Application of metathesis reaction protocols to the stereocontrolled access of some functionalized azaheterocycles

PhD Thesis

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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

RRM: ring-rearrangement metathesis

SG: Stewart–Grubbs catalyst

TFA: trifluoroacetic acid

Ts: tosyl or 4-toluenesulfonyl

1. INTRODUCTION AND AIMS

There is a great interest towards carbocyclic and azaheterocyclic β-amino acids in pharmaceutical and medicinal chemistry. Such molecular entities can be found in a number of natural products, bioactive compounds, and drugs.[1-19] Synthesis of carbocyclic β-amino acid derivatives is a highlighted research topic in the Institute of Pharmaceutical Chemistry at the University of Szeged, and a wide variety of methods were developed to obtain such derivatives.[20-33] Azaheterocyclic β-amino acid derivatives were also synthesized in our Institute through oxidative ring opening followed by double reductive amination.[26,30-36]

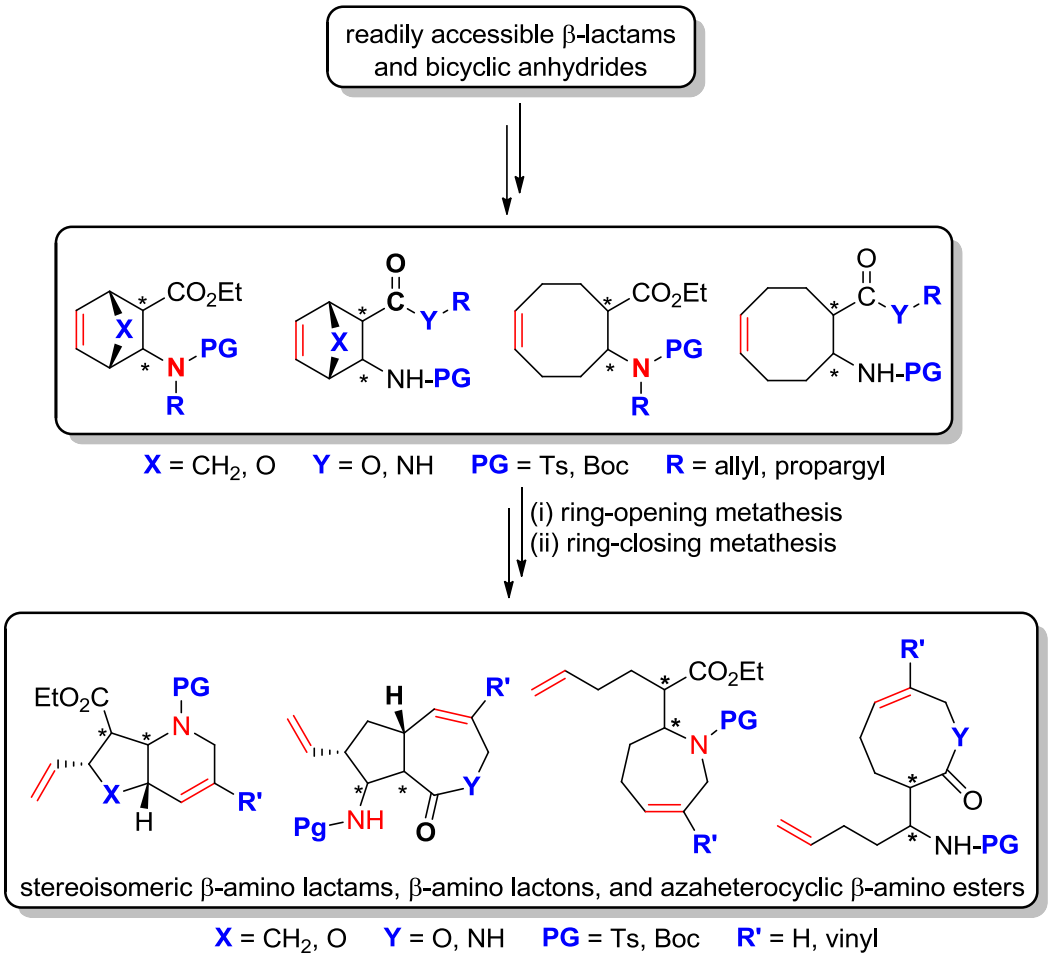
Functionalized azaheterocycles, including azaheterocyclic β-amino acids mentioned above, are an important and highly abundant compound family in pharmaceutical and medicinal chemistry.[14,15,37-43] As a consequence, their synthesis is an important topic in our group. Our research group prepared a number of functionalized azaheterocycles (including many fluorinated ones) from functionalized cycloalkenes via oxidative ring opening followed by double reductive amination.[44-47]

Olefin metathesis uses commercially available metal alkylidenes to cleave olefin bonds, then to reassemble the resulting alkylidene fragments into new olefins.[48-56] Numerous 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 transformation 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) substep.[57-59] Importantly, 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 increasingly used in the chemical industry[60-63] as well as in the synthesis of bioactive compounds and natural products.[64-68] For example, our research group applied ring-opening metathesis and regioselective cross-metathesis to obtain various novel functionalized compounds from cyclic β-amino acid derivatives.[29-33]

Diversity-oriented synthesis (DOS), its dedicated goal being the construction of valuable (structurally and chemically diverse) molecular libraries, has become an important

principle during the last few decades in pharmaceutical chemistry and drug research. 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 rapidly and efficiently generate highly complex frameworks that are difficult to synthesize by conventional methods.[57,58]

The present PhD work focused on the development of a stereocontrolled synthetic route for accessing azaheterocyclic β-amino acid derivatives. The strategy was based on ring-rearrangement metathesis of highly strained unsaturated bicyclic compounds (*Scheme 1*). A number of experimental conditions were used to investigate the effects of the catalysts and the substrates on the yields and conversions of the metathesis reactions.



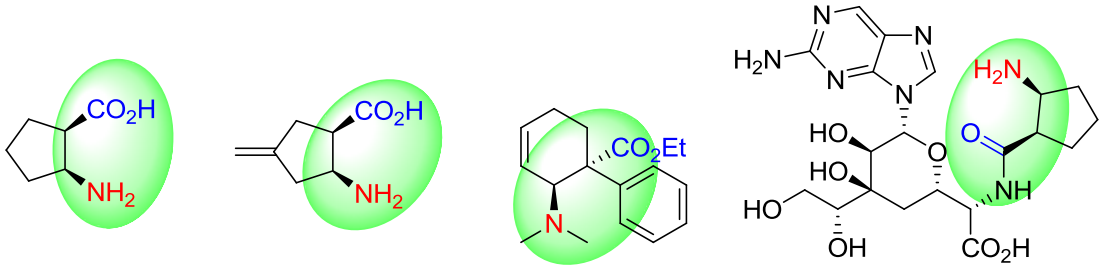
Scheme 1. Aims of the present PhD work

2. LITERATURE BACKGROUND

2.1. Importance of cyclic β-amino acid derivatives

Cyclic β-amino acids possess a wide range of bioactive properties, they can be found in a number of natural products and drugs, and they are promising building blocks of various foldamers (see below). As a result, such compounds and their synthesis have always been an important topic in pharmaceutical and medicinal chemistry.[1-19,82-88]

Figure 1 depicts 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] Its synthetic analogue, icofungipen (**2**), has similar bioactivity (but its development stopped after Phase II trials).[8] Tilidine [(±)-**3**] is a synthetic opioid painkiller drug.[7] Amipurimycin (**4**) is a peptidyl nucleoside antibiotic, which was isolated from *Streptomyces novoguineensis*, and it contains a cispentacin unit.[9]



cispentacin (**1**): natural product (*antifungal effect*) | icofungipen (**2**): bioactive compound (*antifungal effect*) | tilidine [(±)-**3**]: approved drug (*analgesic*) | amipurimycin (**4**): natural product (*antibiotic*)

Figure 1. Carbocyclic β-amino acids in natural products, bioactive compounds and drugs

A number of 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 (to be more exact, a glycoprotein IIb/IIIa antagonist), but its development stopped after Phase II trials.[10] Dexmethylphenidate (**7**) stimulates the central nervous system (probably via blocking dopamine and noradrenaline reuptake), and it is used in the treatment of attention deficit hyperactivity disorder (ADHD).[11] Finally, cucurbitin (**8**) is a natural product that is found in seeds of *Cucurbita* species and possesses activity against *Schistosoma japonicum* (a parasitic worm).[19]

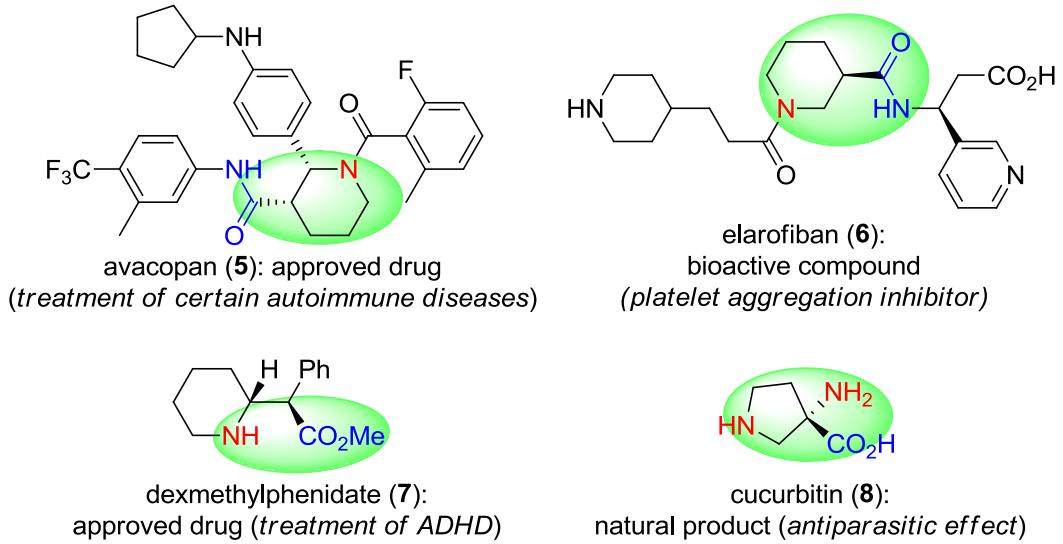


Figure 2. Azaheterocyclic β-amino acids in natural products, bioactive compounds, and drugs

Figure 3 shows some notable 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*, gougerotin (**11**) was isolated from *Streptomyces gougerotii*, while chryscandin (**12**) is produced by a *Chrysosporium pannorum* strain.[7,83,84]

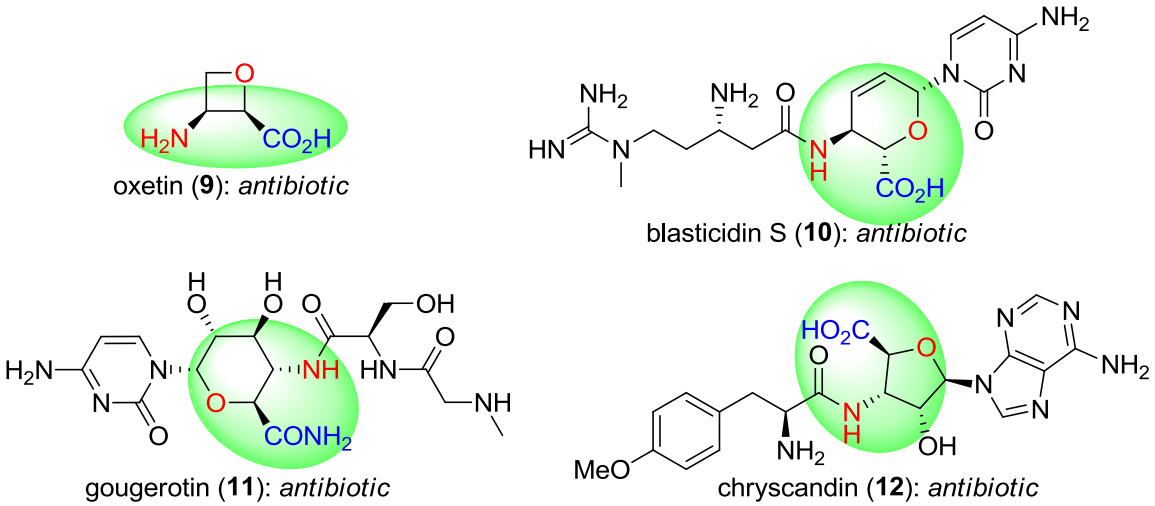
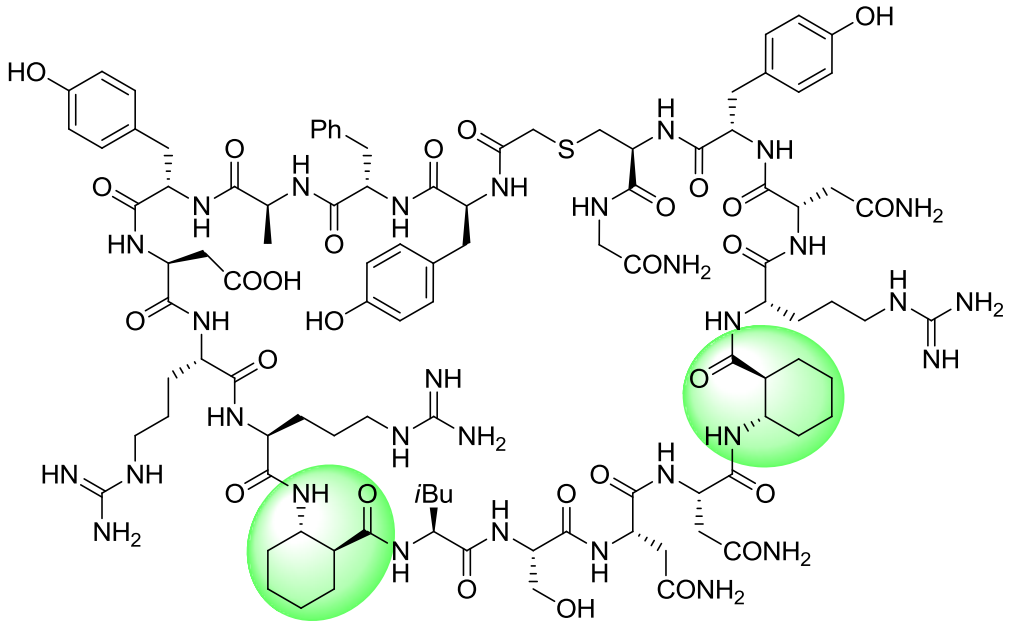
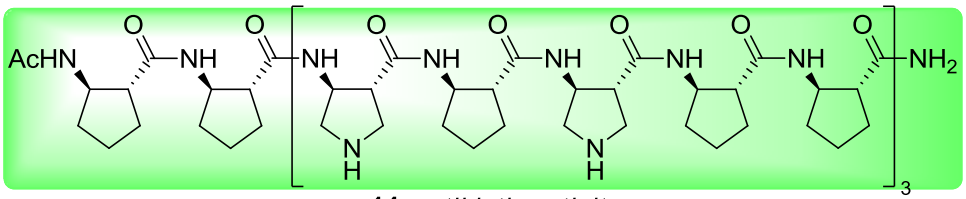


Figure 3. Oxacyclic β-amino acids in natural products

Cyclic β-amino acids are also utilized as building blocks 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 show interesting biological activity (Figure 4).[85-88]



13: *human factor XIIa inhibitor*



14: *antibiotic activity*

Figure 4. Bioactive foldamers containing cyclic β-amino acids

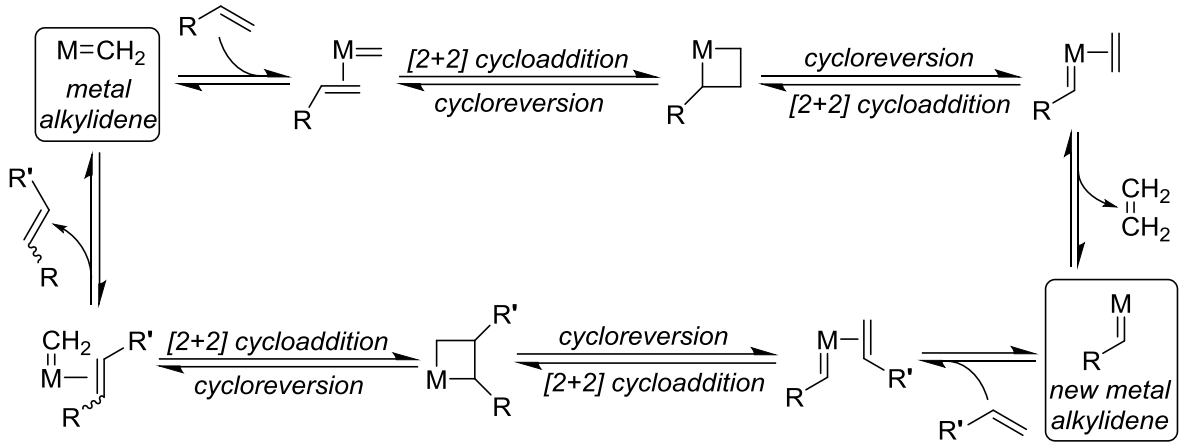
2.2. Olefin bond functionalization of some cycloalkene β-amino acid derivatives through metathesis reactions

Because of the importance of cyclic β-amino acid derivatives, transformation and preparation of such compounds were a highlighted topic in the Institute of Pharmaceutical Chemistry at the University of Szeged, and many synthetic pathways were developed.[20-36] In this section, after a brief introduction to olefin metathesis, synthetic pathways with key steps of ring-opening metathesis and cross-metathesis will be discussed.[29-33]

2.2.1. Introduction to olefin metathesis

Over the past two decades, olefin metathesis has become increasingly important and widely applied in synthetic organic chemistry.[60-68] The accepted mechanism for olefin metathesis was proposed by Chauvin in 1971 (*Scheme 2*).[48] The process starts with [2+2] cycloaddition between the metal alkylidene and an olefin, then the formed metallacyclobutane

intermediate undergoes cycloreversion. The resulting new metal alkylidene then repeats the previous process with another olefin. Importantly, metathesis processes are generally reversible, and the alkylidene fragments of the starting compounds are reassembled in a more or less statistical fashion.[48-53]



Scheme 2. Olefin metathesis mechanism proposed by Chauvin in 1971

The properties of the metal alkylidene catalyst are very important. In the beginning, poorly-defined heterogeneous catalytic systems were used. The first well-defined homogenous catalysts appeared in the late 1970s (after the mechanistic proposal of Chauvin), followed by an amazing development ever since.[50-56]

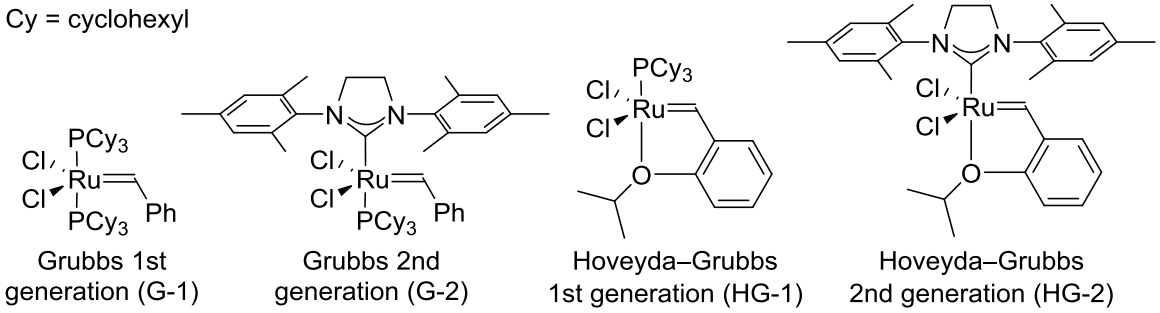


Figure 5. Structures of the most commonly used Ru-based catalysts and their abbreviations

Currently, two types of metathesis catalysts, with somewhat complementary properties, are commonly used. 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 (notably, 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. Furthermore, they have good functional group tolerance and somewhat lower (but still quite sufficient) activity.[50,51,53] In addition, ruthenium-based catalysts are easily accessible, which (together with their advantages) contributed crucially to the current importance of olefin metathesis processes in organic synthesis. Figure 5 shows structures of the most commonly used Ru-based catalysts.[53]

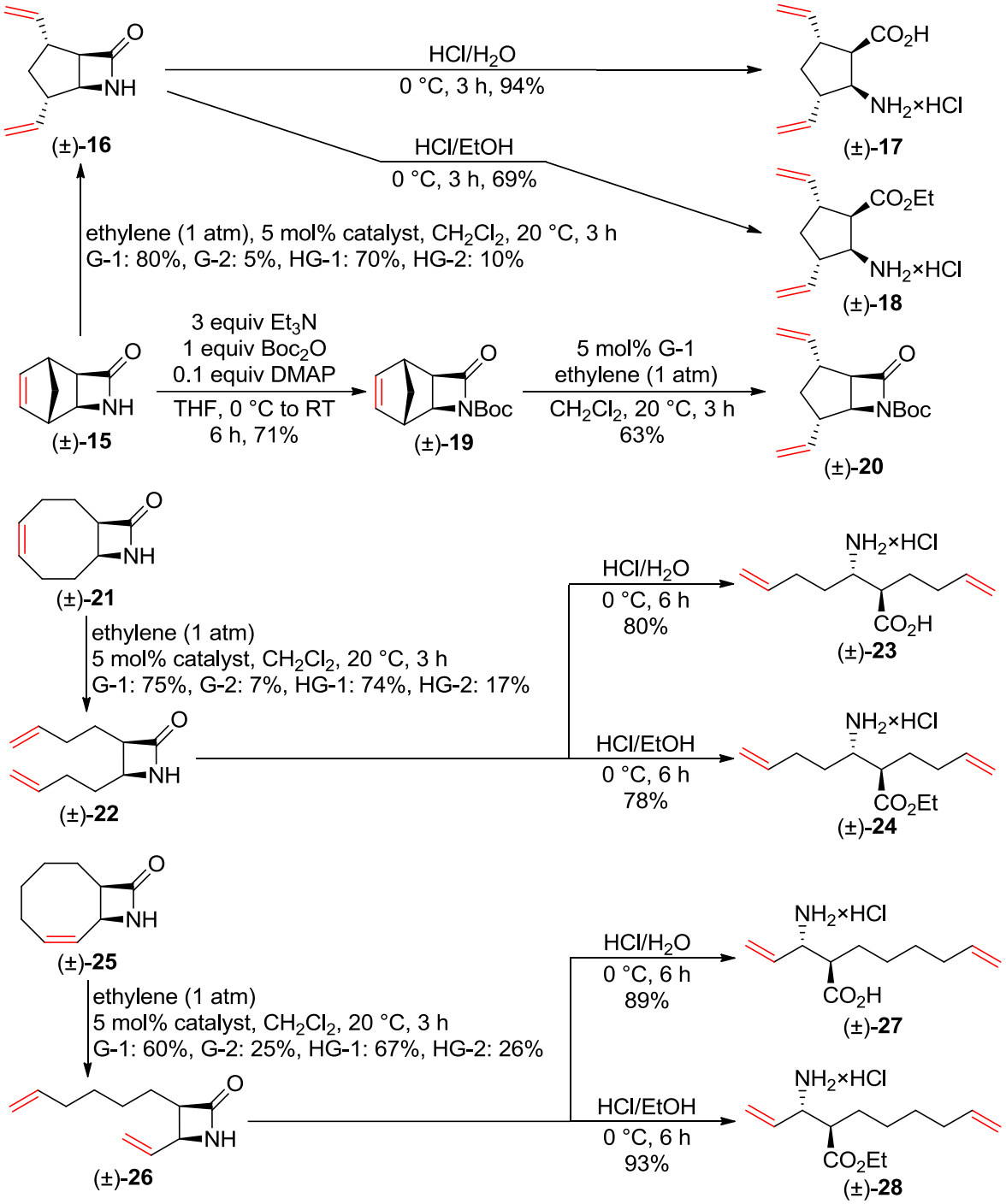
Several classes of metathesis reactions have been developed, such as ring-opening metathesis (ROM), ring-opening metathesis polymerization (ROMP), ring-closing metathesis (RCM), acyclic diene metathesis polymerization (ADMET), cross-metathesis (CM), cross enyne metathesis (CEYM), ring-closing enyne metathesis (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, whereas sp^3 carbons (including asymmetric ones) are untouched. Notably, although all metathesis reactions are reversible, the position of the equilibrium is greatly 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 compounds 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]

