Ph.D. Thesis

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

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1. Introduction and aims

Diversity-oriented synthesis (DOS) aims to construct valuable molecular libraries possessing high structural and chemical diversity. It 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. Ring-rearrangement metathesis (RRM) is one of the methods that can quickly and efficiently generate highly complex frameworks that are difficult to synthesize by conventional methods.

Cyclic β-amino acid derivatives are of high importance in pharmaceutical chemistry. These compounds possess a wide range of bioactive properties, they are present in a number of natural products and drugs, and they are promising building blocks of various foldamers.

Functionalized azaheterocycles (including azaheterocyclic β-amino acids) are an important and highly abundant compound family in pharmaceutical and medicinal chemistry. Therefore, the synthesis of such molecules became a highlighted research topic in our research group. Numerous functionalized azaheterocycles were prepared from functionalized cycloalkenes via an oxidative ring opening/double reductive amination sequence.

The present PhD work focused on the development of stereocontrolled synthetic routes for accessing azaheterocyclic β-amino acid derivatives. The strategy was based on ring-rearrangement metathesis of cycloalkene β-amino acid derivatives. Because such reactions are driven by the release of ring strain, norbornene, oxanorbornene, and cyclooctene derivatives were utilized. A number of experimental conditions were used to investigate the effects of the catalysts (*Figure 1*) and the substrates on the yields and conversions of the metathesis reactions.

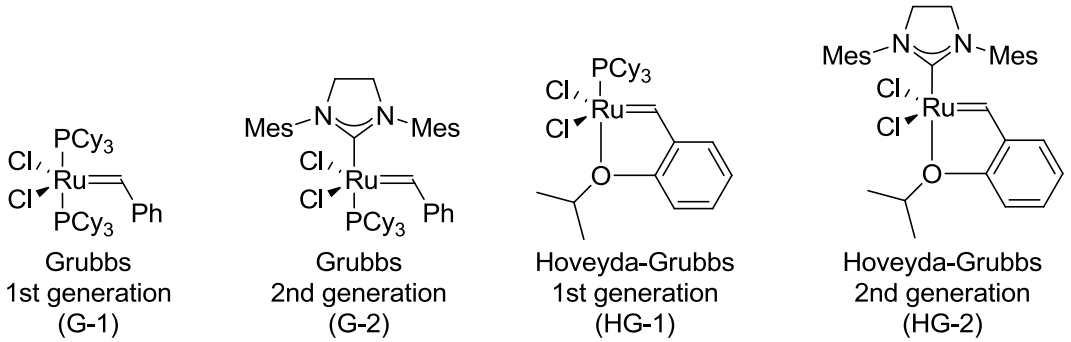


Figure 1. Commercially available catalysts used in this work

2. Methods

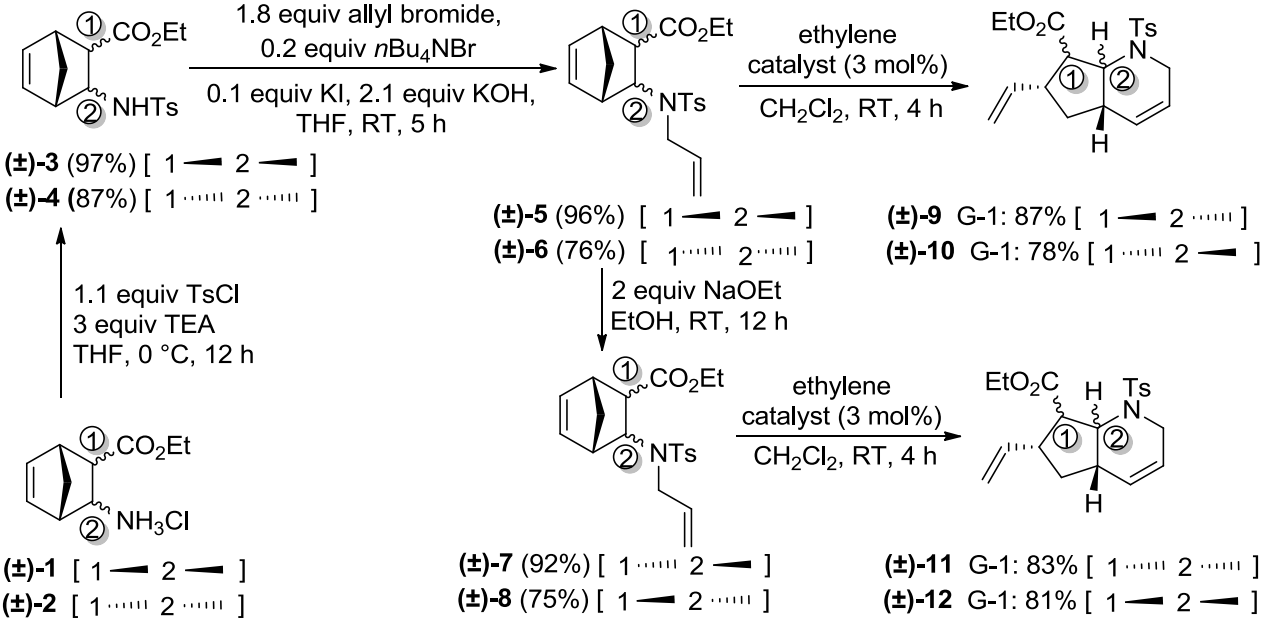
The synthesized compounds were separated and purified by column chromatography on silica gel and by crystallization. The newly prepared compounds were characterized by NMR spectroscopy, high-resolution mass spectrometry, melting point measurement and elemental analysis. For determination of the structure and stereochemistry of the compounds, 2D NMR spectroscopy (COSY, HSQC, HMBC and NOESY) were applied.

