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Synthesis of New β-Amino Acid Scaffolds by Means of Ring-Rearrangement Metathesis

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The synthesis of some novel functionalized azaheterocyclic β-amino esters with multiple chiral centers via a stereocontrolled synthetic route has been carried out using some cyclooctene β-amino acids as starting model compounds. The strategy of the method was planned to create some novel unsaturated *N*-protected cyclic β-amino esters that were subjected to ring-opening metathesis (ROM) followed by selective ring-closing metathesis (RCM). A number of experimental conditions were accomplished to investigate the activity of catalysts, yields, conversions, and substrate effect on ring-rearrangement metathesis (RRM) transformation. Importantly, the procedure used in this synthetic process does not affect the configuration of the chiral centers; therefore, the stereochemistry of the starting cyclooctadiene β-amino acids predetermined the structure of the new azaheterocyclic derivatives.

Introduction

During olefin metathesis, the carbon–carbon double bond of alkenes is cleaved with the help of metal alkylidenes, then the resulting alkylidene groups are reassembled into new alkenes. This process is more and more popular in organic synthesis thanks to its numerous attractive features. First of all, it requires only mild conditions. Furthermore, because olefin metathesis does not affect the configuration of asymmetric carbons, product stereochemistry is controlled solely by the stereochemistry of the starting compound. Finally, the relative robustness and good functional group tolerance of Ru-containing metathesis catalysts also contributed greatly to the success of these reactions. It is important to note that all olefin metathesis processes are reversible, but their equilibrium can be greatly influenced by the used conditions.[1–3]

Azaheterocyclic amino acid derivatives belong to an important family of compounds in pharmaceutical and medicinal chemistry.[4,5] First of all, these compounds show a wide range of biological properties (Figure 1).[6–9] Furthermore, azaheterocyclic amino acid motifs can be found in numerous drugs (Figure 2)[10–13] and bioactive peptides.[14,15]

Taking into account our earlier work on carbocyclic β-amino acid derivatives,[16–18] and the importance of azaheterocyclic amino acids, our research group aimed to synthesize new azaheterocyclic amino acid derivatives. Our first strategy is depicted on Scheme 1. Oxidative ring opening of β-amino esters with a cycloalkene skeleton yielded reactive dialdehydes, which were subjected to double reductive amination without isolation. The latter step involved ring closure and the overall process is ring expansion.[18,19]

Our earlier experiences with olefin metathesis reactions of cyclic β-amino esters[17] led us to realize that ring-rearrangement metathesis (RRM) of easily accessible *N*-alkenylated (or *N*-alkynylated) carbocyclic β-amino esters could be a feasible and stereocontrolled pathway towards novel azaheterocyclic β-amino acid derivatives. Ring-rearrangement metathesis is a two-step process. First, the unsaturated substrate undergoes ring-opening metathesis with ethylene. Entropy does not favor this process, but release of the ring strain present in the starting compound can be a sufficient driving force. Then, the formed intermediate undergoes either ring-closing metathesis (RCM) or ring-closing enyne metathesis (RCEYM). Naturally, these processes work best if the newly formed ring system is not too strained.[2]

According to the above considerations, RRM reactions were performed with *N*-allylated or *N*-propargylated norbornene or oxanorbornene β-amino esters (Scheme 2). To our delight, most of the desired products (azaheterocyclic β-amino esters with a hexahydro-1*H*-cyclopenta[*b*]pyridine or hexahydrofuro[3,2-*b*]pyridine scaffold) were formed in moderate to good yields.[20,21]

The aim of the current work is the extension of the this stereocontrolled synthetic strategy to cyclooctene β-amino acid derivatives and related β-lactams, exploring the chemical behavior of multi-unsaturated scaffolds under metathesis (Scheme 3).

Results and Discussion

Similar to our previous works,[20,21] ring-opening metathesis/ring-closing metathesis (ROM/RCM) and ring-opening meta-

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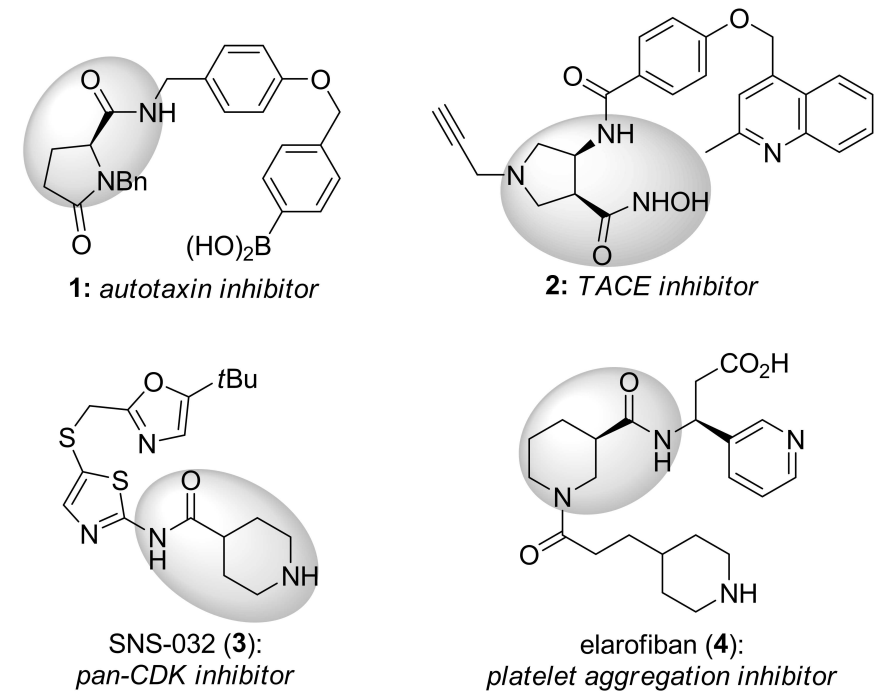


Figure 1. Bioactive azaheterocyclic amino acid derivatives.