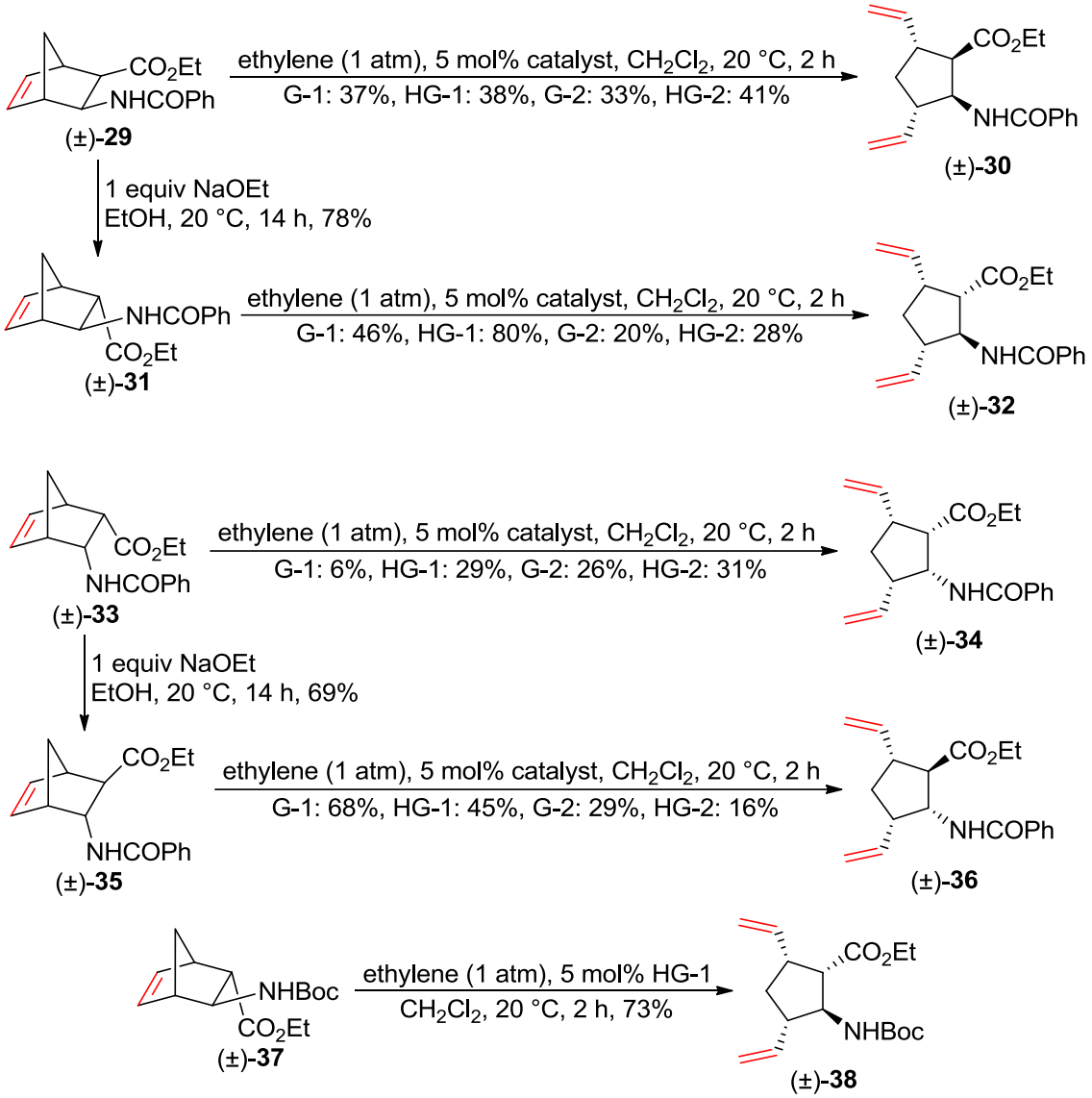
2.2.2. Olefin bond functionalization via ring-opening metathesis

Kardos et al. reported a stereocontrolled approach to functionalized cispentacins and open-chain $\beta^{2,3}$-amino acid derivatives utilizing ring-opening metathesis of the unsaturated bi- or tricyclic β-lactams as the 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 provided the expected ring-opening metathesis products with the highest yields obtained with G-1 and HG-1 catalysts. The formed lactams (±)-**16**, (±)-**22**, and (±)-**26** were subjected to acidic hydrolysis to obtain β-amino acid hydrochlorides (±)-**17**, (±)-**23**, and (±)-**27**. Alternatively, ethanolysis of these lactams afforded β-amino ester hydrochlorides (±)-**18**, (±)-**24**, and (±)-**28**. Neither ROM nor lactam ring opening

affected the configuration of the stereogenic centers.[30] Later, ROM of lactam (±)-**19** (prepared by *N*-Boc protection[22] of (±)-**15**) was also accomplished.[31]



Scheme 3. Synthesis of functionalized cispentacins and open-chain $\beta^{2,3}$-amino acid derivatives

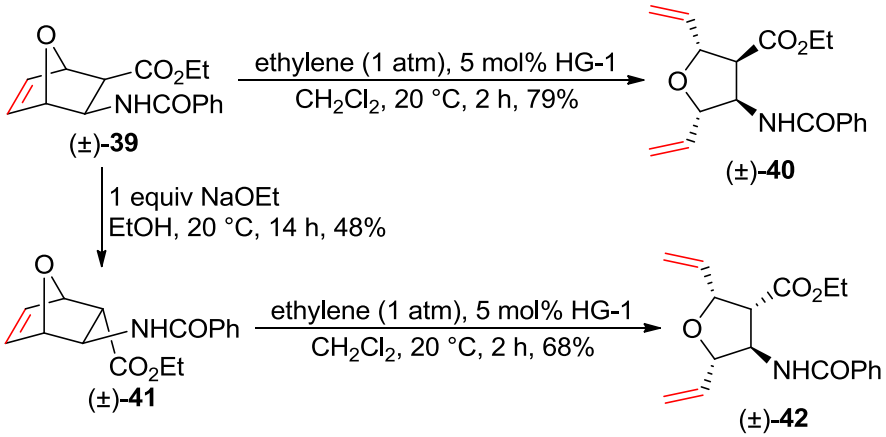


Scheme 4. Synthesis of 3,5-divinylated cispentacin and transpentacin derivatives

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 afforded substrates (±)-**31** and (±)-**35** in which the ester and the amide group 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

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] Later, Kiss and coworkers accomplished transformation of compound (±)-**37** [the *N*-Boc protected analogue of (±)-**31**] as well (*Scheme 4*).[33]

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



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

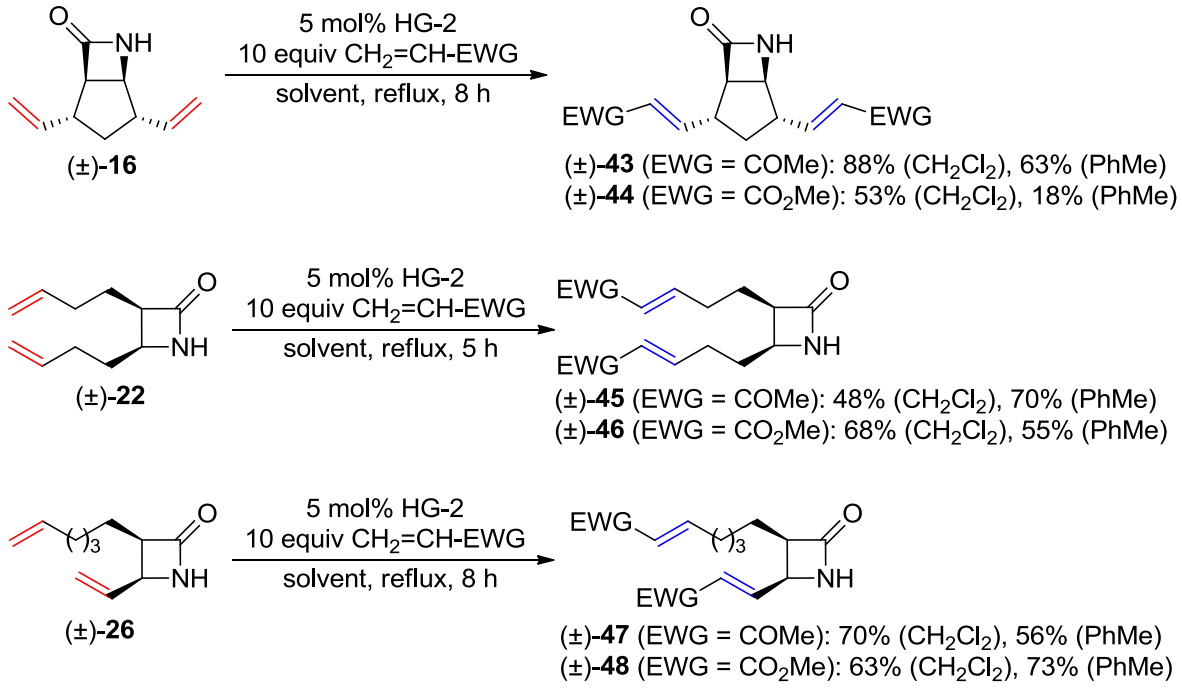
2.2.3. Olefin bond functionalization via cross-metathesis

Cross-metathesis (olefin metathesis reaction between two different olefins) is a commonly applied method for the functionalization of C=C bonds even in complex frameworks.[50,53,56,64] Subjecting the mixture of olefins **A** and **B** to metathesis should give three possible products (**A**+**A** homocoupling, **B**+**B** homocoupling, and **A**+**B** cross-coupling). Consequently, a careful planning is needed to make cross-coupling the dominant outcome. In most cases, cross-metathesis mainly yields the thermodynamic product (usually, an *E* olefin).[53,64]

For further functionalization of the divinylated β-amino acid derivatives discussed in

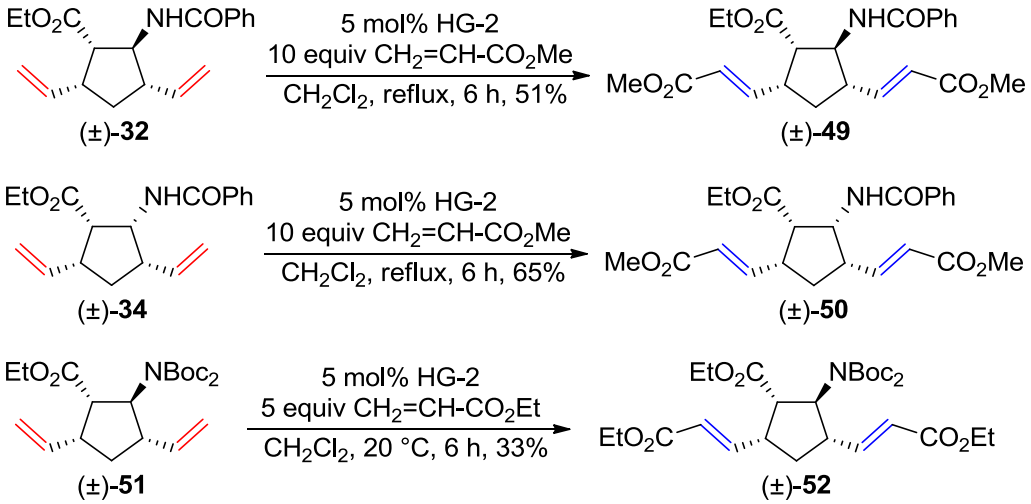
Section 2.2.2, our Institute applied cross-metathesis with a large excess of an electron-deficient alkene (an acrylate or methyl vinyl ketone). Homocoupling of electron-deficient alkenes is slow,[56,89] but they still take part in cross-coupling, and their excess ensures that homocoupling of the divinylated substrates is suppressed (coupling partner/substrate encounters are more frequent than substrate/substrate encounters). Therefore, metathesis of these reaction mixtures mainly provides the desired cross-coupling products.

First, divinylated β-lactams (±)-**16**, (±)-**22**, and (±)-**26** (see *Scheme 3*) were subjected to metathesis. After several preliminary experimental investigations regarding the reaction conditions and the catalysts, the highest conversions were achieved with HG-2 catalyst. Some reactions preferred treatment under reflux conditions in anhydrous CH_2Cl_2, while others favored reflux treatment in anhydrous toluene. In all cases, both terminal olefin functions underwent cross-metathesis, affording 'dicoupled' products with *E* geometry in moderate to good yields (*Scheme 6*).[30]

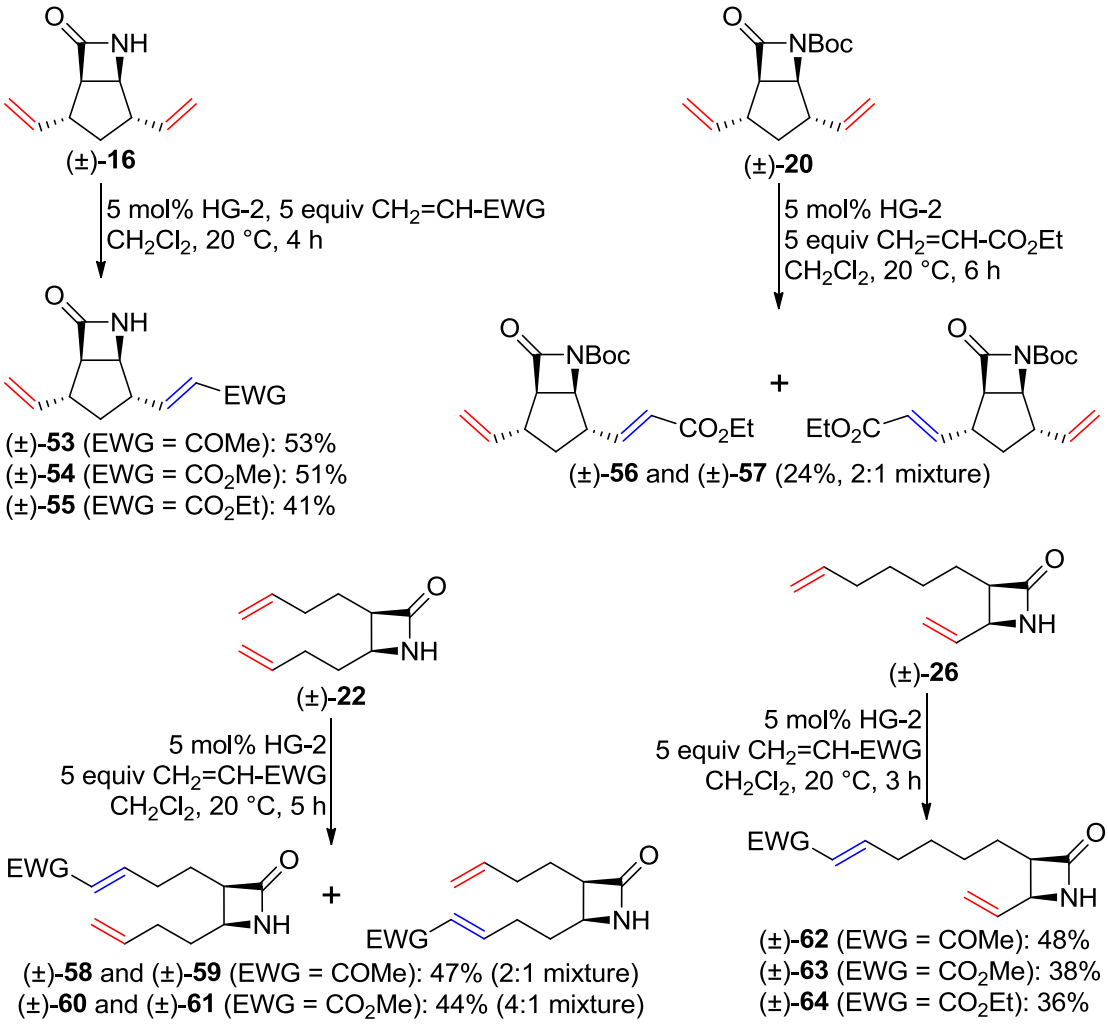


Scheme 6. Synthesis of dialkenylated β-lactam derivatives

The next substrates were *N*-benzoylated amino esters (±)-**32** and (±)-**34.** Their cross-metathesis with methyl acrylate in anhydrous CH_2Cl_2 under reflux yielded the expected 'dicoupled' products.[29] Doubly *N*-Boc protected compound (±)-**51** behaved similarly (*Scheme 7*).[33] Product (±)-**50** was previously prepared via Wittig reaction.[25]

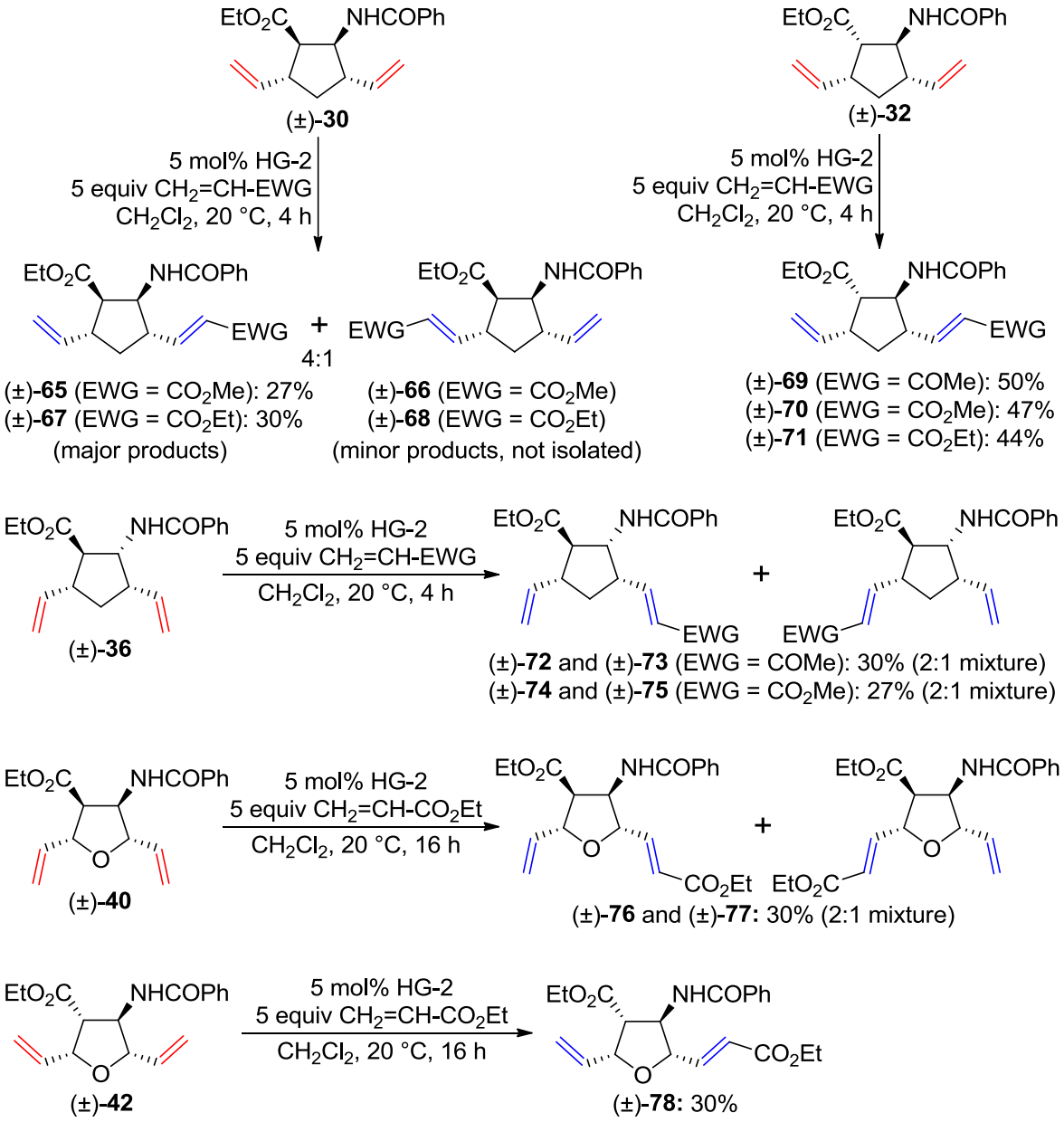


Scheme 7. Synthesis of dialkenylated β-amino esters



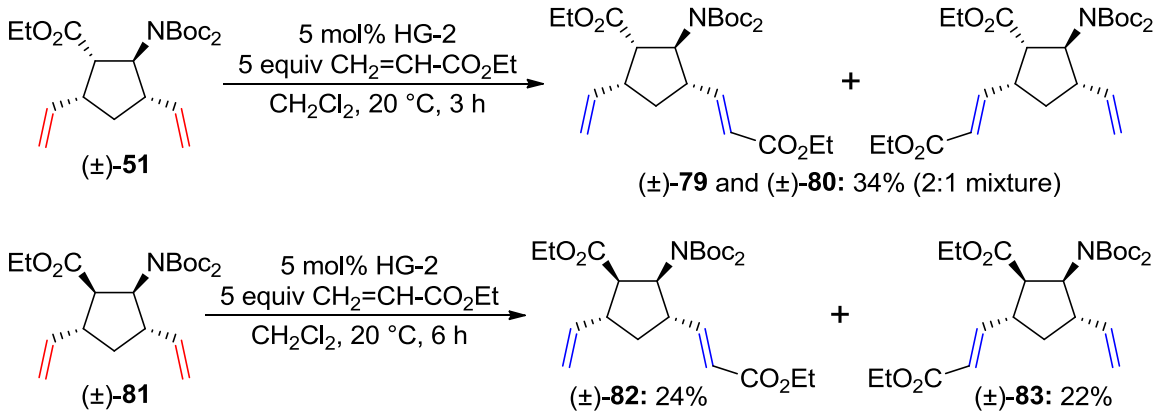
Scheme 8. Chemoselective cross-metathesis of divinylated β-lactams

