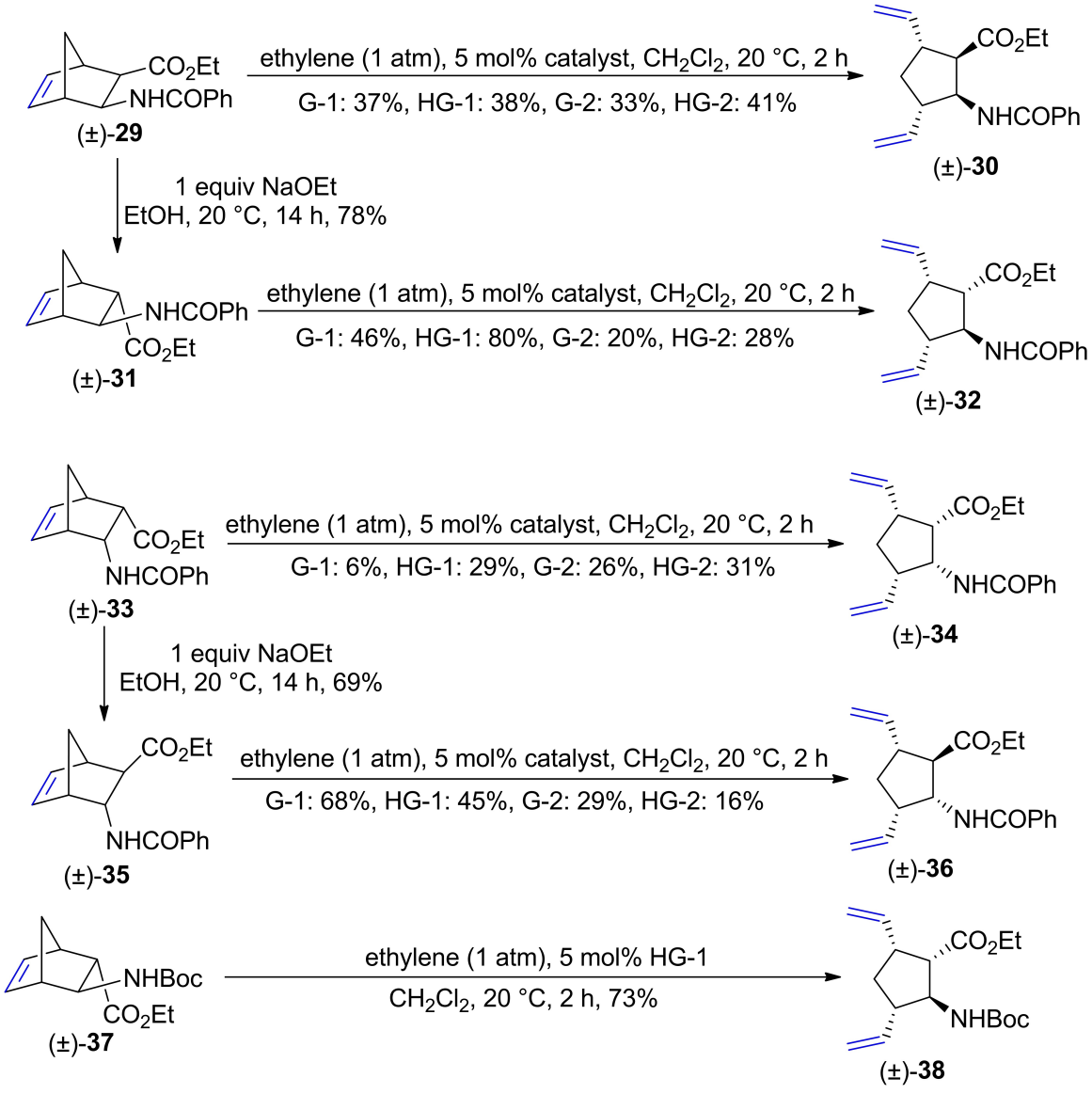
A stereocontrolled approach to functionalized cispentacins and open-chain $\beta^{2,3}$-amino acid derivatives has been reported recently, which utilized ring-opening metathesis of the unsaturated bi- or tricyclic β-lactams as its key step (Scheme 3). The starting lactams [(±)-**15**, (±)-**21** and (±)-**25**] were obtained from readily available cyclic dienes (norbornene, 1,5-cyclooctadiene and 1,3-cyclooctadiene) via [2 + 2] cycloaddition with chlorosulfonyl isocyanate (CSI) followed by partial hydrolysis with an aqueous solution of sodium sulfite and sodium carbonate.[20,21,30] Reaction of these β-lactams with ethylene afforded the expected ring-opening metathesis products, the highest yields were obtained with G-1 and HG-1 catalysts. The formed lactams (±)-**16**, (±)-**22** and (±)-**26** were submitted to acidic hydrolysis to obtain β-amino acid hydrochlorides (±)-**17**, (±)-**23** and (±)-**27**. Alternatively, ethanolysis of these lactams provided β-amino ester hydrochlorides (±)-**18**, (±)-**24** and (±)-**28**. Neither ROM nor lactam ring opening affected the configuration of the stereocenters.[30] ROM of lactam (±)-**19** (prepared by *N*-Boc protection[22] of (±)-**15**) was also accomplished.[31]

Kardos et al. reported that application of *N*-protected β-amino esters instead of β-lactams yielded functionalized *N*-protected cispentacin esters (Scheme 4). *Diexo* amino ester (±)-**29** was obtained from lactam (±)-**15**, while *diendo* amino ester (±)-**33** was synthesized from carbic anhydride. Epimerization of these esters with NaOEt in EtOH furnished



Scheme 3. Synthesis of divinyl-substituted cispentacins and acyclic $\beta^{2,3}$-amino acid derivatives.

substrates (±)-**31** and (±)-**35** in which the ester and the amide groups are *anti* to each other. Treatment of these substrates with metathesis catalysts (G-1, G-2, HG-1, or HG-2) under ethylene atmosphere resulted in the desired ring-opening metathesis products. In the case of racemic *diexo* and *diendo* norbornene β-amino ester substrates (±)-**29** and (±)-**33**, there was no clear correlation between yields and catalysts used, although HG-2 catalyst was slightly more effective in both



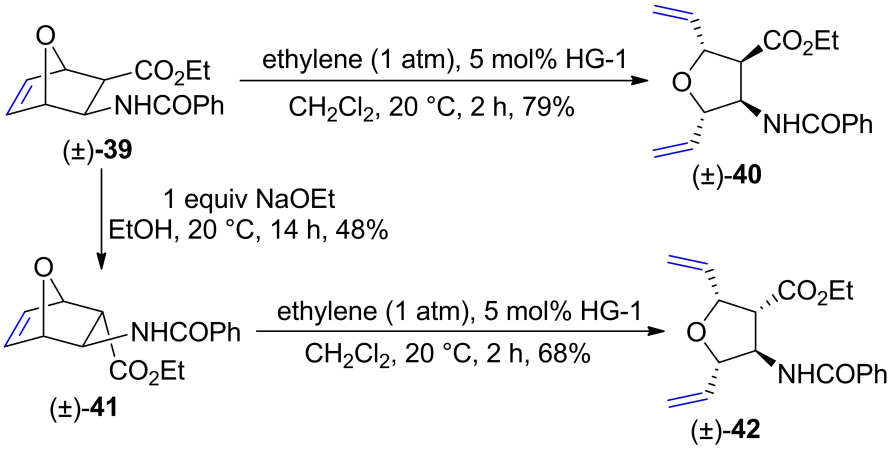
Scheme 4. Synthesis of 3,5-divinylated cispentacin and transpentacin derivatives.

cases (41 % and 31 %). In contrast, for *exo-endo* derivative (±)-**31** and *endo-exo* derivative (±)-**35**, the 1st generation catalysts provided more than two times higher yields than 2nd generation ones.[29] The transformation of compound (±)-**37** [the *N*-Boc protected analogue of (±)-**31**] was accomplished as well (Scheme 4).[33]

In view of the importance of oxygen-containing heterocyclic β-amino acids, Kardos et al. reported the preparation of such compounds using ROM. *diexo*-Oxanorbornene amino ester (±)-**39** was prepared from *exo*-3,6-epoxy-1,2,3,6-tetrahydrophthalic anhydride (the Diels-Alder reaction product between furan and maleic anhydride). Its stereoisomer (±)-**41** was prepared by base-promoted epimerization. Both oxanorbornene compounds were submitted to ROM. The reaction only took place in the presence of HG-1 catalyst, and gave 3,5-divinylated oxacispentacin (±)-**40** and 3,5-divinylated oxatranspentacin (±)-**41** (Scheme 5).[29]

1.2.3. Olefin Bond Functionalization via Cross-Metathesis

Cross-metathesis (metathesis reaction between two different olefins) is a commonly utilized method for the functionalization of C=C bonds.[50,53,56,64] Because subjecting the mixture of olefins **A** and **B** to metathesis should give three possible

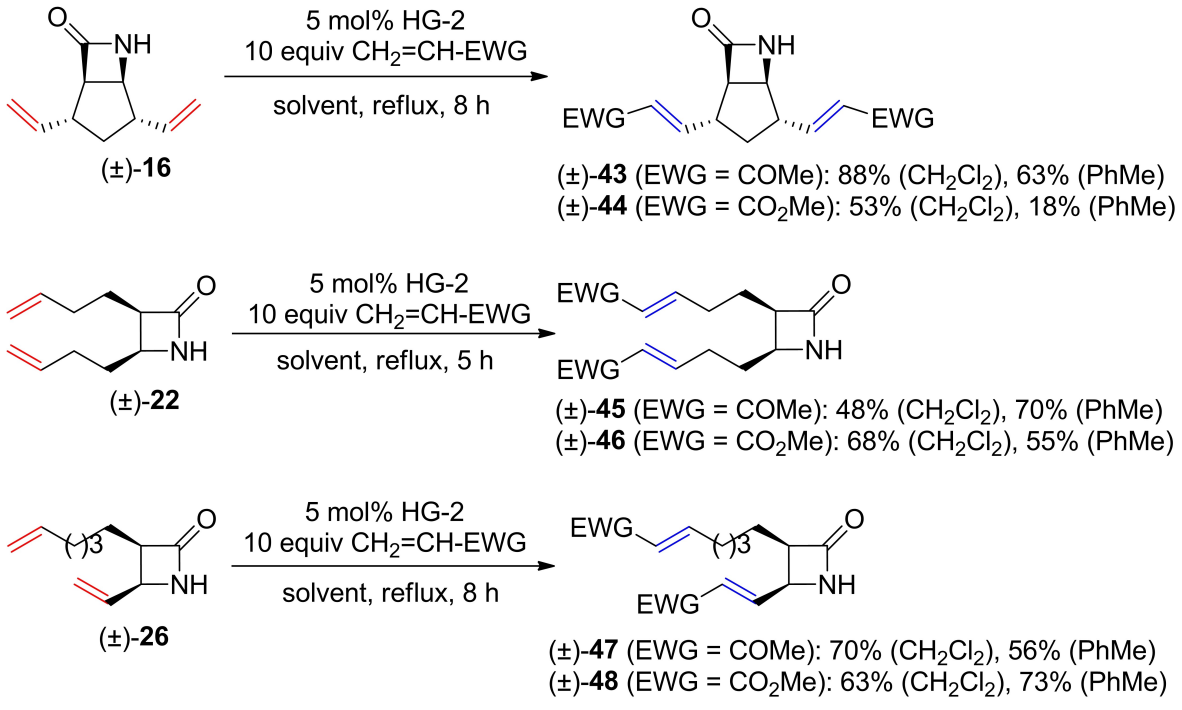


Scheme 5. Synthesis of 3,5-divinylated oxacispentacin derivatives.

products (**A**+**A** homocoupling, **B**+**B** homocoupling, and **A**+**B** cross-coupling), careful planning is required to make cross-coupling the dominant outcome. In most cases, cross-metathesis mainly furnishes the thermodynamic product (usually, an *E* olefin).[53,64] Homocoupling of electron-deficient alkenes is slow,[56,89] but they still take part in cross-coupling, and their excess ensures that homocoupling of the divinylated substrates is suppressed (coupling partner/substrate encounters are more frequent than substrate/substrate encounters).

Divinylated β-lactams (±)-**16**, (±)-**22**, and (±)-**26** (Scheme 3) were submitted to metathesis. The highest conversions were attained with HG-2 catalyst. In all cases, both terminal olefin functions underwent cross-metathesis, giving "decoupled" products with *E* geometry (Scheme 6).[30]

The cross-metathesis of *N*-benzoylated amino esters (±)-**32** and (±)-**34**. with methyl acrylate in refluxing anhydrous CH_2Cl_2 yielded the expected "dimetathesized" products.[29] Doubly *N*-Boc protected amino ester (±)-**51** behaved similarly



Scheme 6. Synthesis of dialkenylated β-lactam derivatives.

(Scheme 7).[33] Product (±)-**50** was earlier prepared through Wittig reaction.[25] The Wittig pathway was not applied for the synthesis of transpentacins (trans-cyclopentane β-amino esters). Note that by applying the metathesis strategy the synthetic procedures could be shortened in comparison with the Wittig protocol as well as the usage of toxic reagents and high amounts of solvents could be reduced.[25] It should also be noted that purification of the metathesis products and elimination of the Ru-based catalyst residues were performed by extraction and gradient column chromatography protocols.

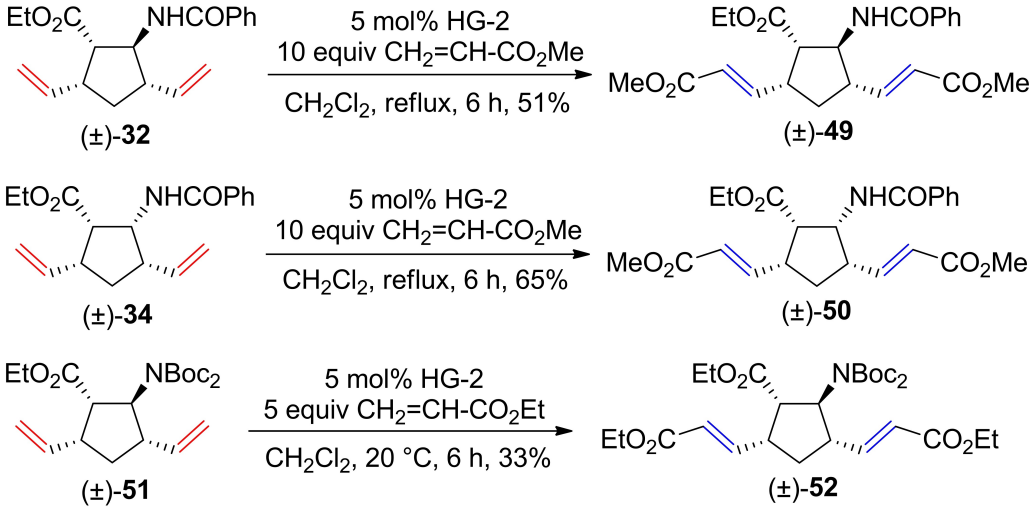
After the above successes, the focus was the regioselectivity of cross-metathesis. It was realized that cross-metathesis of divinylated lactam (±)-**16** under milder conditions (RT instead of reflux, with 5 equiv. electron-deficient olefin coupling partner instead of 10 equiv, shorter reaction time) yielded a single "monocoupled" product.[31] Lactam (±)-**26** behaved similarly, while transformation of lactams (±)-**20** and (±)-**22** provided mixtures of two "monometathesized" products (Scheme 8).[31,33]

Regioselective cross-metathesis was also performed on divinylated cispentacin and transpentacin derivatives (Scheme 9–10). In the case of substrates (±)-**32** and (±)-**42**, CM selectively gave a single "monocoupled" product. For all other substrates [β-amino esters (±)-**30**, (±)-**36**, (±)-**40**, (±)-**51**, and (±)-**81**], cross-metathesis led to a mixture of the two "monocoupled" products. In the case of cispentacin derivative (±)-**30**, the major products were isolated by crystallization and their structure was identified.[31,33]