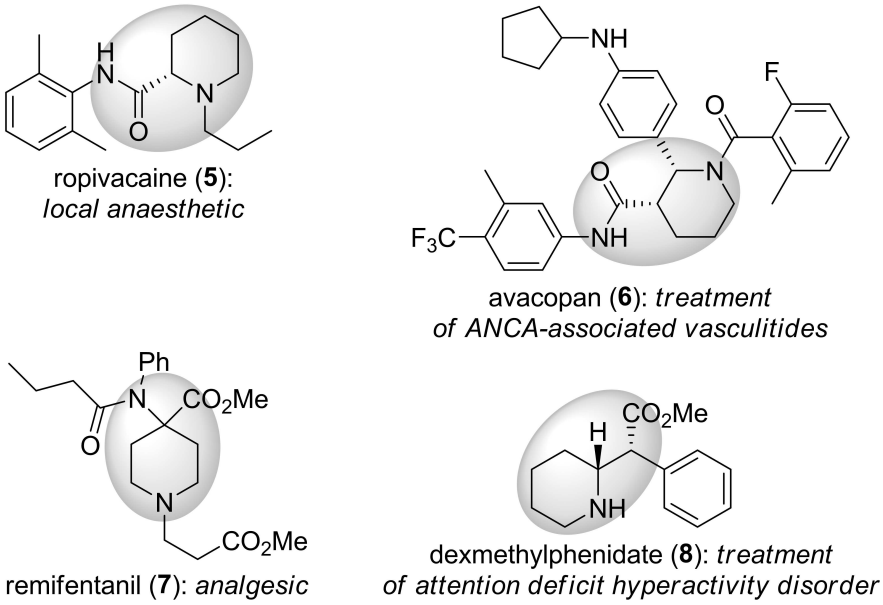
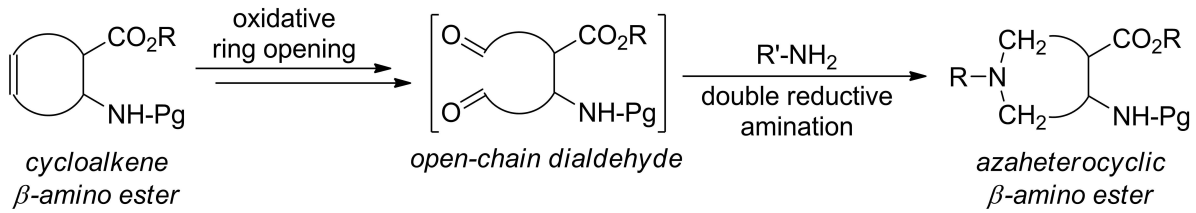
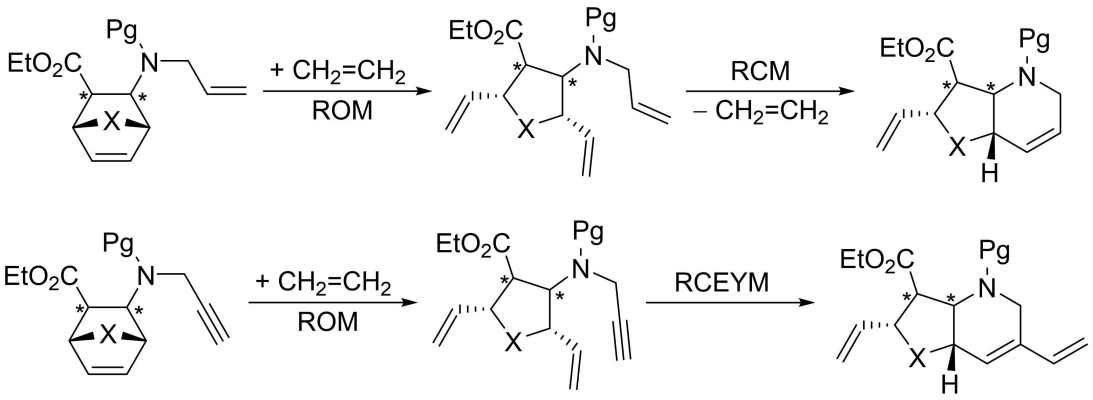


