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Selective Transformation of 1,3-Cyclooctadiene into Novel Functionalized Azaheterocycles, β-Amino Esters, and Lactams by Means of Ring-Rearrangement Metathesis

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Diversity-oriented synthesis of some novel functionalized azaheterocyclic β-amino esters with multiple chiral centers from 1,3-cyclooctadiene-based β-amino acids through a stereocontrolled synthetic route has been accomplished. The strategy was based on the creation of some novel unsaturated *N*-protected cyclic β-amino esters from 1,3-cyclooctadiene. Products were subjected to ring-opening metathesis (ROM) followed by selective ring-closing metathesis (RCM). A comparative investigation on the selectivity, regarding the catalysts, yields, conversions, and substrate directing effect on ring-rearrangement metathesis (RRM) transformation has been accomplished. Importantly, the procedure used in this synthetic process does not affect the configuration of the chiral centers. The pathway takes place across conservation of the configurations of the stereocenters; therefore, the architectural skeleton of the starting cyclooctene-based β-amino acids predetermined the structure of the new azaheterocyclic systems.

Introduction

Olefin metathesis employs metal alkylidenes to cleave the carbon–carbon multiple bond of alkenes and then reassembling the resulting alkylidene fragments into new olefins. This process has gained increasing popularity in organic synthesis due to its appealing characteristics. Notably, olefin metathesis operates under mild conditions, simplifying its application under various conditions, and it is able to preserve the configuration of the asymmetric carbon centers during the process. Moreover, metathesis catalysts based on ruthenium (Ru) are particularly robust, exhibiting good functional group tolerance. Numerous metathesis processes exist, encompassing 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). RRM is a domino metathesis process and it involves a ROM sub-step followed by either RCM or RCEYM.[1–7]

Diversity-oriented syntheses (DOS), in order to fabricate valuable molecular libraries with molecular entities possessing versatile structural and chemical architecture, have numerous advantages. The main feature of these synthetic approaches is the use of readily accessible, relatively inexpensive starting materials for the construction of three-dimensional complex scaffolds. The intricate structures of the resulting compounds play a crucial role in pharmaceutical chemistry and drug discovery.[8–13] RRM is one of the methods, which can easily and efficiently generate highly complex frameworks that would be difficult to synthesize by other conventional common methods.[14–17]

Functionalized azaheterocyclic derivatives belong to an important and highly abundant compound family in pharmaceutical and medicinal chemistry. These compounds exhibit a diverse array of biological properties, such as anticancer, antibacterial, antiviral, and antifungal activities (Figure 1).

Furthermore, azaheterocyclic amino acids or lactams belong to an interesting subgroup of this compound family. Each of these subgroups has its own unique structural features with potential applications and they can be found in numerous drugs (Figure 1).[18–29]

As a consequence, the synthesis of functionalized azaheterocycles and lactams stands out as a highlighted research topic.

Earlier, our research group applied RRM of easily accessible strained carbocyclic β-amino esters to obtain various azaheterocyclic β-amino esters in a stereocontrolled fashion.[30–34] This synthetic approach is particularly noteworthy, because it allows an accurate control of the configurations of the stereocenters within the resulting azaheterocyclic compounds. In addition, it opened up new avenues for the synthesis of diverse and structurally intricate β-amino acids, paving the way for potential