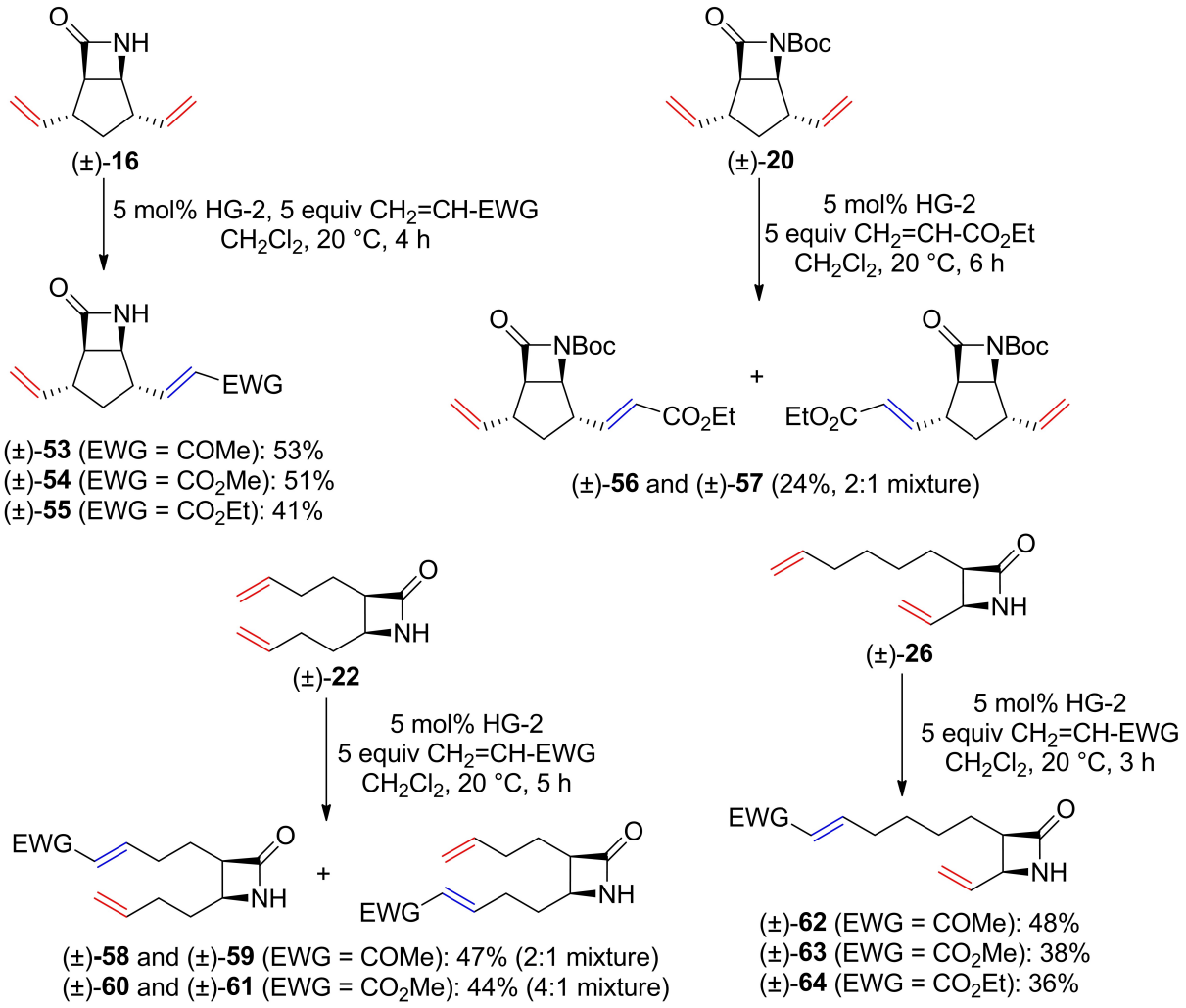
The selectivity in these cross-metathesis reactions is determined by the combined effect of three factors. Coordination with the carbonyl oxygen of the ester group stabilizes the ruthenacyclobutane intermediate, and hinders transformation. In the cases of the substrates depicted on Scheme 8–10, if the ester group and the vicinal vinyl group are *cis* to each other, coordination takes place more readily (because it gives more stable *cis*-annelated rings, not less-favored *trans*-annelated ones), and CM of this vinyl group is more suppressed. This is the reason for the regioselective CM of β-amino esters (±)-**32** and (±)-**42** (Scheme 11).[31]

The second factor is hydrogen bonding interaction between the N–H hydrogen and the chlorine ligand of the catalyst, which facilitates transformation of the vinyl group which is closer to the N–H group. For example, CM of lactam (±)-**16** provides one "monometathesized" product, but its *N*-Boc protected analogue (±)-**20** provides two such products. Furthermore, cross-metathesis of β-amino ester (±)-**32** is much less selective in hydrogen bond acceptor solvents (THF or 1,4-dioxane) which can disrupt substrate-catalyst hydrogen bonding formation (Scheme 11).[31] Finally, compared to its analogues (±)-**32** and (±)-**42**, CM of doubly *N*-Boc protected ester (±)-**51** is much less selective because hydrogen bonding is absent and steric hindrance is increased (see Scheme 12).[33]

The third factor is steric hindrance. If the large Ru-complex cannot approach a vinyl group efficiently, transformation of that vinyl group will be hindered. Cross-metathesis of compound (±)-**51** with a very large $NBoc_2$ group has low selectivity, while analogous reactions of compounds (±)-**32** and (±)-**42** (which contain a smaller NHCOPh group) are completely selective (Scheme 12).[33]



Scheme 7. Synthesis of dialkenylated cispentacins and transpentacins.



Scheme 8. Chemoselective cross-metathesis of divinylated β-lactams.

2. Synthesis of some Azaheterocycles by Ring-Rearrangement Metathesis

2.1. A Brief Insight into the Ring-Rearrangement Metathesis

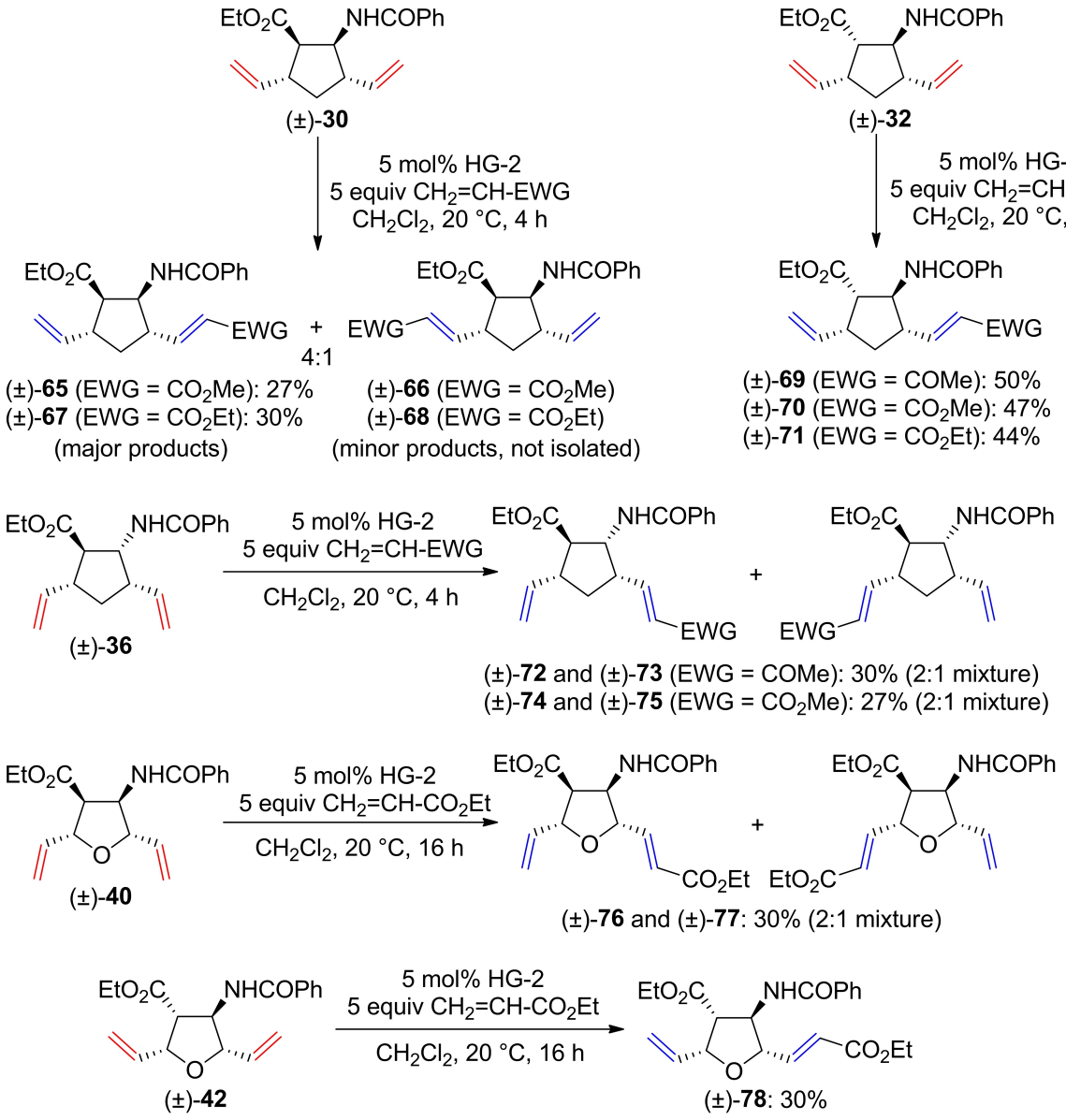
Ring-rearrangement metathesis (RRM) is a domino metathesis process. It starts with a ring-opening metathesis (ROM) step, which is immediately followed by either ring-closure metathesis (RCM) or ring-closing enyne metathesis (RCEYM). Scheme 13–14 depict the general mechanism of these processes.[57]

The ROM/RCM process does not change the overall number of molecules (it transforms one molecule of substrate into one molecule of product), while the ROM/RCEYM process actually decrease it (one molecule of substrate and one molecule of ethylene is transformed into one molecule of product). Release of ring strain is the most common driving force of ring-rearrangement metathesis reactions.[57–59]

Ring-rearrangement metathesis has a number of attractive features. Thus, it is capable of efficiently generating structural complexity in a single process. Furthermore, like all other metathesis processes, it preserves the configurations of the chiral centers. Together with the accessibility of stable and reliable Ru-based metathesis catalysts, application of RRM processes in organic synthesis is highly expanding topic.[57–59]

2.2. Synthesis of some Azaheterocycles by Application of the Metathesis Protocol

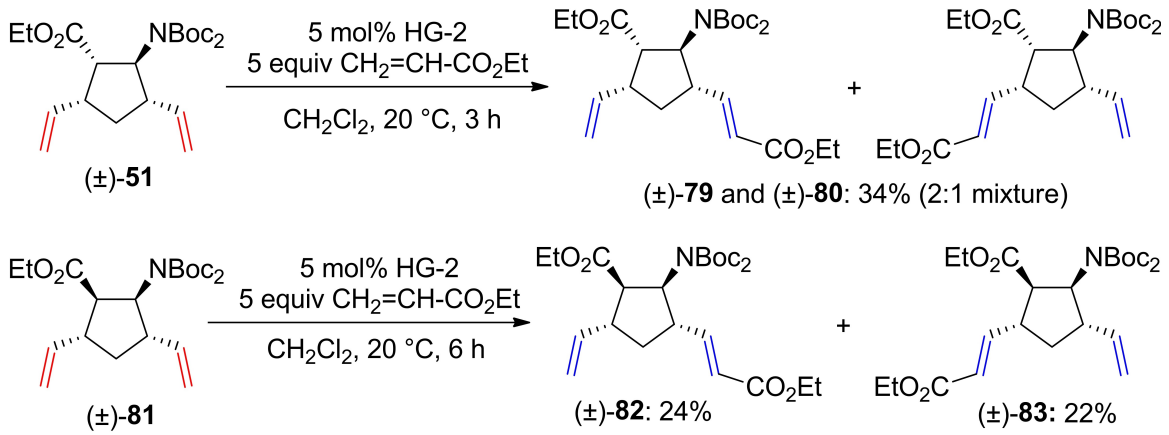
Synthesis of azaheterocycles is a highly important research topic in pharmaceutical and medicinal chemistry, because these compounds are present in a wide variety of drugs, biologically interesting molecules, and natural



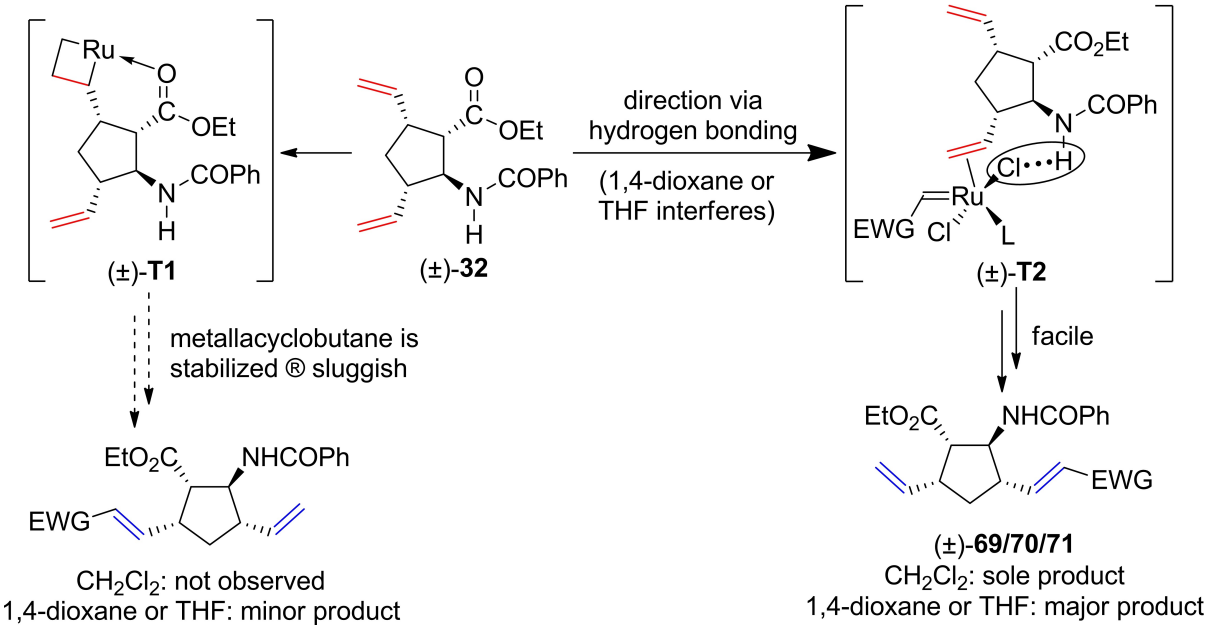
Scheme 9. Synthesis of dialkenylated cispentacins and transpentacins.

products.[10–19,37–43] This subchapter will give some brief insight into the access of azaheterocycles vith ring-rearrangement metathesis.

North and co-authors described metathesis reactions of *N,N'*-diallylated and *N,N'*-dipropargylated derivatives of vicinal diaminocycloalkenes in the presence of G-1 and G-2 catalysts. In metathesis reactions of *N,N'*-diallylated sulfonamide **84**, the dominant pathway was ring-closing metathesis. In fact, with G-1 catalyst, only RCM happened, while G-2 catalyst provided some RRM product **86** and lots of RCM product **85**. *N,N'*-Dipropargylated sulfonamide **87** also disfavored RRM. In this case, CEYM was the dominant pathway, and the highest yield of RRM product **89** was achieved with G-2 catalyst. In contrast, transformation of *N,N'*-dipropargylated sulfonamide (±)-**90** (prepared from commercially available (±)-*trans*-5-norbornene-2,3-dicarbonyl chloride) provided mainly the desired ROM/RCEYM/RCEYM product (±)-**91** (accompanied with two ROM/RCEYM byproducts which were inseparable), and the transformation was the most efficient with G-1 catalyst. Scheme 15 depicts those reactions which provided the best yields for RRM products.[90] The large difference between the RRM reactivities of cyclohexene and norbornene systems can be explained by the lack of ring strain in the former compounds.[91–92]



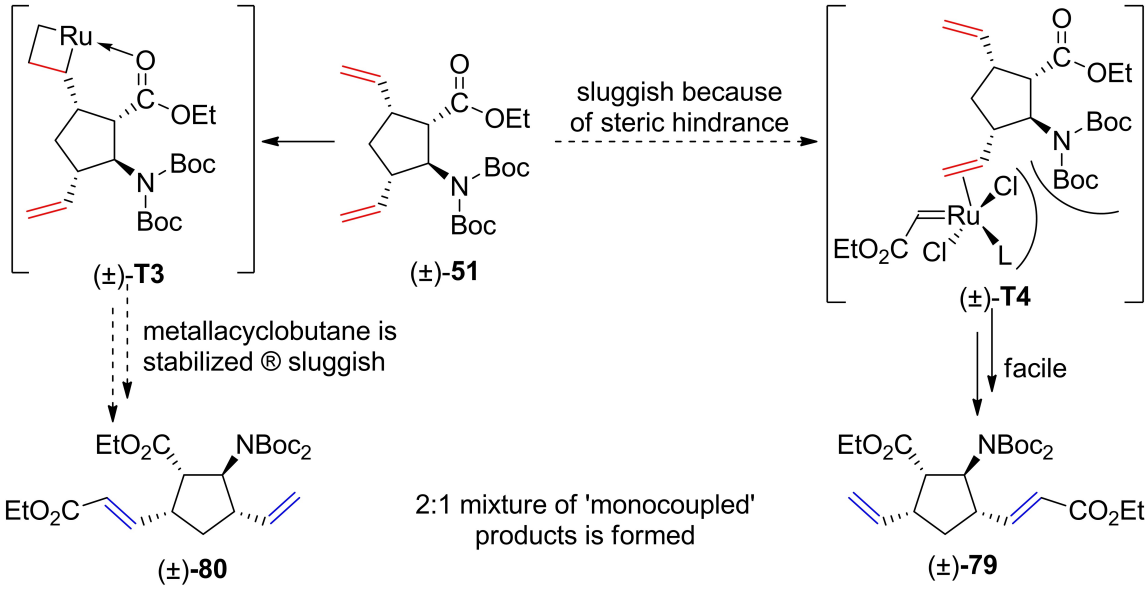
Scheme 10. Synthesis of dialkenylated, doubly *N*-Boc protected β-amino esters.