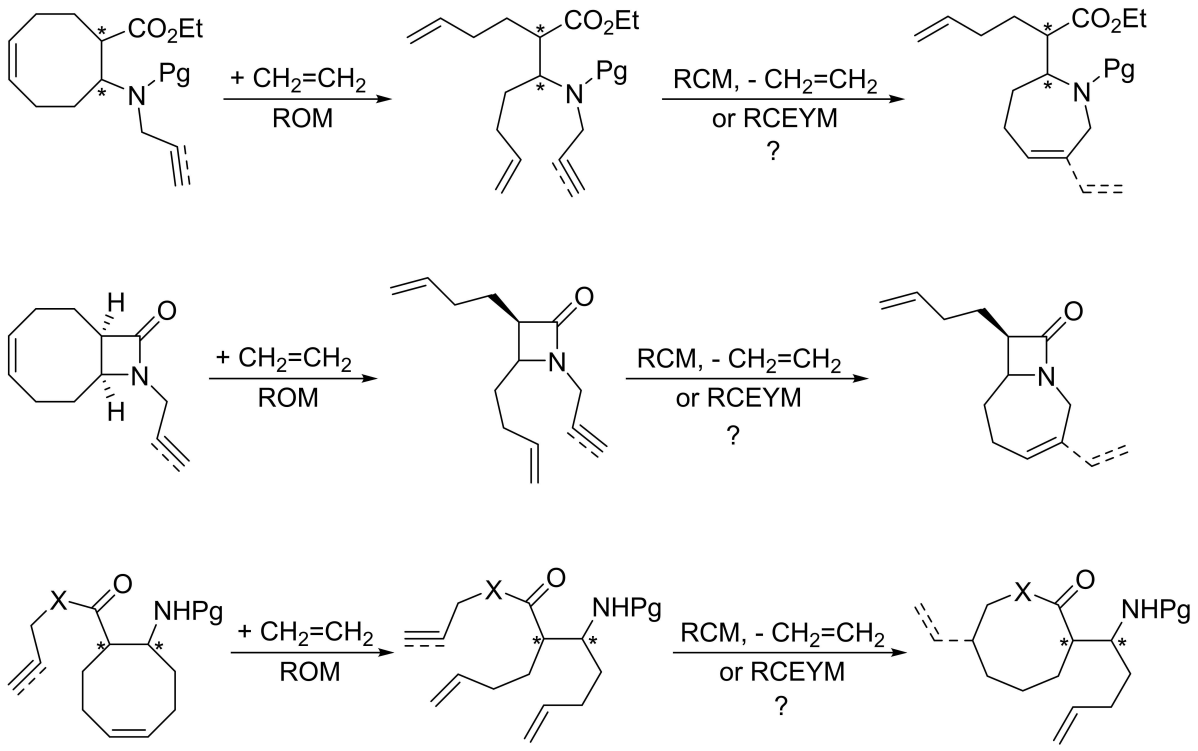
Figure 2. Drugs with an azaheterocyclic amino acid motif.



Scheme 1. Previous work: synthesis of azaheterocyclic β-amino esters via oxidative ring opening/reductive amination. Pg: protecting group.



Scheme 2. Previous work: synthesis of azaheterocyclic β-amino esters from norbornene and oxanorbornene derivatives via ring-rearrangement metathesis. X = O, CH_2. Pg = Boc, Ts.



Scheme 3. Current goal: ring-rearrangement metathesis of β-amino acid and β-lactam derivatives with a cyclooctene skeleton. X = O, NH.

thesis/ring-closing enyne metathesis (ROM/RCEYM) protocols were carried out under ethylene atmosphere.[22] Because the outcome of metathesis reactions depends on the catalyst, too, each reaction was attempted with the four commercially available common catalysts depicted on Figure 3.

First, racemic compound (±)-**9** was prepared from 1,5-cyclooctadiene using a literature method (treatment with chlorosulfonyl isocyanate followed by mild basic workup, then lactam ring opening with HCl/EtOH).[23] This amino ester hydrochloride was converted to compounds (±)-**11** and (±)-**13** using the pathway established earlier[21,22] (*N*-tosylation, then *N*-alkylation). Then, compounds (±)-**11** and (±)-**13** were subjected to olefin metathesis. By varying the experimental conditions, such as the quantity of catalyst, temperature, and reaction time, we found that the optimal conditions are CH_2Cl_2 as solvent, 3 mol% catalyst, room temperature, and 4 h reaction time. Under these conditions, ROM/RCM of amino ester (±)-**11** provided azaheterocyclic product (±)-**12** selectively with chemodifferentiation of the olefin bonds (Scheme 4). Catalyst G-1 provided the best yield and the other catalysts were slightly less efficient. In contrast, transformation of compound (±)-**13** provided two products: azaheterocycle (±)-**14** and a multi-unsaturated β-amino ester (±)-**15** (Scheme 4).