After the above successful syntheses, the focus of Kiss and coworkers shifted to regioselectivity of cross-metathesis. It was quickly realized that cross-metathesis of divinylated lactam (±)-**16** under milder conditions (RT instead of reflux, 5 equiv electron-deficient olefin coupling partner instead of 10 equiv, and shorter reaction time) yields a single 'monocoupled' product.[31] Lactam (±)-**26** behaved similarly, while transformation of lactams (±)-**20** and (±)-**22** resulted in mixtures of two 'monocoupled' products (*Scheme 8*). Separation of these product mixtures failed, and the structure of the major product is unknown.[31,33]



Scheme 9. Synthesis of dialkenylated cispentacin and transpentacin analogues

Regioselective cross-metathesis was also attempted on divinylated cispentacin and transpentacin derivatives (*Schemes 9*, *10*). In the case of substrates (±)-**32** and (±)-**42**, CM selectively led to a single 'monocoupled' product. For all other substrates [β-amino esters (±)-**30**, (±)-**36**, (±)-**40**, (±)-**51**, and (±)-**81**], cross-metathesis afforded 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. Products from substrate (±)-**81** were also separable. However, separation of other 'monocoupled' product mixtures failed, and structures of the major products are unknown.[31,33]

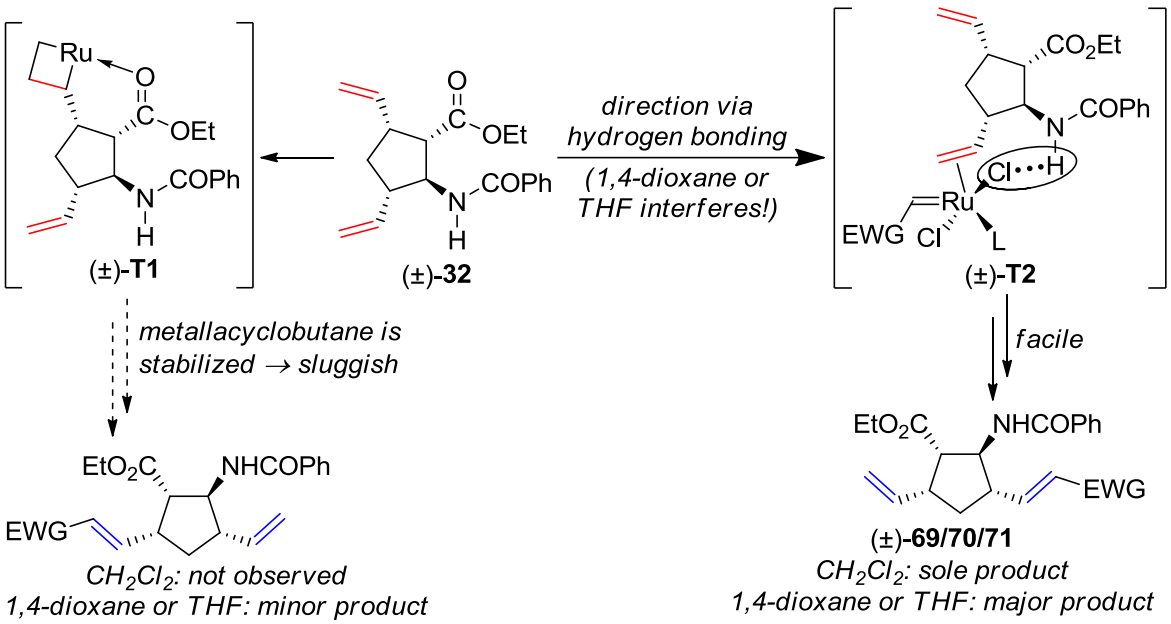


Scheme 10. Synthesis of dialkenylated, doubly *N*-Boc protected β-amino esters

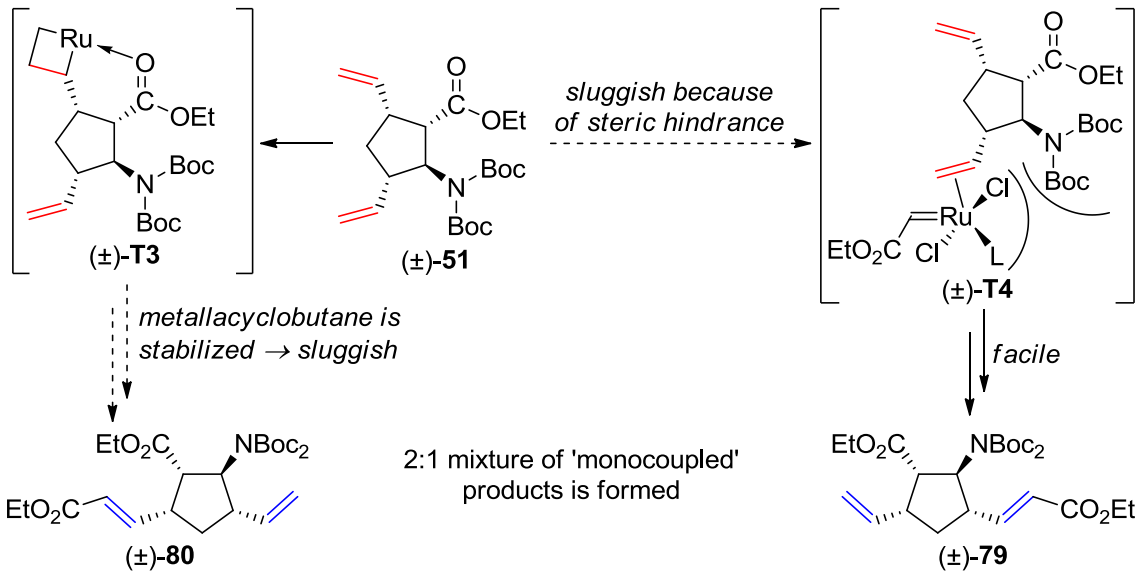
The authors proposed that selectivity in these cross-metathesis reactions is determined by the combined effect of three factors. First of all, coordination with the carbonyl oxygen of the ester group stabilizes the ruthenacyclobutane intermediate of the metathesis process, and hinders transformation. 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 happens more readily (because it yields *cis*-annelated rings, not *trans*-annelated ones), and CM of this vinyl group is more suppressed. This is an important reason behind regioselective CM of β-amino esters (±)-**32** and (±)-**42** (*Scheme 11*).[31]

The second factor is hydrogen bonding between the N–H hydrogen and the chloride ligand of the catalyst, which facilitates transformation of the vinyl group closer to the N–H group. For example, CM of lactam (±)-**16** provides one 'monocoupled' 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 bond formation (*Scheme 11*).[31]

The case of compound (±)-**42** is probably similar. 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]



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



Scheme 12. Reasons of regioselectivity in cross-metathesis reaction of (±)-**49**

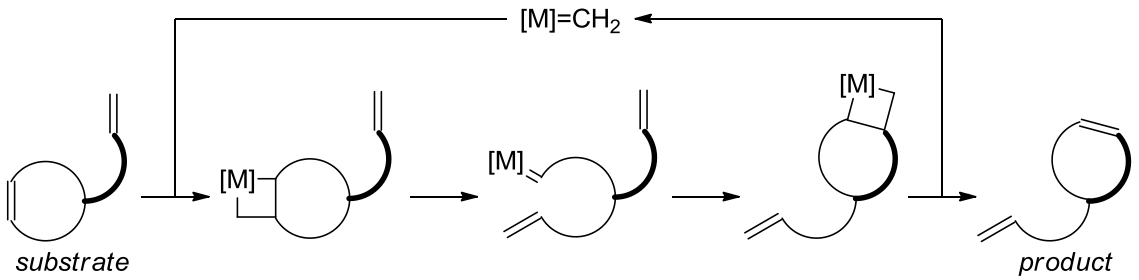
The third factor is steric hindrance. If the large Ru complex cannot approach a vinyl group efficiently, transformation of that vinyl group will be hindered. For example, cross-metathesis of compound (±)-**51** with a bulky $NBoc_2$ group has low selectivity, while analogous reactions of compounds (±)-**32** and (±)-**42** (which contain a smaller NHCOPh group) are

completely selective (*Scheme 12*).[33] Regioselective cross-metathesis of β-lactam (±)-**26** was also attributed to steric hindrance.[33]

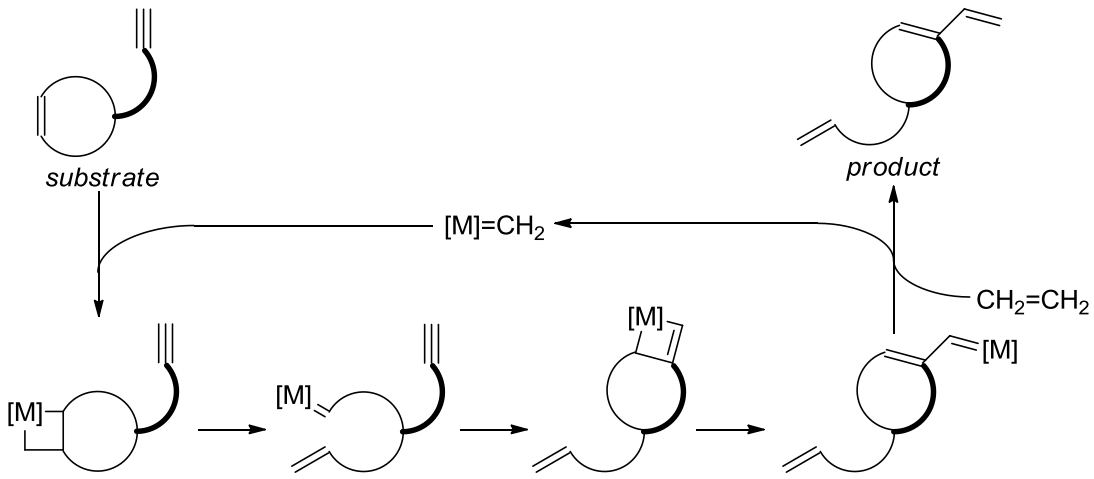
2.3. Synthesis of azaheterocycles by ring-rearrangement metathesis

2.3.1. Introduction to 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-closing metathesis (RCM) or ring-closing enyne metathesis (RCEYM). *Scheme 13* and *14* depict the general mechanism of these processes.[57]



Scheme 13. General mechanism of ROM/RCM sequences



Scheme 14. General mechanism of ROM/RCEYM sequences

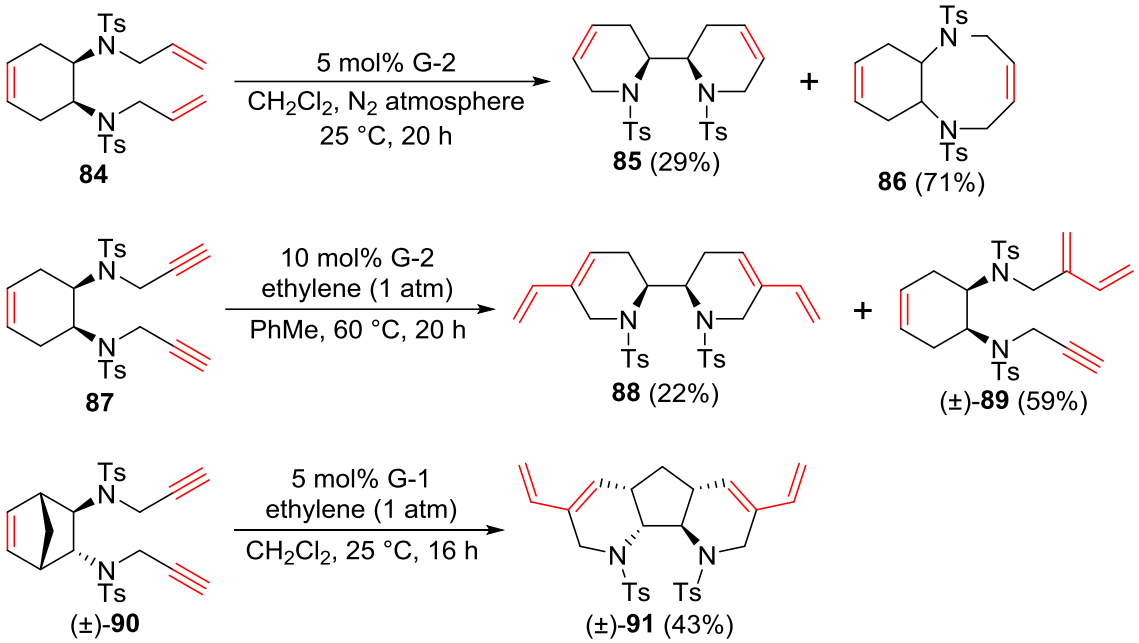
The ROM/RCM process does not change the overall number of molecules (it transforms one molecule of substrate into one molecule of product), while the ROM/RCEYM process actually decreases it (one molecule of substrate and one molecule of ethylene are transformed into a single product molecule). Therefore, the entropy term does not really favor RRM and, consequently, it must be driven by the enthalpy term. 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. First of all, 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 an emerging topic.[57-59]

2.3.2. Synthesis of azaheterocycles by application of the metathesis protocol

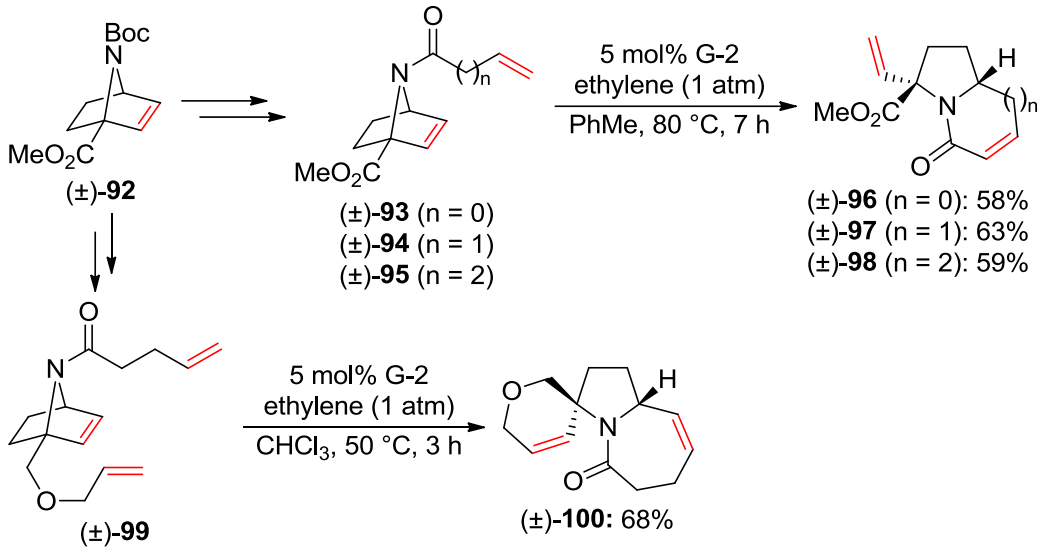
Synthesis of nitrogen-containing heterocycles is a highly important research topic in pharmaceutical and medicinal chemistry, because these compounds are present in a wide variety of drugs, biologically active molecules, and natural products.[10-19,37-43] This section will give some insight into the synthesis of azaheterocycles via ring-rearrangement metathesis.



Scheme 15. RRM reactions of vicinal diaminocycloalkene derivatives

Groaz, Banti, and North 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** too. *N*,*N*'-Dipropargylated sulfonamide **87** also disfavored RRM. In this case, CEYM was the dominant pathway, and the highest yield of RRM product

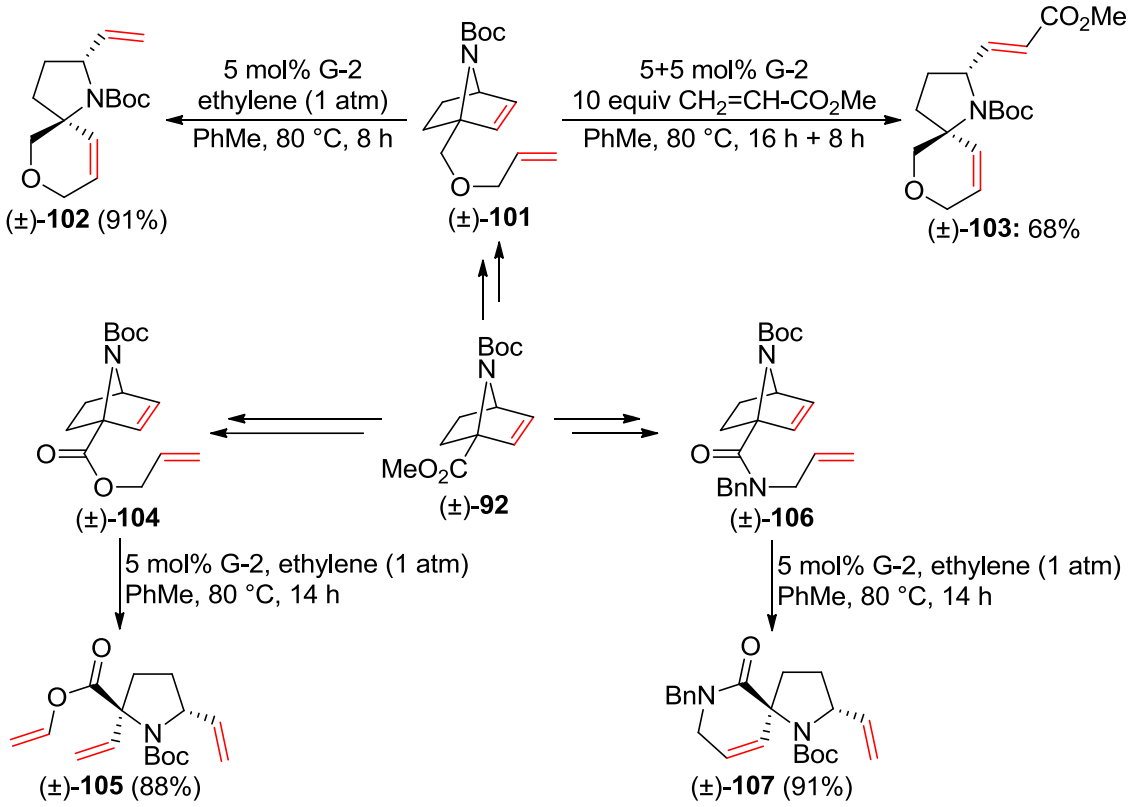
89 was achieved with G-2 catalyst. In contrast, transformation of *N*,*N*'-dipropargylated sulfonamide (±)-**90** (prepared from commercially available (±)-*trans*-5-norbornene-2,3-dicarbonyl chloride) provided mainly the desired ROM/RCEYM/RCEYM product (±)-**91** (accompanied with two ROM/RCEYM byproducts which were inseparable), and the transformation was the most efficient with G-1 catalyst. *Scheme 15* depicts 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 16. Synthesis of pyrrolizidine, indolizidine, and pyrrolo[1,2-*a*]azepine derivatives

Peregrina and coworkers have elaborated an elegant process via 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, which are currently of particular interest.[38,94]

First, 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 with the vinyl group adjacent to the methyl ester group remaining 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]

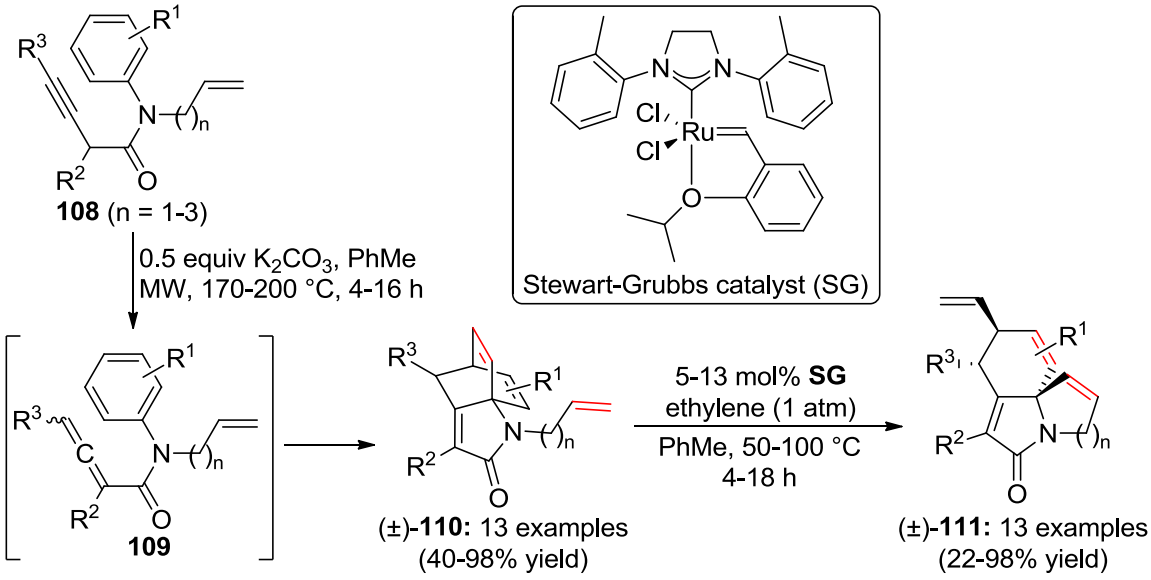


Scheme 17. Synthesis of azaspiro[4.5]decane derivatives

The same group extended the above approach for the synthesis of azaspiro[4.5]decane systems. First, metathesis precursors (±)-**101**, (±)-**104**, and (±)-**106** were synthesized from compound (±)-**92** and then they were subjected to olefin metathesis. Metathesis of allyl ester (±)-**104** was problematic and provided only ROM product (±)-**105**. Under the same conditions, ROM/RCM of (±)-**101** and (±)-**106** was facile and very efficient. In the case of (±)-**106**, the presence of the *N*-benzyl group on the amide function 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 (although it required repeated catalyst addition), providing product (±)-**103** in 68% yield (*Scheme 17*).[95]