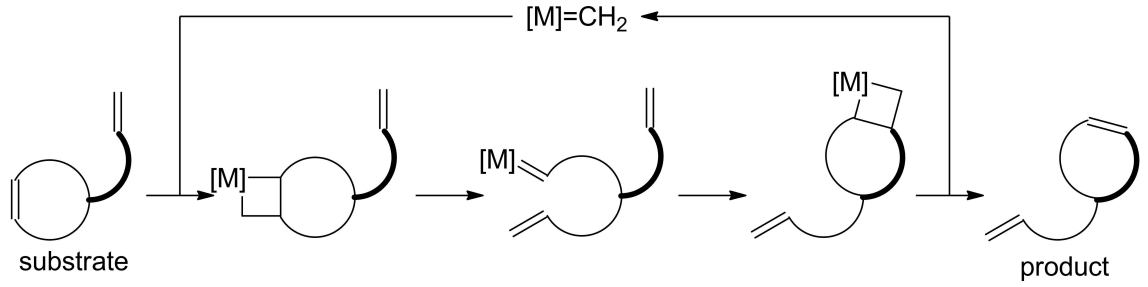
Scheme 11. Regioselectivity in cross-metathesis reactions of (±)-**32.**

Peregrina and coworkers have elaborated an elegant process with ring-rearrangement metathesis for the conversion of 7-azanorbornene systems into pyrrolizidine, indolizidine, and pyrrolo[1,2-a]azepine derivatives (Scheme 16).[93] Such frameworks are found in a wide range of biologically active natural products of particular interest.[38,94] 7-Azanorbornene compound (±)-**92** was subjected to *N*-deprotection and subsequent acylation to obtain substrates (±)-**93**, (±)-**94** and (±)-**95**. Treatment of these substrates with G-2 catalyst in the presence of ethylene provided ROM/RCM products: (±)-**96** (pyrrolizidine skeleton, 58% yield), (±)-**97** (indolizidine skeleton, 63% yield), and (±)-**98** (pyrrolo[1,2-*a*]azepine skeleton, 59% yield). It is worth to note that RCM occurred regioselectively, the vinyl group which was adjacent to the methyl ester group remained intact in the azabicyclo[n.3.0]alkenone products. Compound (±)-**92** was also transformed into allyl ether (±)-**99** whose RRM reaction provided tricyclic product (±)-**100** (Scheme 16).[93]

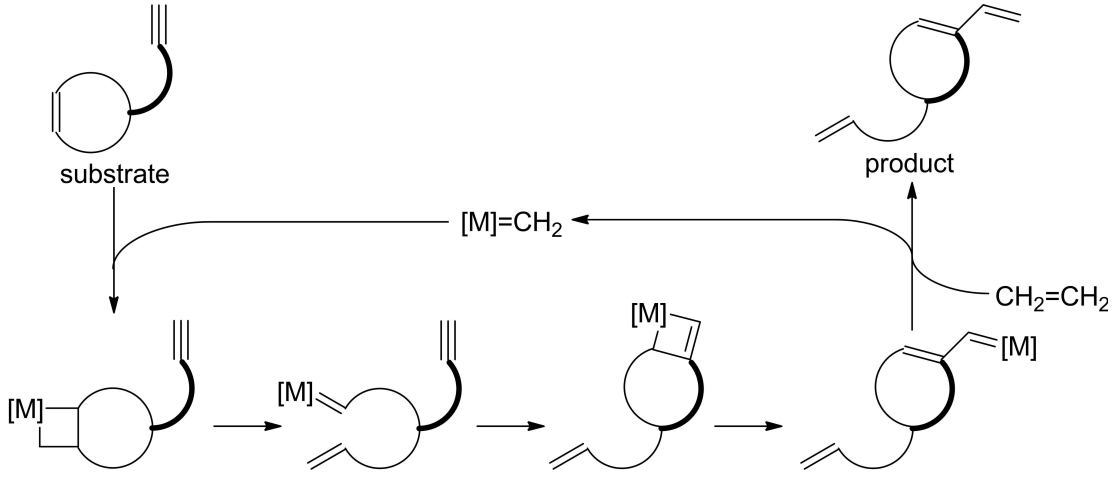
The same group extended the above approach for the synthesis of azaspiro[4.5]decane systems. First, metathesis precursors (±)-**101**, (±)-**104**, and (±)-**106** were prepared from compound (±)-**92**. Then, they were submitted to olefin metathesis. Metathesis of allyl ester (±)-**104** provided only ROM product (±)-**105**. Under the same conditions, ROM/



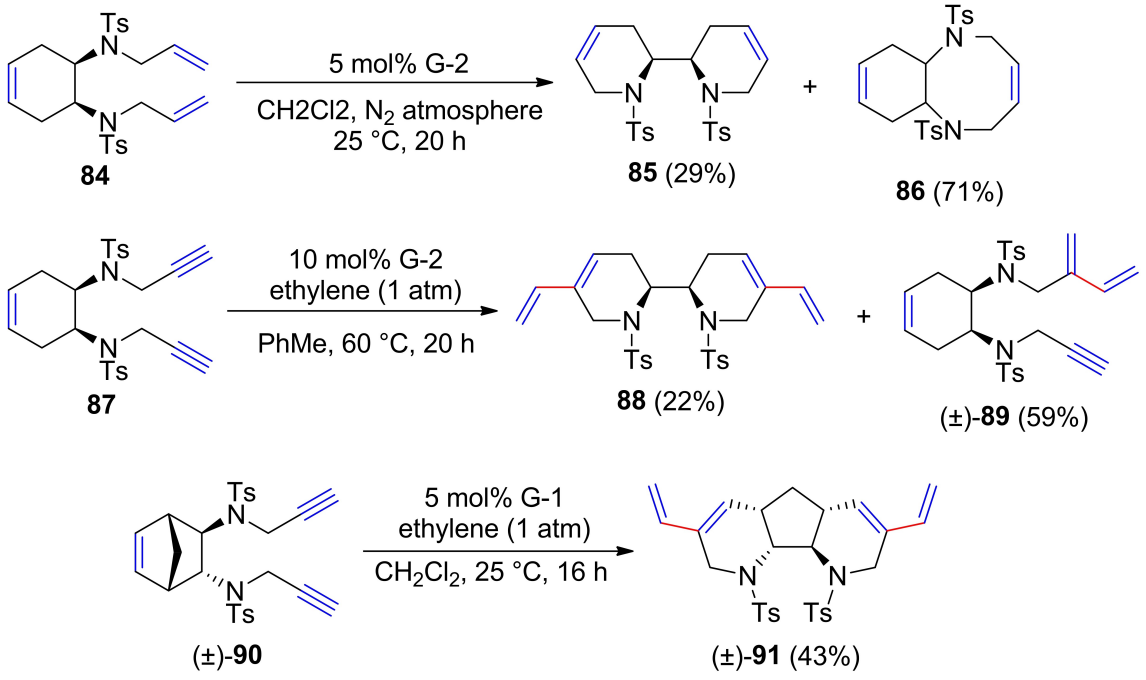
Scheme 12. Regioselectivity in cross-metathesis reaction of (±)-**51.**



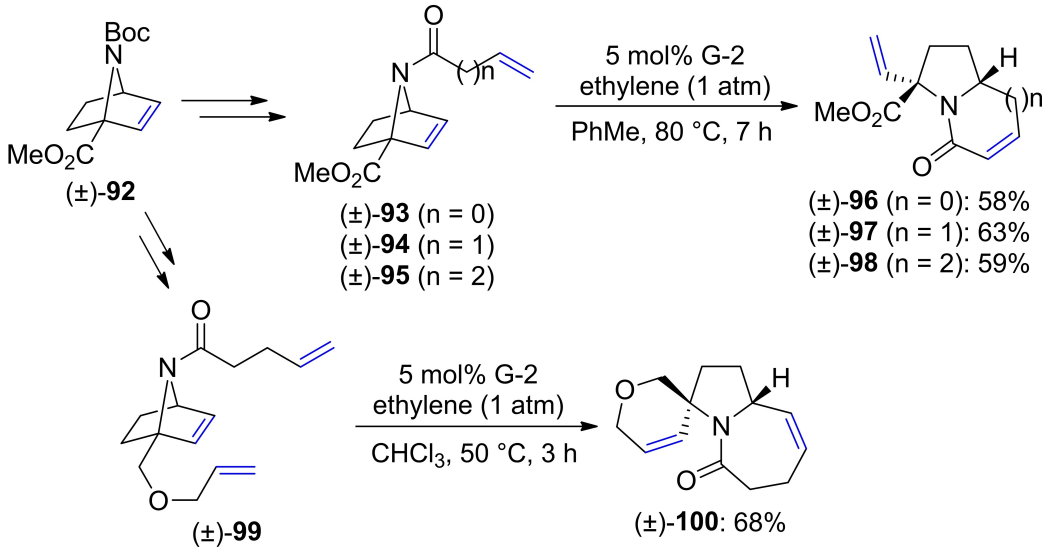
Scheme 13. General mechanism of ROM/RCM.



Scheme 14. General mechanism of ROM/RCEYM.



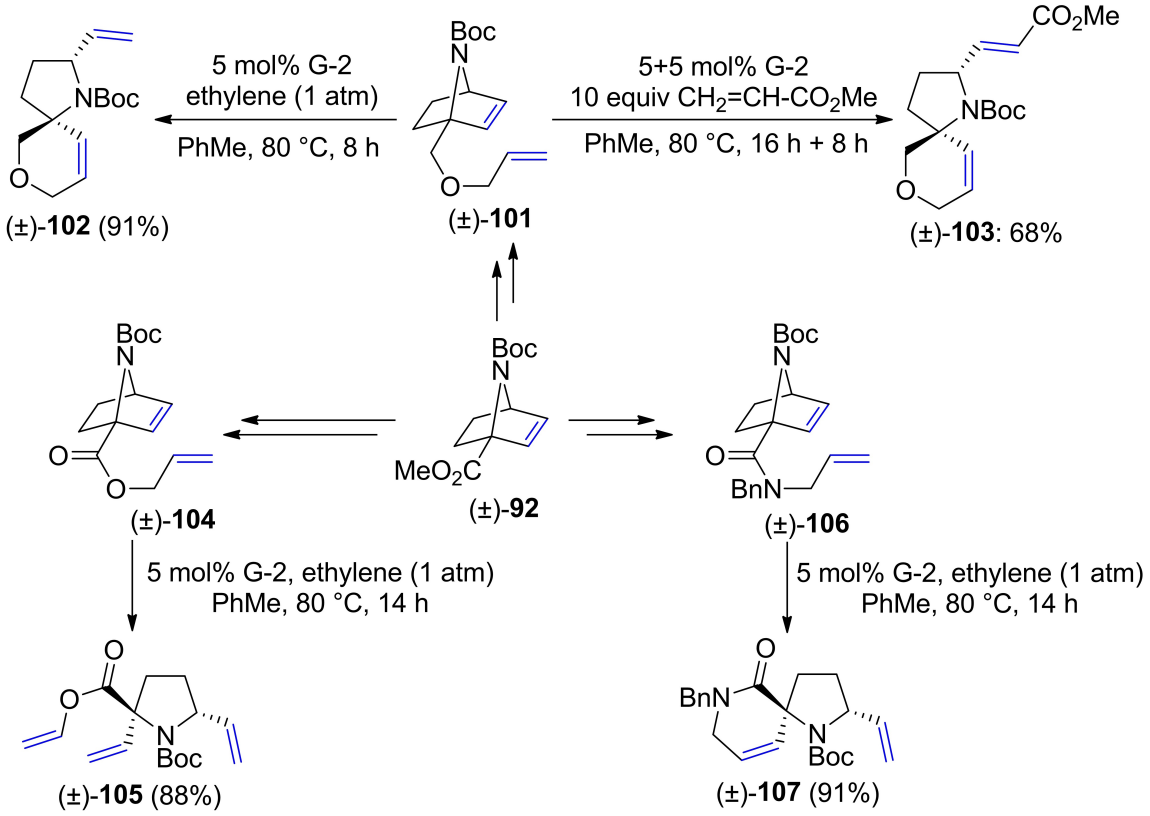
Scheme 15. RRM reactions of diaminocycloalkene derivatives.



Scheme 16. Synthesis of pyrrolizidine, indolizidine, and pyrrolo[1,2-*a*]azepine derivatives.

RCM of (±)-**101** and (±)-**106** was facile and efficient. In the case of (±)-**106**, the presence of the *N*-benzyl group on the amide was necessary (without it, treatment with G-2 catalyst resulted in only carbon-carbon double bond migration). In the case of (±)-**101**, ROM/RCM/CM reaction with methyl acrylate was also successful providing product (±)-**103** (Scheme 17).[95]

Vanderwal and co-authors reported a novel method towards highly complex polycyclic lactams. Heating of propargylanilides **108** in the presence of a base resulted in isomerization to allenecarboxanilides **109** followed by intramolecular Diels-Alder reaction. The formed Himbert cycloadducts (±)-**110** were subjected to ring-rearrangement metathesis. The most efficient catalyst was Stewart-Grubbs catalyst



Scheme 17. Synthesis of azaspiro[4.5]decane derivatives.

(SG), which provided tricyclic lactams (±)-**111** (Scheme 18). The reaction tolerated various substitution patterns on the propargyl group and the arene ring, as well as functional groups, permitting access to a large variety of polycyclic lactams. These compounds are structurally similar to *Erythrina* alkaloids, a large family of natural products with interesting neurobiological activities.[96] Further examples for azaheterocycle synthesis via ring-rearrangement metathesis can be found in Ref. [58–59].

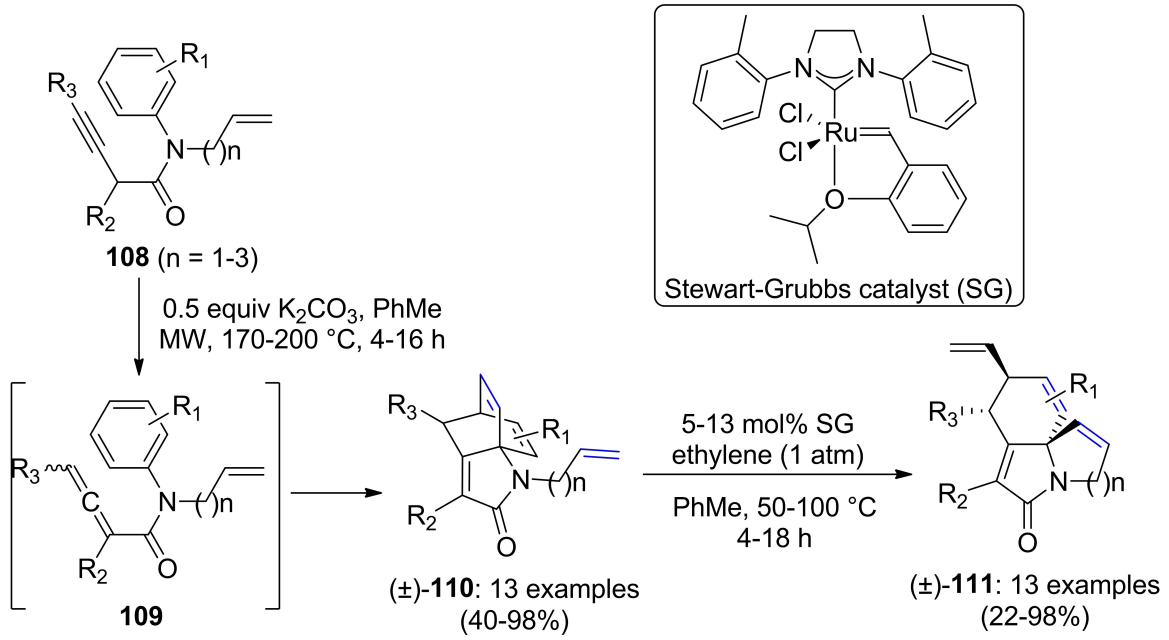
3. Synthesis of some Azaheterocyclic β-Amino Acids

3.1. Synthesis of Azaheterocyclic β-Amino Acids by Application of the Ring-Opening/Cross-Metathesis Protocol

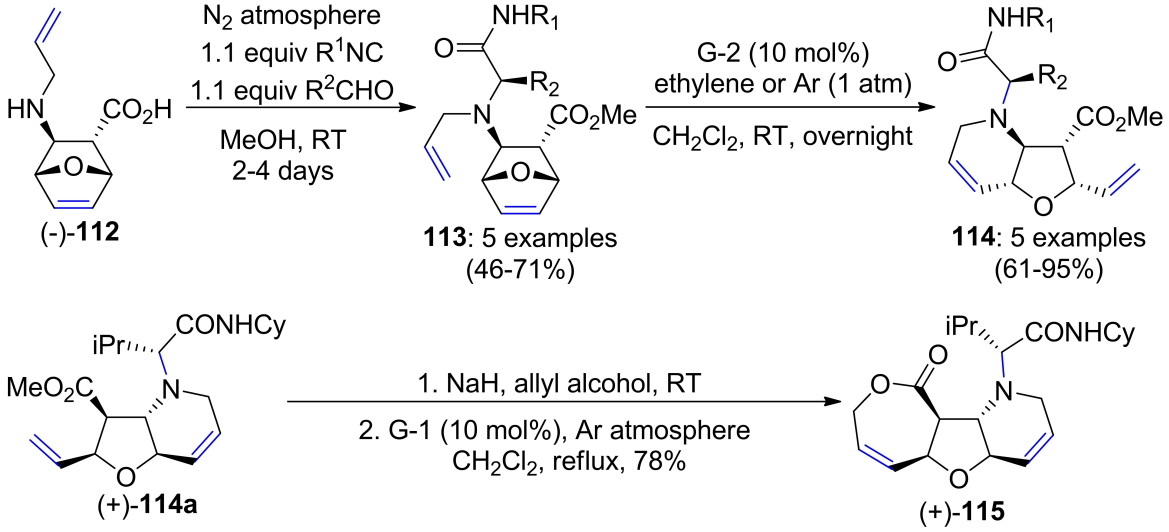
Azaheterocyclic β-amino acids are a special subclass of functionalized azaheterocycles. As earlier mentioned (see Section 2.1, especially Figure 2), azaheterocyclic β-amino acids exert various biological properties, and they are present in a number of natural products, synthetic bioactive compounds, foldamers, and drugs.[10–19] As a consequence, pharmaceutical and medicinal chemistry emerged significant effort to synthetize and study azaheterocyclic β-amino acid derivatives.[10–19,26,36,97–99] This subchapter will discuss examples in which ring-rearrangement metathesis was utilized to obtain such compounds.