3. Results and discussion

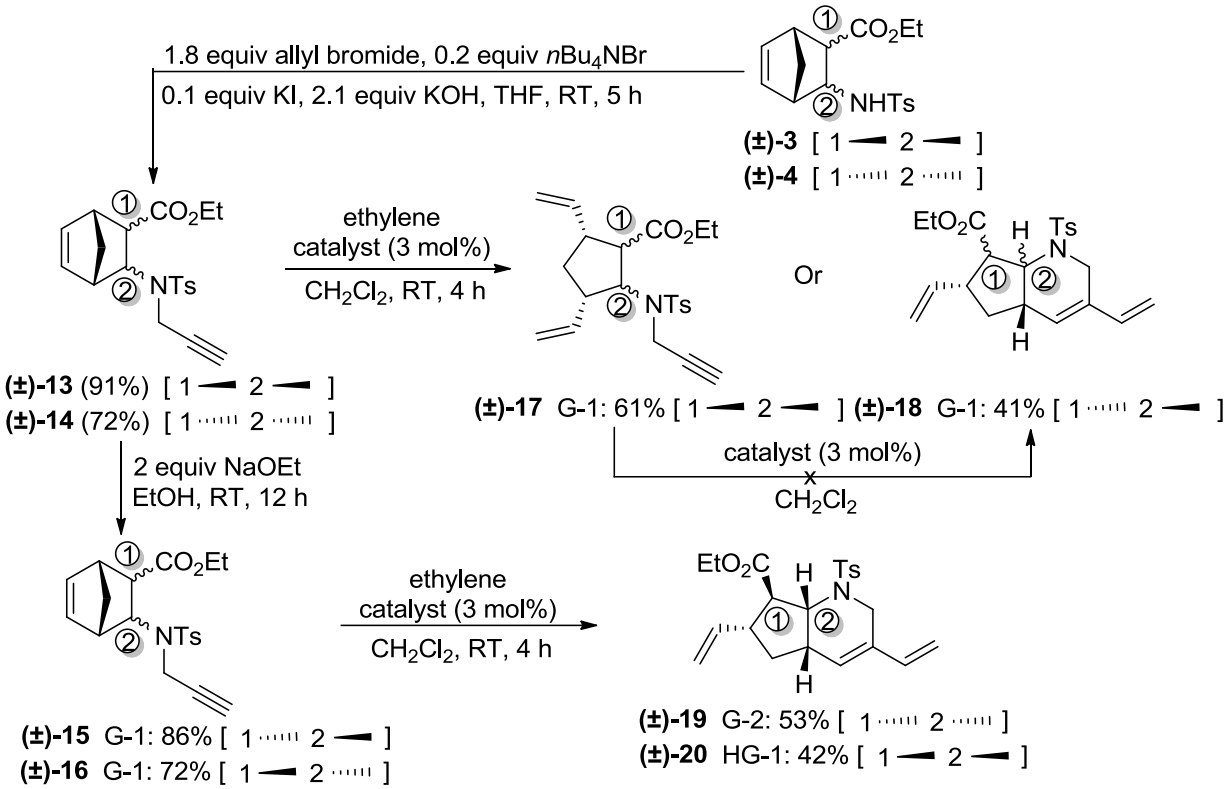
3.1 Stereocontrolled synthesis of some novel azaheterocycles by ring-rearrangement metathesis of norbornene β-amino acid derivatives

Synthesis of novel functionalized azaheterocycles with several chiral centers were accomplished via stereocontrolled synthetic routes: ring-opening metathesis/ring-closing metathesis of norbornene β-amino esters with an allyl group, and ring-opening metathesis/ring-closing enyne metathesis of analogous propargylated compounds. In all cases, thorough investigation of the experimental conditions found that the highest isolated yields of the desired azaheterocyclic products were obtained under the following conditions: 3 mol% catalyst, ethylene atmosphere, CH_2Cl_2 solvent, RT, 4 h reaction time.

Synthesis and RRM of *N*-allylated substrates (±)-**5**, (±)-**6**, (±)-**7**, and (±)-**8** is depicted on *Scheme 1*. Synthesis and RRM of the analogous *N*-propargylated substrates (±)-**13**, (±)-**14**, (±)-**15**, and (±)-**16** is depicted on *Scheme 2*.