Vanderwal and coworkers reported a novel approach towards highly complex polycyclic lactams. First, strong heating of readily available propargylanilides **108** in the presence of a base resulted in isomerization to allenecarboxanilides **109** followed by intramolecular Diels–Alder reaction. Then, the formed Himbert cycloadducts (±)-**110** were subjected to ring-rearrangement metathesis. The most efficient catalyst was Stewart–Grubbs catalyst (SG), which provided tricyclic lactams (±)-**111** in good to excellent yields in most cases

(*Scheme 18*). The reaction tolerated various substitution patterns on the propargyl group and the arene ring, as well as numerous 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, which often possess interesting neurobiological activities.[96]



Scheme 18. Synthesis of complex polycyclic lactams via RRM

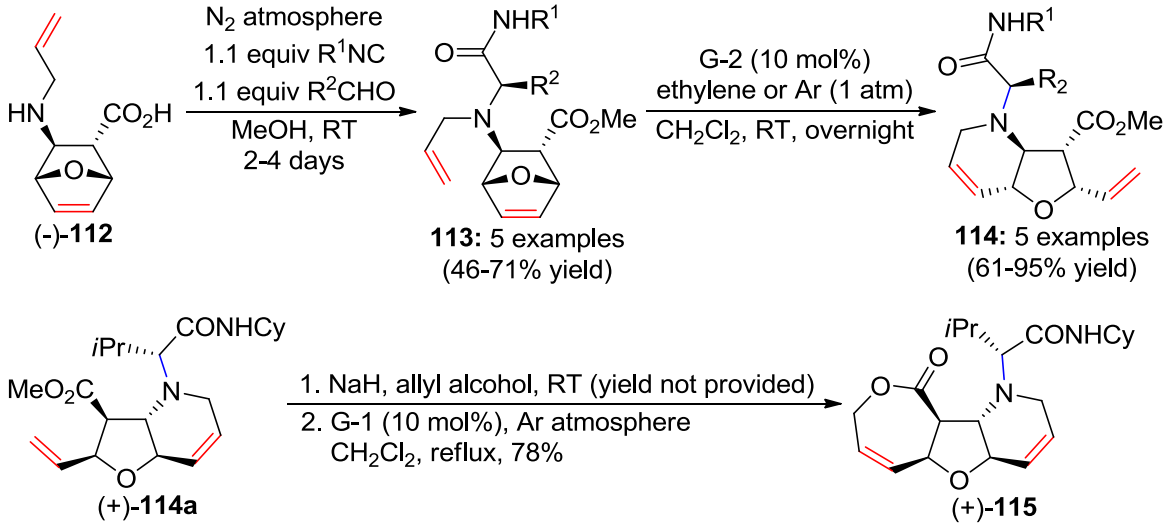
Further examples for azaheterocycle synthesis via ring-rearrangement metathesis can be found in Ref. 58 and 59.

2.3.3. Synthesis of azaheterocyclic β-amino acids by application of the metathesis protocol

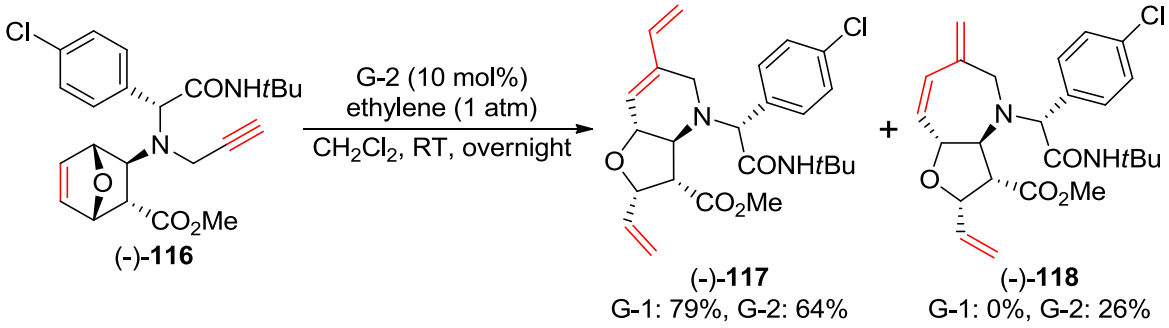
Azaheterocyclic β-amino acids are a special subtype of functionalized azaheterocycles. As previously mentioned (see *Section 2.1*, especially *Figure 2*), azaheterocyclic β-amino acids show various biological activities, and they are present in a number of natural products, synthetic bioactive compounds (including foldamers), and drugs.[10-19] As a consequence, pharmaceutical and medicinal chemistry put significant effort to prepare and study azaheterocyclic β-amino acid derivatives.[10-19,26,36,97-99] This section will discuss examples, where ring-rearrangement metathesis was utilized to obtain such compounds.

Guanti and coworkers described a synthesis route, which utilized Ugi reaction of 7-oxanorbornene β-amino acids. First, enantiopure amino acid (–)-**112** was reacted with an aldehyde and an isocyanide in methanol. This Ugi reaction was completely diastereoselective, yielding compounds **113**. Treatment of these with 10 mol% G-2 catalyst in CH_2Cl_2 under ethylene or argon atmosphere delivered the desired azaheterocyclic β-amino esters **114** in

61-95% yields (Scheme 19). Notably, G-1 catalyst performed poorly in this reaction. Product (+)-**114a** was transformed further via transesterification and subsequent RCM to tricyclic compound (+)-**115**. This RCM reaction only succeeded with the less reactive G-1 catalyst under reflux in CH_2Cl_2 (*Scheme 19*).[97]

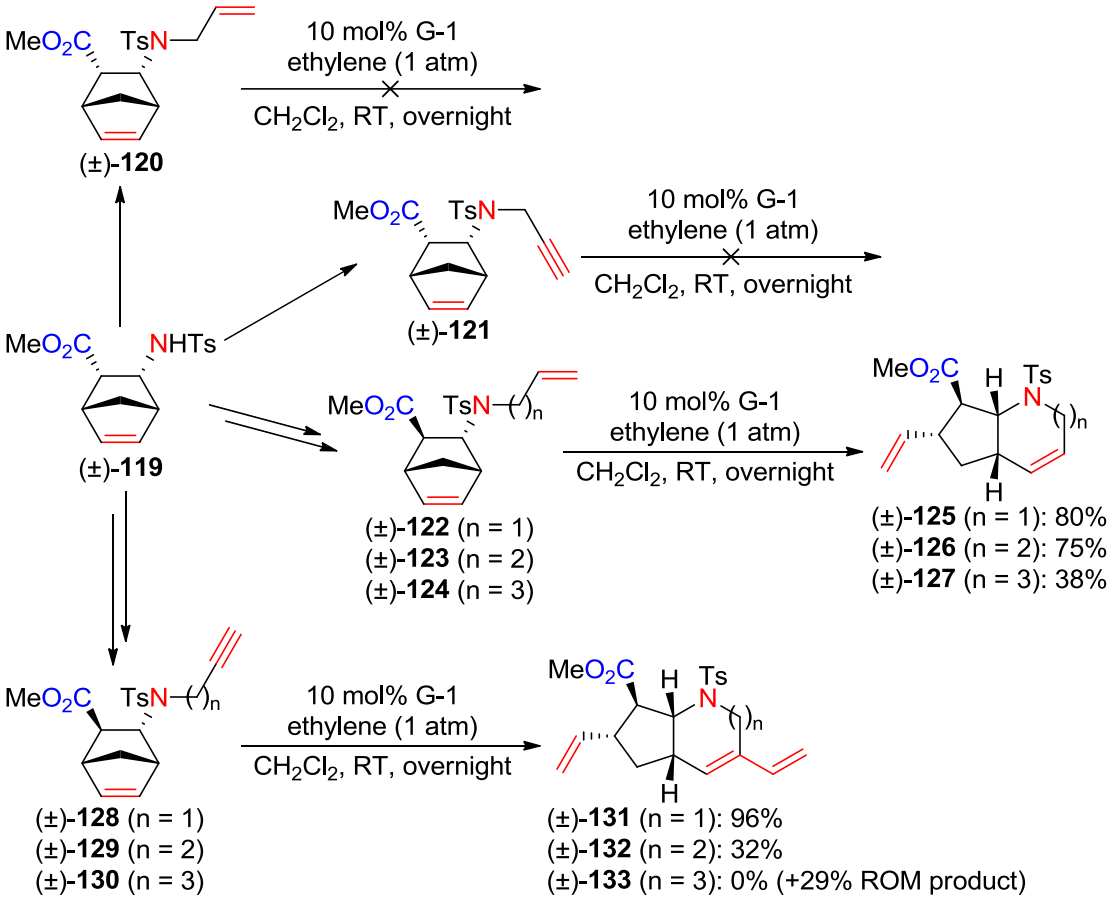


Scheme 19. Synthesis of fused bi- and tricyclic β-amino acid derivatives via Ugi/RRM sequence



Scheme 20. Synthesis of fused bicyclic β-amino acid derivatives via enyne metathesis

Ugi reactions of the *N*-propargylated analogue of (–)-**112** were not completely diastereoselective. However, major product (–)-**116** was successfully isolated in pure form and subjected to olefin metathesis. This reaction needed an ethylene atmosphere. In the presence of G-1 catalysts, 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]

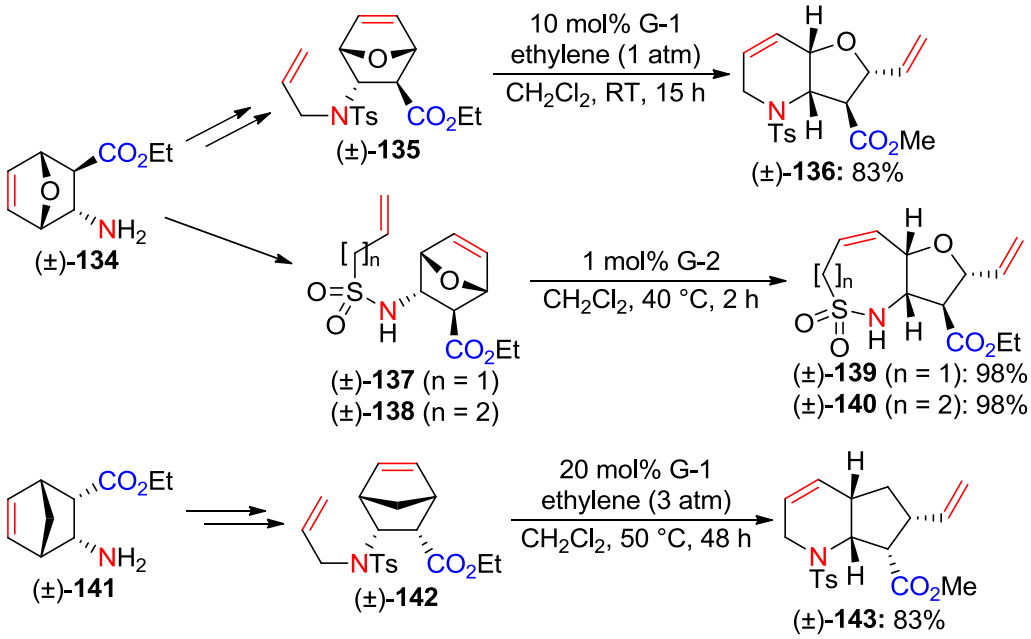


Scheme 21. Synthesis of fused azaheterocyclic β-amino esters from norbornene derivatives

Nadany and Mckendrick reported the synthesis of azaheterocyclic β-amino acid derivatives via a series of tandem metathesis reactions utilizing norbornene β-amino esters. First, compound (±)-**119** was transformed into various substrates via *N*-alkylation and, when necessary, NaOMe-promoted epimerization. Interestingly, transformation of *diendo* compounds [(±)-**120** and (±)-**121**] failed, but the reaction of *endo-exo* compounds [ROM/RCM of (±)-**122**–**124** and ROM/RCEYM of (±)-**128**–**130**] was mostly successful (*Scheme 21*). The trend in the RRM yields is easy to notice. 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 in 29% yield.[98]

McKendrick, Blechert, and coworkers reported RRM reactions with a number of oxanorbornene β-amino esters (*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 the 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]

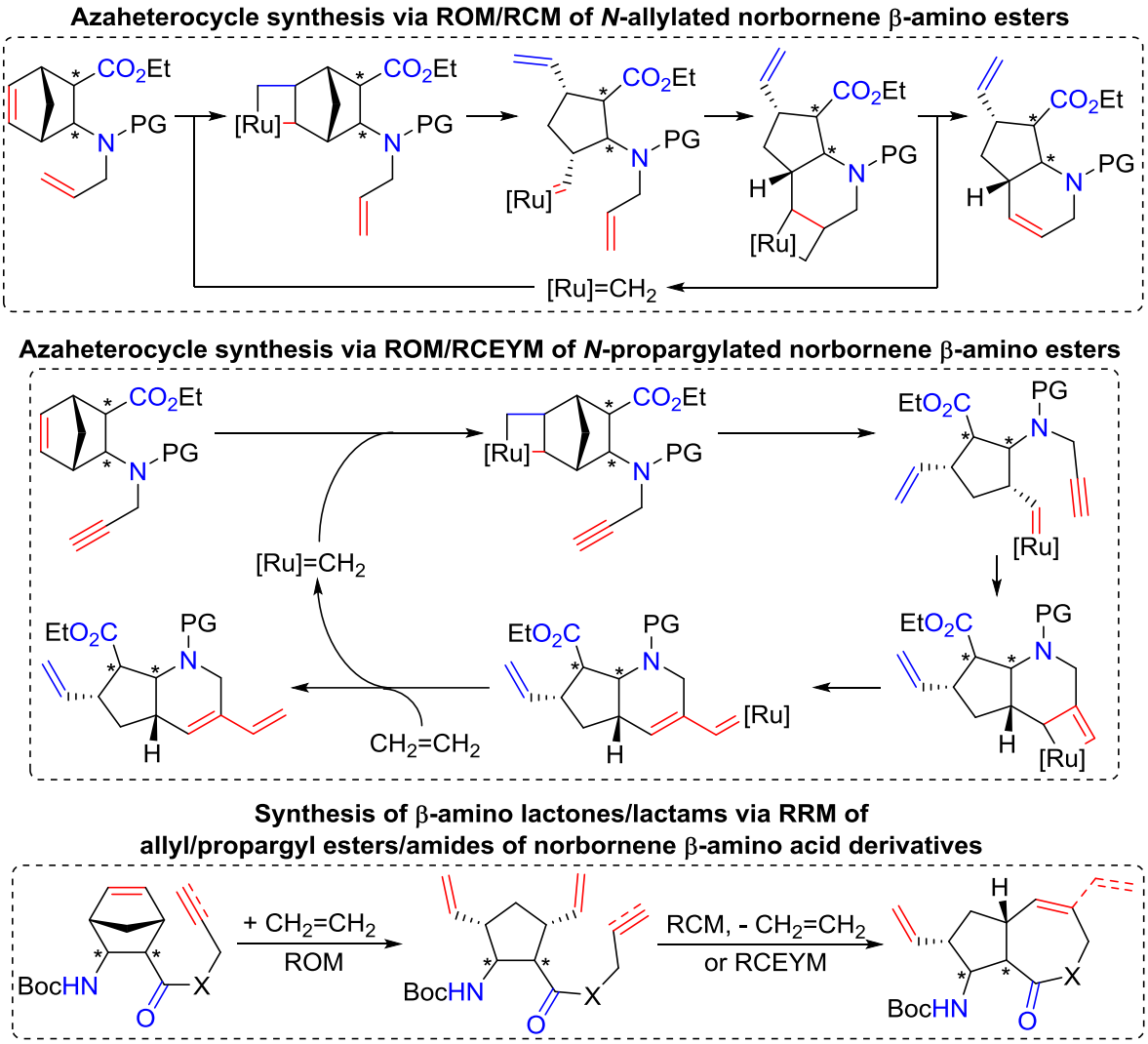


Scheme 22. Synthesis of bicyclic β-amino esters from oxanorbornene derivatives

3. RESULTS AND DISCUSSION

3.1. Stereocontrolled syntheses via ring-rearrangement metathesis of norbornene β-amino acid derivatives

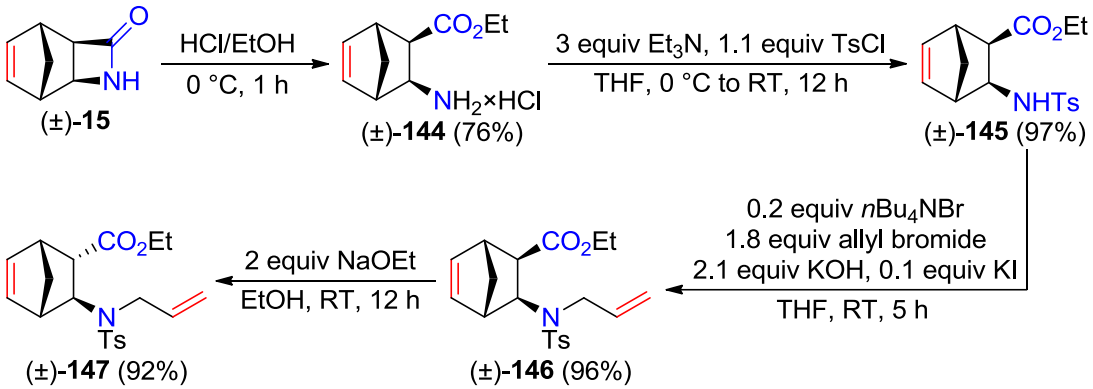
Our initial goal in this work was the stereocontrolled synthesis of novel functionalized azaheterocycles with multiple chiral centers through ring-rearrangement metathesis (ROM/RCM or ROM/RCEYM) of *N*-allylated/*N*-propargylated norbornene β-amino esters. The latter compounds could be prepared from readily available norbornene β-amino acid derivatives. Then, allyl/propargyl esters of norbornene β-amino acids and the analogous amides were also subjected to RRM in order to access β-amino lactones and β-amino lactams (*Scheme 23*).



Scheme 23. Planned RRM reactions of norbornene derivatives (X = O, NH; PG = Boc, Ts)

3.1.1. Synthesis of azaheterocyclic β-amino acid derivatives through ROM/RCM of *N*-allylated norbornene β-amino esters

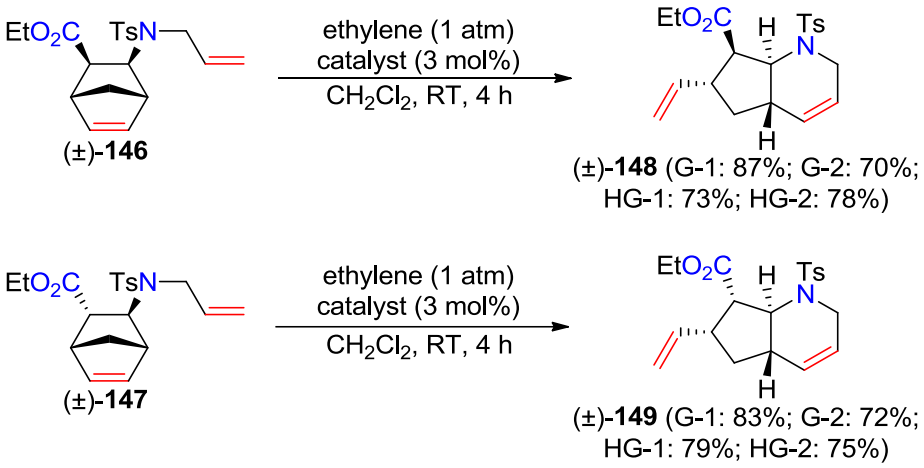
Our stereocontrolled synthetic strategy towards novel azaheterocyclic β-amino acid derivatives utilized ring-opening metathesis/ring-closing metathesis (ROM/RCM) of *N*-allylated norbornene β-amino esters. The synthesis of the first substrates, *diexo* compound (±)-**146** and *exo-endo* compound (±)-**147**, is depicted on *Scheme 24*. First, racemic lactam (±)-**15**, prepared by cycloaddition of chlorosulfonyl isocyanate and norbornadiene followed by partial hydrolysis,[21] was subjected to heteroring opening with HCl/EtOH.[35] Then, *N*-Ts protection of the amino group gave β-amino ester (±)-**145**, whose *N*-allylation afforded the desired *diexo* β-amino ester (±)-**146** in excellent yield (96%).[101] The used *N*-allylation protocol was based on a literature protocol, which was originally reported for β-lactams.[102] Epimerization of compound (±)-**146** with NaOEt gave *exo-endo* compound (±)-**147**, in which the ester and the amide group are in *trans* arrangement.[101]



Scheme 24. Synthesis of *N*-allylated norbornene β-amino esters (±)-**146** and (±)-**147**

Although ROM/RCM reactions do not consume ethylene, the presence of ethylene is still beneficial in a number of cases. It can transform the ruthenium alkylidene metathesis catalysts to more reactive ruthenium methylidenes, and it can suppress substrate oligomerization.[103] Therefore, we performed ROM/RCM reactions under ethylene atmosphere. Both *N*-allylated β-amino esters were treated with four commercially available Ru-based catalysts (see *Figure 5*) under various experimental conditions to investigate the effects of substrate stereochemistry, catalyst type, quantity of catalyst, temperature, and reaction time on the metathesis reaction. The highest conversions and isolated yields 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 25*). 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 products.[101]



Scheme 25. Synthesis of azaheterocyclic compounds (±)-**148** and (±)-**149** via ROM/RCM

All compounds depicted on *Scheme 25* have a rigid structure. Namely, the starting β-amino esters (±)-**146** and (±)-**147** have a norbornene skeleton, while our azaheterocyclic products (±)-**148** and (±)-**149** have a *trans*-annelated ring system. This was a great help in confirming their stereochemistry by NMR (*Figure 6*). First of all, fixed W arrangement of the single bonds can result in noticeable ^{4}J coupling. In the case of β-amino ester (±)-**146**, COSY shows that one H-7 hydrogen has ^{4}J couplings both with H-2 and H-3. In contrast, according to COSY of compound (±)-**147**, this H-7 hydrogen has ^{4}J coupling with H-3, but no coupling with H-2. This clearly suggests that norbornene β-amino ester (±)-**146** is a *diexo* compound, while norbornene β-amino ester (±)-**147** has a protected *exo* amino group and an *endo* ester group. Stereochemistry of norbornene β-amino ester (±)-**146** is further corroborated by the lack of H-2↔H-7 and H-3↔H-7 NOESY interactions, and the value of the ^{3}J coupling constant between H-2 and H-3 (according to the Karplus equation, ^{3}J couplings are large between synperiplanar and antiperiplanar hydrogens, but much smaller between anticlinal ones). In the case of norbornene β-amino ester (±)-**147**, we could not determine the ^{3}J coupling constant between H-2 and H-3, but one of its H-7 hydrogens (the one which do **not** have ^{4}J coupling with H-3) shows a NOESY interaction with the H-2 hydrogen (but not with H-3). This supports its *exo-endo* stereochemistry.[101]

Stereochemical assignment of azaheterocyclic products (±)-**148** and (±)-**149** was mostly based on the stereocontrolled nature of the metathesis reaction and stereochemistry of the starting β-amino esters (±)-**146** and (±)-**147**.[101] But this is somewhat supported by NOESY interactions. In azaheterocycle (±)-**148**, there is a NOESY interaction between the H-7 and H-7a hydrogens. In azaheterocyclic (±)-**149**, such an interaction cannot be observed. Furthermore, the lack of NOESY interaction between the H-4a and H-7a hydrogens in both heterocycles is in agreement with the *trans*-annelation (*Figure 6*).