Guanti and co-workers described a synthetic route which used Ugi reaction of 7-oxanorbornene β-amino acids. Enantiopure amino acid (−)-**112** was reacted with an aldehyde and an isocyanide in MeOH. The reaction was completely diastereoselective, furnishing compounds **113**. Treatment of this with 10 mol% G-2 catalyst in CH_2Cl_2 under ethylene or argon atmosphere afforded the azaheterocyclic β-amino esters **114** (Scheme 19). Product (+)-**114a** was transformed further via transesterification and subsequent RCM to tricyclic derivative (+)-**115** (Scheme 19).[97]

Ugi reaction of the *N*-propargylated analogue of (−)-**112** was not totally diastereoselective. However, major product (−)-**116** was successfully isolated in pure form and subjected to metathesis. In the presence of G-1 catalysts and ethylene atmosphere only the expected ROM/RCEYM product (−)-**117** was formed. However, when the reaction was performed with G2 catalyst, product (−)-**117** was accompanied with CEYM/ROM/RCM product (−)-**118** (Scheme 20).[97]



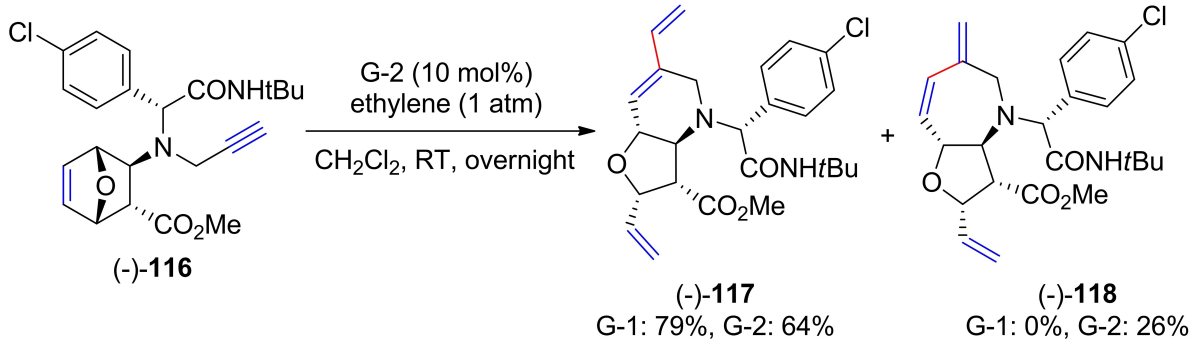
Scheme 18. Synthesis of polycyclic lactams via RRM.



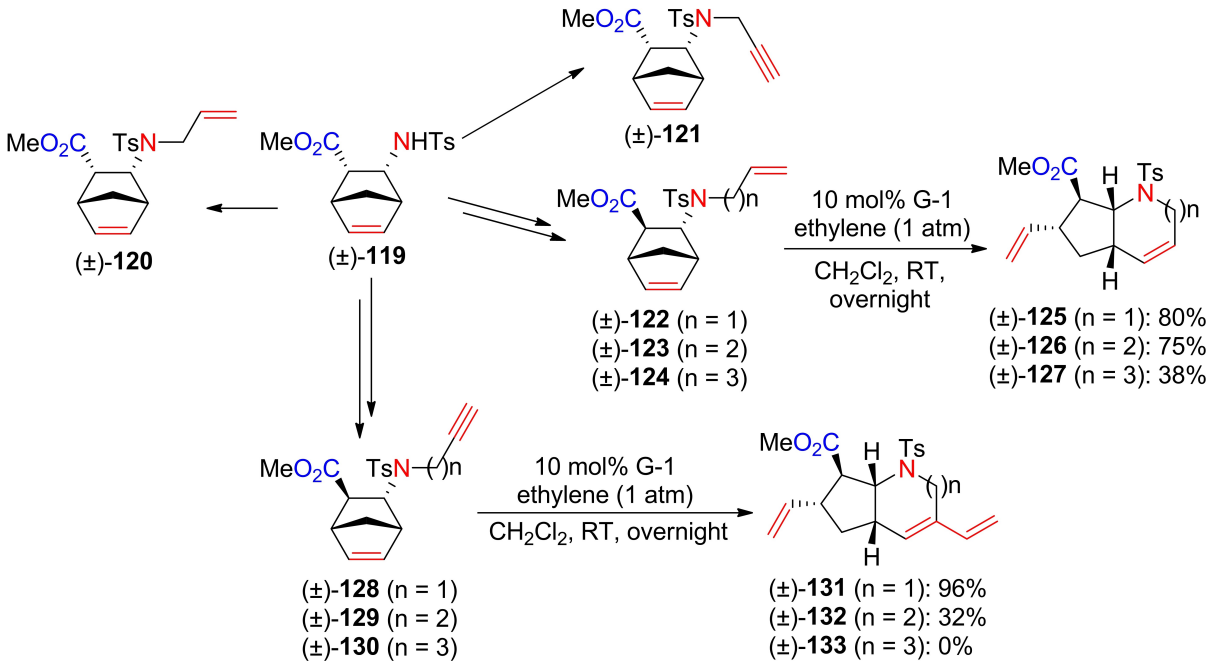
Scheme 19. Synthesis of fused bi- and tricyclic derivatives via Ugi/RRM reactions.

Nadany and Mckendrick reported synthesis of azaheterocyclic β-amino acid derivatives through tandem metathesis reactions on norbornene β-amino esters. Compound (±)-**119** was transformed into various substrates via *N*-alkylation (and by NaOMe-promoted epimerization). Transformation of *diendo* compounds [(±)-**120** and (±)-**121**] failed, but transformation of *endo-exo* compounds [ROM/RCM of (±)-**122-124** and ROM/RCEYM of (±)-**128-130**] was successful (Scheme 21). The trend in the RRM yields is easy to observe. In the cases of both kinds of tandem metathesis processes, more strained products form in lower yields. This is why closure of 6-membered rings was efficient, closure of 7-membered rings was less efficient, and closure of 8-membered rings was inefficient. In fact, closure of the azacyclooctene ring only succeeded in the case of substrate (±)-**124**, while substrate (±)-**130** provided only a ROM product.[98]

McKendrick, Blechert, and coworkers reported RRM reactions on a number of oxanorbornene β-amino esters



Scheme 20. Synthesis of fused bicyclic derivatives via enyne metathesis.



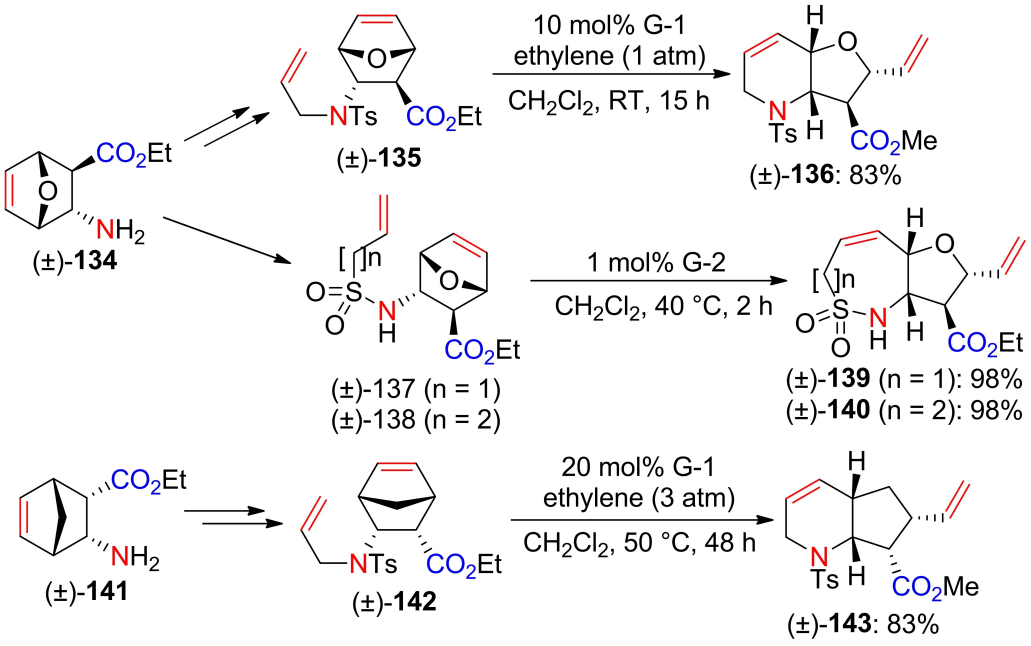
Scheme 21. Synthesis of fused azaheterocyclic β-amino esters from norbornene scaffolds.

(Scheme 22). First, *endo-exo* compound (±)-**134** was transformed to *N*-allylated β-amino ester (±)-**135** as well as alkenylsulfonylated compounds (±)-**137** and (±)-**138**. Then, the prepared substrates were subjected to olefin metathesis. RRM of substrate (±)-**135** proceeded smoothly with G-1 catalyst. RRM of (±)-**137** and (±)-**138** was more challenging, the key factors of success were utilization of G-2 catalyst (which is more reactive than G-1) and use of 0.5 mM substrate concentration. Norbornene β-amino ester (±)-**142** was also prepared and subjected to metathesis. Under forcing conditions, the reaction was successful and provided the desired ROM/RCM product (±)-**143** in 88% yield.[99] This is in strong contrast with the behavior of the analogous methyl ester (±)-**120**, where olefin metathesis did not happen.[98] Furthermore, according to our own experiences, RRM of (±)-**142** proceeds well even under mild conditions (see *Section 3.1.1*, Scheme 26).[100]

3.2. Stereocontrolled Syntheses Across Ring-Rearrangement Metathesis of Norbornene β-Amino Amino Acid Derivatives

3.2.1. Synthesis of Azaheterocyclic β-Amino Acid Derivatives through ROM/RCM of N-Allylated Norbornene β-Amino Esters

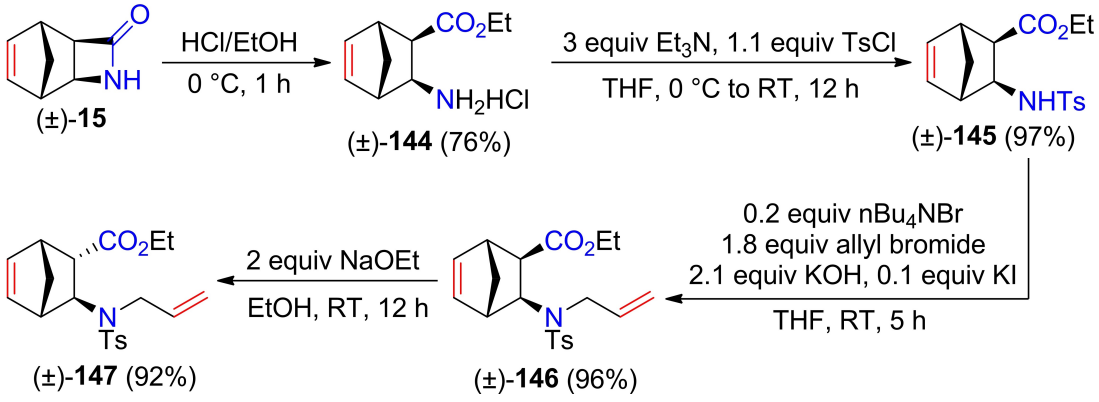
A stereocontrolled synthetic strategy towards novel azaheterocyclic β-amino acid derivatives used ROM/RCM of *N*-



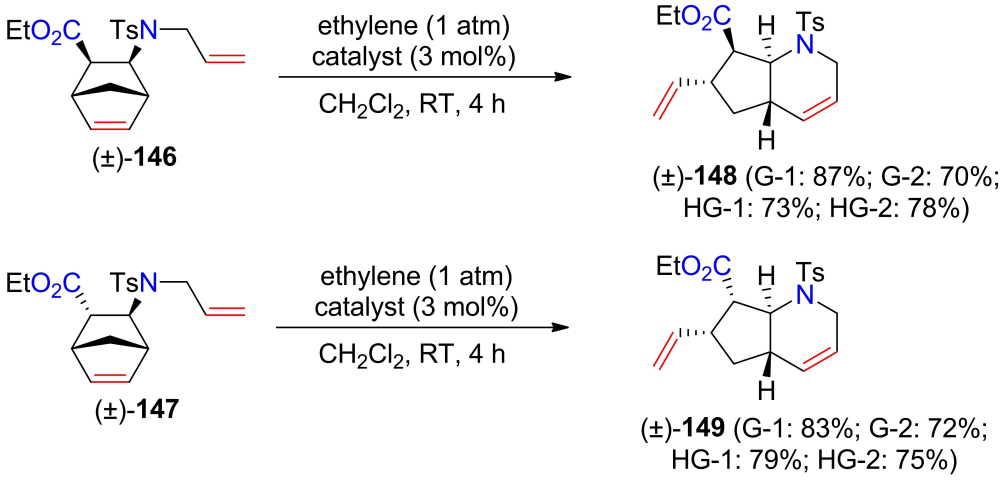
Scheme 22. Synthesis of bicyclic β-amino esters from oxanorbornene scaffolds.

allylated norbornene β-amino esters. The synthesis of *diexo* compound (±)-**146** and *exo-endo* compound (±)-**147**, is depicted on Scheme 23. Racemic lactam (±)-**15** (prepared by cycloaddition of chlorosulfonyl isocyanate and norbornadiene followed by partial hydrolysis)[21] was subjected to lactam-ring opening with HCl/EtOH.[35] Then, *N*-Ts protection of the amino group delivered β-amino ester (±)-**145**, whose *N*-allylation afforded the *diexo* β-amino ester (±)-**146**.[101] The *N*-allylation protocol was based on a literature protocol.[102] Epimerization of compound (±)-**146** with NaOEt provided *exo-endo* compound (±)-**147**.[101]

The presence of ethylene is beneficial in ROM. It can transform the ruthenium alkylidene metathesis catalysts to more reactive ruthenium methylidenes, and it can suppress substrate oligomerization.[103] The highest conversions and isolated yields in ROM/RCM of the desired azaheterocyclic β-amino esters (±)-**148** and (±)-**149** were obtained in CH_2Cl_2 using 3 mol% catalyst at room temperature for 4 h (Scheme 24). Amongst the catalysts, G-1 provided the best results [(±)-**148**: 87%, (±)-**149**: 83%]. In all cases, the nitrogen atom of the exocyclic amino group of the norbornene β-amino ester substrate was incorporated into the dihydropyridine ring of the fused-ring azaheterocyclic scaffold.[101]



Scheme 23. Synthesis of *N*-allylated norbornene β-amino esters (±)-**146** and (±)-**147.**

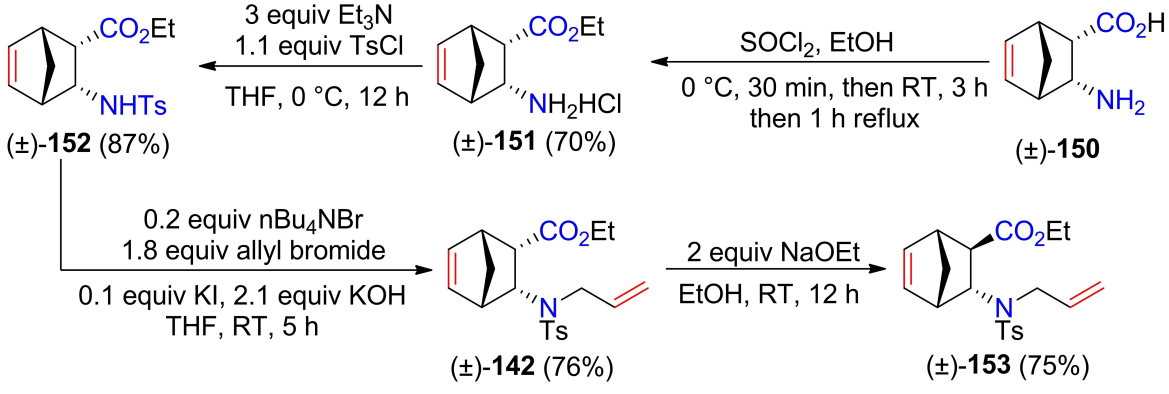


Scheme 24. Synthesis of azaheterocyclic derivatives (±)-**148** and (±)-**149** through ROM/RCM.