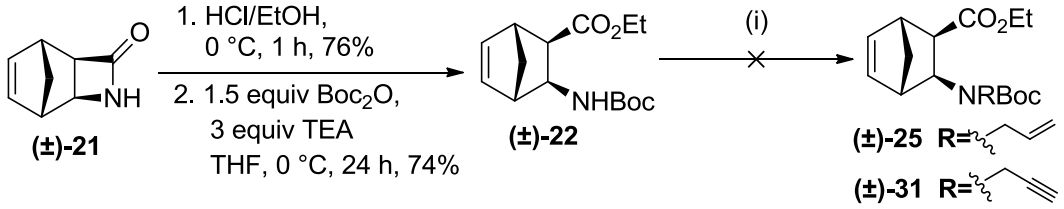


Scheme 1. Synthesis of azaheterocyclic β-amino esters (±)-**9**, (±)-**10**, (±)-**11**, and (±)-**12**



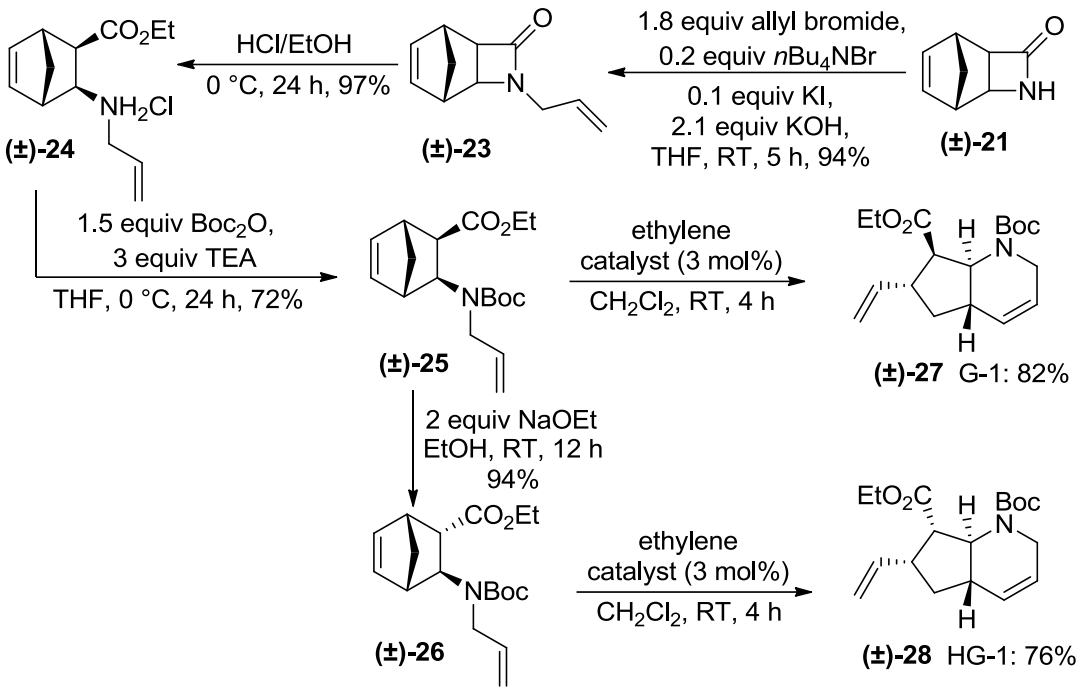
Scheme 2. Synthesis of azaheterocyclic β-amino esters (±)-**18**, (±)-**19**, and (±)-**20**

The removal of *N*-tosyl protection can be a challenging process. Therefore, our next objective was the synthesis of analogous *N*-Boc protected scaffolds whose deprotection is easier. Unfortunately, despite using several varieties of bases (sometimes in combination with additives), solvents, and reaction temperatures, *N*-allylation and *N*-propargylation of *N*-Boc-protected β-amino ester **(±)-22** failed (*Scheme 3*).



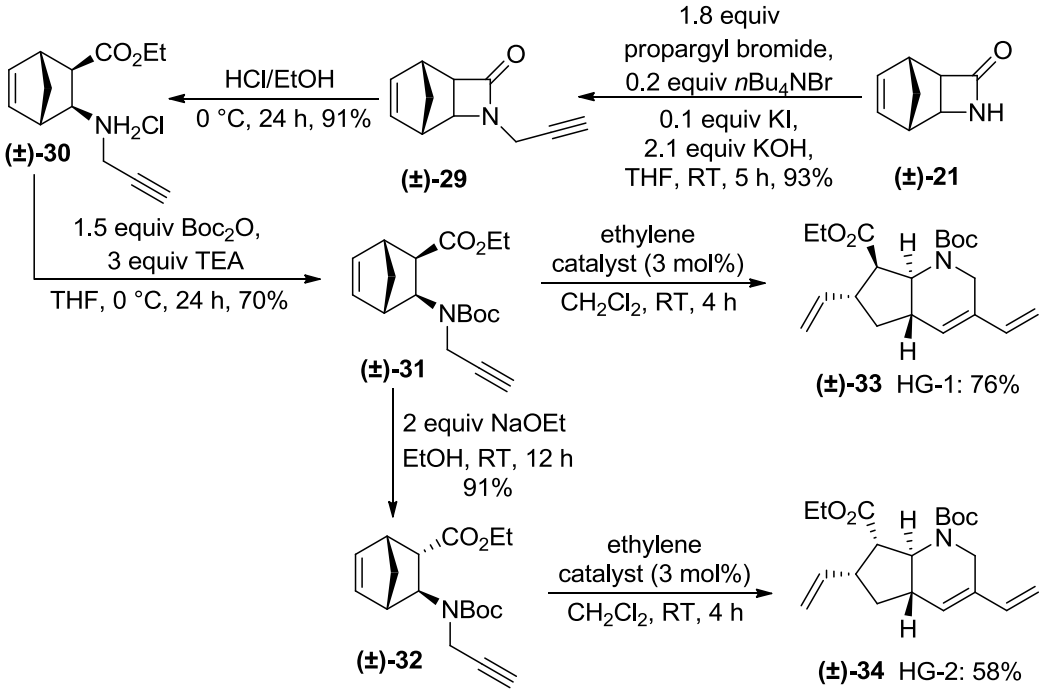
Scheme 3. Attempts for the synthesis of *N*-Boc β-amino esters **(±)-25** and **(±)-31**
(i) (allyl bromide or propargyl bromide)/base (Cs_2CO_3, Et_3N, DBU, *t*BuOK, K_2CO_3, NaH or KOH)/solvent (DMF, MeCN, THF)/additives (*n*Bu_4NBr or KI)/temperature (RT or reflux)