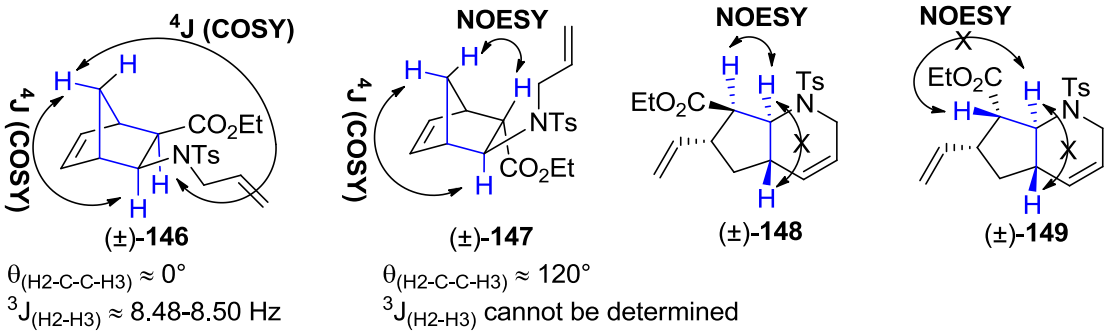
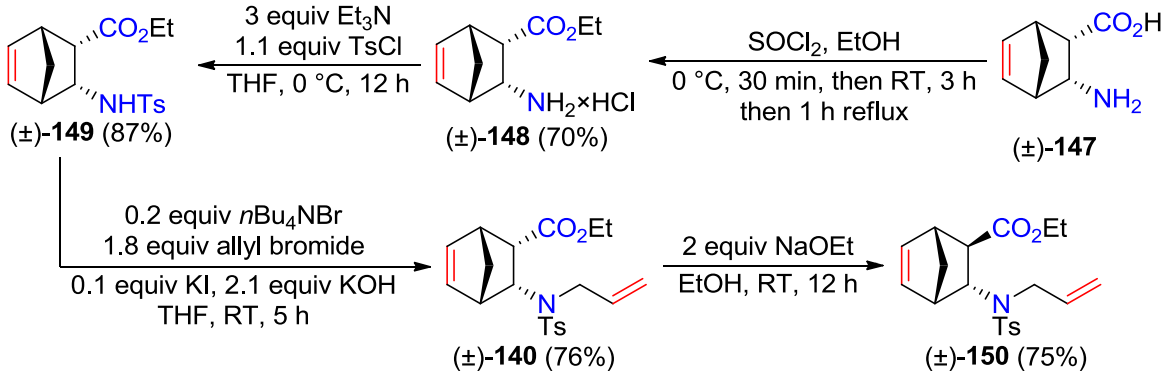


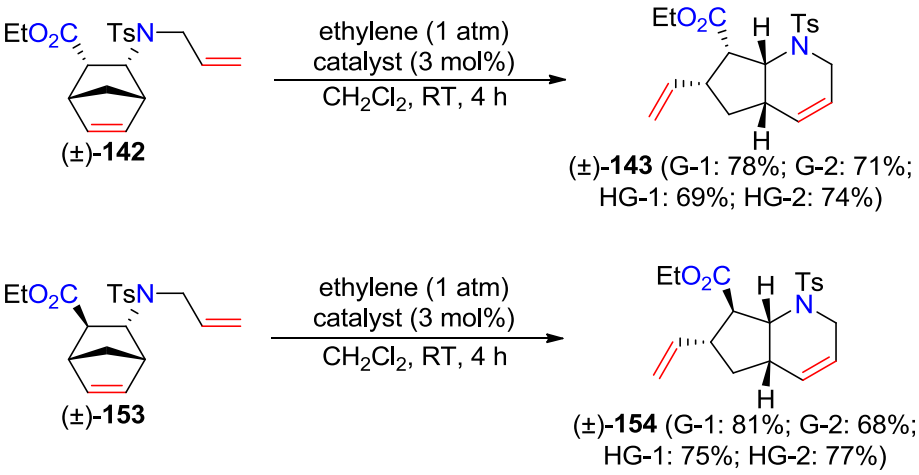
Figure 6. Confirmation of the stereochemistry of the compounds depicted on *Scheme 25*

Encouraged by the above results, we extended this stereocontrolled synthetic strategy to access stereoisomers of products (±)-**148** and (±)-**149**. First, amino acid (±)-**150** (obtained from cheap carbic anhydride)[104] was subjected to esterification[105] followed by *N*-tosyl protection of the amino group. Then, the resulting *diendo* norbornene β-amino ester (±)-**152** was subjected to *N*-allylation under the previously established conditions[101] to obtain RRM substrate (±)-**142**. Then, base-promoted epimerization of *diendo* amino ester (±)-**142** yielded RRM substrate (±)-**153**, where the ester group is in *exo* position, but the protected amino group is still in *endo* position (*Scheme 26*).[100]



Scheme 26. Synthesis of *N*-allylated norbornene β-amino esters (±)-**142** and (±)-**153**

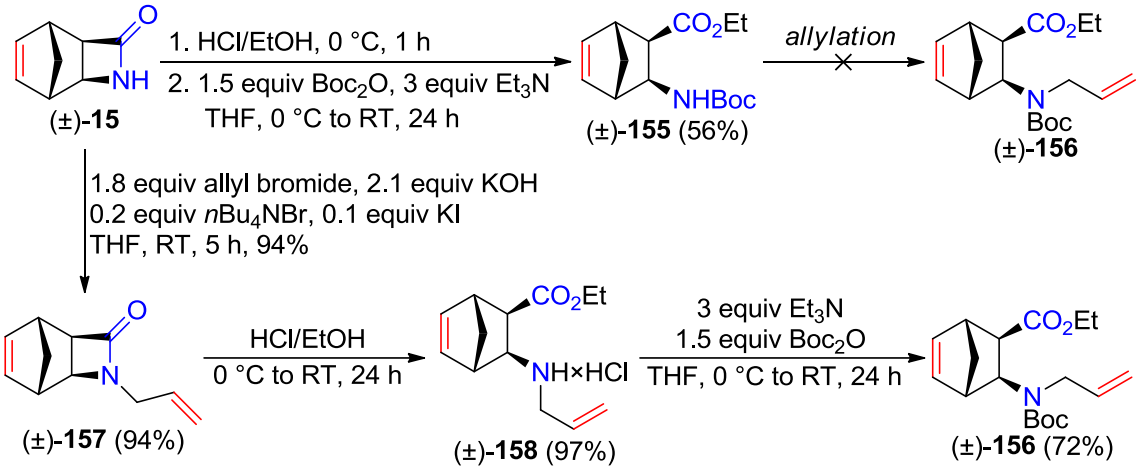
With unsaturated amino ester derivatives (±)-**142** and (±)-**153** in our hands, we performed the ring-rearrangement metathesis reaction. The previously established conditions (3 mol% catalyst, anhydrous CH_2Cl_2 solvent, room temperature)[101] were the most effective. The highest yields of the desired azaheterocyclic β-amino acid derivatives [78% yield for product (±)-**143**, 81% yield for product (±)-**154**] were obtained with G-1 catalyst (*Scheme 27*).[100] According to literature, the yield of (±)-**143** can be increased to 88% under more extreme conditions (20 mol% G-1 catalyst, 3 atm ethylene pressure, CH_2Cl_2, 50 °C, 48 h; see *Scheme 22*).[99] The synthesis of the methyl ester analogue of (±)-**154** was reported previously by Nadany and Mckendrick (*Scheme 21*).[98]



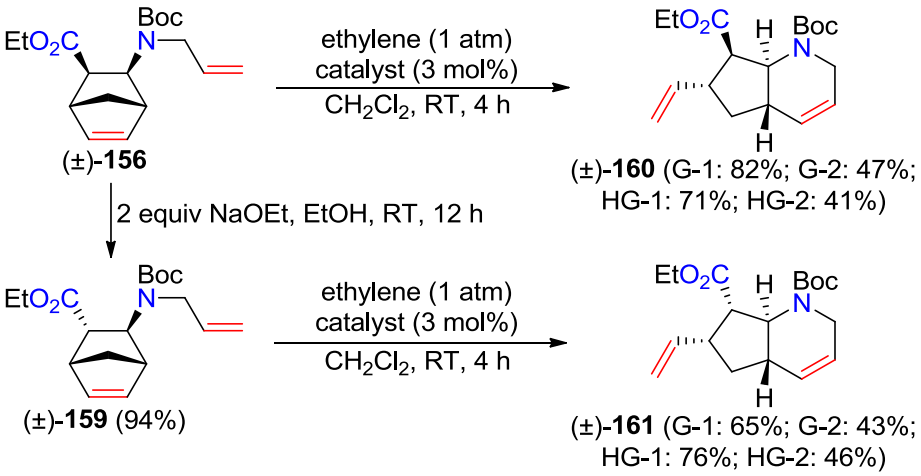
Scheme 27. Synthesis of azaheterocyclic compounds (±)-**143** and (±)-**154** via ROM/RCM

Unfortunately, *N*-detosylation can be a difficult process, which limits usefulness of *N*-tosyl protected compounds in organic synthesis or peptide chemistry. In the light of this fact, we also intended to prepare the analogous Boc-protected compounds, because removal of *N*-Boc groups is usually easy. First, *N*-allylation of the readily available *N*-Boc protected β-amino ester (±)-**155**[34] was attempted. Unfortunately, none of the methods probed [allyl bromide+K_2CO_3 (with or without *n*Bu_4NBr) in DMF at RT; allyl bromide+Cs_2CO_3 in DMF at RT, allyl bromide and Cs_2CO_3 under reflux in MeCN; allyl bromide and Et_3N (with or without 4-dimethylaminopyridine) in THF at RT; allyl bromide and DBU, MeCN, reflux; allyl bromide and *t*BuOK in THF at RT] provided the desired product (±)-**156**. Fortunately, we were able to find an alternative pathway, which utilizes the same steps (lactam ethanolysis, *N*-Boc protection, and *N*-alkylation), however, in a different order. *N*-Allylation of β-lactam (±)-**15** according to a literature protocol[102] provided compound (±)-**157** rapidly and in excellent yield.

Ethanolysis of *N*-allyl lactam (±)-**157** was efficient, although isolation of *N*-allylated amino ester hydrochloride (±)-**158** was more troublesome than expected. Most amino ester hydrochlorides, such as (±)-**144**, have low solubility in EtOH and can be isolated in pure form with simple filtration. In contrast, *N*-allylated amino ester hydrochloride (±)-**158** had very good solubility in HCl/EtOH; therefore the solvent had to be evaporated to obtain the product. Finally, *N*-Boc protection of (±)-**158** proceeded without any problem, and afforded the desired compound (±)-**156** (*Scheme 28*).[101]



Scheme 28. Synthesis pathways towards amino ester (±)-**156**



Scheme 29. Synthesis of azaheterocyclic compounds (±)-**160** and (±)-**161** via ROM/RCM

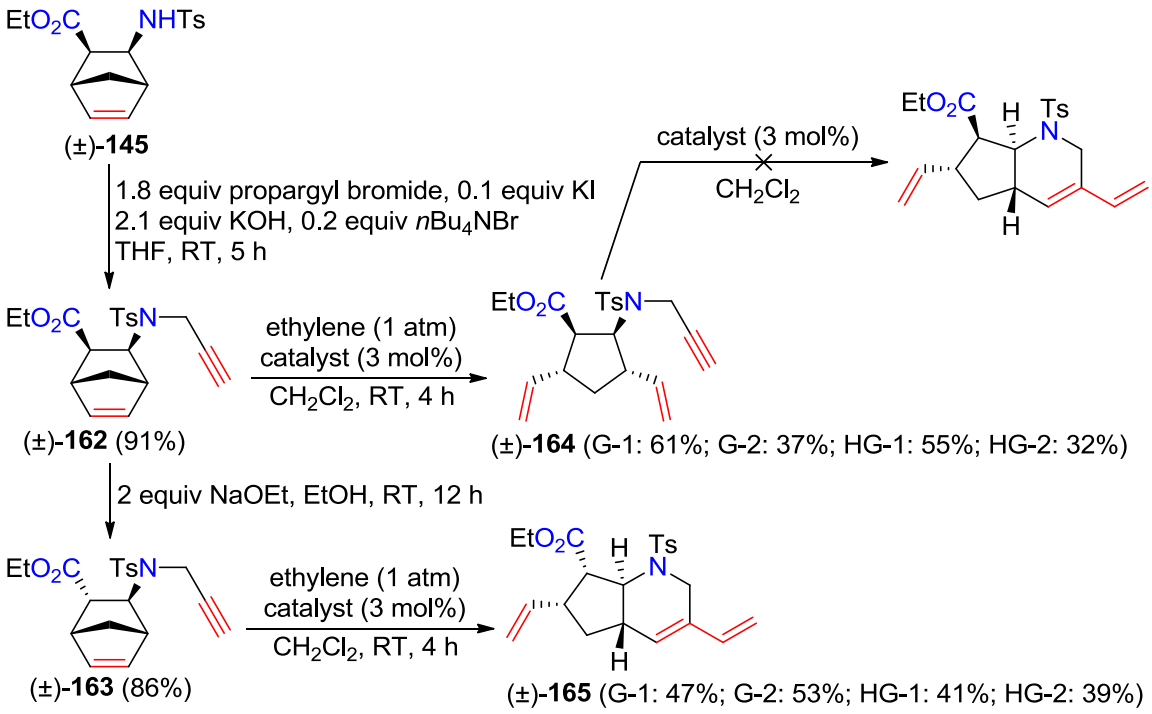
Base-promoted epimerization of *diexo* compound (±)-**156** gave *exo-endo* compound (±)-**159**. Then, both *N*-Boc protected β-amino esters were subjected to olefin metathesis, which provided the expected ROM/RCM products (±)-**160** and (±)-**161** (*Scheme 29*). With first-generation catalysts, the yields were close to the RRM yields of the analogous *N*-tosylated

compounds (see *Scheme 25*), but second-generation catalysts were markedly less efficient with *N*-Boc protected substrates. The best yield of product (±)-**160** was achieved with G-1 catalyst, while HG-1 catalyst was the best in the synthesis of (±)-**161**.[101]

3.1.2. Synthesis of azaheterocyclic β-amino acid derivatives through ROM/RCEYM of *N*-propargylated norbornene β-amino esters

Because the ROM/RCM strategy discussed in Section 3.1.1 was successful, we started to work on the related ROM/RCEYM strategy. It was decided that ROM/RCEYM reactions of *N*-propargylated norbornene β-amino esters will be performed under the conditions optimized for ROM/RCM of *N*-allylated norbornene β-amino esters. That method operated under an ethylene atmosphere (importantly, ROM/RCEYM reactions consume stoichiometric amounts of ethylene), and it was our hope that the structural similarity of *N*-propargylated and *N*-allylated substrates results in similar condition preferences.

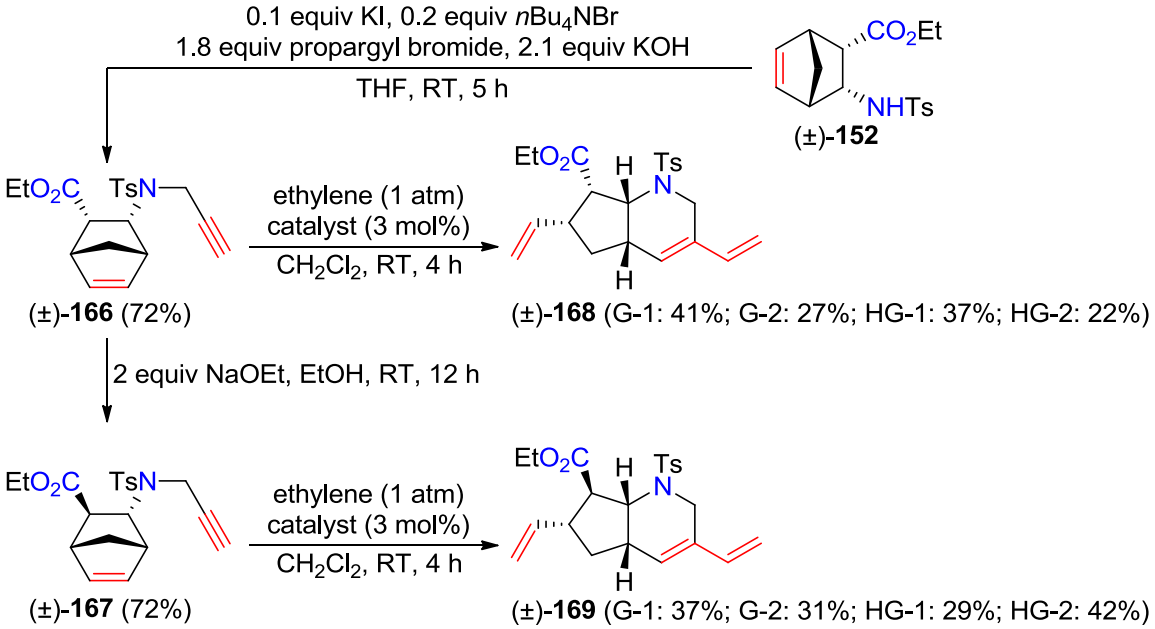
Luckily, it turned out that quick and efficient *N*-propargylation can be achieved analogously to *N*-allylation by replacing allyl bromide with propargyl bromide in the synthesis. As a result, the synthesis of *N*-propargylated metathesis substrates proceeded without any new difficulty.