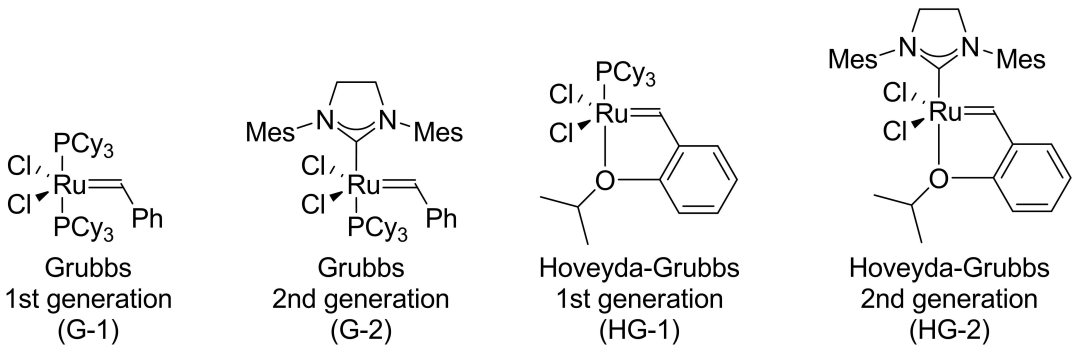
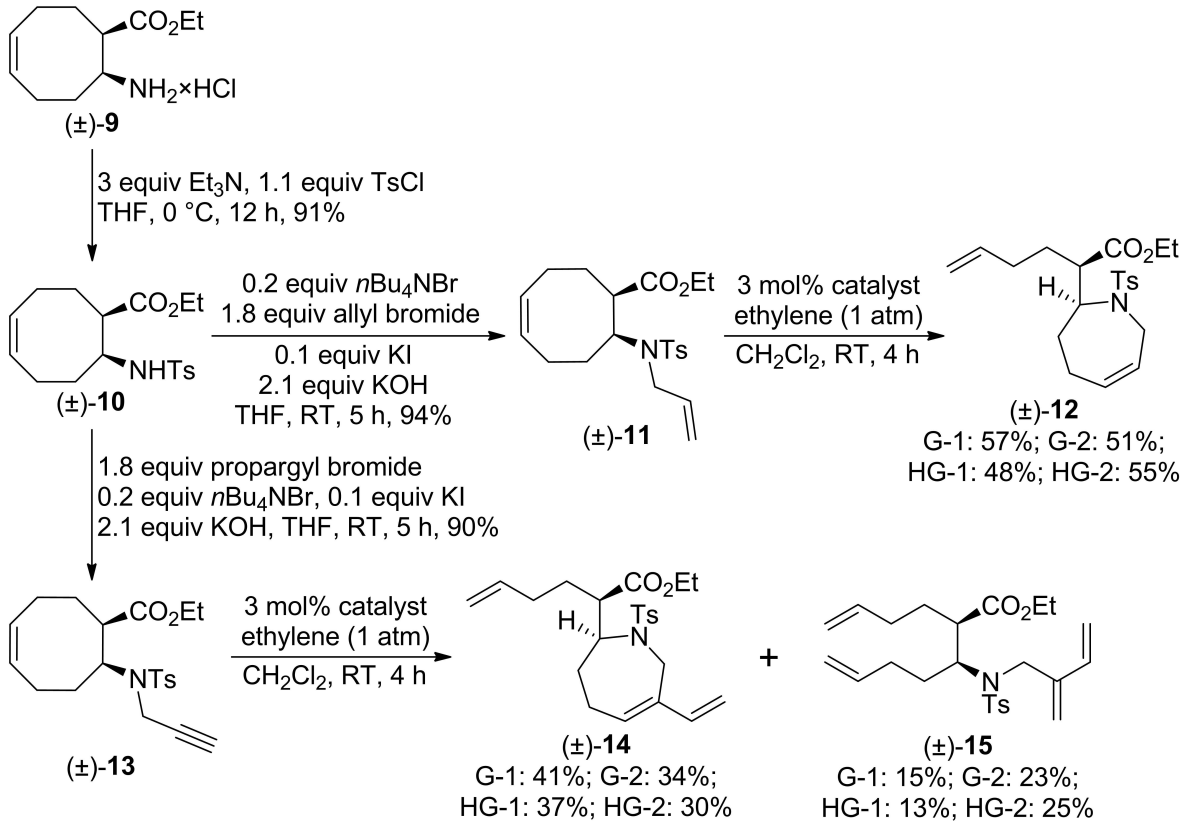


Figure 3. Commercially available metathesis catalysts used in this work. Cy = cyclohexyl, Mes = 2,4,6-trimethylphenyl.



Scheme 4. Synthesis and metathesis reactions of amino esters (±)-**11** and (±)-**13**.

Based on the literature,[24] this can be explained by the competition between the ROM/RCEYM and ROM/CEYM processes (CEYM: cross enyne metathesis). Ring-opening metathesis of amino ester (±)-**13** can undergo both RCEYM [yielding product (±)-**14**] and CEYM with ethylene [yielding product (±)-**15**]. With all four catalysts, the combined yields were similar and compound (±)-**14** was the main product, but first-generation catalysts were more selective towards the formation of the azaheterocycle. As a result, G-1 provided the highest yield of (±)-**14** (41%), while the best yield for (±)-**15** (25%) was achieved in the presence of HG-2 (Scheme 4).