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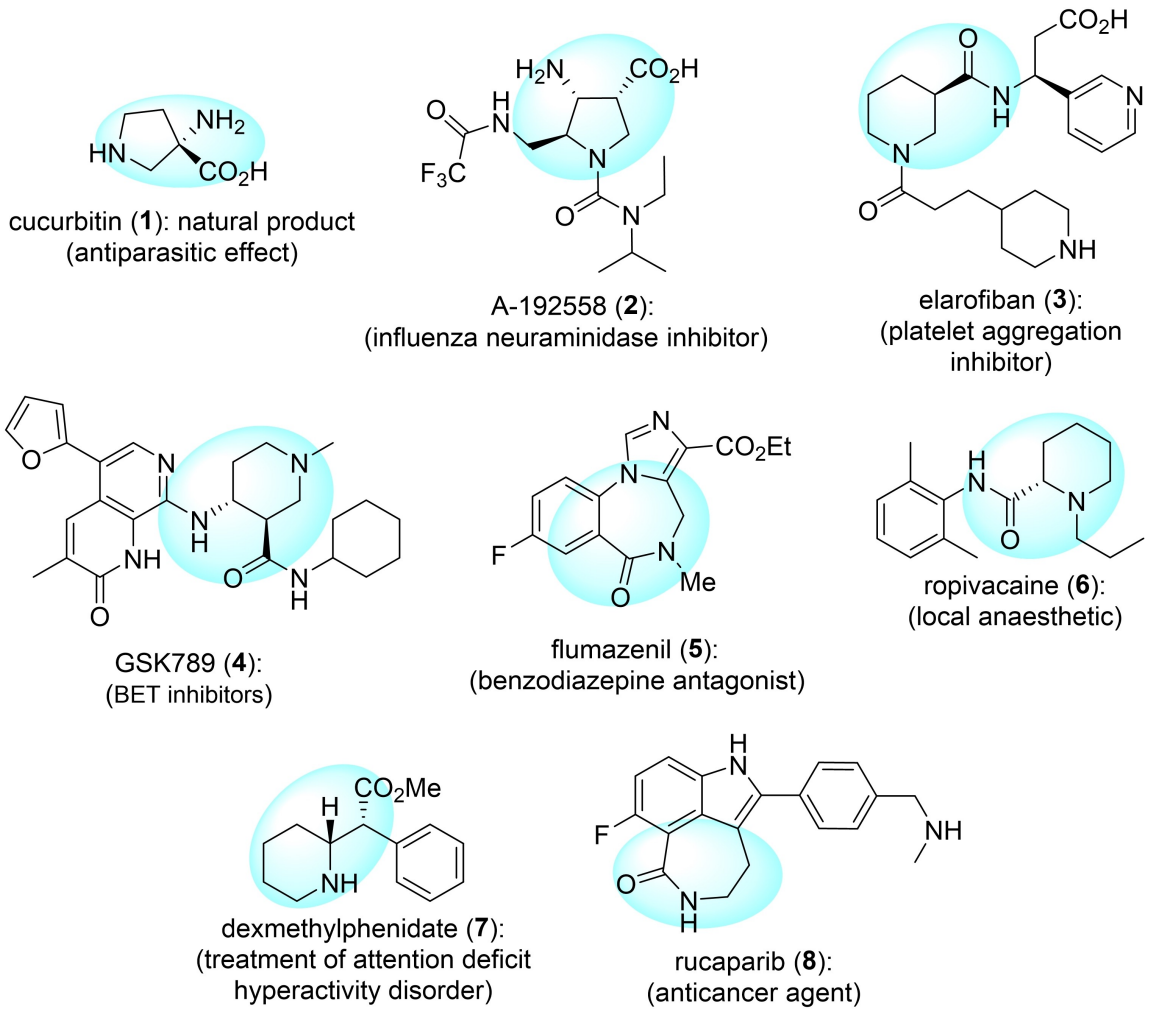

Figure 1. Azaheterocyclic β-amino acid derivatives found in natural products and in synthetic bioactive compounds and marketed drugs containing an azaheterocylic amino acid or a lactam structural unit.

applications in pharmaceutical and medicinal chemistry. Diversity-oriented syntheses have used the easily available norbornadiene-, oxanorbornadiene-, and 1,3-cyclooctadiene-derived starting compounds to form the corresponding azaheterocyclic β-amino esters (Scheme 1).[30–35]

To extend and demonstrate the versatility and reliability of the method, the aim of the current work was the application of RRM to access other azaheterocyclic β-amino esters, β-amino lactones, and β-amino lactams, which might be considered to be highly valuable building blocks in organic synthesis. The starting compounds for this investigation comprised either allyl/propargyl cyclooctene β-lactams or β-amino esters or the analogous *N*-allylated/*N*-propargylated amides or esters derived from 1,3-cyclooctadiene, showcasing our commitment to explore future diverse structural motifs (Scheme 2).

Results and Discussion

Based on our previous research endeavours,[30–34] we accomplished the ROM/RCM and ROM/RCEYM protocols of 1,3-cyclooctadiene-based amino esters in ethylene atmosphere. We systematically explored each reaction using four common, commercially available Ru-based catalysts illustrated in Figure 2. This approach allowed us to investigate the influence of catalyst selection on the outcome of the metathesis reactions in a comprehensive manner, and to determine the optimal conditions for achieving the formation of the desired products.

First, compound (±)-**11** was synthesized utilizing a literature method involving the treatment of 1,3-cyclooctadiene with chlorosulfonyl isocyanate followed by a mild, basic workup.[36] Subsequently, lactam (±)-**10** was subjected to ring opening with HCl/EtOH. The resulting amino ester hydrochloride (±)-**11** served as the precursor for the synthesis of compounds (±)-**13** and (±)-**15**, employing a pathway described earlier,[30–32] which involved *N*-tosylation followed by *N*-alkylation. The RCM was carried out by varying the experimental conditions including the quantity and loading of catalyst, reagent, temperature, and reaction time. The highest conversions and isolated yields of the desired pyrrolidine products were obtained in CH_2Cl_2, with 3 mol% catalyst, at room temperature in 4-h reactions. Under these optimized conditions, ROM/RCM of amino ester (±)-**13**