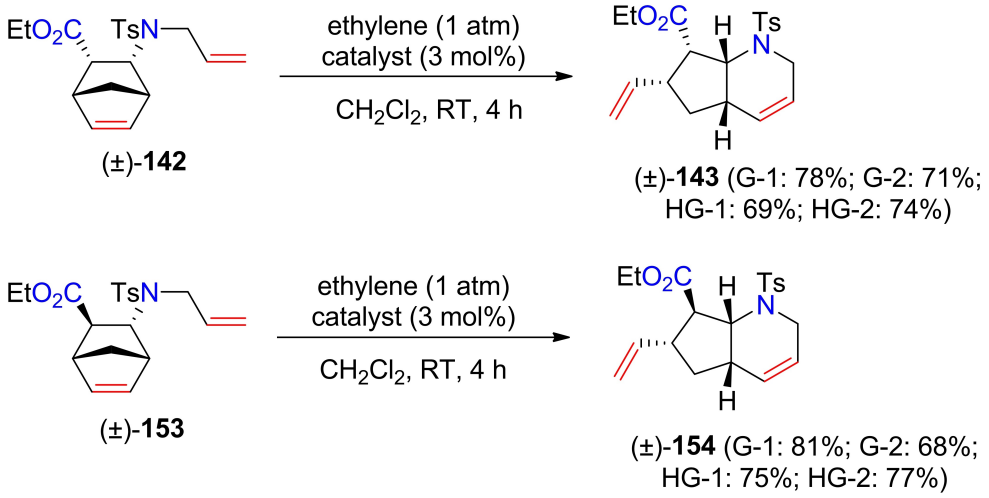
This stereocontrolled strategy was extended to access stereoisomers of products (±)-**148** and (±)-**149**. Aamino acid (±)-**150** (obtained from cheap carbic anhydride)[104] was subjected to esterification[105] followed by *N*-tosyl protection of the amino group. The resulting *diendo* norbornene β-amino ester (±)-**152** was submitted to *N*-allylation[101] to obtain RRM substrate (±)-**142**. Then, base-promoted epimerization of *diendo* amino ester (±)-**142** afforded RRM substrate (±)-**153**, where the ester group is in *exo* position, but the protected amino group is still in *endo* position (Scheme 25).[100]

Amino ester derivatives (±)-**142** and (±)-**153** were subjected to the ring-rearrangement metathesis reaction. The previously established conditions (3 mol% catalyst, anhydrous CH_2Cl_2 solvent, room temperature)[101] were the most effective. The highest yields of the azaheterocyclic β-amino acid derivatives [78% yield for product (±)-**143**, 81% yield for product (±)-**154**] were obtained with G-1 catalyst (Scheme 26).[100]

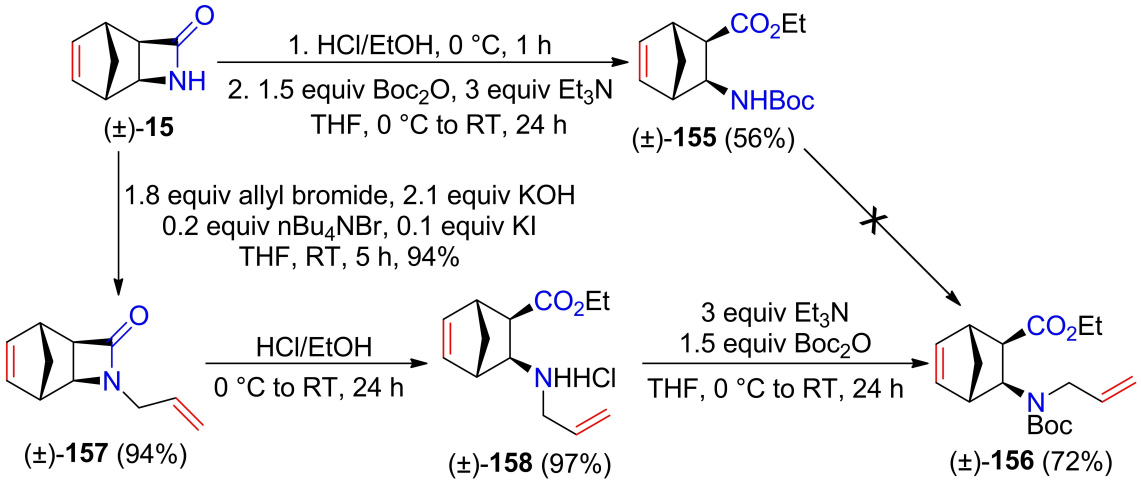
It is known that *N*-detosylation is in general a difficult process, which limits usefulness of *N*-tosyl protected compounds in organic synthesis or peptide chemistry. In light of this fact, the analogous Boc protected compounds were prepared, because removal of *N*-Boc group is usually easy. *N*-allylation of the *N*-Boc-protected β-amino ester (±)-**155**[34] could not be accomplished. An alternative pathway, was performed, which utilizes the same steps (lactam ethanolysis, *N*-Boc protection, and *N*-alkylation), just in a different order. *N*-Allylation of β-lactam (±)-**15** according to a literature protocol[102] gave compound (±)-**157**. Ethanolysis of *N*-allyl lactam (±)-**157** was efficient. Finally, *N*-Boc protection of (±)-**158** proceeded smoothly, and afforded compound (±)-**156** (Scheme 27).[101]



Scheme 25. Synthesis of *N*-allylated norbornene β-amino esters (±)-**142** and (±)-**153.**



Scheme 26. Synthesis of azaheterocyclic compounds (±)-**143** and (±)-**154** via ROM/RCM.

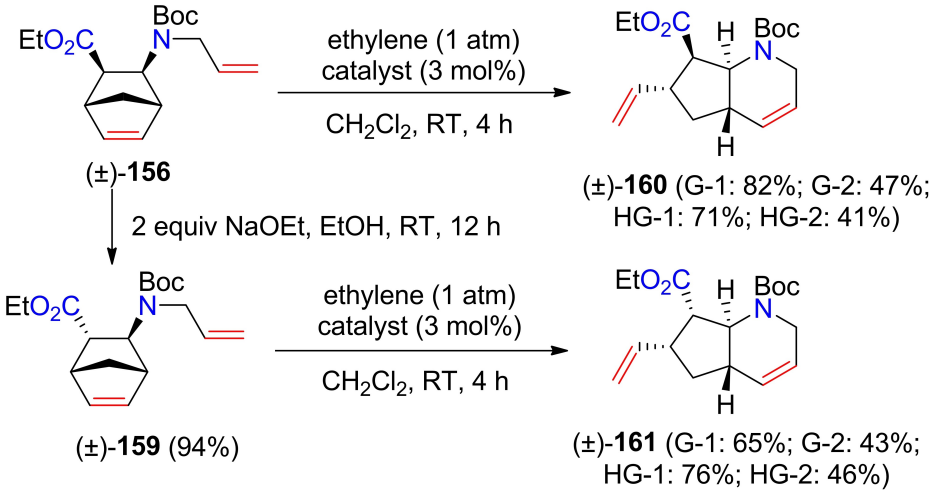


Scheme 27. Synthesis of amino ester (±)-**156.**

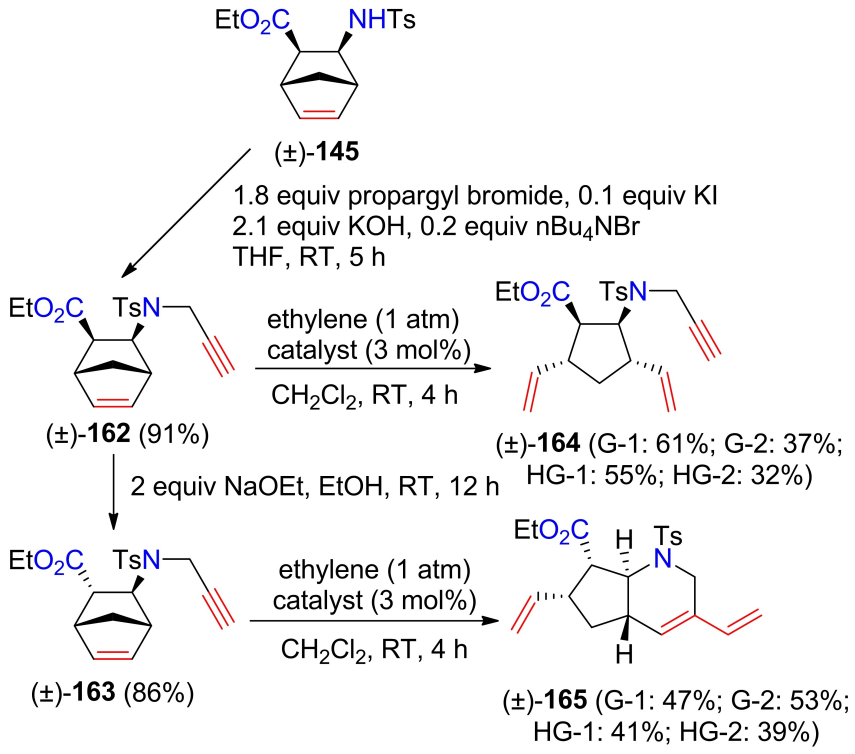
Base-promoted epimerization of *diexo* compound (±)-**156** afforded *exo-endo* compound (±)-**159**. Then, both *N*-Boc protected β-amino esters were submitted to olefin metathesis, which gave the expected ROM/RCM products (±)-**160** and (±)-**161** (Scheme 28). With first generation catalysts, the yields were close to the RRM yields of the analogous *N*-tosylated compounds, but second generation catalysts were less efficient with *N*-Boc protected substrates. The best yield of product (±)-**160** was accomplished with G-1 catalyst, while HG-1 catalyst was the best in the synthesis of (±)-**161**.[101]

3.2.2. Synthesis of Azaheterocyclic β-Amino Acid Derivatives through ROM/RCEYM of N-Propargylated Norbornene β-Amino Esters

ROM/RCEYM reactions of *N*-propargylated norbornene β-amino esters were performed under the conditions optimized for ROM/RCM of *N*-allylated norbornene β-amino esters. Efficient *N*-propargylation was achieved analogously to *N*-allylation. *N*-propargylated β-amino esters (±)-**162** and (±)-**163** were synthesized and subjected to olefin metathesis (Scheme 29). RRM reactions of *diexo* substrate (±)-**162** were not successful, the process always stopped after the ring-opening step. Attempts to trigger ring-closing ene–yne metathesis of the formed cispentacin derivative (±)-**164** by reacting with metathesis catalysts in the absence of ethylene also failed.



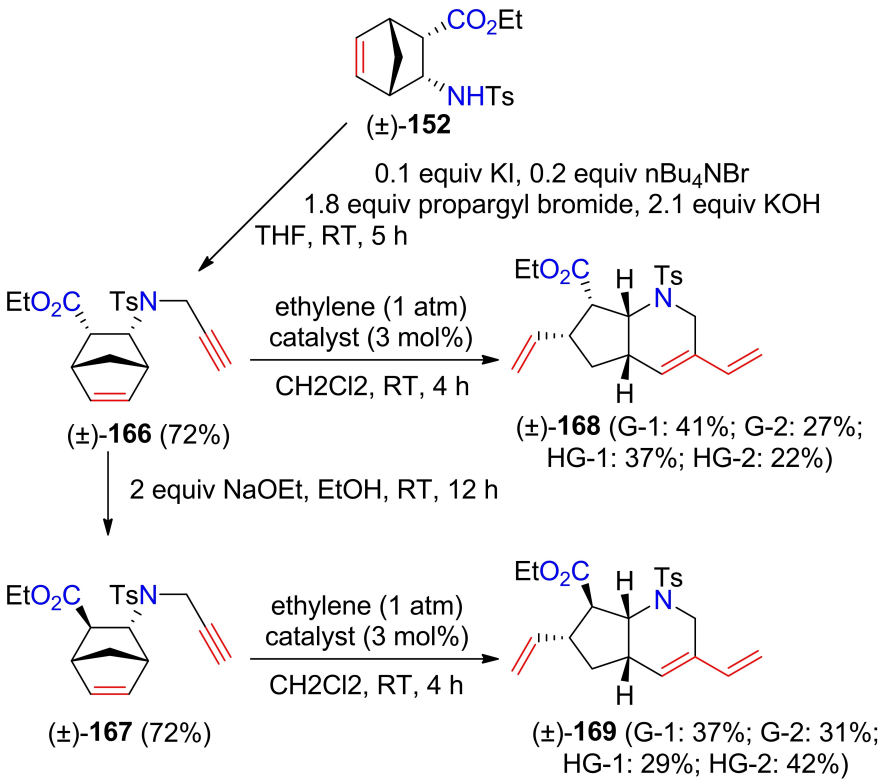
Scheme 28. Synthesis of azaheterocyclic compounds (±)-**160** and (±)-**161** via ROM/RCM.



Scheme 29. Synthesis of amino ester derivative (±)-**164** and azaheterocycle (±)-**165.**

In contrast, olefin metathesis of *exo-endo* compound (±)-**163** provided ROM/RCEYM product (±)-**165**. The process was most efficient with G-2 catalyst.[101]

Stereoisomers of azaheterocyclic compound (±)-**165** were also synthtized. *N*-Propargylation of norbornene β-amino ester (±)-**152** delivered *diendo* RRM substrate (±)-**166**, whose epimerization with NaOEt resulted in *endo-exo* RRM substrate (±)-**167**. In the presence of metathesis catalysts under ethylene atmosphere, both compounds afforded the unsaturated azaheterocyclic products. G-1 catalyst provided the best performance in transformation of (±)-**166**, while transformation of stereoisomeric substrate (±)-**167** was the most efficient with HG-2 catalyst (Scheme 30).[100]



Scheme 30. Synthesis of azaheterocyclic compounds (±)-**168** and (±)-**169** via ROM/RCEYM.

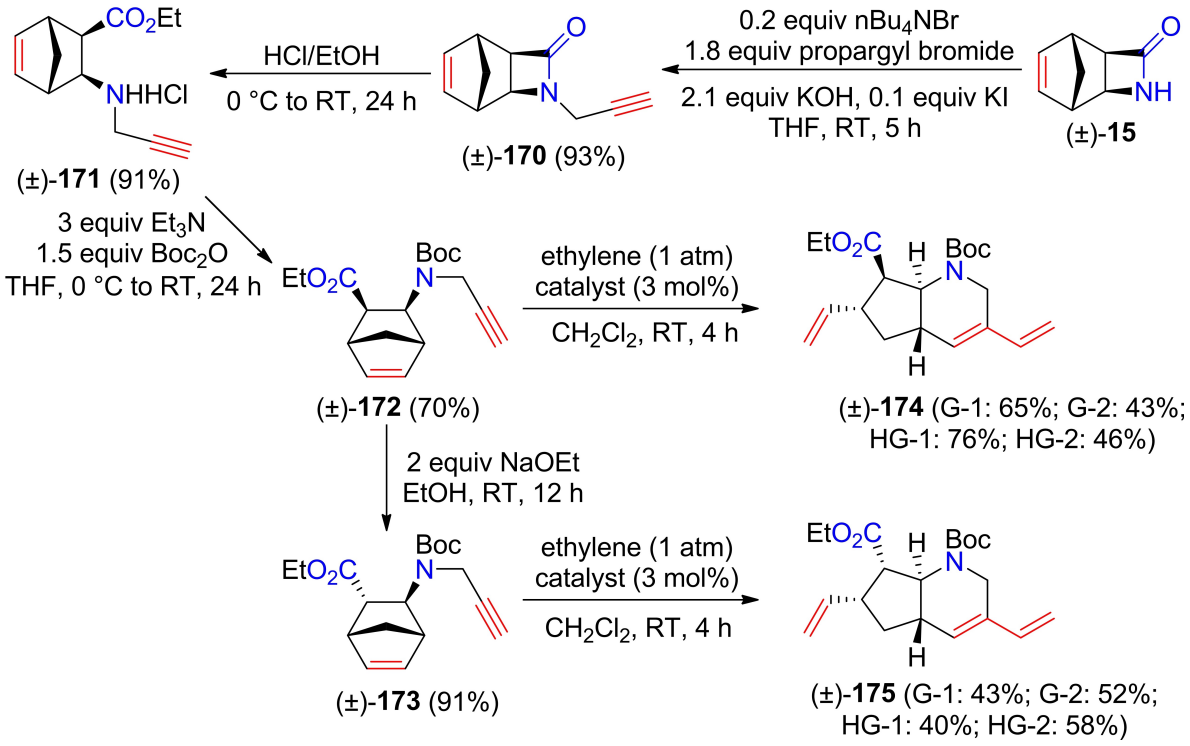
Diexo compound (±)-**172** was synthesized from lactam (±)-**15** with an *N*-propargylation/lactam ethanolysis/*N*-Boc protection sequence, while *exo-endo* compound (±)-**173** was obtained via NaOEt-promoted epimerization of (±)-**172**. ROM/RCEYM reactions of both *N*-Boc protected β-amino esters resulted in azaheterocyclic products (Scheme 31). First generation catalysts (especially HG-1) performed better in transformation of *diexo* compound (±)-**172**, while second generation catalysts (especially HG-2) were more efficient in transformation of *exo-endo* compound (±)-**173**.[101]

3.2.3. Transformation of other Norbornene β-amino Acid Derivatives

Applicability of metathesis for the preparation of β-amino lactones and β-amino lactams was investigated. *Diexo* amino acid (±)-**176**[106] was subjected to *O*-allylation and the resulting ester (±)-**177** was treated with various metathesis catalysts under ethylene atmosphere. Only ring opening metathesis occured, delivering novel cispentacin (±)-**178** with all four catalysts. Attempts to force RCM by treating isolated (±)-**178** with metathesis catalysts failed. *N*-Allylated amide (±)-**179** was prepared via DCC-mediated coupling of amino acid (±)-**176** with allylamine. When amide (±)-**179** was subjected to metathesis, it behaved in the same way as its ester analogue (±)-**177** (Scheme 32).[107]

Substrates ester (±)-**182** and amide (±)-**184** were synthesized from *N*-Boc protected *diendo* amino acid (±)-**181**[106]. When they were subjected to olefin metathesis, ROM took place instead of RRM. Products (±)-**183** and (±)-**185** were formed in good yields with all catalysts (especially G-2). Attempts to trigger ring-closing metathesis by treatment of isolated (±)-**183** and (±)-**185** with metathesis catalysts in the absence of ethylene failed (Scheme 33).[107]

Diexo β-amino ester (±)-**186** was prepared by *O*-propargylation of compound (±)-**176**, and then it was subjected to olefin metathesis. With second generation catalysts, the only product was cispentacin derivative (±)-**187**, which was formed via ROM. In contrast, first-generation catalysts provided ROM compound (±)-**187**, ROM/CEYM compound (±)-**188** (this was the major product), and ROM/RCEYM product (±)-**189** (this product was formed in the lowest yield). D*iexo* amide (±)-**190** was synthesized via DCC-mediated coupling of compound (±)-**176** with propargylamine, and it was subjected to olefin metathesis as well. Two products were formed: the ROM/RCEYM product (±)-**192** (this was the major product with first generation catalysts) and



Scheme 31. Synthesis of azaheterocyclic compounds (±)-**174** and (±)-**175** via ROM/RCEYM.