Scheme 30. Synthesis of cispentacin derivative (±)-**164** and azaheterocycle (±)-**165**

First, *N*-propargylated β-amino esters (±)-**162** and (±)-**163** were synthesized and subjected to olefin metathesis (*Scheme 30*). RRM reactions of *diexo* substrate (±)-**162** were not successful, since the process always stopped after the ring-opening step. Attempts to trigger ring-closing ene–yne metathesis of the formed cispentacin derivative (±)-**164** by treatment with metathesis catalysts in the absence of ethylene also failed. In contrast, olefin metathesis of *exo-endo* compound (±)-**163** provided the desired ROM/RCEYM product (±)-**165**. The process was most efficient with G-2 catalyst.[101]

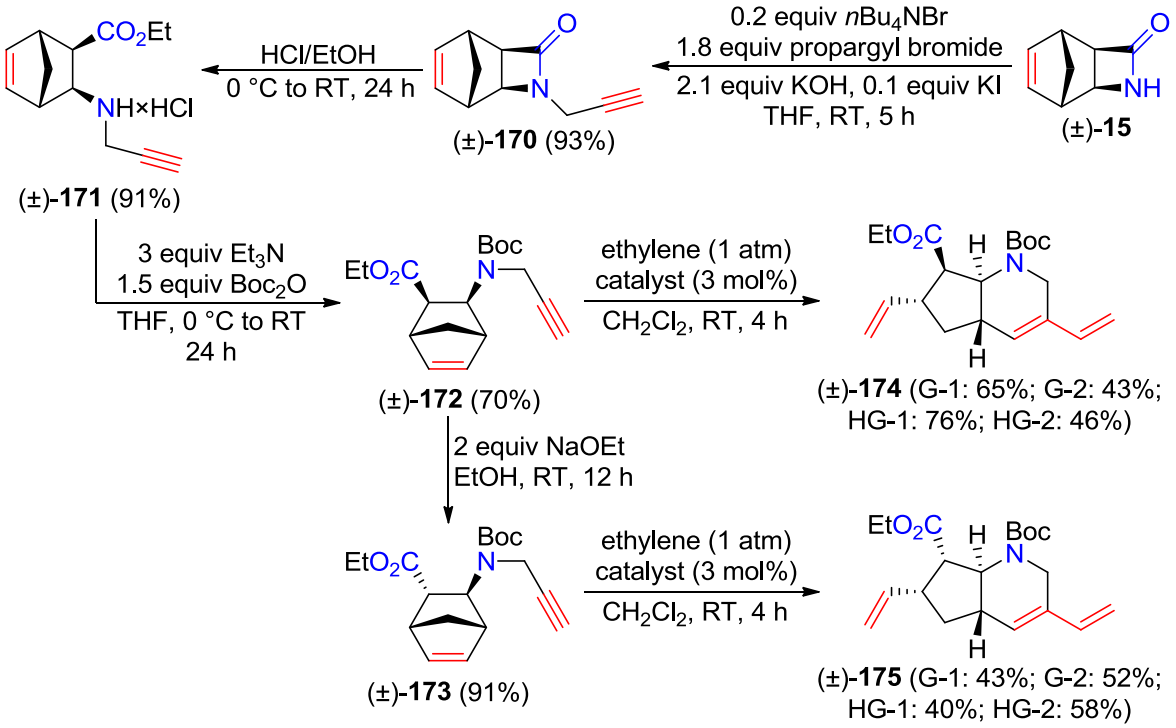
We continued our work by synthesizing additional stereoisomers of azaheterocyclic compound (±)-**165**. *N*-Propargylation of norbornene β-amino ester (±)-**152** provided *diendo* RRM substrate (±)-**166**, whose epimerization with NaOEt resulted in *endo-exo* RRM substrate (±)-**167**. In the presence of metathesis catalysts under ethylene atmosphere (1 atm), both compounds provided the expected unsaturated azaheterocyclic products. G-1 catalyst showed the best performance in the transformation of (±)-**166**, while the transformation of stereoisomeric substrate (±)-**167** was the most efficient with HG-2 catalyst (*Scheme 31*).[100] Synthesis of the methyl ester analogue of (±)-**169** was reported previously by Nadany and Mckendrick (*Scheme 21*).[98]



Scheme 31. Synthesis of azaheterocyclic compounds (±)-**168** and (±)-**169** via ROM/RCEYM

We also intended to prepare azaheterocyclic scaffolds whose deprotection is easier, facilitating their application in syntheses and peptide chemistry. Based on our previous results

(*Scheme 28*), *N*-alkylation of the easily accessible *N*-Boc protected analogues of (±)-**145** and (±)-**152** was not attempted. Instead, *diexo* compound (±)-**172** was synthesized from lactam (±)-**15** via 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 gave the desired azaheterocyclic products (*Scheme 32*). This is noteworthy, because RRM of (±)-**162** (the *N*-Ts protected analogue of (±)-**172**) failed. First generation catalysts (especially HG-1) performed better in the transformation of *diexo* compound (±)-**172**, while second generation catalysts (especially HG-2) were more efficient in the transformation of *exo-endo* compound (±)-**173**.[101]



Scheme 32. Synthesis of azaheterocyclic compounds (±)-**174** and (±)-**175** via ROM/RCEYM

Stereochemistry of unsaturated β-amino esters (±)-**172** and (±)-**173** was confirmed by NMR measurements. First of all, both compounds have a rigid structure, which results in fixed W arrangement and detectable ^4J couplings between one of the bridge methylene protons (H-7) and the *endo* hydrogens. Because COSY shows that H-7 of compound (±)-**172** has cross peaks with both H-2 and H-3, while H-7 of compound (±)-**173** has a cross peak with just H-3, we can conclude that (±)-**172** is a *diexo* compound, but (±)-**173** has an *exo* protected amino group and an *endo* ester group (*Figure 7*). This is corroborated by the values of the ^3J coupling constants

between H-2 and H-3 [compound (±)-**172:** H-2 and H-3 are synperiplanar and ^{3}J = 8.40 Hz, compound (±)-**173:** H-2 and H-3 are anticlinal and ^{3}J = 3.80–3.93 Hz] and the NOESY interaction between H-7 and H-2 (the *exo* hydrogen) in (±)-**173**.[101]

Stereochemical assignment of azaheterocyclic products (±)-**174** and (±)-**175** was mostly based on the stereocontrolled nature of the metathesis reaction and the stereochemistry of their RRM precursors.[101] A NOESY cross peak between the H-7 and H-7a hydrogens of (±)-**174** indicates that they are *syn* relative to each other (the analogous hydrogens of (±)-**175** do not have a NOESY interaction). The *trans*-annelation of these azaheterocycles is also supported by the lack of NOESY interaction between the H-4a and H-7a hydrogens. However, H-2 of both heterocycles has a NOESY cross peak with the terminal olefin CH_2 group, as expected from a mostly *s-trans* conjugated diene (*Figure 7*).

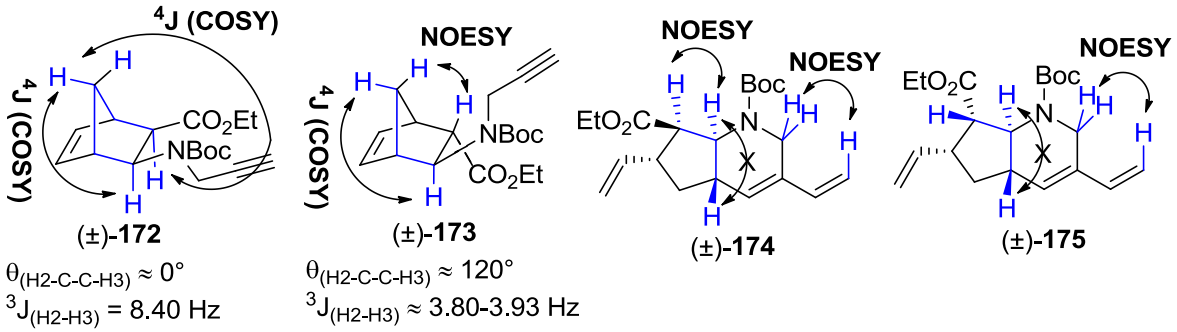
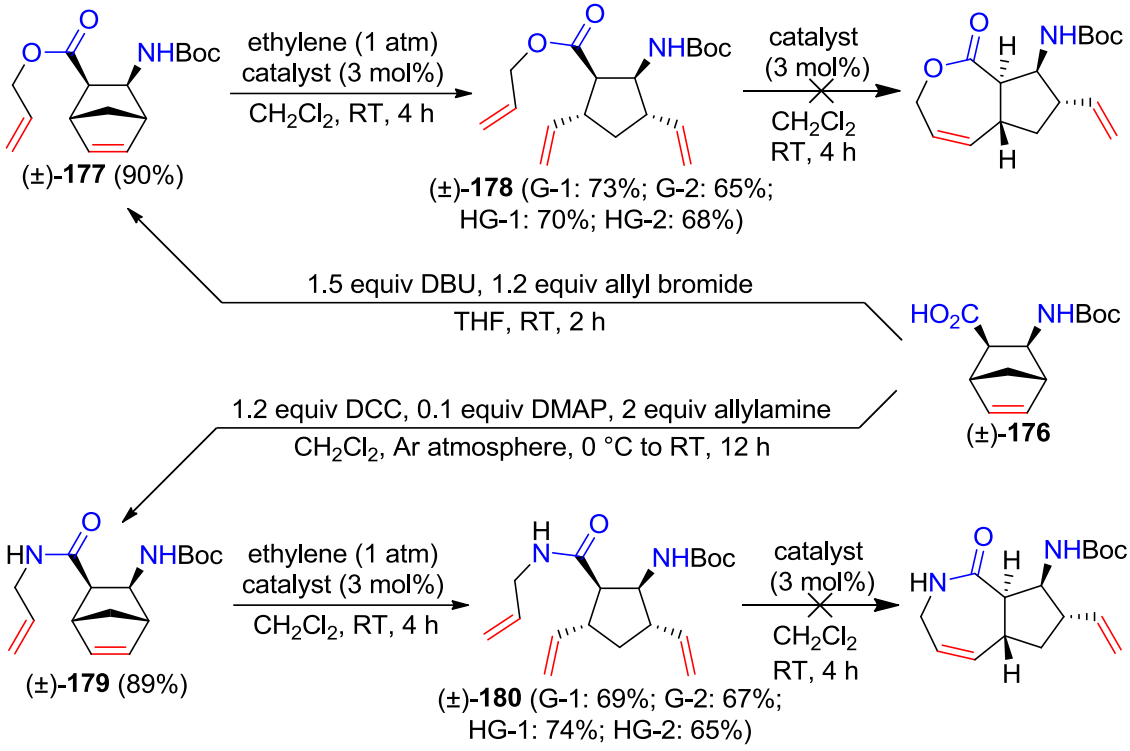


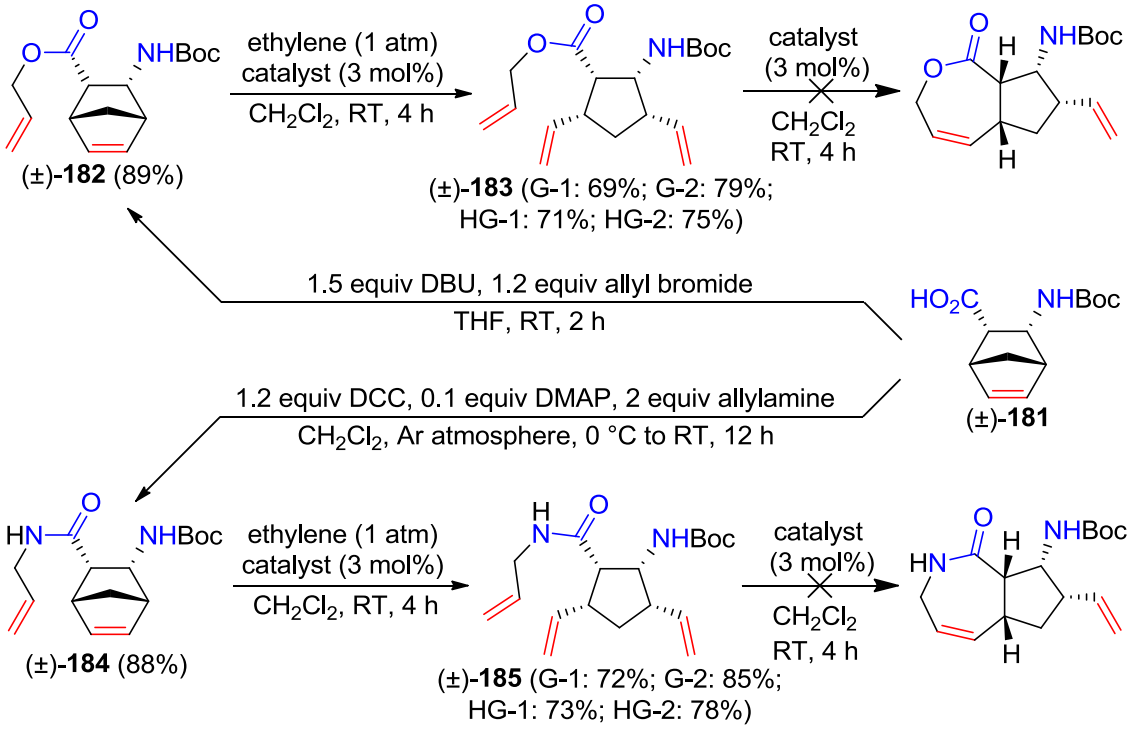
Figure 7. Confirmation of the stereochemistry of compounds (±)-**172** to (±)-**175**

3.1.3. Transformation of other norbornene β-amino acid derivatives

Since our new RRM strategy demonstrated its usefulness in the synthesis of azaheterocyclic β-amino esters, we investigated its applicability for the preparation of β-amino lactones and β-amino lactams. First, *N*-protected *diexo* amino acid (±)-**176**[106] was subjected to *O*-allylation. The resulting ester (±)-**177** was then treated with various metathesis catalysts under ethylene atmosphere. Unfortunately, only ring opening metathesis happened, delivering novel cispentacin (±)-**178** in good yields with all four catalysts. Attempts to force RCM by treating isolated (±)-**178** with metathesis catalysts failed. After this, *N*-allylated amide (±)-**179** was prepared via DCC-mediated coupling of amino acid (±)-**176** with allylamine. Unfortunately, when amide (±)-**179** was subjected to metathesis, it behaved in the same way as its ester analogue (±)-**177** (*Scheme 33*).[107]



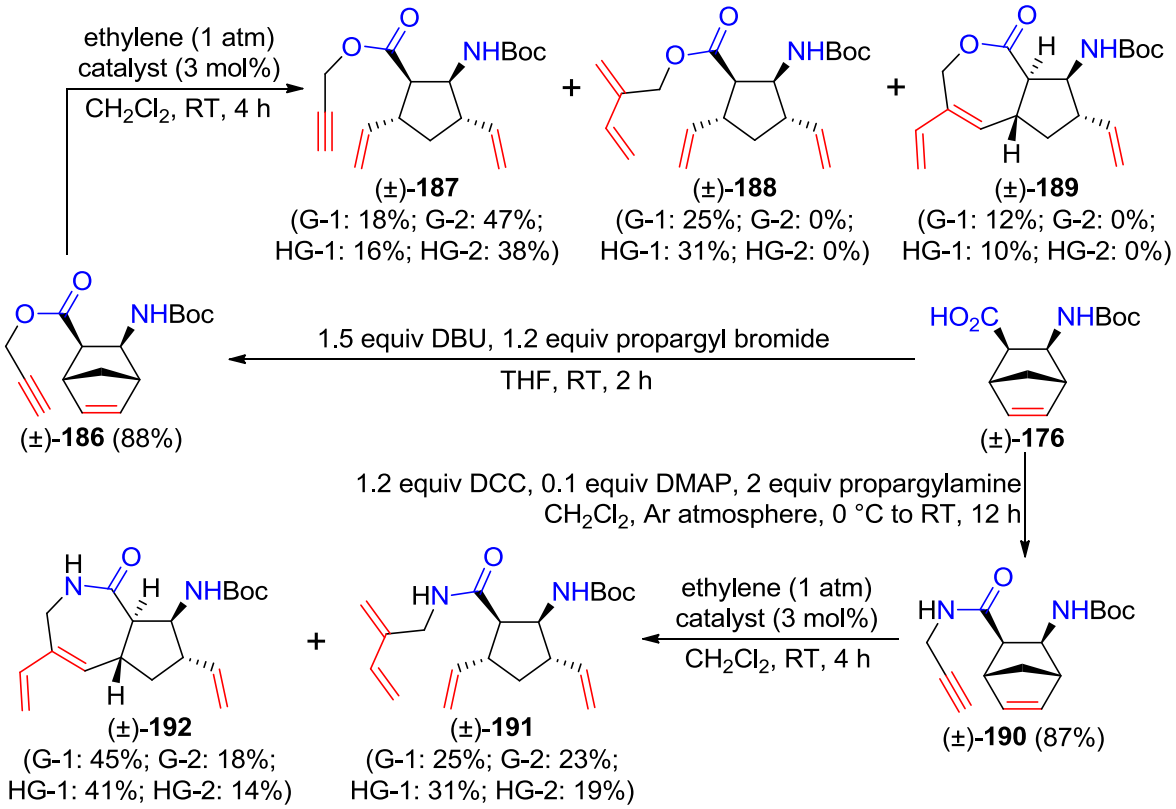
Scheme 33. Synthesis of cispentacins (±)-**178** and (±)-**180**; and attempts for their RCM



Scheme 34. Synthesis of cispentacins (±)-**183** and (±)-**185**; and attempts for their RCM

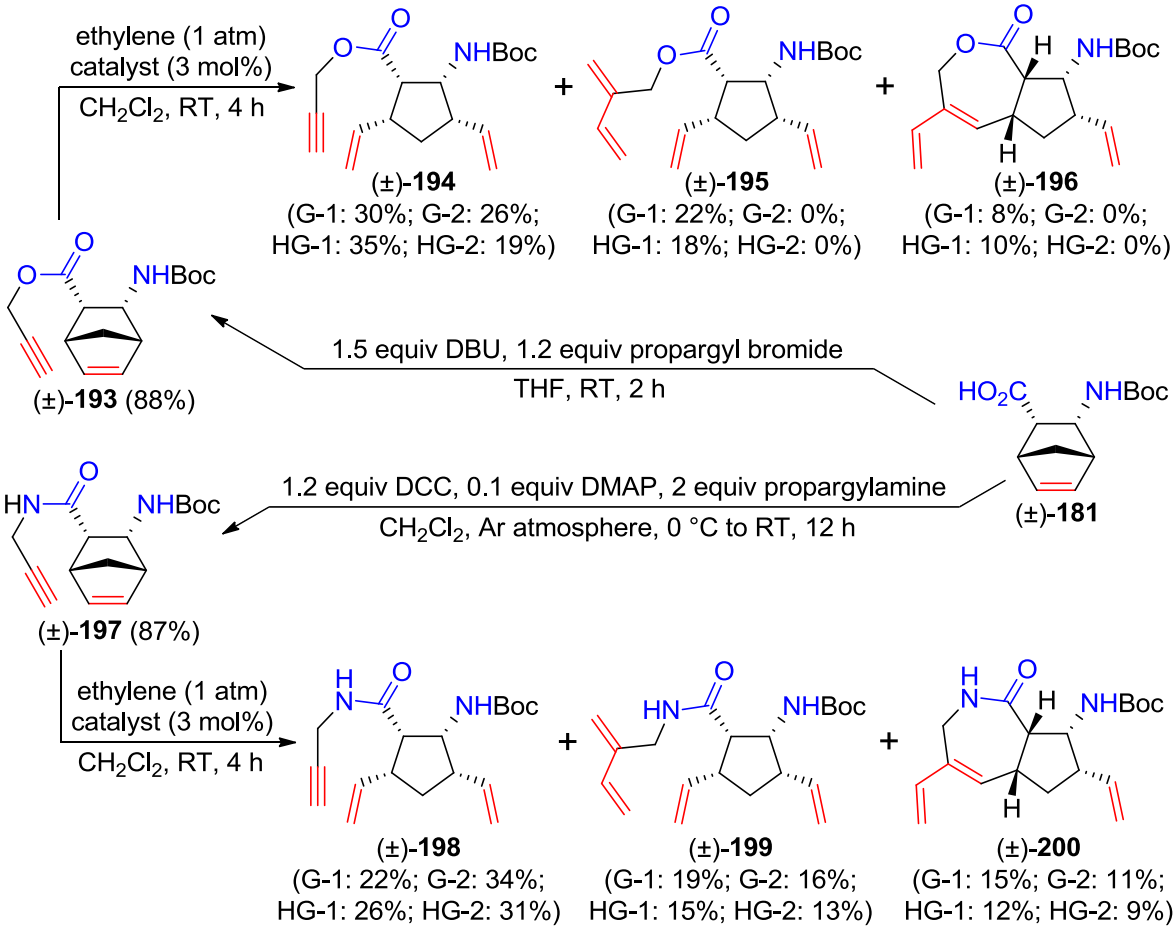
Our next substrates were ester (±)-**182** and amide (±)-**184**. These were synthesized from *N*-Boc protected *diendo* amino acid (±)-**181**[106] in a similar fashion to the one shown on

Scheme 33. Unfortunately, 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 34*).[107]



Scheme 35. Ring-rearrangement metathesis of β-amino acid derivatives (±)-**186** and (±)-**190**

The ROM/RCM synthetic pathway was unsuccessful, but we still had some hope in the ROM/RCEYM pathway. First, *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** (the main product), and ROM/RCEYM product (±)-**189** (formed in the lowest yield). Subsequently, *diexo* 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 desired ROM/RCEYM product (±)-**192** (this was the main product with first generation catalysts) and ROM/CEYM compound (±)-**191** (this was the main product with second generation catalysts). These results are summarized on *Scheme 35*.[107]

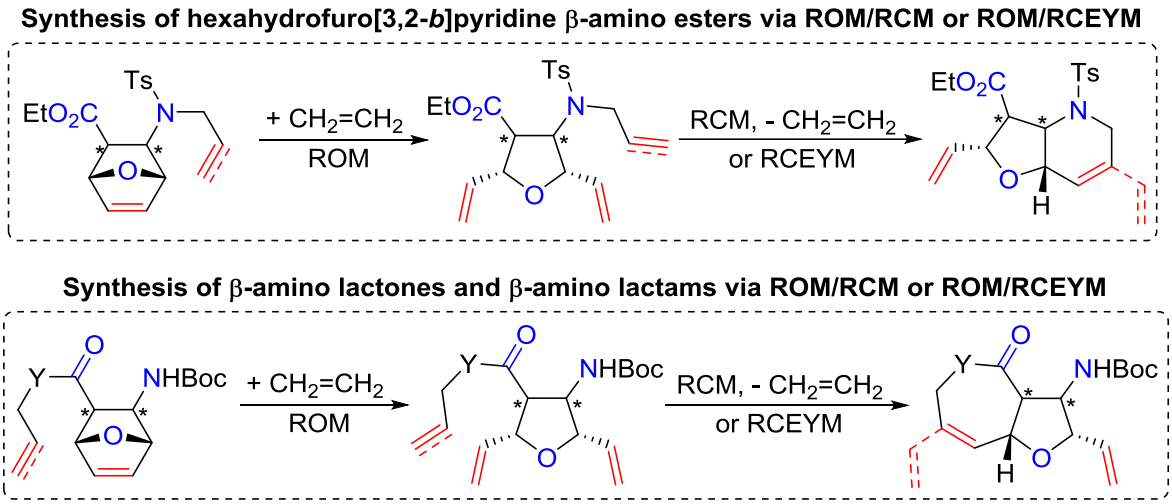


Scheme 36. Ring-rearrangement metathesis of β-amino acid derivatives (±)-**190** and (±)-**194**

Finding that the ROM/RCEYM strategy is viable, we continued our work with two *diendo* compounds: β-amino ester (±)-**193** and β-amino amide (±)-**197**. These were synthesized from *N*-protected *diendo* β-amino acid (±)-**181** using the same methods depicted on *Scheme 35* (*O*-propargylation and DCC-mediated amidation with propargylamine). When it was subjected to olefin metathesis, ester (±)-**193** behaved in the same way as its *diexo* analogue (±)-**186**: first generation catalysts provided 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 provided ROM compound (±)-**194** as a single 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**). These results are summarized on *Scheme 36*.[107]

3.2. Stereocontrolled syntheses via ring-rearrangement metathesis of oxanorbornene β-amino acid derivatives

In view of the relevance of oxygen-containing cyclic β-amino acids (as discussed by examples in *Section 2.1*), our RRM-based stereocontrolled synthetic strategies were extended to oxanorbornene β-amino acid derivatives. Our goals were the synthesis of tetrahydrofuran-annelated azaheterocyclic β-amino esters, tetrahydrofuran-annelated β-amino lactones, and tetrahydrofuran-annelated β-amino lactams (*Scheme 37*).