Upon reviewing the applied synthetic pathway, we devised an alternative route. To our delight, *N*-allylation of β-lactam **(±)-21**, ethanolysis of the formed *N*-allyl lactam **(±)-23**, and finally *N*-Boc protection provided compound **(±)-25**. Its epimerization yielded *trans* β-amino ester **(±)-26**. Upon subjecting to ring-rearrangement metathesis, both substrates afforded the desired azaheterocycles **(±)-27** and **(±)-28** (*Scheme 4*).



Scheme 4. Synthesis of *N*-Boc protected azaheterocyclic β-amino esters via ROM/RCM

Using the already established synthetic pathway, *N*-propargyl lactam **(±)-29** was synthesized and transformed into azaheterocycles **(±)-33** and **(±)-34** (*Scheme 5*). Note that synthesis of the *N*-tosylated analogue of **(±)-33** failed previously (*Scheme 2*).



Scheme 5. Synthesis of *N*-Boc protected azaheterocyclic β-amino esters via ROM/RCEYM

The stereochemistry of the above synthesized azaheterocyclic products and their β-amino ester precursors were determined by 2D NMR (COSY, NOESY, HSQC, and

HMBC) spectral data. Some examples are depicted in *Figure 2*.

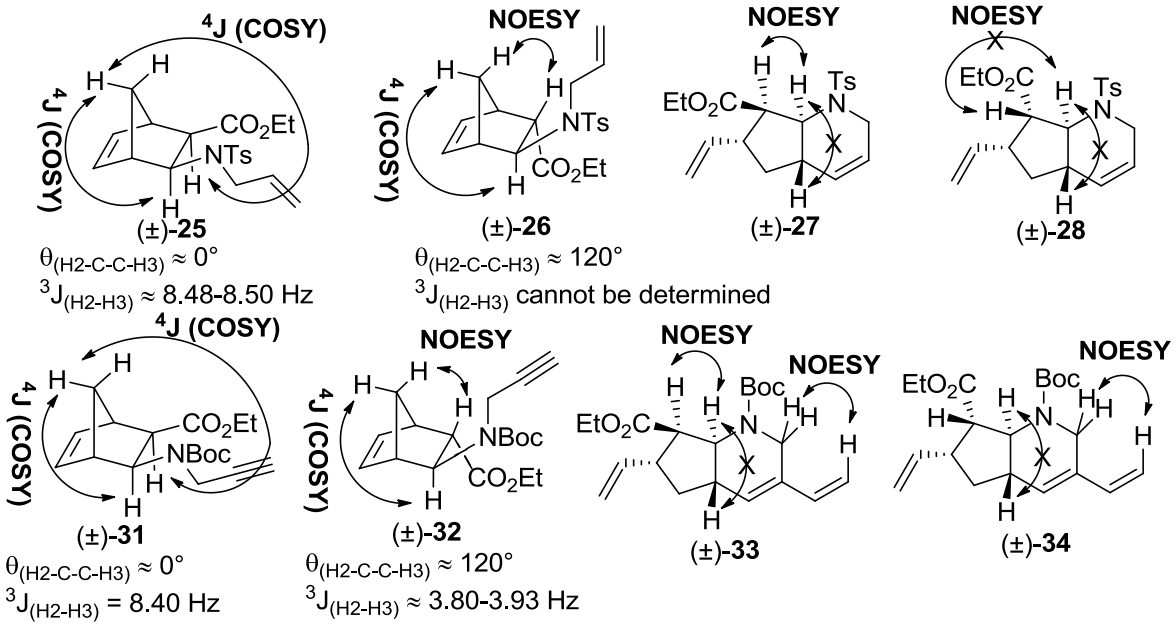
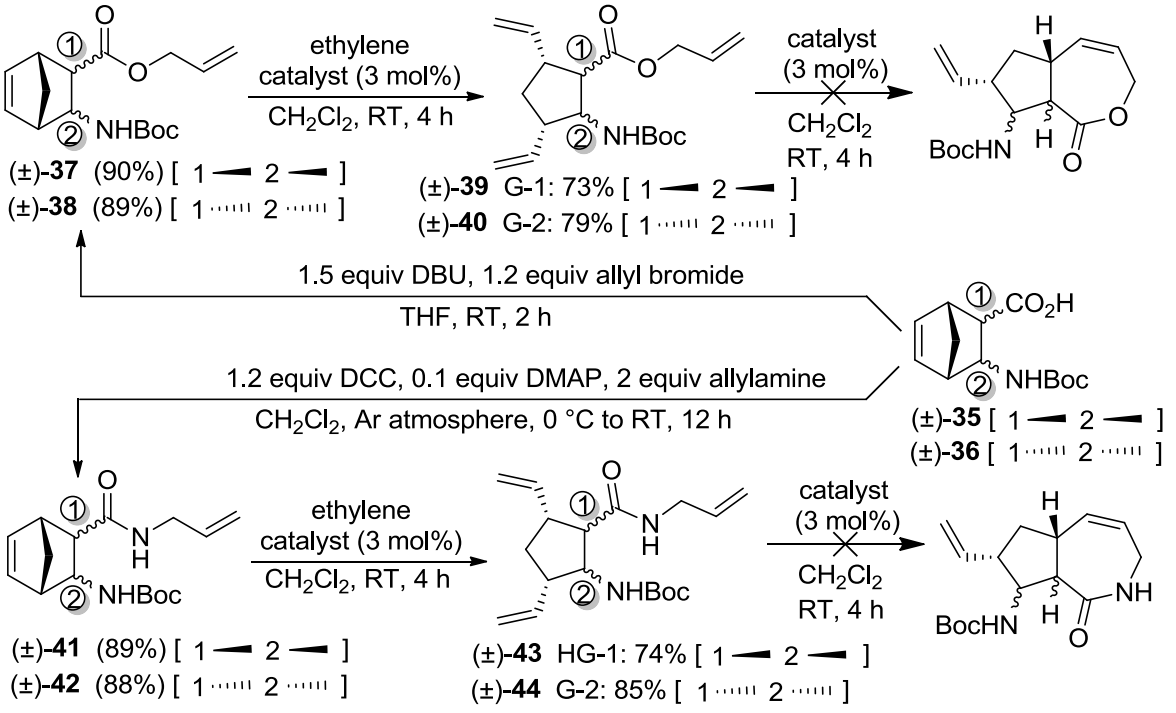