ROM/CEYM compound (±)-**191** (this was the major product with second generation catalysts) (Scheme 34).[107]

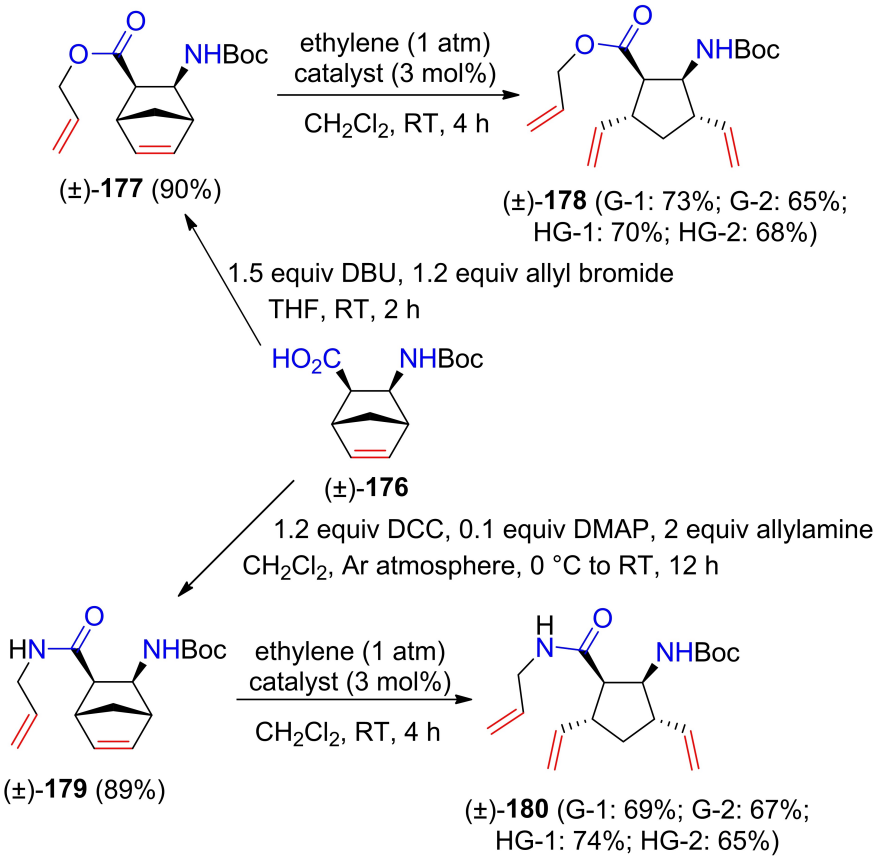
Diendo compounds: β-amino ester (±)-**193** and β-amino amide (±)-**197** were synthesized from *N*-protected *diendo* β-amino acid (±)-**181**. When subjected to olefin metathesis, ester (±)-**193** behaved in the same way as its *diexo* analogue (±)-**186**: first generation catalysts furnished a three-component mixture (in decreasing order of yields: ROM/CEYM compound (±)-**195**, ROM compound (±)-**194**, and the desired RRM product (±)-**196**), while second generation catalysts gave ROM compound (±)-**194** as sole product. Metathesis of amide (±)-**197**, however, was slightly different than metathesis of its stereoisomer (±)-**190**: all four catalysts provided a three-component mixture (in decreasing order of yields: ROM product (±)-**198**, ROM/CEYM product (±)-**199**, and the desired RRM product (±)-**200**) (Scheme 35).[107]

3.3. Stereocontrolled Syntheses Across Ring-Rearrangement Metathesis of Oxanorbornene β-Amino Acid Derivatives

In view of the relevance of oxygen-containing cyclic β-amino acids the RRM-based stereocontrolled synthetic strategies were extended to oxanorbornene β-amino acid derivatives.

3.3.1. Synthesis of Azaheterocyclic β-Amino Acid Derivatives through ROM/RCM of N-Allylated Oxanorbornene β-Amino Esters

Diexo β-amino ester hydrochloride (±)-**201** (it is available via esterification of the corresponding oxanorbornene β-amino acid with EtOH and $SOCl_2$).[108] by tosylation yielded β-amino ester (±)-**202**. *N*-allylation of this β-amino ester was unsuccessful (probably the oxanorbornene skeleton was sensitive to KOH), but a new synthetic pathway which used DBU as a base was rapid and successful. The resulting oxanorbornene compound (±)-**203** was submitted to base-promoted epimerization to obtain *exo-endo* compound (±)-**204**. Both *diexo* ester (±)-**203** and *exo-endo* ester (±)-**204** were subjected to RRM. The highest conversions and isolated yields of tetrahydrofuran-fused azaheterocycles (±)-**205** and (±)-**206** were obtained using the same conditions as the analogous cyclopentane-fused azaheterocycles (±)-**148** and (±)-**149** (CH_2Cl_2 solvent, 3 mol% catalyst, ethylene atmosphere, room temperature, 4 h). In both cases, the process was the efficient with all catalysts (G-1 catalyst was the best, closely followed by HG-1 catalyst) (Scheme 36).[100]



Scheme 32. Synthesis of cispentacin derivatives (±)-**178** and (±)-**180.**

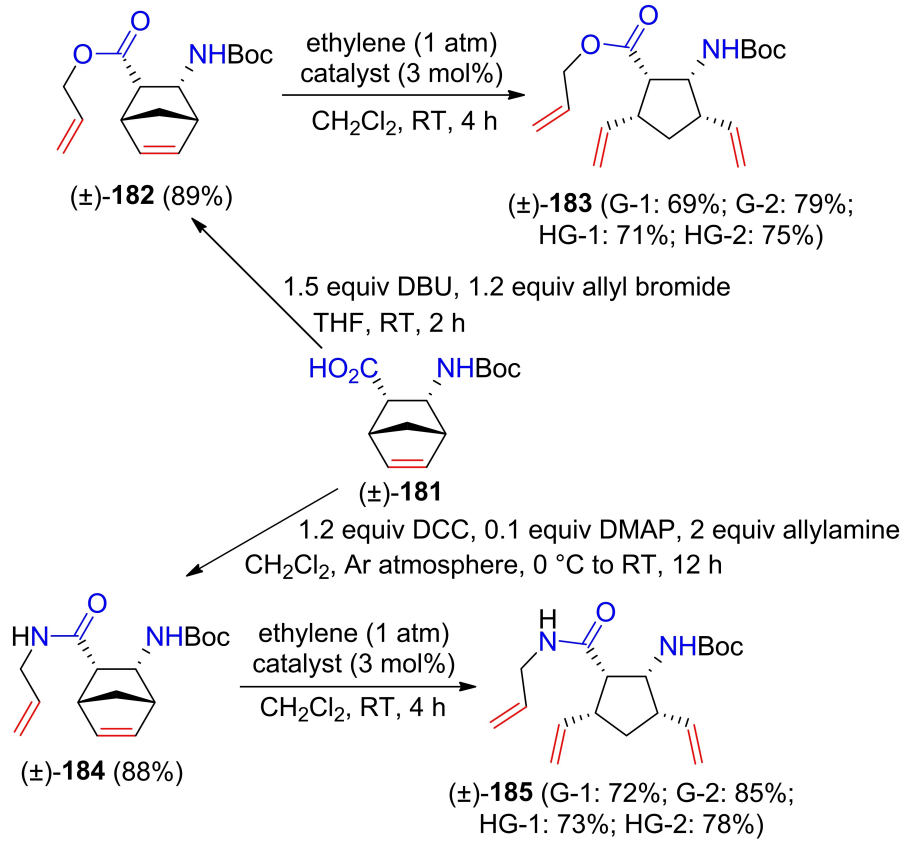
3.3.2. Synthesis of Azaheterocyclic β-Amino Acid Derivatives through ROM/RCEYM of N-Propargylated Oxanorbornene β-Amino Esters

RRM of compound (±)-**207** provided azaheterocycle (±)-**209**, the highest yield was achieved with G-1 catalyst. Interestingly, transformation of compound (±)-**208** provided a product mixture. With first generation catalysts, ROM product (±)-**210** was the main product, while second generation catalysts provided comparable amounts of ROM product (±)-**210** and ROM/RCEYM product (±)-**211**. During transformation of substrate (±)-**208**, ring-opening metathesis is faster and/or more efficient than the subsequent ring-closing enyne metathesis (Scheme 37).[100]

3.3.3. Transformation of other Oxanorbornene β-Amino Acid Derivatives

The applicability of metathesis for the access of tetrahydrofuran-fused β-amino lactones and tetrahydrofuran-fused β-amino lactams was investigated. Oxanorbornene ester (±)-**213** was prepared by *O*-allylation of *N*-Boc protected amino acid (±)-**212**,[109] while oxanorbornene amide (±)-**215** was obtained by reacting protected amino acid (±)-**212** with allylamine and DCC. When subjected to olefin metathesis (CH_2Cl_2 solvent, 3 mol% catalyst, ethylene atmosphere, room temperature, 4 h), compounds (±)-**213** and (±)-**215** behaved in the same way as their norbornene analogues (±)-**177** and (±)-**179**: only highly efficient ring opening occurred (G-1 catalyst provided the best performance). Even treatment of isolated ROM products (±)-**214** and (±)-**216** with metathesis catalysts in the absence of ethylene was unsuccessful in triggering RCM (Scheme 38).[107]

After reaching the target products by ROM/RCM failed, we switched to ROM/RCEYM. Thus, oxanorbornene derivatives (±)-**217** (a propargyl ester) and (±)-**220** (an *N*-propargylated amide) were synthesized and treated with metathesis catalysts under ethylene atmosphere. The minor products [(±)-**218** and (±)-**221**] were formed via ROM, while the main products [(±)-**219** and (±)-**222**] were formed via ROM/CEYM. Even when isolated ROM products were treated with metathesis catalysts, RCEYM did not happen (Scheme 39). This is in strong contrast with the cases of propargyl esters and *N*-propargylated amides of norbornene β-



Scheme 33. Synthesis of cispentacin derivatives (±)-**183** and (±)-**185.**

amino acids, where ROM/RCEYM was moderately successful.[107]

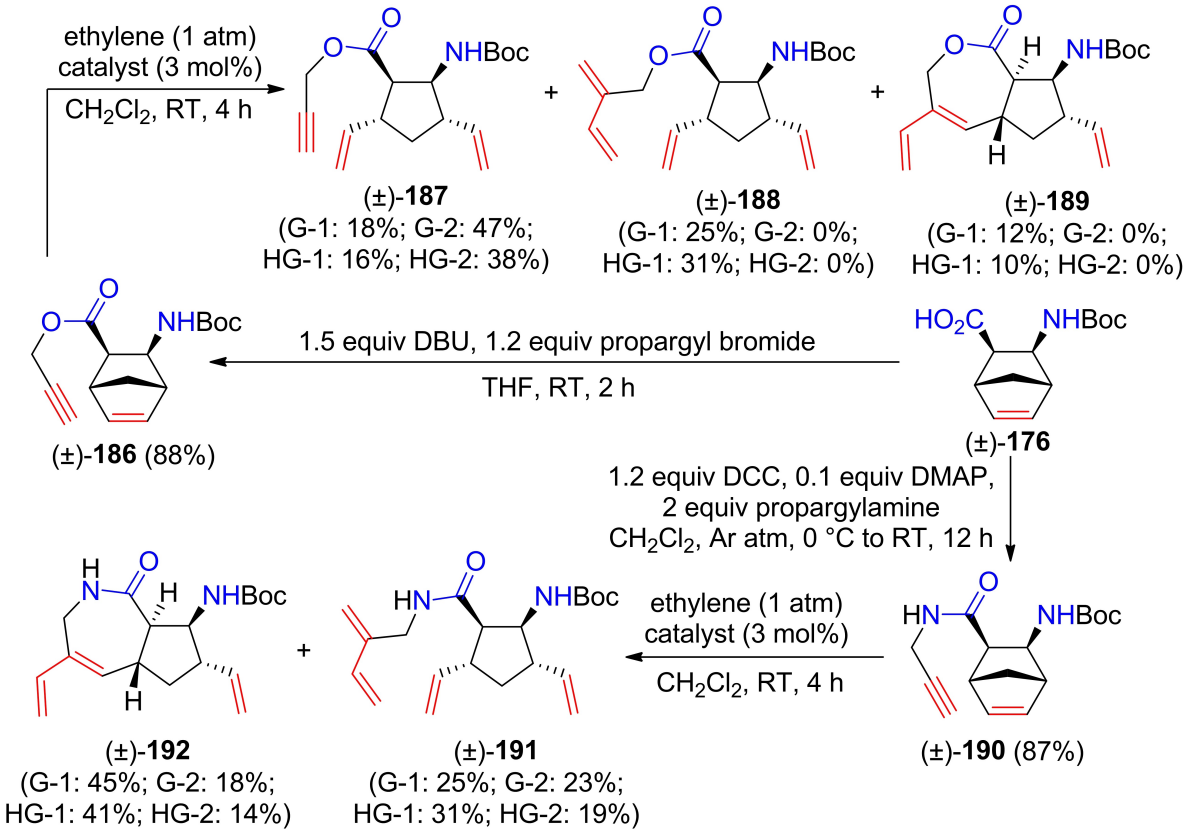
3.4. Stereocontrolled Syntheses via Ring-Rearrangement Metathesis of Cyclooctene β-Amino Acid Derivatives

Application of the stereocontrolled synthetic metathesis approaches to cyclooctene β-amino acid derivatives and the related β-lactams, to obtain various novel functionalized compounds (azaheterocycles, β-amino lactones, and β-amino lactams) was also studied.

3.4.1. Synthesis of Azaheterocyclic β-Amino Acid Derivatives via ROM/RCM of N-Allylated Cyclooctene β-Amino Esters

Cyclooctene β-amino ester (±)-**225**, was prepared from β-lactam (±)-**21** in three steps (lactam ethanolysis,[20] *N*-tosylation, and *N*-allylation). Compound (±)-**21** is readily available from 1,5-cyclooctadiene using a literature method: [2+2] cycloaddition of 1,5-cyclooctadiene and chlorosulfonyl isocyanate yields the *N*-chlorosulfonyl derivative of (±)-**21**, which undergoes partial hydrolysis during mild basic workup to yield free β-lactam (±)-**21**.[20,23] The optimal conditions for the ring-rearrangement metathesis of compound (±)-**225** (CH_2Cl_2 as solvent, 3 mol% catalyst, RT, and 4 h reaction time) were identical to the conditions utilized for RRM of norbornene and oxanorbornene derivatives, and resulted in seven-membered azaheterocycle (±)-**226** as the single product (Scheme 40). The other possible product (an eight-membered azaheterocycle) did not form. Probably, this is a consequence of the lower ring strain of seven-membered cyclic alkenes compared to eight-membered ones.[91–92] All 4 catalysts had comparable performance, but the highest yield was achieved with the G-1 catalyst.[110]

N-Boc protected analogue (±)-**229** was synthesized from lactam (±)-**21** by *N*-allylation, lactam ethanolysis, and *N*-Boc protection. (*N*-Allylation of the *N*-Boc protected analogue of cyclooctene β-amino ester (±)-**224** was not attempted.) Then, RRM of substrate (±)-**229** provided seven-membered azaheterocycle (±)-**230** as the lonely product. Notably, second generation catalysts (especially G-2) provided much better yields of (±)-**30** than first generation ones (Scheme 41).[110]



Scheme 34. Ring-rearrangement metathesis of β-amino acid derivatives (±)-**186** and (±)-**190.**

3.4.2. Synthesis of Azaheterocyclic β-Amino Acid Derivatives via ROM/RCEYM of N-Propargylated Cyclooctene β-Amino Esters

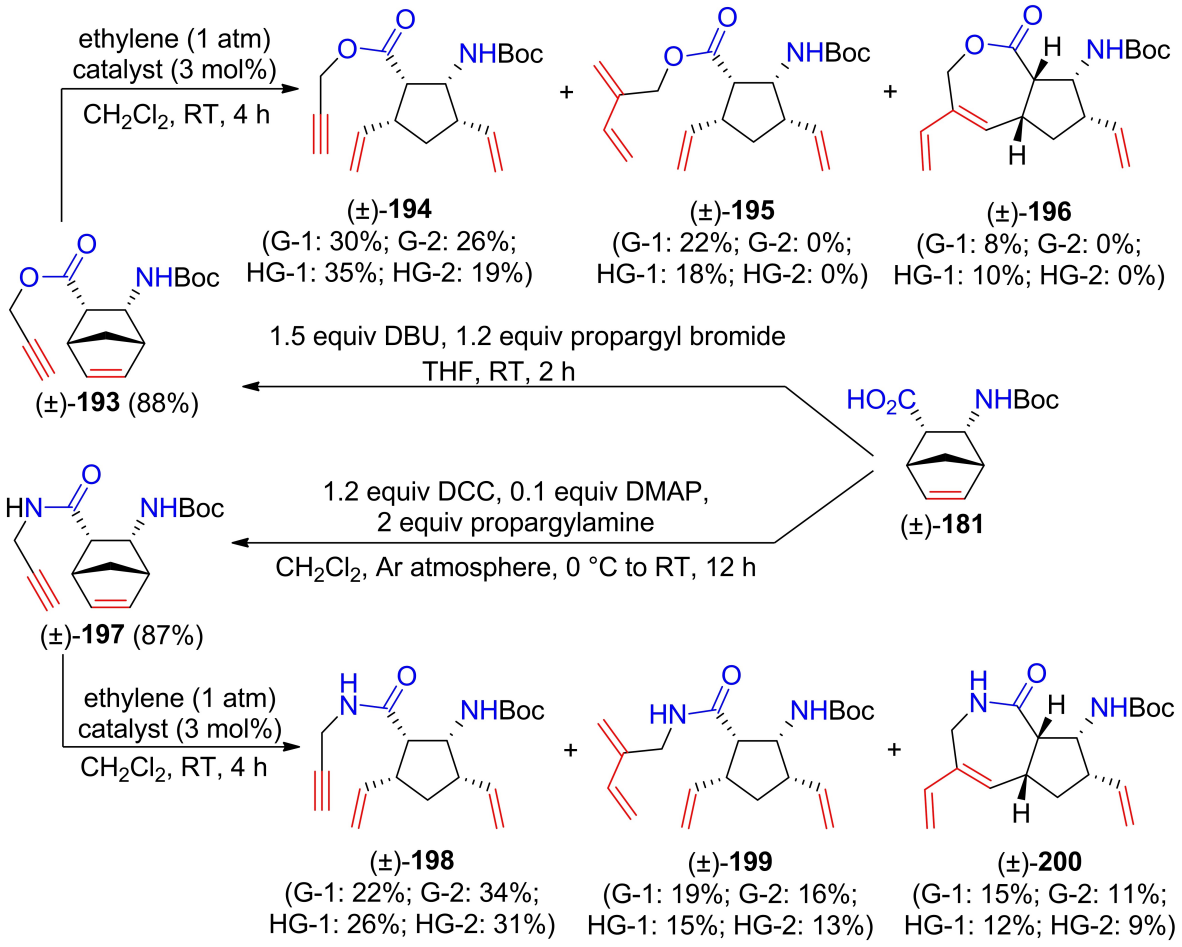
The scope of the above method was extended to ROM/RCEYM reactions of the closely related *N*-propargylated cyclooctene β-amino esters. Hence, *N*-tosylated RRM substrate (±)-**231** was synthesized utilizing a process similar to the preparation of (±)-**225**. Olefin metathesis of this amino ester resulted in azaheterocycle (±)-**232** and open-chain unsaturated β-amino ester (±)-**233** (Scheme 42).[110]

As depicted on Scheme 43, ring-opening metathesis of amino ester (±)-**231** results in open-chain intermediate (±)-**T5** which can undergo both RCEYM [yielding product (±)-**232**] and CEYM with ethylene [yielding product (±)-**233**]. With all four catalysts, the combined yields were similar and compound (±)-**232** was the major product, but first generation catalysts were more selective towards formation of the azaheterocycle. The highest yield of (±)-**232** was 41% (with G-1 catalyst), while the highest yield for (±)-**233** was 25% (with HG-2 catalyst).