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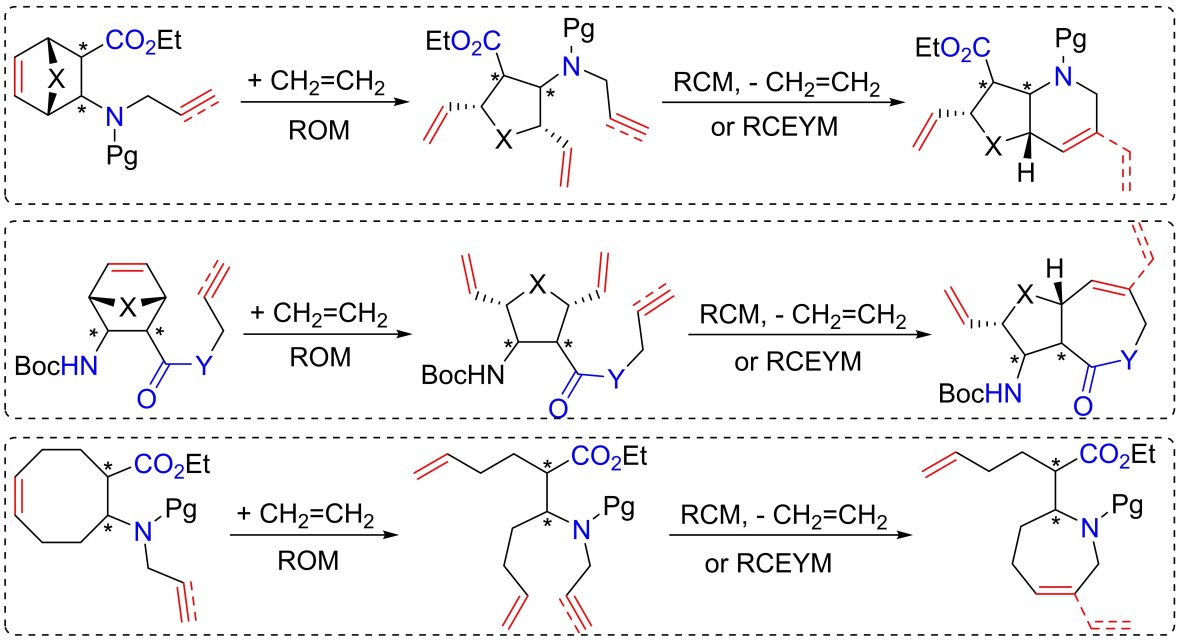
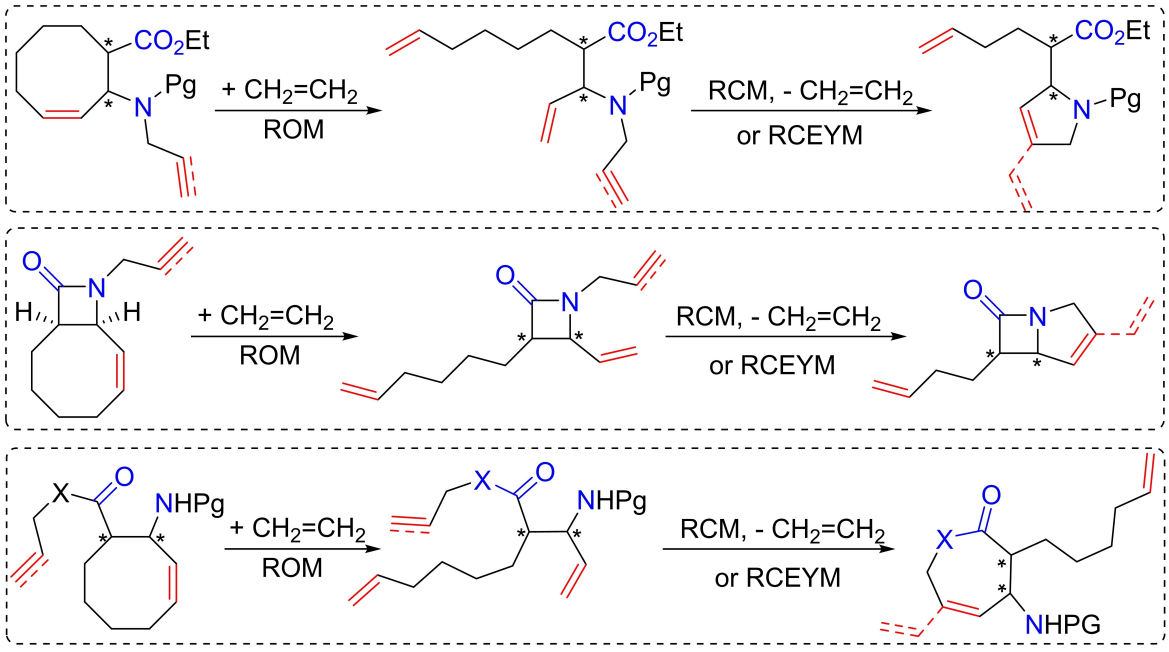


Scheme 1. Earlier work: synthesis of diverse azaheterocyclic β-amino esters via ring-rearrangement metathesis; X = O, CH_2; Y = O, N; Pg = Boc, Ts.[30–35]



Scheme 2. Current goal: synthesis of novel azaheterocyclic β-amino esters, β-amino lactones, and β-amino lactams through ring-rearrangement metathesis; X = O, NH.

yielded the expected azaheterocyclic product (±)-**14**, with G-1 catalyst proving to be the most efficient (Scheme 3). Interestingly, the transformation of amino ester (±)-**15** gave the desired azaheterocycle (±)-**16** as the sole product. The highest yield was achieved with the G-1 (68%) and HG-2 catalysts (66%).