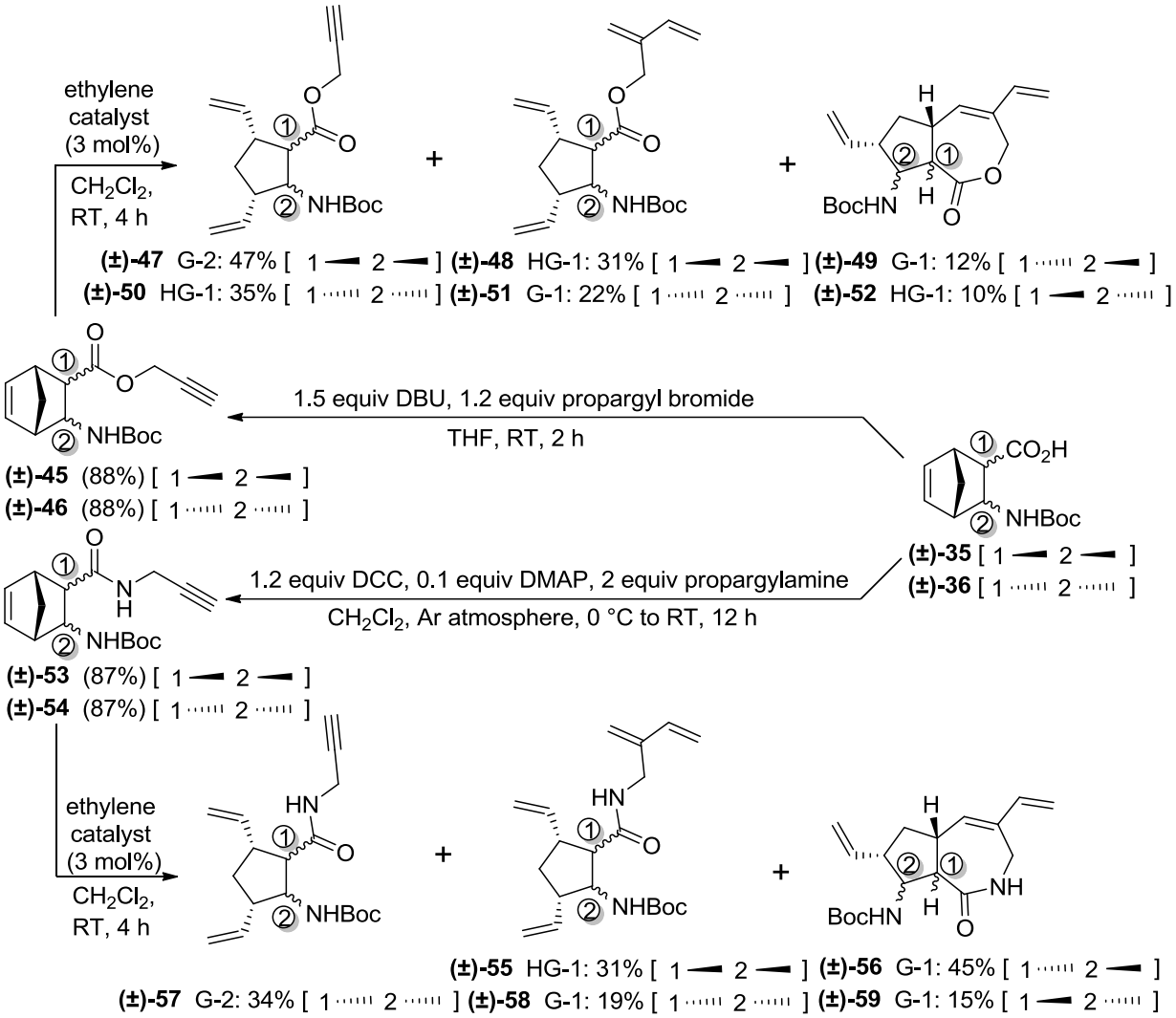
Figure 2. Confirmation of the stereochemistry of some compounds depicted on *Scheme 4-5*

The synthetic methodology was further extended to access novel β-amino lactones and β-amino lactams. Thus, *N*-Boc protected amino acids **(±)-35** and **(±)-36** were subjected to *O*-allylation or amidation. Then, the resulting compounds were subjected to RRM. Unfortunately, olefin metathesis stopped after the ring opening step, delivering novel cis- and transpentacin products (*Scheme 6*). Attempts to force RCM of these products failed.