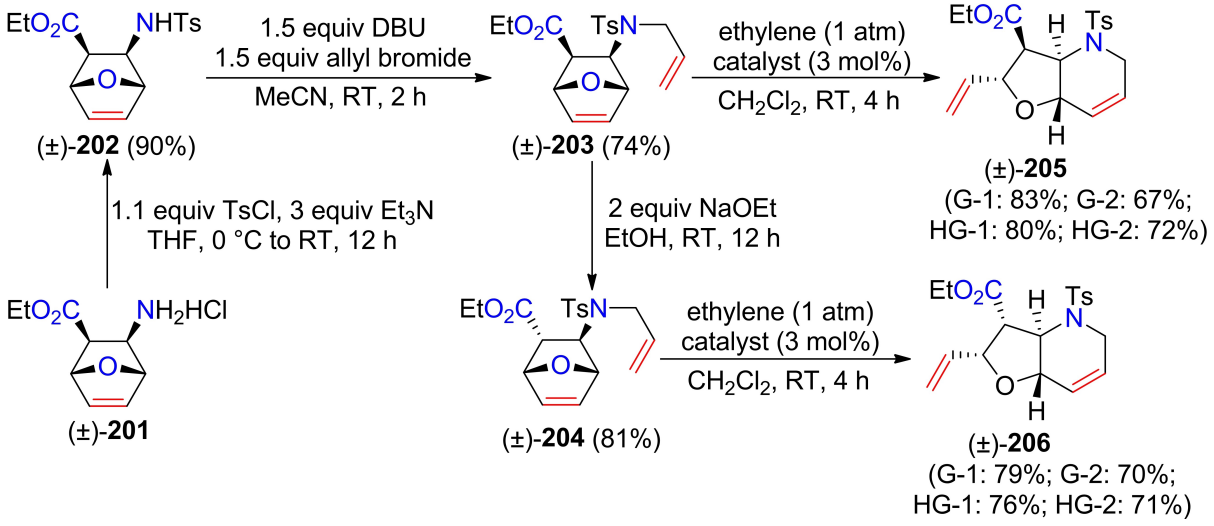
N-Boc protected RRM substrate (±)-**236** was prepared by using a similar route as its *N*-allylated analogue (±)-**229**: *N*-propargylation of lactam (±)-**21**, ethanolysis of the formed *N*-propargyl lactam, then *N*-Boc protection. Subjecting this amino ester to metathesis gave azaheterocycle (±)-**237** as single product (Scheme 44). This is in contrast with the case of *N*-tosylated analogue (±)-**231**, where a ROM/CEYM byproduct was also formed. The highest yields were attained with G-2 catalyst (45%) and HG-2 catalyst (44%).[110]

3.4.3. Transformation of other Cyclooctene β-Amino Acid Derivatives

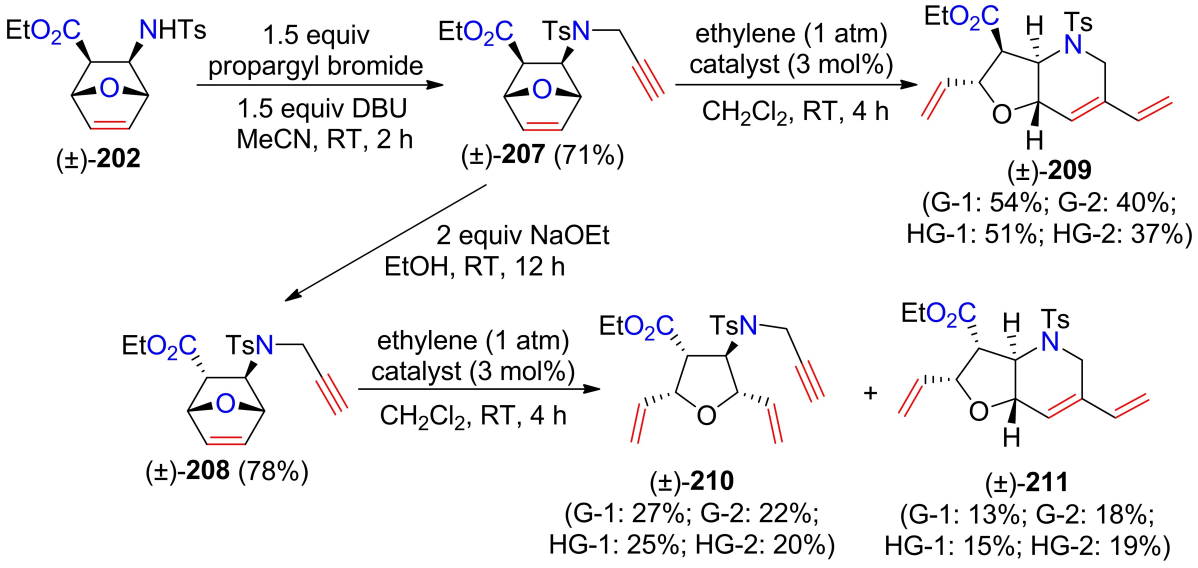
β-Lactams (±)-**227** and (±)-**234** were also submitted to metathesis (Scheme 45). When *N*-allylated β-lactam (±)-**227** was treated with metathesis catalysts in the presence of ethylene, only ring-opening metathesis occurred in low yield (the highest yield of product (±)-**238**, 25%, was achieved by G-1 catalyst). Treatment of isolated ROM product (±)-**238** with metathesis catalysts in the absence of ethylene resulted in fast and efficient ring-closing metathesis, providing the desired azaheterocycle (±)-**239** in an excellent yield with all four catalysts. When *N*-propargylated β-lactam (±)-**234** with metathesis catalysts in the presence of ethylene, ROM product (±)-**240** and ROM/RCEYM product (±)-**241** were formed. The



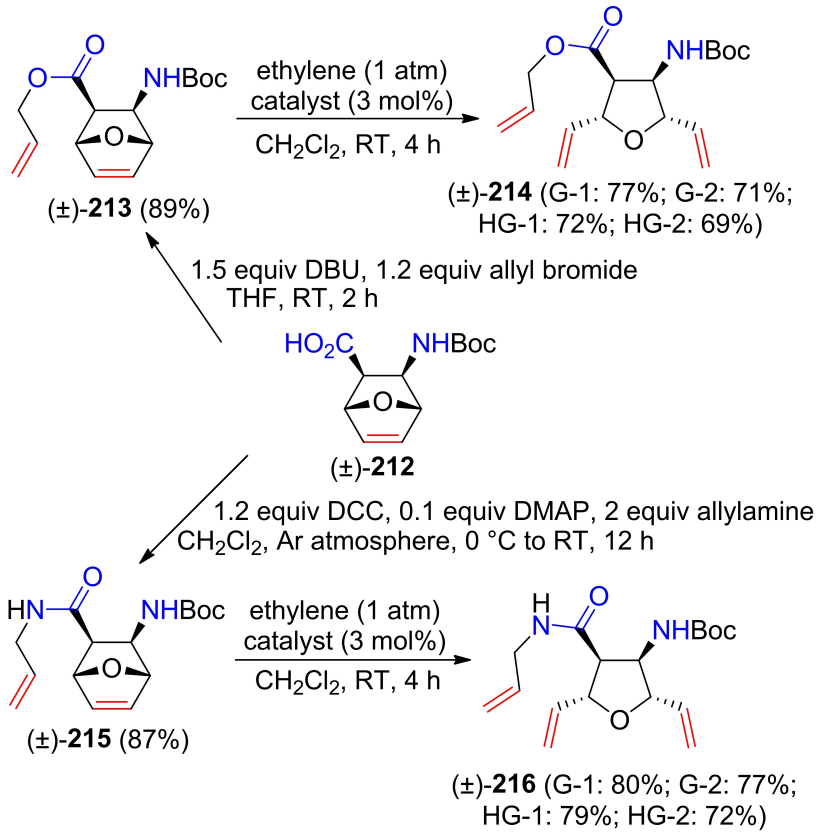
Scheme 35. Ring-rearrangement metathesis of β-amino acid derivatives (±)-**190** and (±)-**194.**



Scheme 36. Synthesis and ROM/RCM of oxanorbornene derivatives (±)-**203** and (±)-**204.**

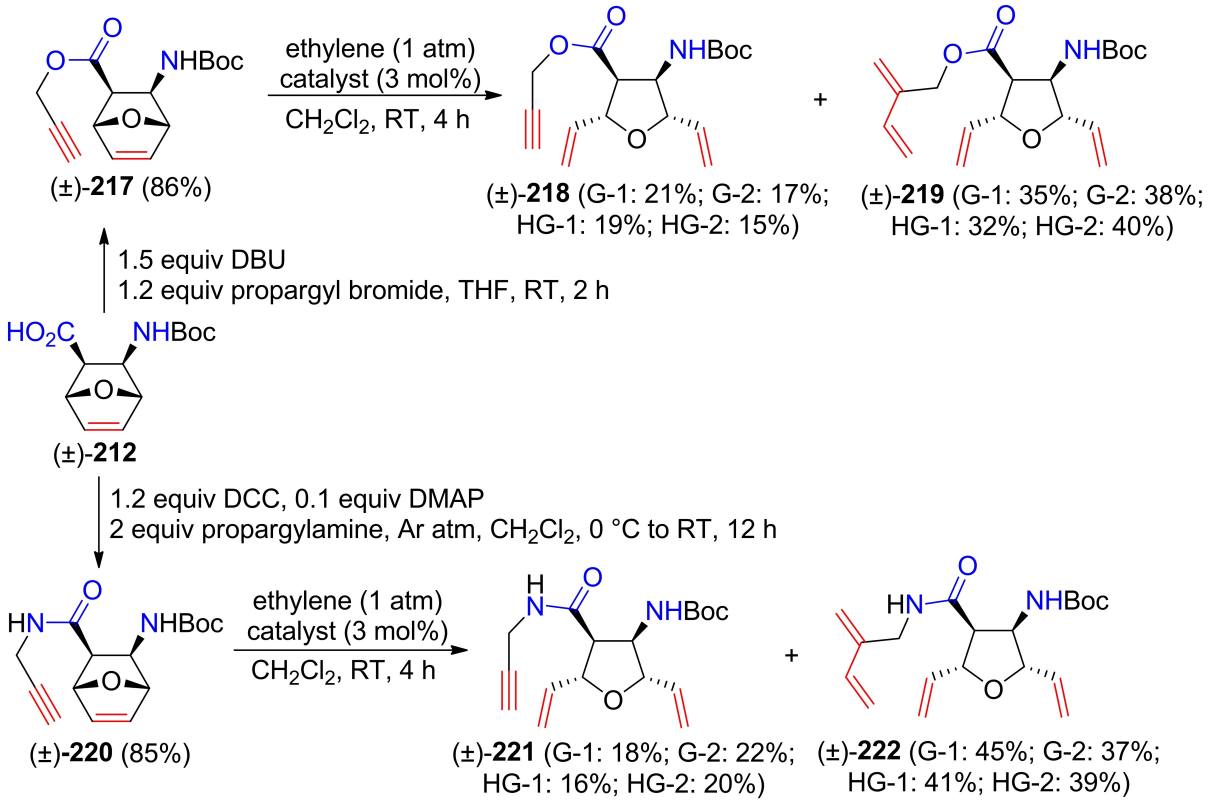


Scheme 37. Synthesis and ROM/RCEYM of oxanorbornene compounds (±)-**207** and (±)-**208.**

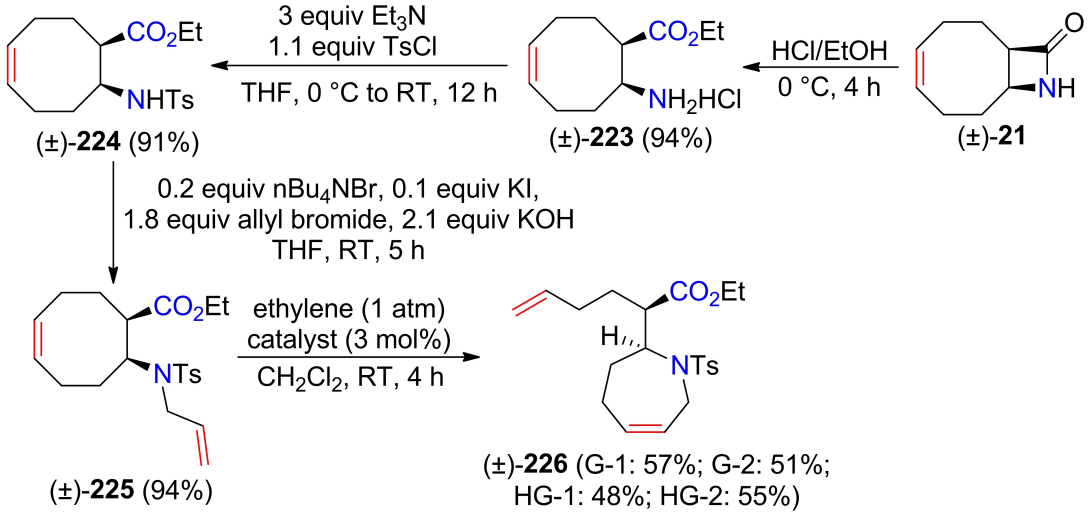


Scheme 38. Synthesis of cispentacin derivatives (±)-**214** and (±)-**216.**

best result [23% (±)-**240** and 13% (±)-**241**] was achieved with G-1 catalyst. Treatment of isolated (±)-**240** with metathesis catalysts in the absence of ethylene resulted in rapid and highly efficient RCEYM reaction with all four catalysts.[109]

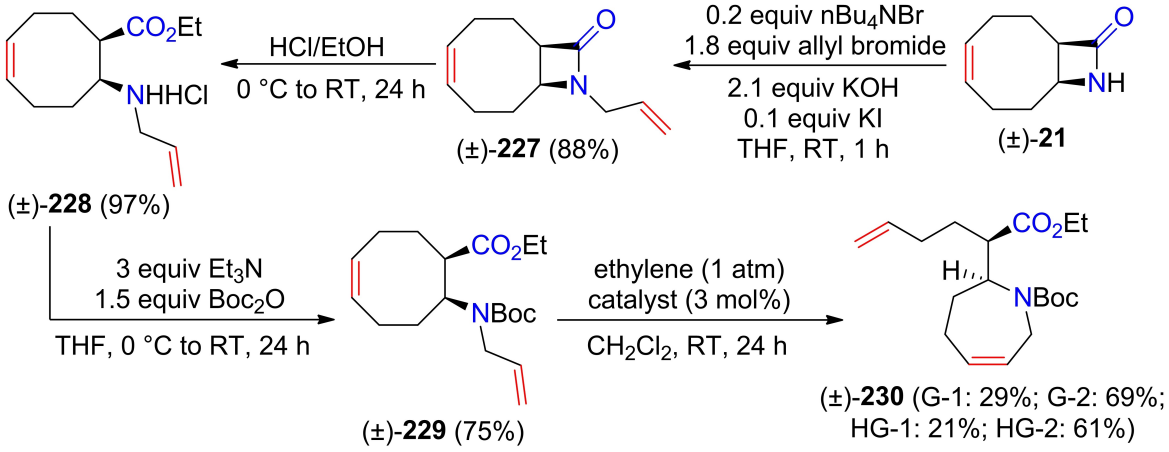


Scheme 39. Unsuccessful RRM of oxanorbornene derivatives (±)-**217** and (±)-**220.**

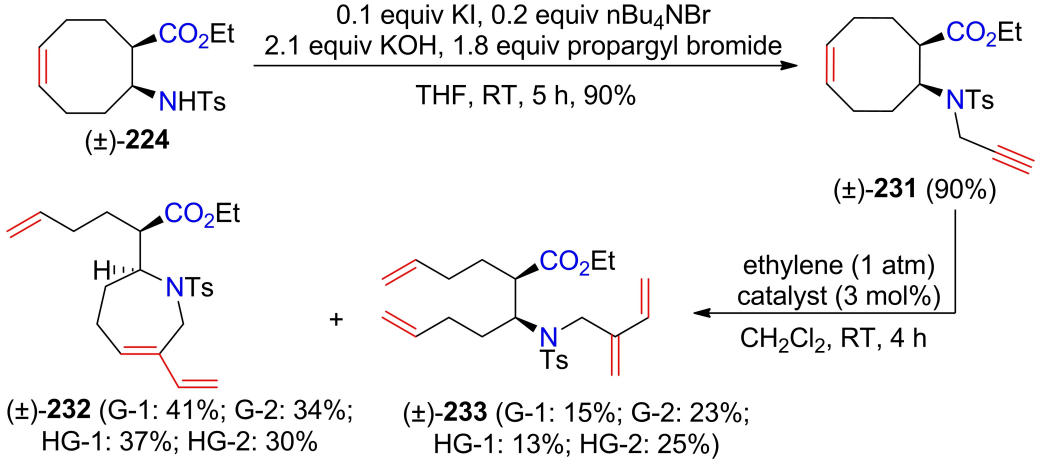


Scheme 40. Synthesis of azaheterocyclic compound (±)-**226** via ROM/RCM.