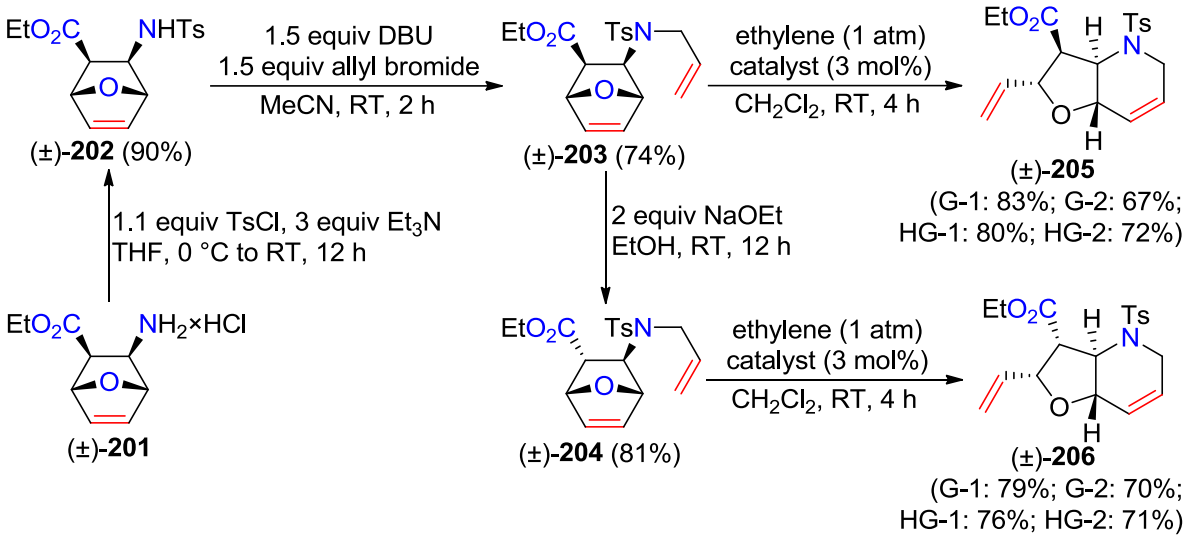


Scheme 37. Synthesis of tetrahydrofuran-containing β-amino acid derivatives from oxanorbornene derivatives through ring-rearrangement metathesis. Y = O, NH

3.2.1. Synthesis of azaheterocyclic β-amino acid derivatives through ROM/RCM of *N*-allylated oxanorbornene β-amino esters

Our first starting compound was *diexo* β-amino ester hydrochloride (±)-**201** (it is available via esterification of the corresponding oxanorbornene β-amino acid with EtOH and $SOCl_2$).[108] Tosylation of its amino group yielded β-amino ester (±)-**202**. Using the conditions depicted on *Scheme 24*, *N*-allylation of this β-amino ester was unsuccessful (presumably, the oxanorbornene skeleton was sensitive to KOH), but a new synthetic pathway using DBU as a base was rapid and successful. The resulting oxanorbornene compound (±)-**203** was subjected to base-promoted epimerization to obtain *exo-endo* compound (±)-**204**. Both *diexo* ester (±)-**203** and *exo-endo* ester (±)-**204** were subjected to RRM. In this way, we could investigate the effects of substrate stereochemistry. After several preliminary experiments, the highest conversions and isolated yields of tetrahydrofuran-fused azaheterocycles (±)-**205** and (±)-**206** were obtained

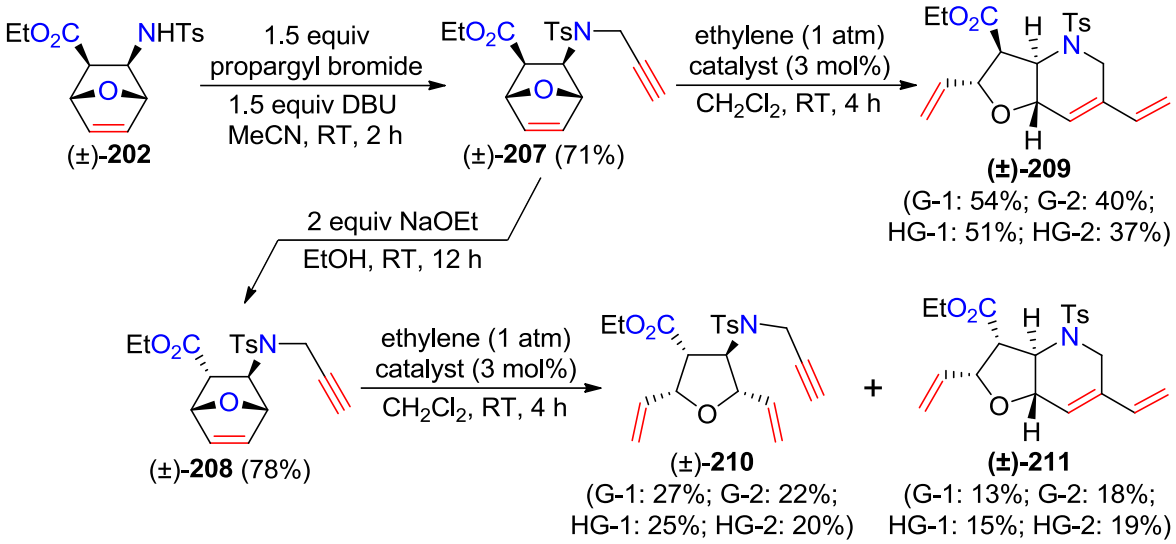
using the same conditions as the analogous cyclopentane-fused azaheterocycles (±)-**148** and (±)-**149** (CH_2Cl_2 solvent, 3 mol% catalyst, ethylene atmosphere, room temperature, 4 h). In both cases, the process was efficient with all catalysts (G-1 catalyst was the best, closely followed by HG-1 catalyst). These results are summarized on *Scheme 38*.[100] RRM of *endo-exo* ester (±)-**135** [a stereoisomer of (±)-**203** and (±)-**204**] was reported previously.[94]



Scheme 38. Synthesis and ROM/RCM of oxanorbornene compounds (±)-**203** and (±)-**204**

3.2.2. Synthesis of azaheterocyclic β-amino acid derivatives through ROM/RCEYM of *N*-propargylated oxanorbornene β-amino esters

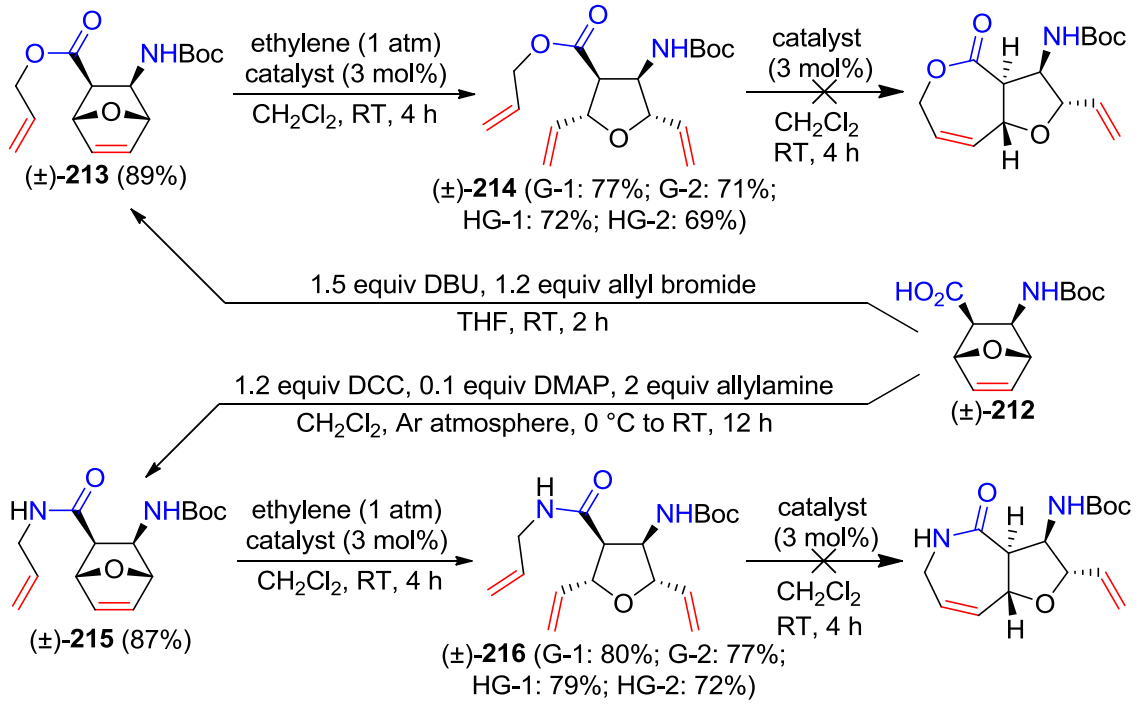
After the success of the ROM/RCM protocol, we also tried the ROM/RCEYM pathway. *N*-Propargylated diastereomeric β-amino esters (±)-**207** and (±)-**208** were synthesized utilizing a process analogous to that established as shown on *Scheme 38*, with the only difference in the alkylating agent used. RRM of compound (±)-**207** afforded the expected azaheterocycle (±)-**209**, with G-1 catalyst giving the highest yield. Strangely, transformation of compound (±)-**208** provided a product mixture. With first generation catalysts, ROM product (±)-**210** was clearly the major product, while second generation catalysts provided comparable amounts of ROM product (±)-**210** and ROM/RCEYM product (±)-**211**. It seems that during transformation of substrate (±)-**208**, ring-opening metathesis is faster and/or more efficient than the subsequent ring-closing enyne metathesis. These results are summarized on *Scheme 39*.[100]



Scheme 39. Synthesis and ROM/RCEYM of oxanorbornene compounds (±)-**207** and (±)-**208**

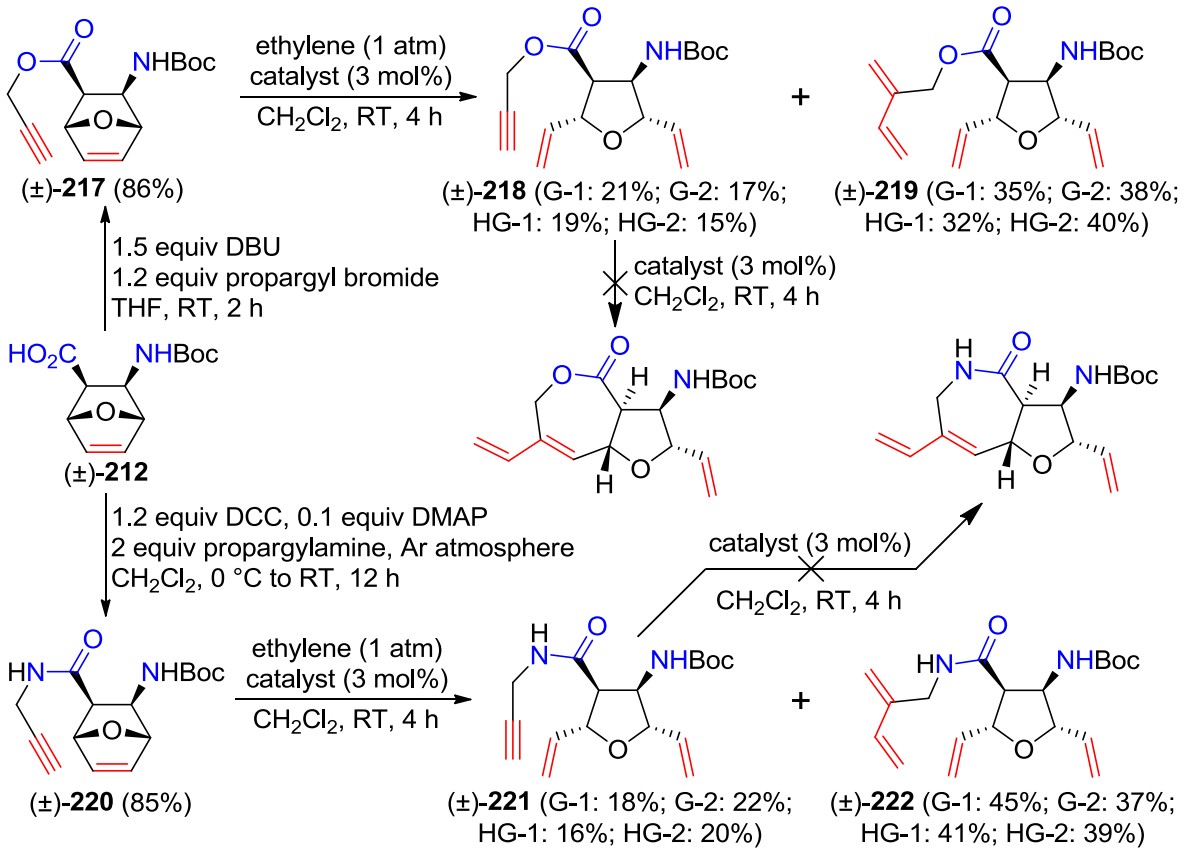
3.2.3. Transformation of other oxanorbornene β-amino acid derivatives

Since our method demonstrated its efficiency in the synthesis of β-amino esters with a hexahydrofuro[3,2-*b*]pyridine scaffold, we investigated its applicability for the access of tetrahydrofuran-fused β-amino lactones and tetrahydrofuran-fused β-amino lactams.



Scheme 40. Synthesis of cispentacins (±)-**214** and (±)-**216**; and attempts for their RCM

Similar to the case of norbornene β-amino acid derivatives (see *Scheme 33, 34*), 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. Unfortunately, when subjected to olefin metathesis using the well-established conditions (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 happened (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 40*).[107]



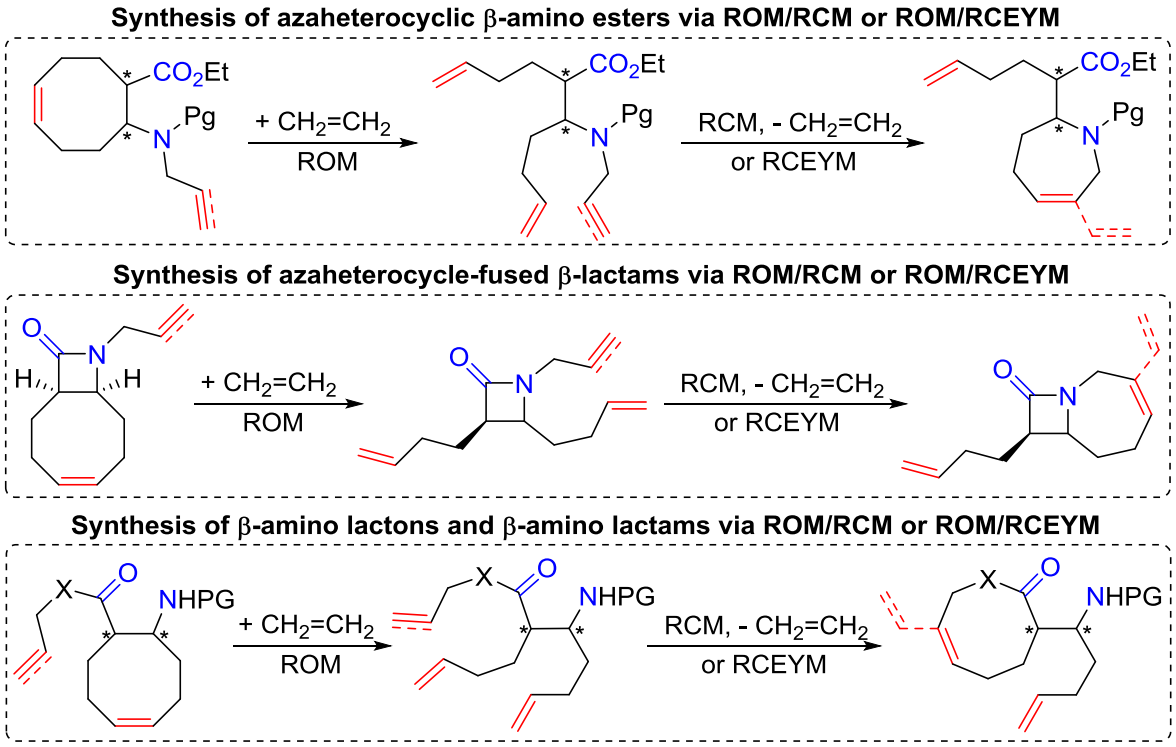
Scheme 41. Unsuccessful RRM of oxanorbornene derivatives (±)-**217** and (±)-**220**

After the attempt to reach 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 take place (*Scheme 41*). This is in strong contrast with the cases of propargyl esters and *N*-propargylated amides of norbornene β-amino acids, where ROM/RCEYM was moderately successful.[107]

3.3. Stereocontrolled syntheses via ring-rearrangement metathesis of cyclooctene β-amino acid derivatives

The aim of the next work was application of the above stereocontrolled synthetic approaches to cyclooctene β-amino acid derivatives and related β-lactams, to obtain various novel functionalized compounds (azaheterocycles, β-amino lactones, and β-amino lactams). Such substances have increasing applications in pharmaceutical and medicinal chemistry. The planned reactions are depicted on *Scheme 42*.

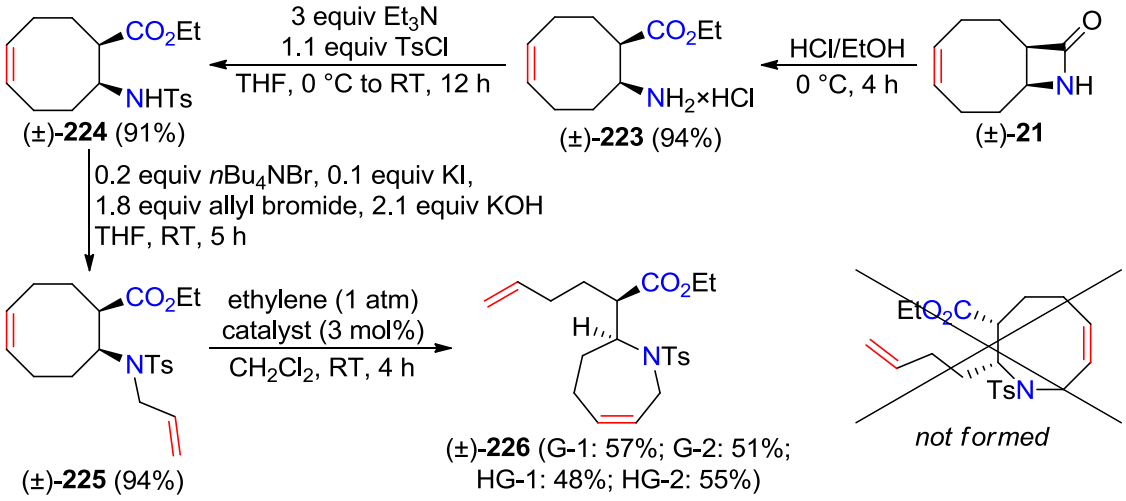


Scheme 42. Planned RRM reactions of cyclooctene derivatives. X = O, NH. PG = Boc, Ts.

3.3.1. Synthesis of azaheterocyclic β-amino acid derivatives through ROM/RCM of *N*-allylated cyclooctene β-amino esters

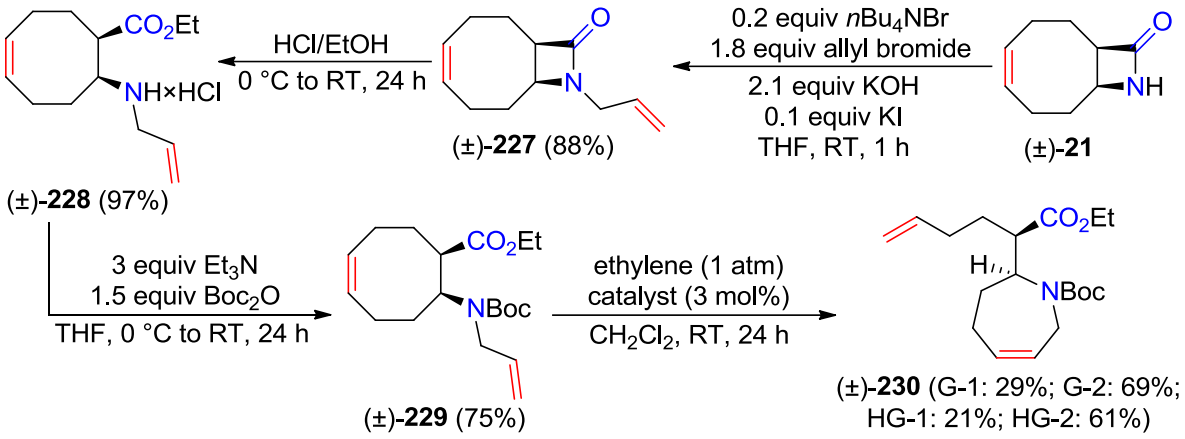
Our first cyclooctene β-amino ester substrate, compound (±)-**225**, was prepared from β-lactam (±)-**21** in three steps (lactam ethanolysis,[20] *N*-tosylation, and *N*-allylation). Compound

(±)-**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 sole product (*Scheme 43*). Note that the other possible product (an eight-membered azaheterocycle) did not form. We assumed, that this is a consequence of the lower ring strain of seven-membered cyclic alkenes compared to eight-membered ones.[91,92] All four catalysts had comparable performance, but the highest yield was achieved with the G-1 catalyst.[110]