Scheme 6. Synthesis of cispentacin analogues and attempts for their RCM

Seeing the failure of the ROM/RCM protocol, we shifted our attention toward the ROM/RCEYM pathway. To our delight, this new synthetic route was successful. All four catalysts afforded a mixture of ROM products [**(±)-47**, **(±)-50**, and **(±)-57**)], ROM/CEYM products [**(±)-48**, **(±)-51**, **(±)-55**, and **(±)-58**)] and the desired RRM products [**(±)-49**, **(±)-52**, **(±)-56**, and **(±)-59**)]. The highest yields were achieved mostly with G-1 and HG-1 catalysts (*Scheme 7*).

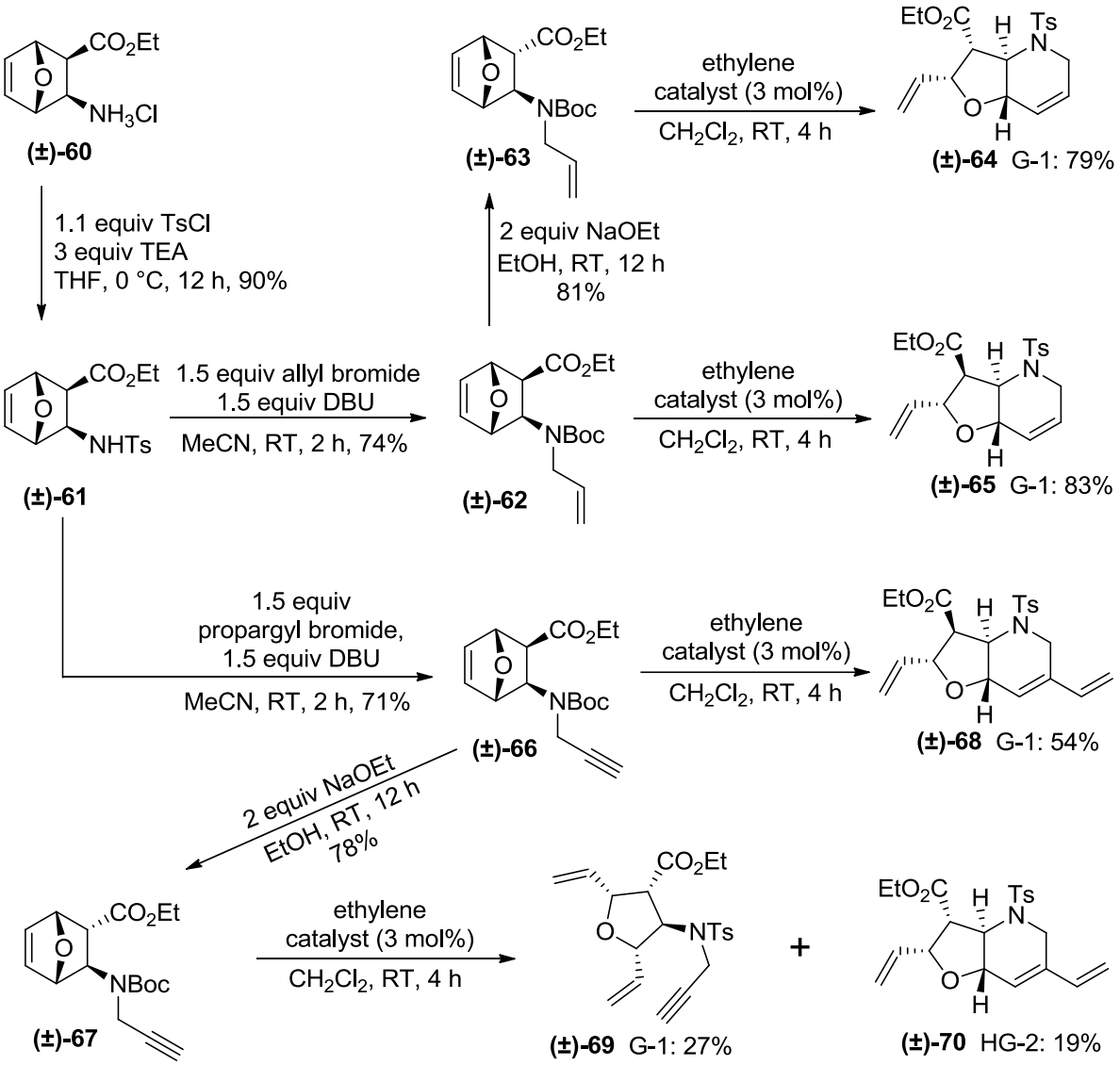


Scheme 7. Synthesis of β-amino lactones and β-amino lactams

3.2 Stereocontrolled synthesis of some novel azaheterocycles by ring-rearrangement metathesis of oxanorbornene β-amino acid derivatives