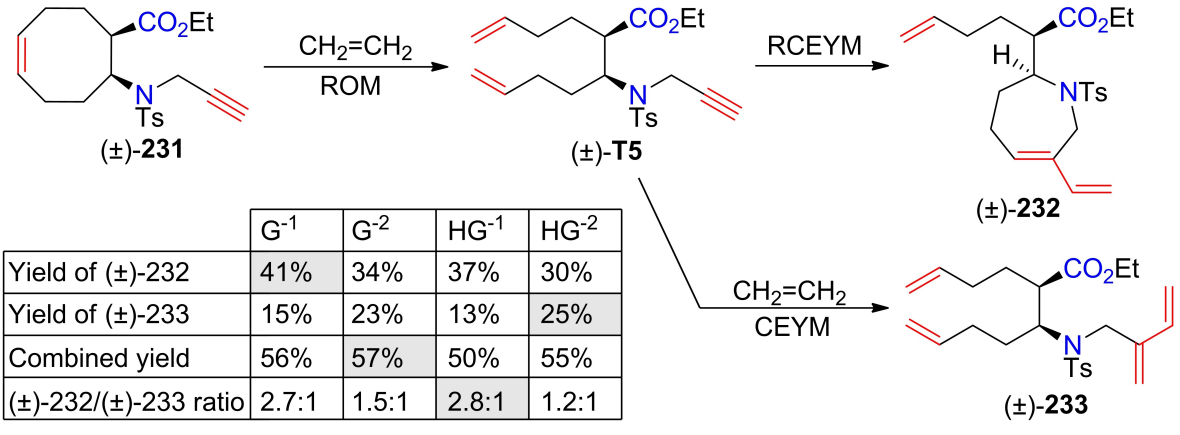
After this, we planned to continue our work with the synthesis of β-amino lactones and β-amino lactams. Thus, *N*-Boc protected amino acid (±)-**242**[23] was subjected to *O*-allylation (allyl bromide in the presence of DBU) or DCC-mediated amidation to prepare RRM substrates (±)-**243** (an allyl ester) and (±)-**245** (an *N*-allylated amide). ROM/RCM of these cyclooctene derivatives would yield an unsaturated lactone with an 8-membered or a 9-membered ring (the



Scheme 41. Synthesis and ROM/RCM of *N*-Boc protected cyclooctene β-amino ester (±)-**229.**

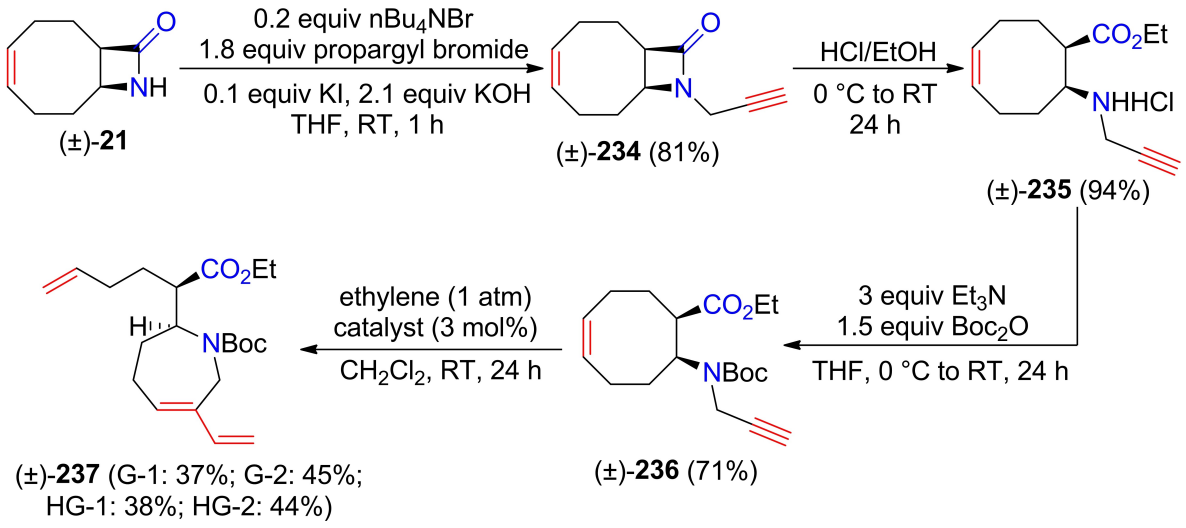


Scheme 42. Synthesis and ROM/RCEYM of cyclooctene β-amino ester (±)-**231.**

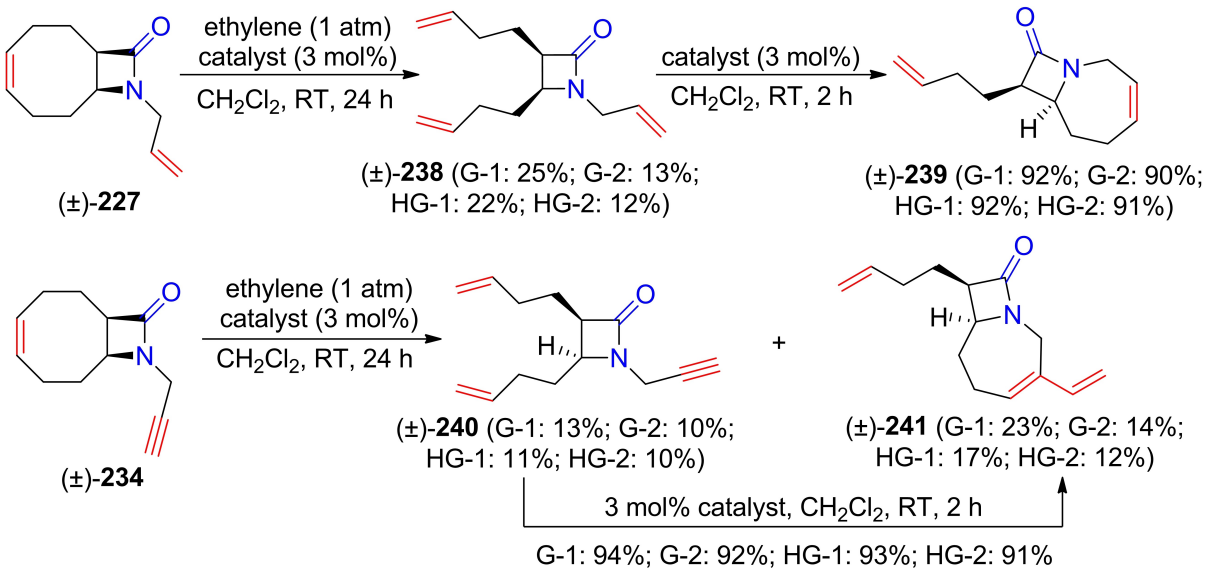


	G^{-1}	G^{-2}	HG^{-1}	HG^{-2}
Yield of (±)-232	41%	34%	37%	30%
Yield of (±)-233	15%	23%	13%	25%
Combined yield	56%	57%	50%	55%
(±)-232/(±)-233 ratio	2.7:1	1.5:1	2.8:1	1.2:1

Scheme 43. Transformation of compound (±)-**231** with metathesis.



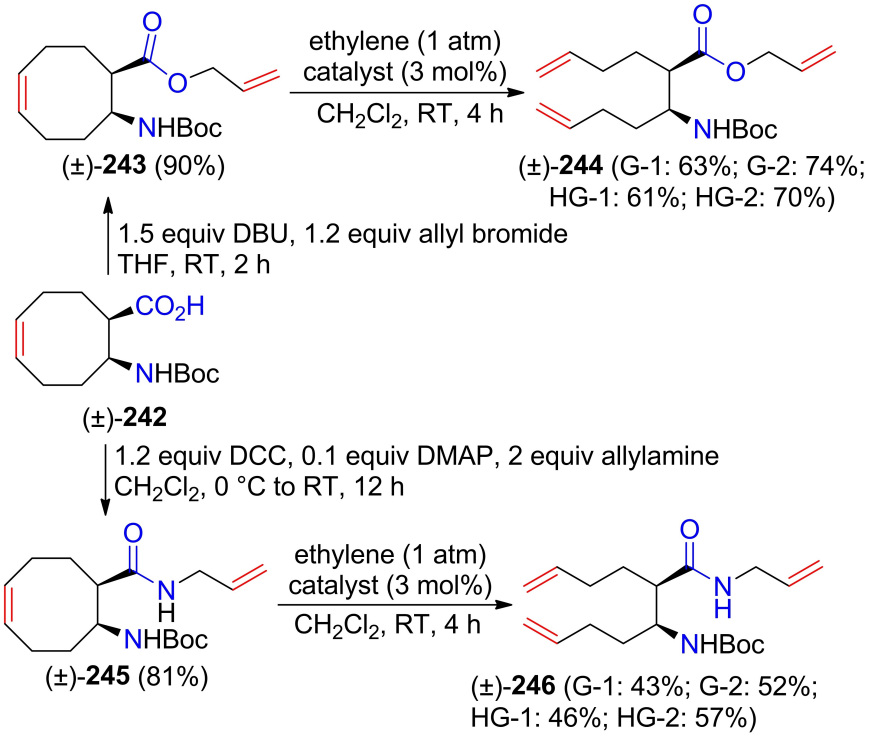
Scheme 44. Synthesis of azaheterocycle (±)-**237** vith ROM/ RCEYM.



Scheme 45. Metathesis of *N*-allylated or *N*-propargylated cyclooctene-fused lactams.

former is more plausible). Because the possible RRM products have comparable (or higher) ring strain to the substrates, it is not surprising that one-step ROM/RCM failed, and metathesis of these substrates in the presence of ethylene afforded only ROM products (Scheme 46). Second generation catalysts were more efficient than first generation ones, the best yields were 74% for (±)-**244** (G-2 catalyst) and 57% for (±)-**246** (HG-2 catalyst). Unfortunately, treatment the isolated ROM products with metathesis catalysts in the absence of ethylene failed to achieve RCM.[110]

Metathesis of ester (±)-**247** in the presence of ethylene failed to achieve one-step ROM/RCEYM (probably because the RRM products would have similar ring strain as the substrate). ROM product (±)-**248** and ROM/CEYM product (±)-**249** were formed. Second generation catalysts were really inefficient in this transformation. In contrast, first generation catalysts were moderately efficient (48% overall yield with both G-1 and HG-1). The best yields were of 23% for (±)-**248** (HG-1 catalyst) and 28% for (±)-**249** (G-1 catalyst). Both products resisted to ring closure attempts. In contrast, transformation of compound (±)-**250** furnished directly the



Scheme 46. ROM/RCM of β-amino acid derivatives (±)-**243** and (±)-**245.**

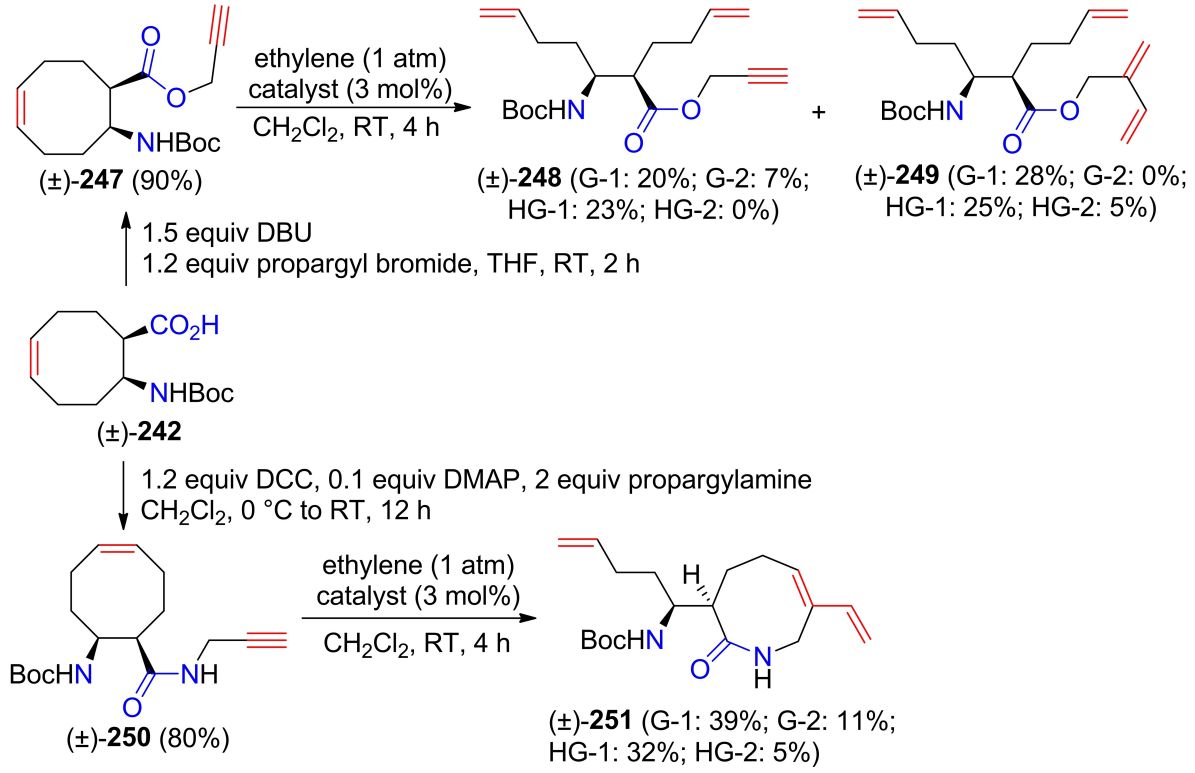
ROM/RCEYM product (±)-**251**. Second generation catalysts were highly inferior to first generation ones, the highest yield of the RRM product was accomplished with G-1 catalyst (39%) (Scheme 47).[110]

4. Summary and Outlook

Olefin metathesis as a powerful tool to create C=C bond containing molecular entities has been effectively applied to create various unsaturated azaheterocyles and amino acid derivatives. Various types of metathesis protocols (ROM, RCM, CM, RCEYM, RRM) gave access to this class of compounds with stereocontrolled manner to synthesize β-amino lactams/lactones and azaheterocyclic β-amino esters with multiple chiral centers. The key step was ring-rearrangement metathesis (RRM) of strained cycloalkene β-amino acid derivatives. The metathesis techniques were carried out with commercial Ru-based catalysts. The metathesis catalyst performance greatly depended on a number of factors: stereochemistry and skeleton of substrate, type of RRM, functional group directing effects, however it is difficult to make general conclusions. The metathesis transformations were dependent on the molecular architecture of the substrates and proceeded under stereocontrol with conservation of the configurations of the stereocenters: thus the structure of the starting compounds predetermined the structure of the formed products. The presence of one or more olefin bonds in the products may allow further C=C bond functionalizations of the structurally, and chemically diverse molecular entities.

List of Abbreviations

ADMET	acyclic diene metathesis polymerization
Boc	*tert*-butyl-oxycarbonyl
CEYM	cross enyne metathesis
CM	cross-metathesis
Cy	cylohexyl
CSI	chlorosulfonyl isocyanate
DMF	dimethylformamide
DOS	diversity-oriented synthesis
EWG	electron-withdrawing group
G-1	1st generation Grubbs catalyst
G-2	2nd generation Grubbs catalyst
HG-1	1st generation Hoveyda–Grubbs catalyst
HG-2	2nd generation Hoveyda–Grubbs catalyst
PG	protecting group
RCEYM	ring-closing enyne metathesis
RCM	ring-closing metathesis
ROM	ring-opening metathesis



Scheme 47. Metathesis reactions of β-amino acid derivatives (±)-**247** and (±)-**250.**

RRM	ring-rearrangement metathesis
SG	Stewart-Grubbs catalyst
TFA	trifluoroacetic acid
Ts	tosyl or 4-toluenesulfonyl

Acknowledgements

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