Considering the challenges and difficulties associated with the removal of the *N*-Ts protecting group, our subsequent goal was the synthesis of analogous *N*-Boc-protected compounds with a more straightforward deprotection strategy. Building upon our earlier findings,[30,32] *N*-alkylation of the easily accessible *N*-Boc analogue of (±)-**12** was achieved. Compounds (±)-**19** and (±)-**23** were synthesized from lactam (±)-**10** through an *N*-alkylation/lactam alcoholysis/*N*-Boc protection sequence. In the presence of metathesis catalysts under ethylene atmosphere (1 atm), both compounds provided the expected unsaturated azaheterocyclic products (±)-**20** and (±)-**24**. Transformation of (±)-**19** and (±)-**23** was somewhat more efficient with the HG-1 catalyst than with the others (Scheme 4).

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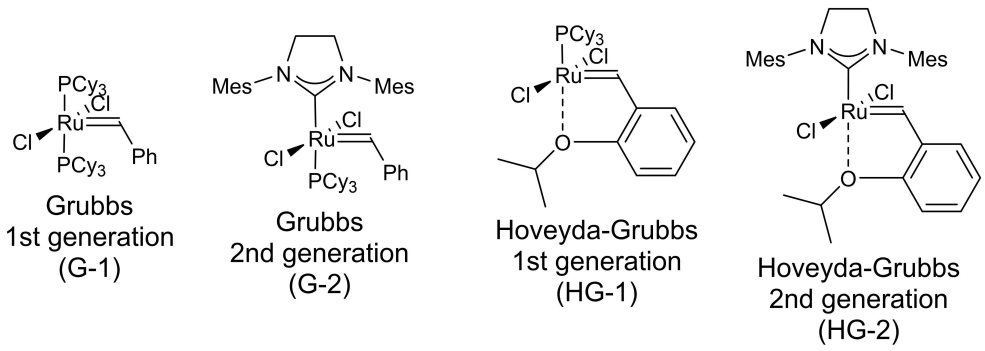
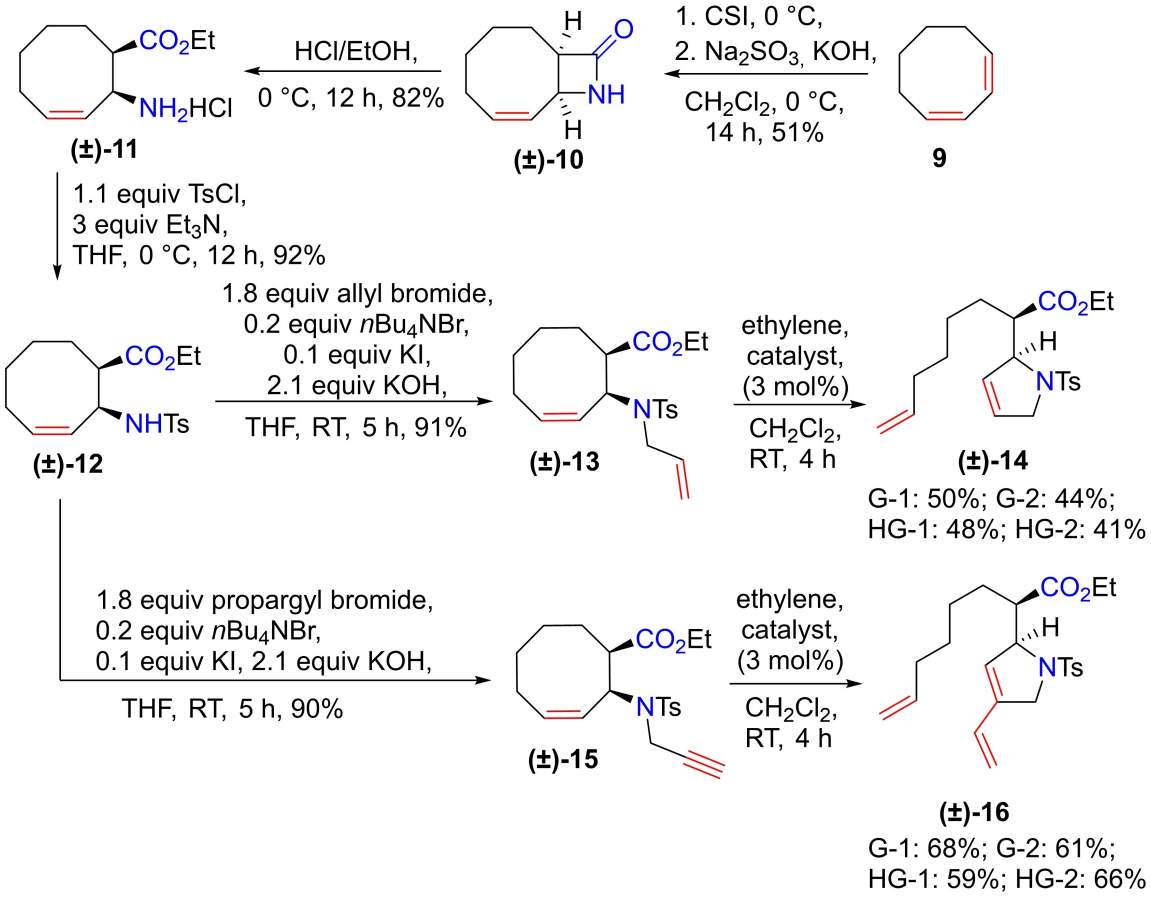