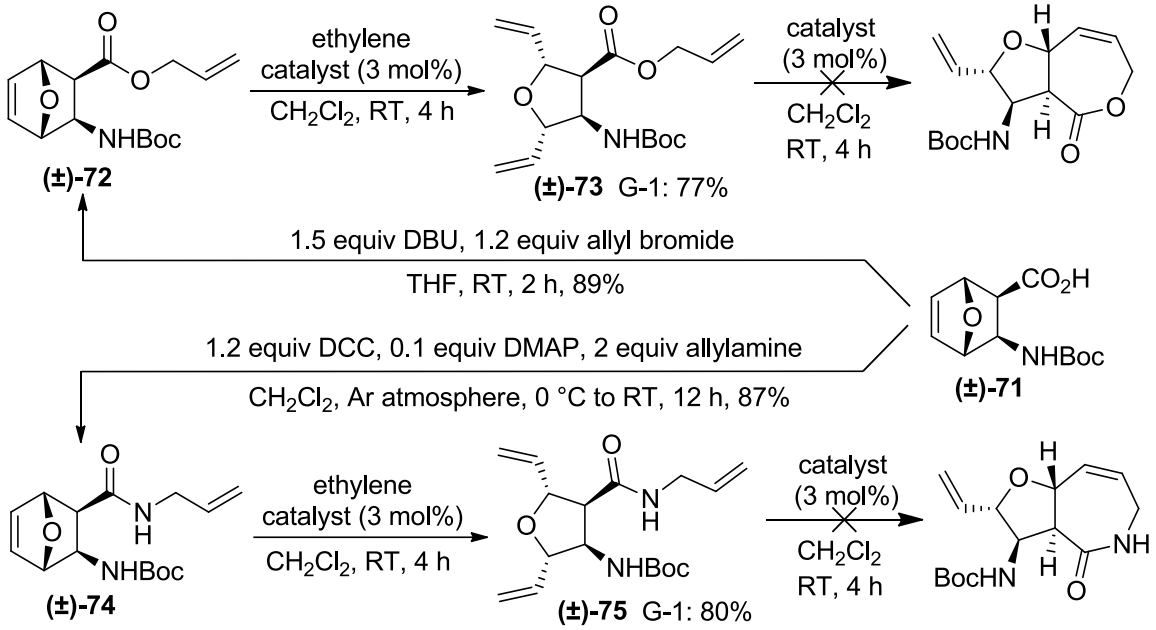
In view of the relevance of oxygen-containing cyclic β-amino acids, the above described stereocontrolled methods were extended towards the synthesis of tetrahydrofuran-fused azaheterocyclic β-amino acids. For this purpose, oxanorbornene β-amino ester **(±)-60** was subjected to *N*-tosylation and subsequent *N*-alkylation (the latter step used DBU as a

base). The resulting compounds [**(±)-62** and **(±)-66**)] and their epimerized derivatives [**(±)-63** and **(±)-67**)] were subjected to ring-rearrangement metathesis, yielding the desired azaheterocycles [**(±)-64**, **(±)-65**, **(±)-68**, and **(±)-70)**] as depicted on *Scheme 8*.



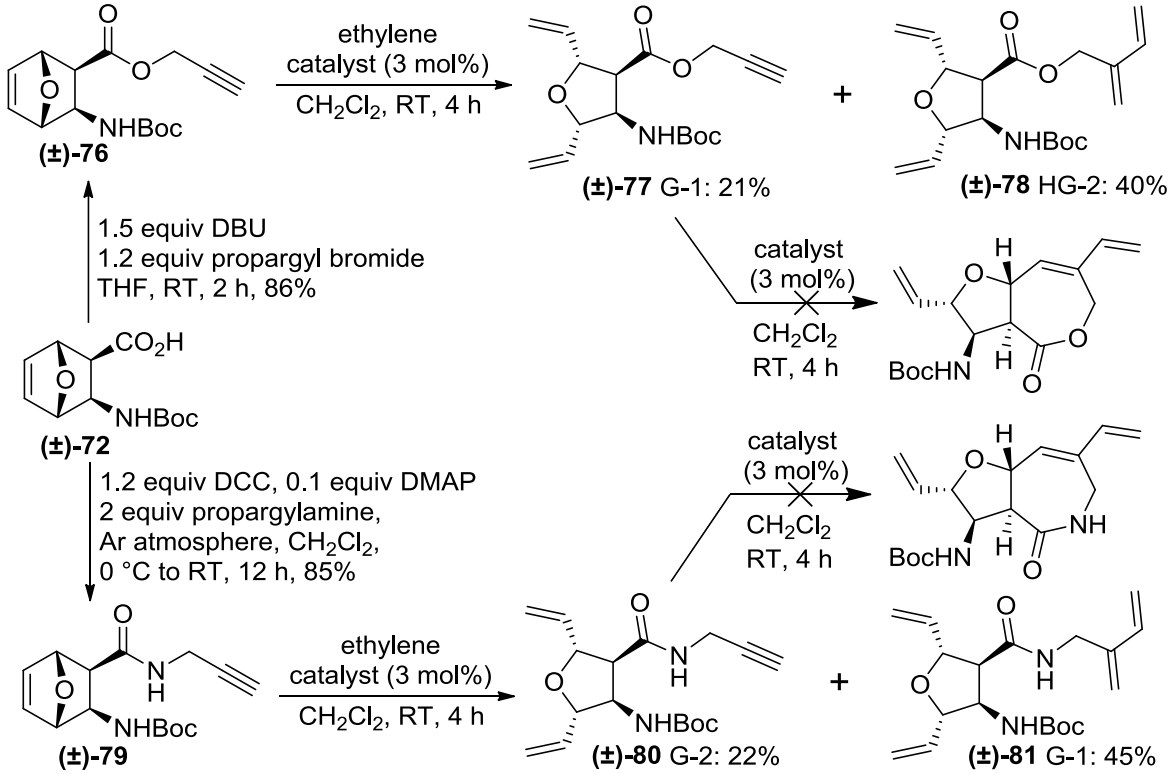
Scheme 8. Synthesis of tetrahydrofuran-fused azaheterocyclic β-amino esters