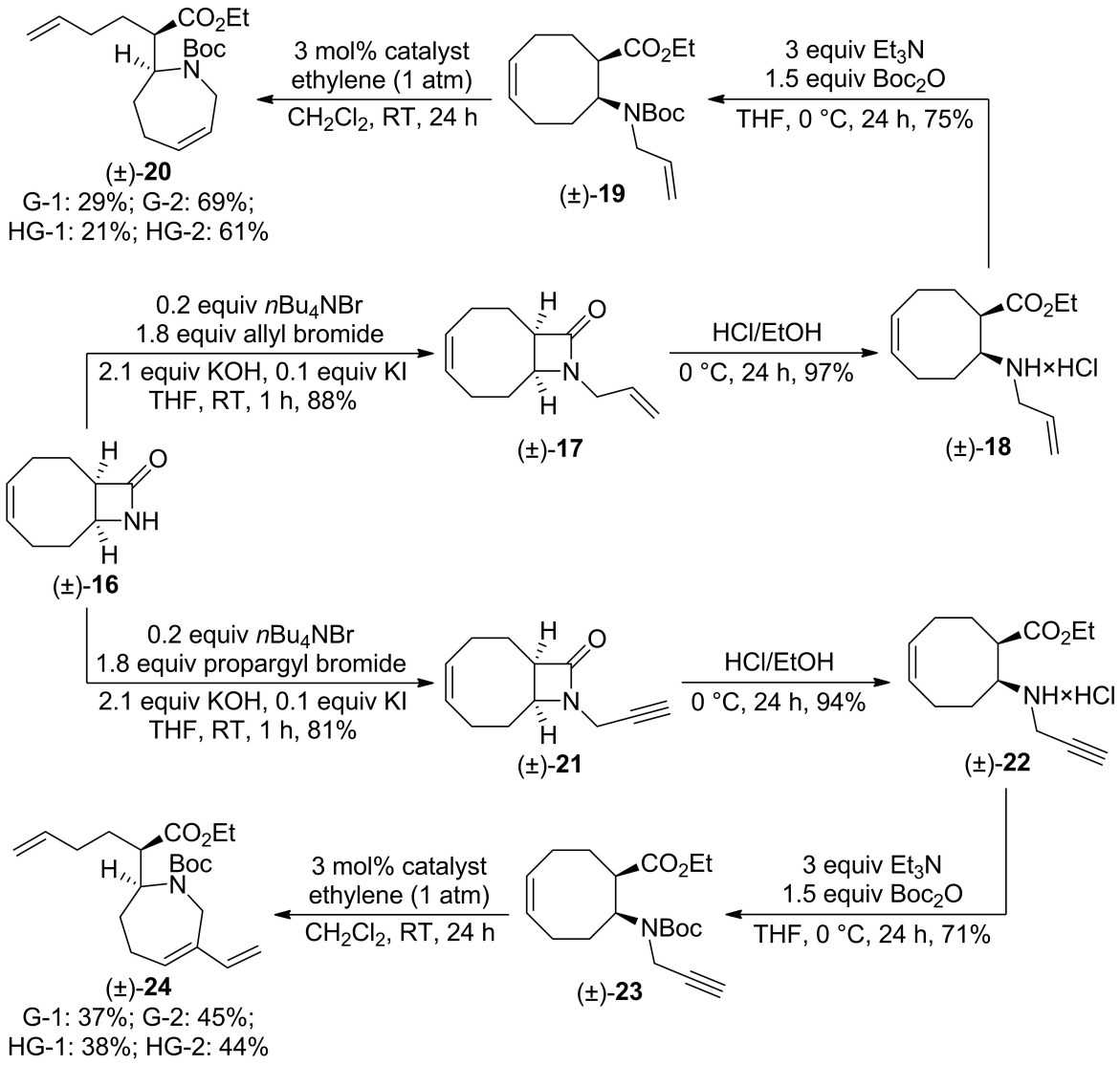
It is important to note, that both metathesis products (±)-**12** and (±)-**14** contain a strained (seven-membered) unsaturated ring system and an alkenylidene element in their structure, similarly to derivatives (±)-**11** and (±)-**13** (with an eight-membered ring and an alkenyl group). In contrast, however these two latter compounds, namely (±)-**12** and (±)-**14** did not undergo further ROM/CM transformations.

Taking into account that removal of the *N*-Ts protecting group is difficult, our next objective was the synthesis of analogous *N*-Boc-protected compounds whose deprotection is easier. Note that these derivatives may receive application in syntheses and peptide chemistry. Based on our previous

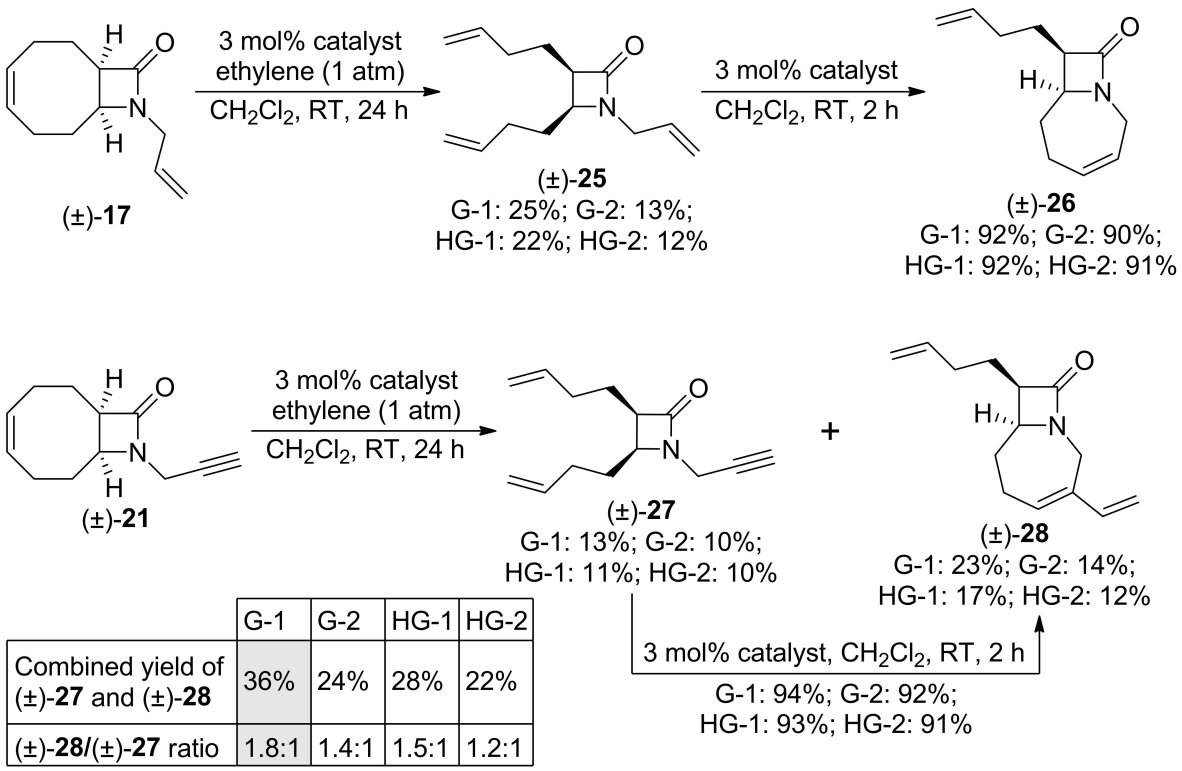
results,[20,21] when by investigating a number of experimental conditions the allylation of *N*-Boc cyclooctene amino ester failed the *N*-alkylation of the easily accessible *N*-Boc analogue of (±)-**10** was not attempted. Instead, compounds (±)-**19** and (±)-**23** were synthesized from lactam (±)-**16** via an *N*-alkylation/lactam alcoholysis/*N*-Boc protection sequence. ROM/RCM of substrate (±)-**19** provided, across chemodifferentiation of the olefin bonds, azaheterocycle (±)-**20** with the highest yield of 69% achieved with G-2 catalyst. Interestingly, ring-rearrangement metathesis of amino ester (±)-**23** gave azaheterocycle (±)-**24** as a sole product, without formation of ROM/CEYM byproduct. The highest yield was achieved with the G-2 (45%) and HG-2 catalysts (44%). Scheme 5 summarizes these results.