Figure 2. Some commercially available catalysts used in this work; Cy = cyclohexyl, Mes = 2,4,6-trimethylphenyl.



Scheme 3. Synthesis and metathesis reactions of allyl and propargyl amino esters (±)-**13** and (±)-**15** (CSI = chlorosulfonyl isocyanate).

The outcome of the RRM transformation of amino esters (±)-**13** and (±)-**15** as well as (±)-**19** and (±)-**23** is unequivocal. In all processes a higher ring strain of the seven-membered skeletons in the starting compounds versus the five-membered ring system of the product is a driving force of these processes.

In order to obtain further novel azaheterocyclic scaffolds, β-lactam derivatives (±)-**17** and (±)-**21** were also subjected to ring-rearrangement metathesis (Scheme 5). In the case of compound (±)-**17**, the process stopped after the ring-opening step and afforded multi-unsaturated β-lactam (±)-**25** in moderate yields (the highest yield of 53% was achieved by HG-2 catalyst). Attempts under various experimental conditions to trigger ring-closing metathesis of (±)-**25** were unsuccessful (Scheme 5). In contrast, the transformation of compound (±)-**21** provided directly the desired ROM/RCEYM product (±)-**27**. The first-generation catalysts provided β-lactam product (±)-**27** more efficiently, than second-generation catalysts.

Next, we investigated the possibilities for the preparation of β-amino lactones and β-amino lactams. First, *N*-protected amino acid (±)-**28** was subjected to *O*-allylation. The resulting ester (±)-**29** was then investigated in ROM/RCM with various metathesis catalysts under ethylene atmosphere. Unfortunately,