Scheme 43. Synthesis of azaheterocyclic compound (±)-**226** via ROM/RCM

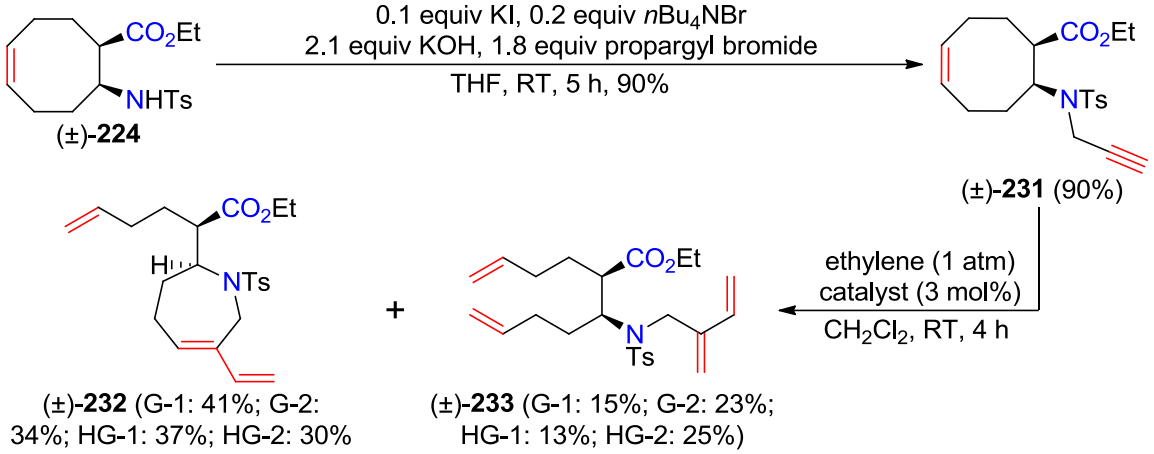
Because *N*-Ts deprotection is often troublesome, our next objective was the synthesis of analogues whose deprotection is easier, which could facilitate their application in foldamer and peptide chemistry. Based on our earlier experiences with norbornene β-amino esters (*Scheme 28, 29*),[101] *N*-Boc protected analogue (±)-**229** was synthesized from lactam (±)-**21** by *N*-allylation, lactam ethanolysis, and *N*-Boc protection. Note that *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 sole product. Notably, second generation catalysts (especially G-2) provided much better yields of (±)-**30** than first generation ones. The above results are summarized on *Scheme 44*.[110]



Scheme 44. Synthesis and ROM/RCM of *N*-Boc protected cyclooctene β-amino ester (±)-**229**

3.3.2. Synthesis of azaheterocyclic β-amino acid derivatives through ROM/RCEYM of *N*-propargylated cyclooctene β-amino esters

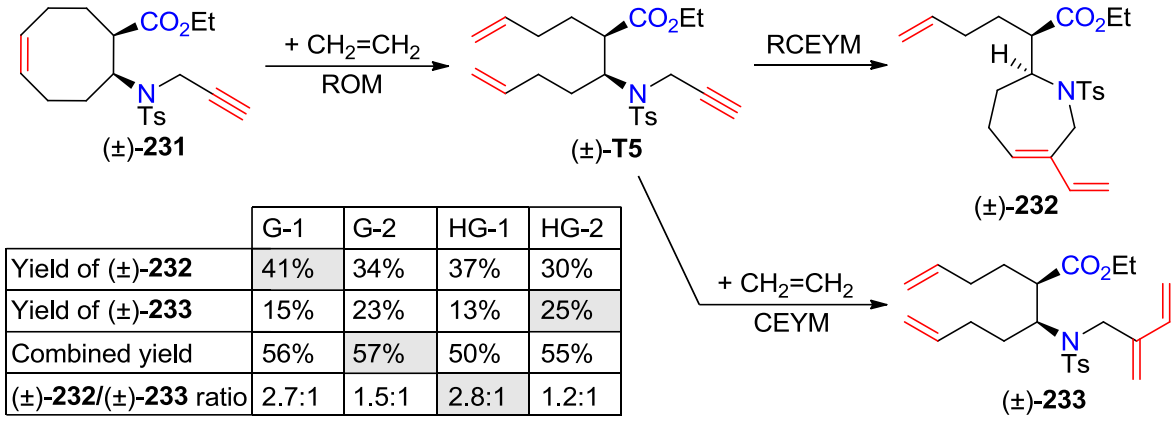
After successfully achieving ROM/RCM reactions of *N*-allylated cyclooctene β-amino esters, we intended to extend the scope of our method to ROM/RCEYM reactions of the closely related *N*-propargylated cyclooctene β-amino esters.



Scheme 45. Synthesis and ROM/RCEYM of cyclooctene β-amino ester (±)-**231**

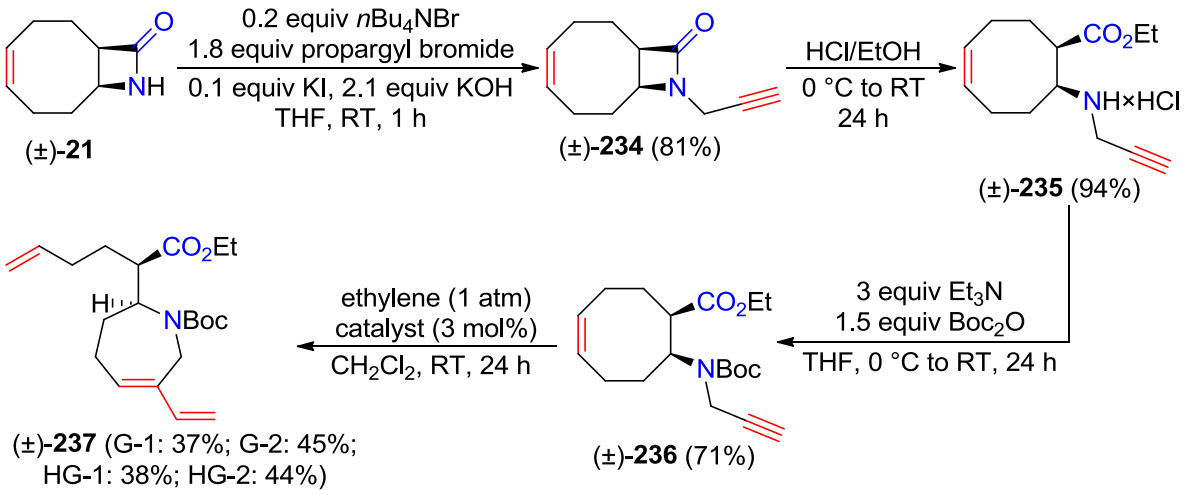
Hence, *N*-tosylated RRM substrate (±)-**231** was synthesized utilizing a process similar to the preparation of (±)-**225** (we only had to replace allyl bromide with propargyl bromide). Olefin metathesis of this amino ester resulted in azaheterocycle (±)-**232** and open-chain unsaturated β-amino ester (±)-**233** (*Scheme 45*).[110] As depicted on *Scheme 46*, 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 main product, but first generation catalysts were more selective towards formation of the azaheterocycle. In the end, the highest yield of (±)-**232** was 41% (with G-1 catalyst), while the highest yield for (±)-**233** was 25% (with HG-2 catalyst).



	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 46. Detailed analysis of transformation of compound (±)-**231**

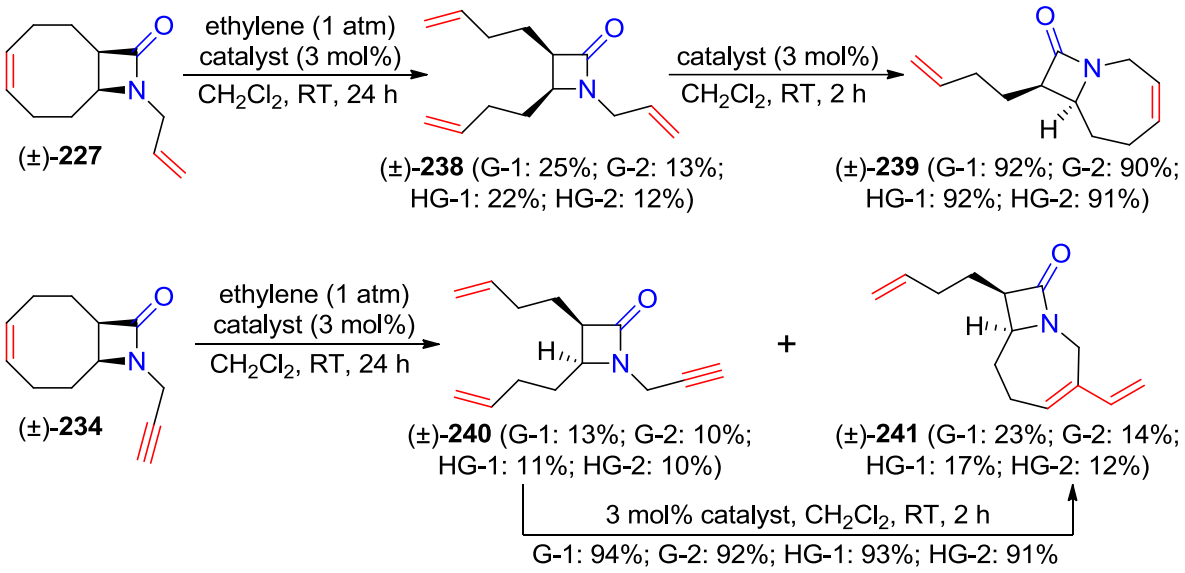


Scheme 47. Synthesis of azaheterocycle (±)-**237** via ROM/ RCEYM

N-Boc protected RRM substrate (±)-**236** was synthesized using a similar pathway as its *N*-allylated analogue (±)-**229**: *N*-propargylation of lactam (±)-**21**, ethanolysis of the formed *N*-propargyl lactam, and then *N*-Boc protection. Subjecting this amino ester to olefin metathesis afforded azaheterocycle (±)-**237** as a sole product (*Scheme 47*). This is in stark contrast to the case of *N*-tosylated analogue (±)-**231**, where a ROM/CEYM byproduct was also formed. The highest yields were achieved with G-2 catalyst (45%) and HG-2 catalyst (44%). It is also worth to note that this substrate needed rather long reaction time.[110]

3.3.3. Transformation of other cyclooctene β-amino acid derivatives

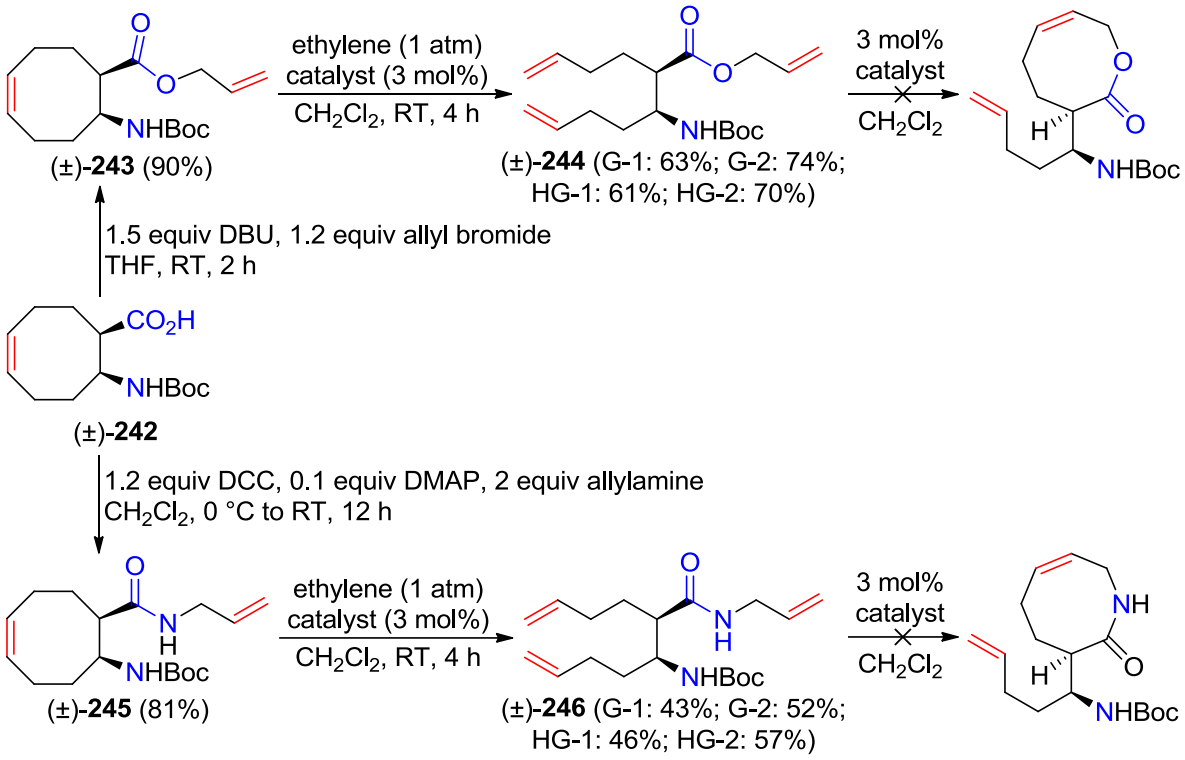
In order to obtain further azaheterocycles, β-lactams (±)-**227** and (±)-**234** were also subjected to olefin metathesis (*Scheme 48*). When *N*-allylated β-lactam (±)-**227** was treated with metathesis catalysts in the presence of ethylene, only ring-opening metathesis happened in low yield [the highest yield of product (±)-**238**, 25%, was achieved by G-1 catalyst]. Fortunately, 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 excellent yields with all four catalysts. When *N*-propargylated β-lactam (±)-**234** was treated with metathesis catalysts in the presence of ethylene, ROM product (±)-**240** and ROM/RCEYM product (±)-**241** were formed in low yields. Again, the best result [23% (±)-**240** and 13% (±)-**241**] was achieved with G-1 catalyst. Notably, treatment of isolated (±)-**240** with metathesis catalysts in the absence of ethylene resulted in rapid and highly efficient RCEYM reactions with all four catalysts.[109]



Scheme 48. Olefin metathesis of *N*-allylated or *N*-propargylated cyclooctene-fused lactams

Next, 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 former is more plausible). Because the possible RRM products have comparable (or higher)

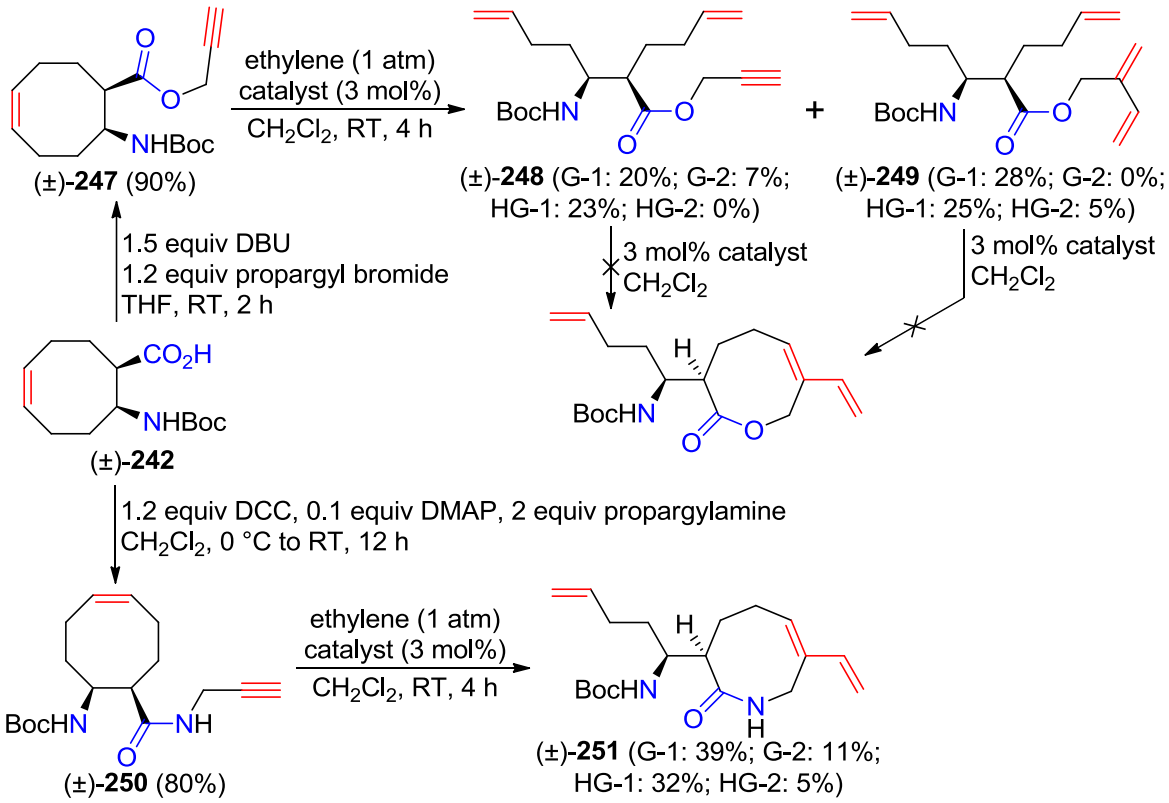
ring strain to the substrates, it is not surprising that one-step ROM/RCM failed, and metathesis of these substrates in the presence of ethylene afforded only ROM products (*Scheme 49*). Second generation catalysts were more efficient than first generation ones, with the best yields of 74% for (±)-**244** (G-2 catalyst) and 57% for (±)-**246** (HG-2 catalyst). Unfortunately, treatment of the isolated ROM products with metathesis catalysts in the absence of ethylene failed to achieve RCM.[110]



Scheme 49. Attempted ROM/RCM of β-amino acid derivatives (±)-**243** and (±)-**245**

Afterwards, we attempted the ROM/RCEYM strategy. Propargyl ester (±)-**247** and *N*-propargylated amide (±)-**250** were prepared using essentially the same pathway depicted on *Scheme 49*, but propargyl compounds were utilized instead of allyl compounds. 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). Instead, 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). In the end, 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** provided

directly the desired ROM/RCEYM product (±)-**251**. Second generation catalysts were greatly inferior to first generation ones, with the highest yield of the RRM product achieved with G-1 catalyst (39%). The above results are summarized on *Scheme 50*.[110]



Scheme 50. Metathesis reactions of β-amino acid derivatives (±)-**247** and (±)-**250**

4. SUMMARY

- A novel stereocontrolled synthetic route was developed 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.
- Based on their functional groups, the utilized RRM substrates can be divided into four groups: *N*-allylated/*N*-propargylated β-amino esters, allyl/propargyl esters of β-amino acids, *N*-allylamides/*N*-propargylamides of β-amino acids, and *N*-allylated/*N*-propargylated cyclooctene β-lactams. Based on the expected RRM process, all four groups can be divided to two subgroups (substrates containing allyl groups were expected to undergo ROM/RCM, while their propargylated analogues were expected to undergo ROM/RCEYM).
- The majority of *N*-allylated/*N*-propargylated β-amino esters were synthesized from readily available β-lactams (±)-**15** and (±)-**21**. *N*-Alkylation, lactam ethanolysis, and *N*-protection (the exact order of these steps depended on the *N*-protecting group) yielded RRM substrates, where the amino group and the ester group were *syn* to each other. Diastereomeric *anti* RRM substrates were prepared by epimerization of *syn* substrates. However, norbornene β-amino esters with an *endo* amino group and oxa-norbornene β-amino esters were obtained from β-amino ester hydrochlorides (±)-**151** and (±)-**201** (*N*-protection and subsequent *N*-alkylation yielded *syn* RRM substrates, which can be epimerized into *anti* RRM substrates).
- Synthesis of other RRM substrates was easier. Allyl esters, propargyl esters, *N*-allylamides, and *N*-propargylamides of β-amino acids were obtained from *N*-Boc protected *syn* amino acids (esters via *O*-alkylation, amides via DCC-mediated coupling with allyl- or propargyl-amine). *N*-Alkylation of cyclooctene-fused β-lactam (±)-**21** yielded (±)-**227** and (±)-**234**.
- The synthesized RRM substrates were subjected to olefin metathesis in the presence of commercially available Ru-based catalysts (G-1, G-2, HG-1, and HG-2). The optimal conditions were 3 mol% catalyst, anhydrous CH_2Cl_2 solvent, ethylene atmosphere, RT.
- In the case of all *N*-allylated β-amino esters (10 compounds), ROM/RCM reactions were successful, and provided the desired RRM compounds as the sole products in good yields.
- In the case of *N*-propargylated β-amino esters (10 compounds), ROM/RCEYM reactions were usually successful, and provided the desired RRM compounds as sole products in moderate to good yields. Exceptions were *diexo* norbornene compound (±)-**162** (only ROM happened), *exo-endo* oxanorbornene compound (±)-**208** (product mixture, up to 19% RRM product), and

cyclooctene compound (±)-**231** (product mixture, up to 41% RRM product).

- In the case of allyl esters (four compounds) and *N*-allylamides (four compounds) of β-amino acids, ROM/RCM reactions failed. Only ROM products were formed, which resisted RCM.
- In the case of β-amino acid propargyl esters (four compounds), ROM/RCEYM of norbornene compounds (±)-**186** and (±)-**193** were moderately successful. G-1 and HG-1 catalysts provided the desired RRM products (in low yields) and two byproducts. In contrast, ROM/RCEYM of oxanorbornene compound (±)-**220** and cyclooctene compound (±)-**247** failed (a mixture of ROM and ROM/CEYM products were formed, which resisted RCEYM).
- In the case of β-amino acid *N*-propargylamides (four compounds), ROM/RCEYM of norbornene compounds was moderately successful. *Diexo* compound (±)-**190** provided RRM product (±)-**192** in moderate yield (together with a ROM/CEYM product), while *diendo* compound (±)-**197** provided RRM product (±)-**200** in low yield (together with a ROM and a ROM/CEYM product). ROM/RCEYM of oxanorbornene compound (±)-**220** failed (a mixture of ROM and ROM/CEYM products were formed, which resisted RCEYM). Interestingly, ROM/RCEYM of cyclooctene compound (±)-**250** was completely successful, and provided the desired RRM compound as a sole product (best yields: 39% with G-1, 32% with HG-1).
- One-step ROM/RCM of *N*-allylated β-lactam (±)-**227** failed, but sequential ROM and RCM was successful (the ROM reaction had a low yield, but the RCM reaction had excellent yield).
- One-step ROM/RCEYM of *N*-propargylated β-lactam (±)-**234** provided ROM product (±)-**240** in low yields and the desired RRM product (±)-**241** in low to moderate yields. RCEYM of isolated (±)-**240** proceeded with excellent yield.
- Generally, the success of a certain RRM reaction was determined by the release of ring strain. Conversion of (oxa)norbornene systems to fused bicyclic systems usually proceeded (except for ROM/RCM of allyl esters and *N*-allylamides to 5:7 fused ring systems; but ROM/RCEYM of analogous propargyl esters and *N*-propargylamides mostly worked). For cyclooctene rings, conversion to an azacycloheptene ring worked, but transformation to another unsaturated 8-membered ring usually failed with (±)-**250** as the only exception.
- Because catalyst performance greatly depended on a number of factors (e.g., stereochemistry and skeleton of substrate, type of RRM), it is difficult to make general conclusions. In simple ROM and ROM/RCM reactions, (oxa)norbornene esters preferred first generation catalysts (especially G-1), while cyclooctene systems preferred second generation catalysts.

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ANNEX