In order to obtain further azaheterocyclic scaffolds, β-lactam derivatives (±)-**17** and (±)-**21** were also subjected to ring-rearrangement metathesis (Scheme 6). In the case of compound (±)-**17**, the one-step ROM/RCM transformation to form a cyclized product failed. However, performing the two metathesis steps sequentially provided cyclized derivative azaheterocycle (±)-**26**. The ROM reaction was rather problematic. Namely compound (±)-**25** formed only in low yields (the highest yield, provided by G-1 catalyst, was 25%). In contrast, the RCM reaction was rapid and it gave excellent yields with all four catalysts. In the case of compound (±)-**21**, the one-step ROM/RCEYM transformation was only partially successful, since both ROM product (±)-**27** and RRM product (±)-**28** were formed in low yields. The ratio of RRM and ROM products was the highest with G-1 catalyst, which also provided the highest yields [23% (±)-**28** and 13% (±)-**27**]. Notably, RCEYM reaction of isolated (±)-**27** was quick and highly efficient with all four catalysts.

Our next goal was the extension of the RRM protocol by the transformation to other highly unsaturated cyclooctene β-amino acid derivatives. These syntheses started from *N*-Boc-protected amino acid (±)-**29** obtained according to an earlier



Scheme 5. Synthesis and ring-rearrangement metathesis of amino esters (±)-**19** and (±)-**23**.

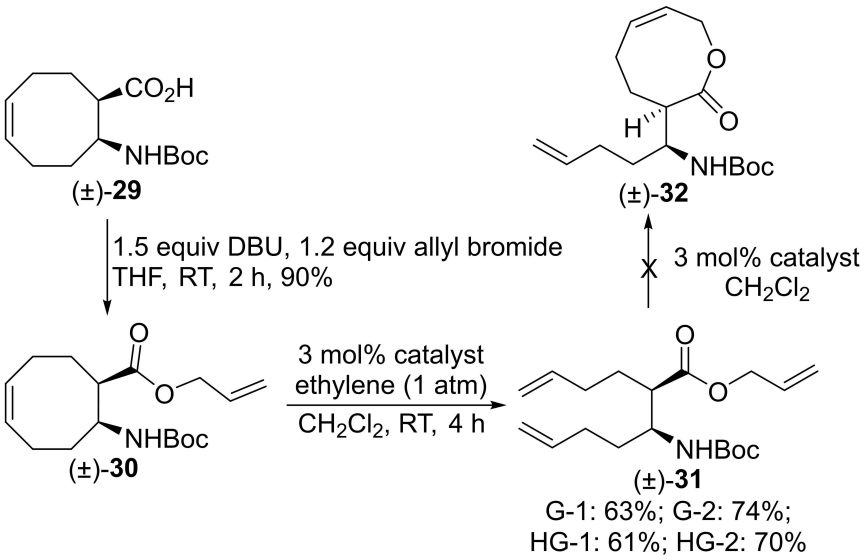


	G-1	G-2	HG-1	HG-2
Combined yield of (±)-**27** and (±)-**28**	36%	24%	28%	22%
(±)-**28**/(±)-**27** ratio	1.8:1	1.4:1	1.5:1	1.2:1

Scheme 6. Metathesis transformations of β-lactams (±)-**17** and (±)-**21**.

procedure.[25] First, the reaction of compound (±)-**29** with allyl bromide in the presence of DBU resulted in allyl ester (±)-**30**. When compound (±)-**30** was treated with ethylene in the presence of a metathesis catalyst, the ROM step took place readily, but the intended RCM step failed. Instead, compound (±)-**31** was isolated as the sole product. The ROM process was efficient with all four catalysts with the highest yield achieved with G-2 catalyst (74%). However, attempts to trigger ring-closing metathesis of (±)-**31** were unsuccessful (Scheme 7).

Reaction of compound (±)-**29** with propargyl bromide in the presence of DBU resulted in the desired ester (±)-**33**. Under our usual RRM conditions, it behaved similarly to its allyl ester