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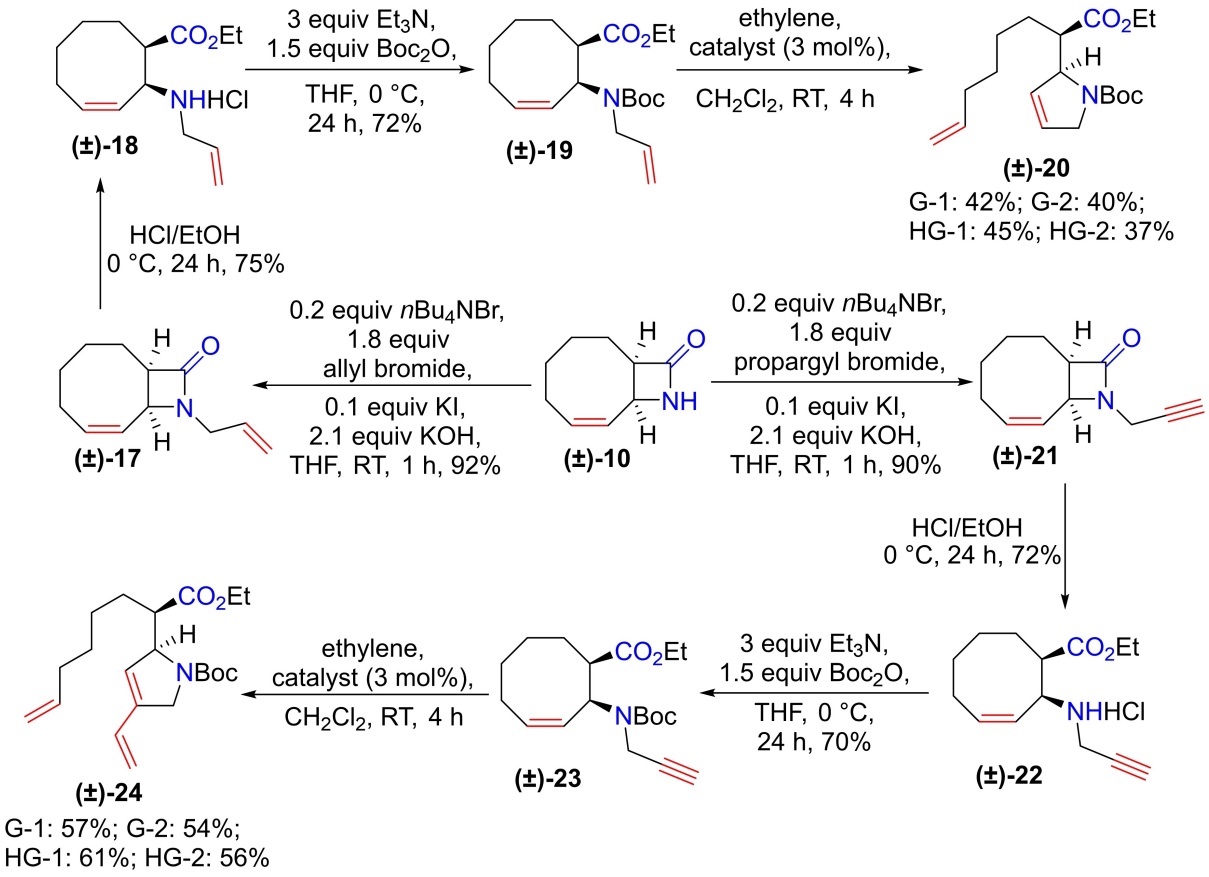
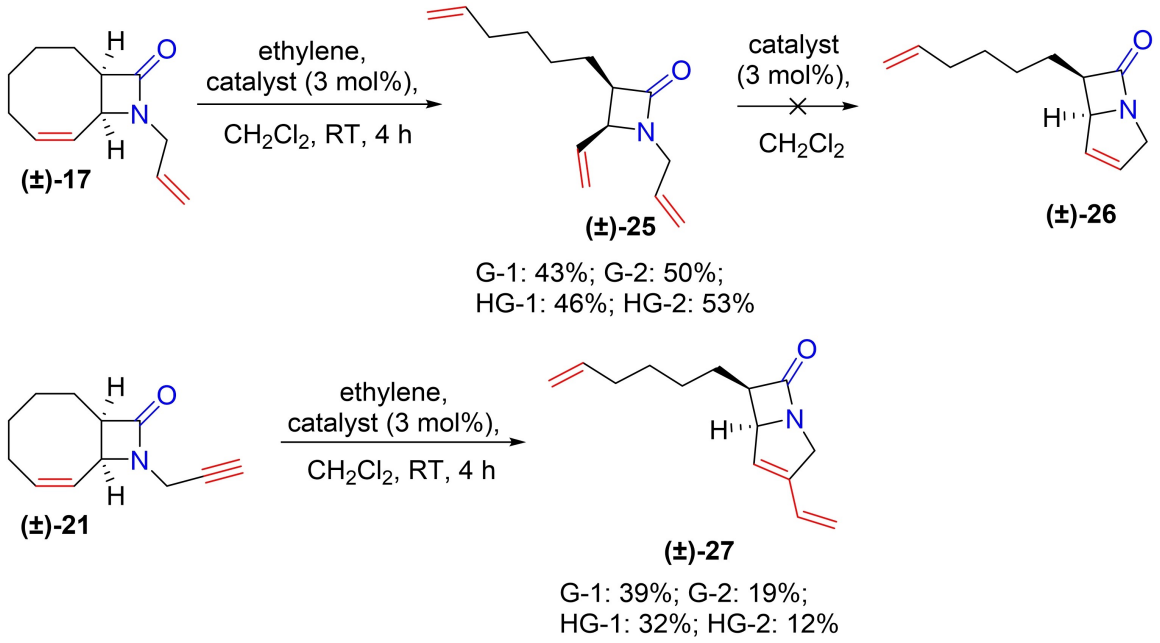


Scheme 4. Synthesis and ring-rearrangement metathesis of allyl and propargyl amino esters (±)-**19** and (±)-**23**.



Scheme 5. Metathesis transformations of β-lactams (±)-**17** and (±)-**21**.

olefin metathesis stopped after the ring opening step delivering a novel tri-unsaturated product (±)-**30** (Scheme 6). The most efficient catalyst was HG-2. Attempts under a number of experimental conditions, by variations of solvent, temperature, and catalyst loading, to force RCM by treating isolated (±)-**30** with metathesis catalysts failed (Scheme 6).

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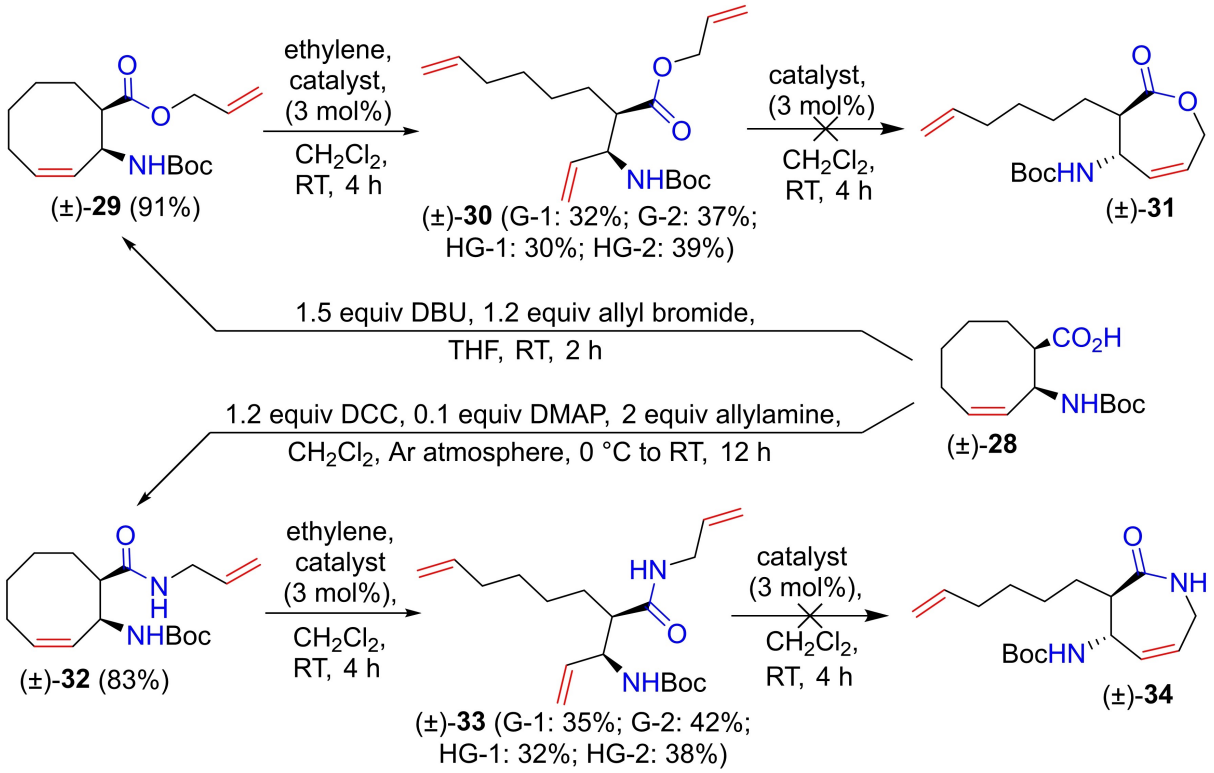

Scheme 6. Synthesis and metathesis transformation of allyl ester (±)-**29** and *N*-allylated amide (±)-**32**.

N-Allylated amide (±)-**32** (obtained via DCC-mediated coupling of amino acid (±)-**28** with allylamine) behaved analogously to allyl ester (±)-**29**, and only ROM product (±)-**33** could be isolated in moderate yields (Scheme 6).

Experiencing the failure of the ROM/RCM protocol, we shifted our attention towards ROM/RCEYM. To our delight, this novel synthetic pathway was successful. First, ester (±)-**35** and amide (±)-**37** were synthesized from *N*-Boc amino acid (±)-**28** in a similar fashion shown on Scheme 6. In the presence of metathesis catalysts under ethylene atmosphere (1 atm), the transformation of compound (±)-**35** provided directly the desired β-amino lactone (±)-**36**, the highest yield being achieved with HG-1 catalyst (45%). Catalyst G-1 provided the highest yield of the formation of β-amino lactam product (±)-**38** (51%) (Scheme 7).

Based on the results depicted on Schemes 6 and 7, *N*-propargylated ester (±)-**35** and amide (±)-**37** derivatives appear to be more susceptible to RRM in comparison with their *N*-allylated counterparts (±)-**29** and (±)-**32**. Based on these observations in might be assumed that the C–C triple bond of the propargyl unit is likely to participate in RRM, in comparison of the olefin bond (of the allylic moiety), however most probably the formation of a conjugated π-π system in (±)-**36** and (±)-**38** (which is not observed in case of (±)-**31** and (±)-**34**) might be a driving force in these transformations. Similar findings were observed earlier.[33,34,37] Note, however, that the reason of this observation is currently unknown.

Conclusions

The application of olefin metathesis on β-amino acid derivatives bearing a cyclooctene skeleton, serving as model starting compounds, allowed the generation of diverse azaheterocyclic β-amino acid frameworks, as well as the synthesis of polyunsaturated linear β-amino acid and lactam derivatives. These procedures are based on the ring-opening metathesis (ROM) of the cyclooctene-based amino acid derivatives, followed by selective cyclization through ring-closing metathesis (RCM) or ring-closing enyne metathesis (RCEYM). The outcomes of RRM transformations depend on both the catalyst and the substrate.