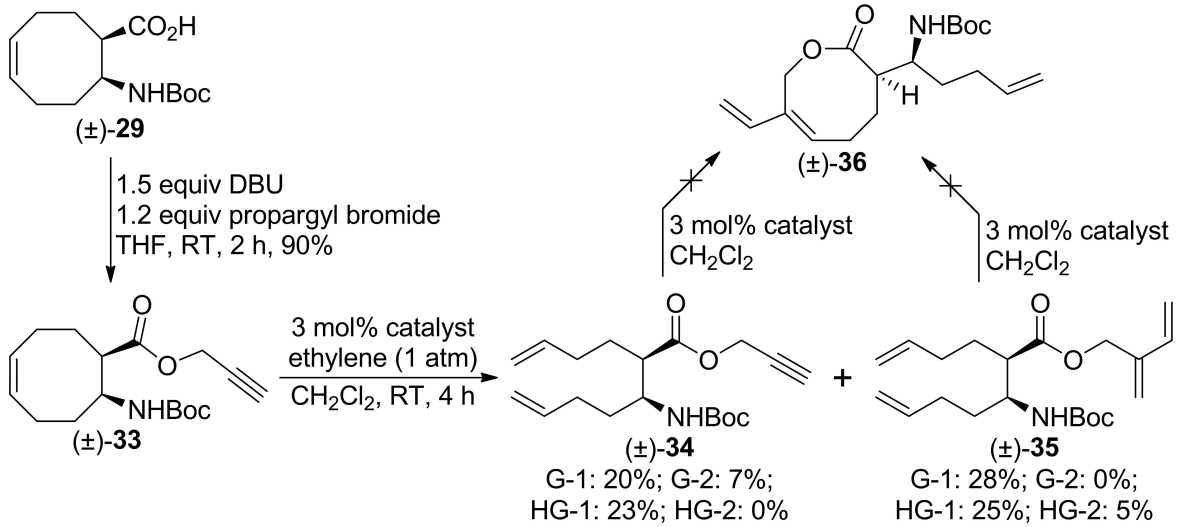
Scheme 7. Synthesis and metathesis transformation of allyl ester (±)-**30**.

analogue, that is, the initial ROM step was not followed by ring closure. However, the presence of ethylene enabled CEYM reactions with the outcome greatly depending on the type of the catalyst. With catalyst G-2, only low amounts of ROM product (±)-**34** were formed. With catalyst HG-2, only low amounts of ROM/CEYM product (±)-**35** were formed. In contrast, G-1 and HG-1 catalysts provided mixtures of the two products with 48% overall yields. The G-1 catalyst noticeably favored ROM/CEYM over simple ROM, while HG-1 was less selective. As a result, G-1 provided the highest yield of (±)-**35** (28%), while HG-1 provided the highest yield of (±)-**34** (23%). Both products resisted to ring closure attempts (Scheme 8).

Finally, using *N*,*N*′-dicyclohexylcarbodiimide (DCC) and 4-dimethylaminopyridine (DMAP), *N*-Boc-protected amino acid (±)-**29** was coupled with allylamine and propargylamine in order to obtain amides (±)-**37** and (±)-**40** as model compounds. In the presence of ethylene and metathesis catalysts, *N*-allylated amide (±)-**37** behaved analogously to allyl ester (±)-**33**, and only ROM product (±)-**38** was formed. HG-2 catalyst provided the highest yield (57%). Attempts to promote RCM of compound (±)-**38** were unsuccessful. In contrast, transformation of compound (±)-**40** provided directly the desired ROM/RCEYM product (±)-**41**. The highest yield was achieved with G-1 catalyst (39%). Scheme 9 summarizes the above results.