The transformation of *N*-allyl β-amino esters (±)-**13** and (±)-**19** with a cyclooctene skeleton was highly successful, yielding the corresponding azacyclopentene scaffolds. The achievement of high yields was attributed to the use of the first-generation catalysts. *N*-Propargyl β-amino esters (±)-**15** and (±)-**23** exhibited high selectivity in this transformation, providing only the ROM/RCEYM products. The yields were approximately equal when utilizing both first- and second-generation catalysts. Metathesis reactions of cyclooctene β-amino acid propargyl ester (±)-**35** and related *N*-propargylated amide (±)-**37** succeeded to deliver β-amino lactone or lactam products. In contrast, attempts with allyl esters (±)-**29** and *N*-allylamides (±)-**32** in RRM reactions were unsuccessful, yielding only ROM products that were resistant to further RCM transformation.

To sum up, based on our findings and the data reported, it is evident that ring-rearrangement metathesis proved to be a potent synthetic route for the creation of diverse azaheterocy-

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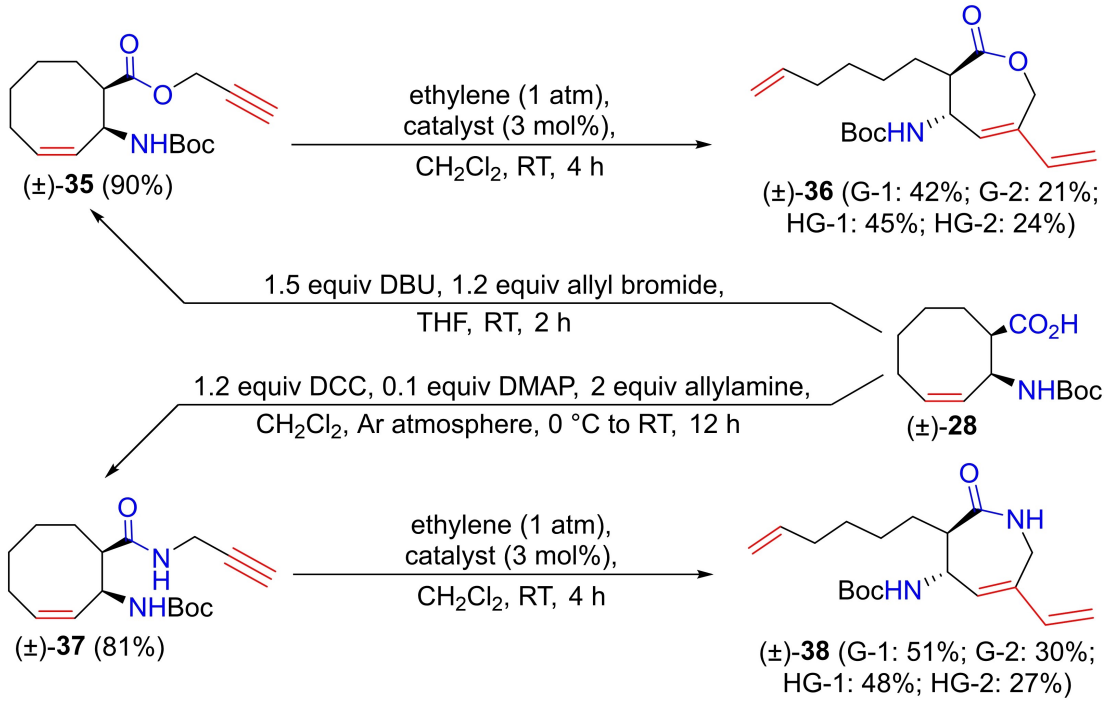

Scheme 7. Synthesis and metathesis transformation of propargyl ester (±)-**35** and *N*- propargylated amide (±)-**37**.

clic β-amino acid derivatives. However, the success of this method depends on the careful design of substrates. Keeping these considerations in mind, the potential for accessing novel compounds through this synthetic pathway is apparent and further experiments are under investigation in our laboratory.

Supporting Information Summary

Experimental procedures, characterization data, and NMR and MS spectra of the synthesized compounds are found in the Supporting Information.

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Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

Research data are not shared.

Keywords: amino esters · azaheterocycles · amino lactones · amino lactams · cyclization · metathesis · stereocontrol

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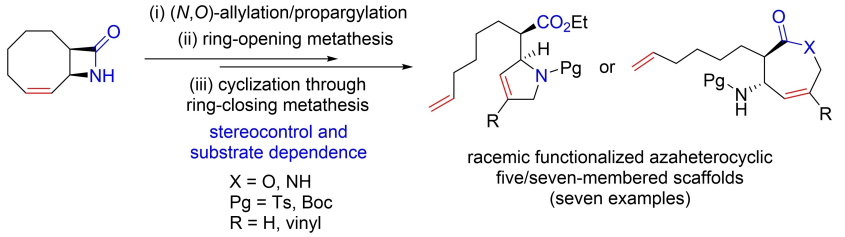

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Selective Transformation of 1,3-Cyclooctadiene into Novel Functionalized Azaheterocycles, β-Amino Esters, and Lactams by Means of Ring-Rearrangement Metathesis

Diversity-oriented synthesis of some novel functionalized azaheterocyclic β-amino esters with multiple chiral centers from 1,3-cyclooctadiene-based β-amino acids has been accomplished through stereocontrolled metathesis protocols.

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