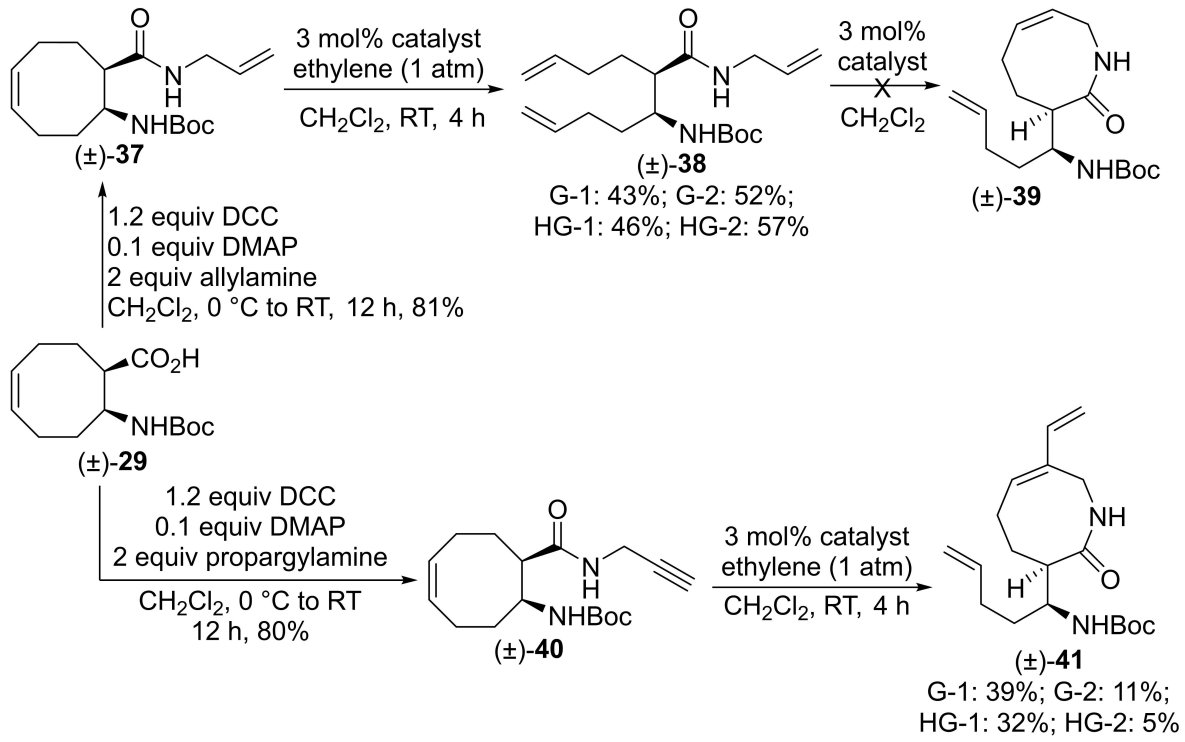
Conclusion

Olefin metathesis transformations of some β-amino acid derivatives with a cyclooctene skeleton, as model compounds, provided access to various azaheterocyclic β-amino acid scaffolds as well as polyunsaturated open-chain β-amino acid derivatives. The success of the desired ring-rearrangement metathesis processes mostly depended on the ring strain of the products and the starting compounds. Of six cases, where the desired RRM process involved transformation of a cyclooctene ring into an azacycloheptene ring, three were completely successful (only the RRM product was formed), two were mostly successful (a product mixture was formed with the RRM product as the major component), while one required performing the ROM and RCM steps separately (but still provided the desired product). This is in agreement with literature data about ring strain (a cycloheptene ring is less strained than a cyclooctene ring).[2] In contrast, RRM sequences, which would transform a cyclooctene ring into an eight-membered unsaturated lactone or lactam ring failed in most cases. Four such comparative transformations were attempted, but only a single succeeded. In the other three cases, only ROM products were formed resisting to ring closure attempts. In these cases, the substrate and the products have comparable ring strains, which makes the overall RRM process thermodynamically less feasible. Therefore, the reaction usually stops after the ROM sub-step (which is driven by the release of ring strain). Our previous results[20,21] and the data reported herein demonstrate that ring-rearrangement metathesis can be a powerful synthetic pathway towards novel azaheterocyclic β-amino acid derivatives, but it requires carefully designed substrates. With these considerations in mind, we plan further investigations of RRM transformations of β-amino acid derivatives with an unsaturated, strained ring system.



	G-1	G-2	HG-1	HG-2
Combined yield	48%	7%	48%	5%
(±)-**35**/(±)-**34** ratio	1.4:1	0:1	1.1:1	1:0

Scheme 8. Synthesis and metathesis transformation of propargyl ester (±)-**33**.



Scheme 9. Syntheses and metathesis transformations of amides (±)-**37** and (±)-**40**.

Experimental part

General information

Chemicals were purchased from Sigma–Aldrich. Solvents were used as received from suppliers. The melting points of the materials were determined using a Kofler apparatus. Silica gel 60 F_{254} was purchased from Merck. NMR spectra were acquired at room temperature on a Bruker Avance Neo 500 spectrometer with 11.75 T magnetic field strength (^{1}H frequency 500.20 MHz, ^{13}C frequency 125.78 MHz) in $CDCl_3$ solution, using the deuterium signal of the solvent to lock the field. The ^{1}H and ^{13}C chemical shifts are given relative to TMS. The HRMS flow injection analysis was performed with Waters Acquity I-Class UPLC system coupled to a Thermo Scientific Q Exactive Plus hybrid quadrupole-Orbitrap mass spectrometer. Using positive heated electrospray ionization as the method, the following settings were made for the mass spectrometer: capillary temperature 250 °C, spray voltage 3.5 kV, sheath gas flow 50, spare gas flow 1, and auxiliary gas flow 10 in arbitrary units. Using an injection time of 100 ms and a mass range of 100 to 1000 m/z, a resolution of 75,000 (FWHM) was selected for the full scan, and the automatic gain control setting was set at 3×106 charges. During analysis, the mobile phase of acetonitrile/water/formic acid (80/20/0.1 v/v/v) flowed at 0.4 mL/min.

Synthesis of new compounds

General procedure for N-alkylation

To a solution of 1.00 g *N*-Ts protected ester or β-lactam, 1.8 equiv. allyl bromide or propargyl bromide, 0.2 equiv. tetrabutylammonium bromide, 0.1 equiv. potassium iodide, and 2.1 equiv. freshly crushed KOH were sequentially added in THF (30 mL) at room temperature. The reaction mixture was stirred vigorously for 1–5 h, then it was quenched with 50 mL saturated aqueous NH_4Cl solution. Afterwards, the phases were separated and the aqueous layer was extracted with 3×50 mL EtOAc. The combined organic layers were dried over Na_2SO_4, evaporated under reduced pressure and the residue was purified by column chromatography on silica gel.

General procedure for Boc protection

To a stirred solution of 1.00 g *N*-allylated or *N*-propargylated amino ester hydrochloride and 3 equiv. Et_3N in 100 mL THF, 1.5 equiv. Boc_2O was added in portions at 0 °C. The mixture was stirred for 24 hours at room temperature. After that, it was diluted with 50 mL EtOAc, then washed with 3×60 mL water. The organic layer was dried over Na_2SO_4 and concentrated under vacuum. The crude products were purified by column chromatography on silica gel.

General procedure for the ring-rearrangement metathesis process

To a solution of 100 mg of *N*-allylated or *N*-propargylated *N*-protected ester in 10 mL anhydrous CH_2Cl_2, ethylene and 3 mol% metathesis catalyst (G-1, G-2, HG-1 or HG-2) were added. The reaction mixture was stirred at room temperature for 4–24 h. Then, in order to decompose the catalyst, a mixture of water (12 mL), methanol (2 mL) and $NaHCO_3$ (0.1 g) was added, and the reaction mixture was stirred for an additional 2 hours. Afterwards, the phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3×15 mL). The combined organic layers were dried over Na_2SO_4, concentrated under reduced pressure, and the residue was purified by column chromatography on silica gel.

Supporting Information Summary

Characterization data and ^{1}H, ^{13}C spectra of the newly synthetized compounds are found in the Supporting Information.

Acknowledgements

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

Research data are not shared.

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

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