Since our strategy demonstrated its efficiency in the synthesis of tetrahydrofuran-fused azacyclic β-amino esters, we investigated its applicability for the access of tetrahydrofuran-fused β-amino lactones or β-amino lactams. Our first substrates were oxanorbornene ester **(±)-72** (prepared by *O*-allylation of compound **(±)-71**) and oxanorbornene amide **(±)-74** (prepared via DCC-mediated amidation of compound **(±)-71** with allylamine). When these substrates were subjected to olefin metathesis, the transformation stopped after the ROM step. Attempts to force RCM of products **(±)-73** and **(±)-75** were unsuccessful (*Scheme 9*).



Scheme 9. Attempted synthesis of tetrahydrofuran-fused β-amino lactones or β-amino lactams

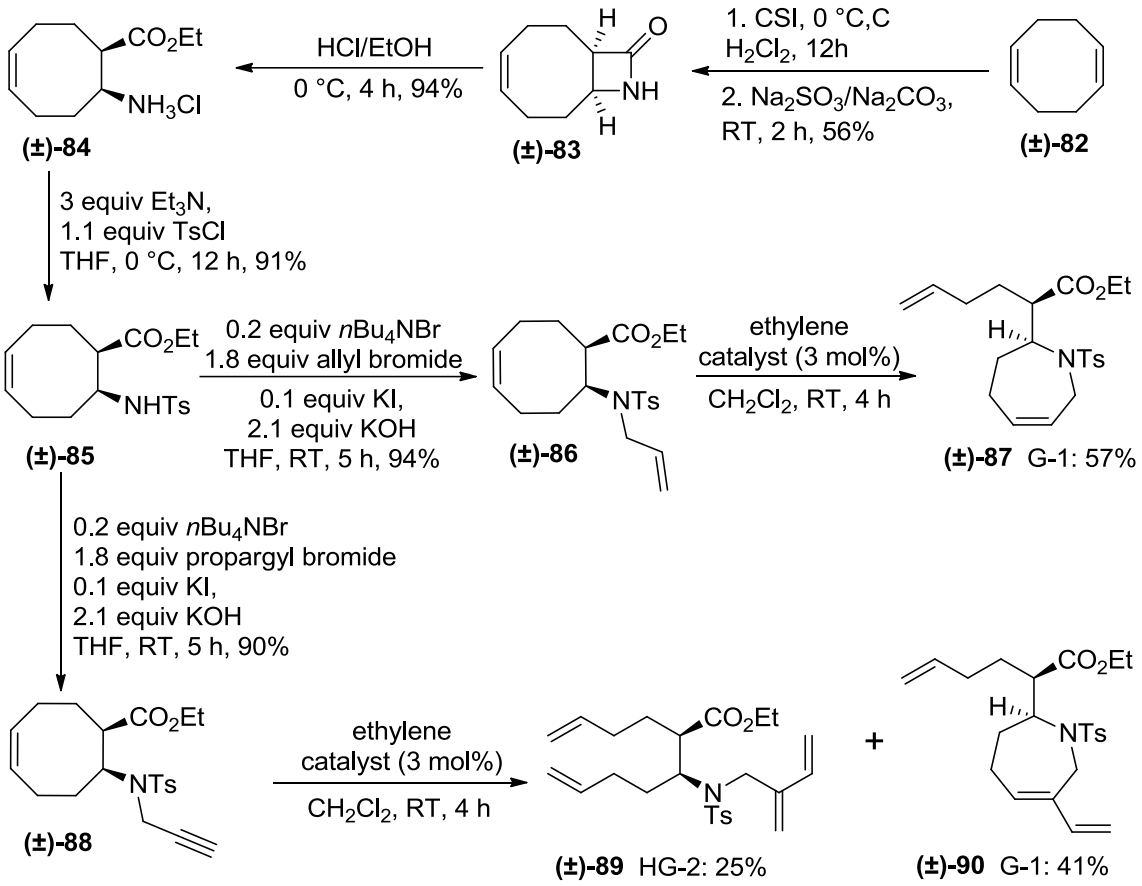
After failing to reach the target product using ROM/RCM, we switched to ROM/RCEYM. Synthesis of substrates **(±)-76** and **(±)-79** was successful, but their olefin metathesis (*Scheme 10*) failed to provide the desired azaheterocycles. The minor products [**(±)-77** and **(±)-80**] were formed by ROM, while the major products [**(±)-78** and **(±)-81**] were formed by ROM/CEYM.



Scheme 10. Attempted RRM of propargylated oxanorbornene compounds **(±)-76** and **(±)-79**

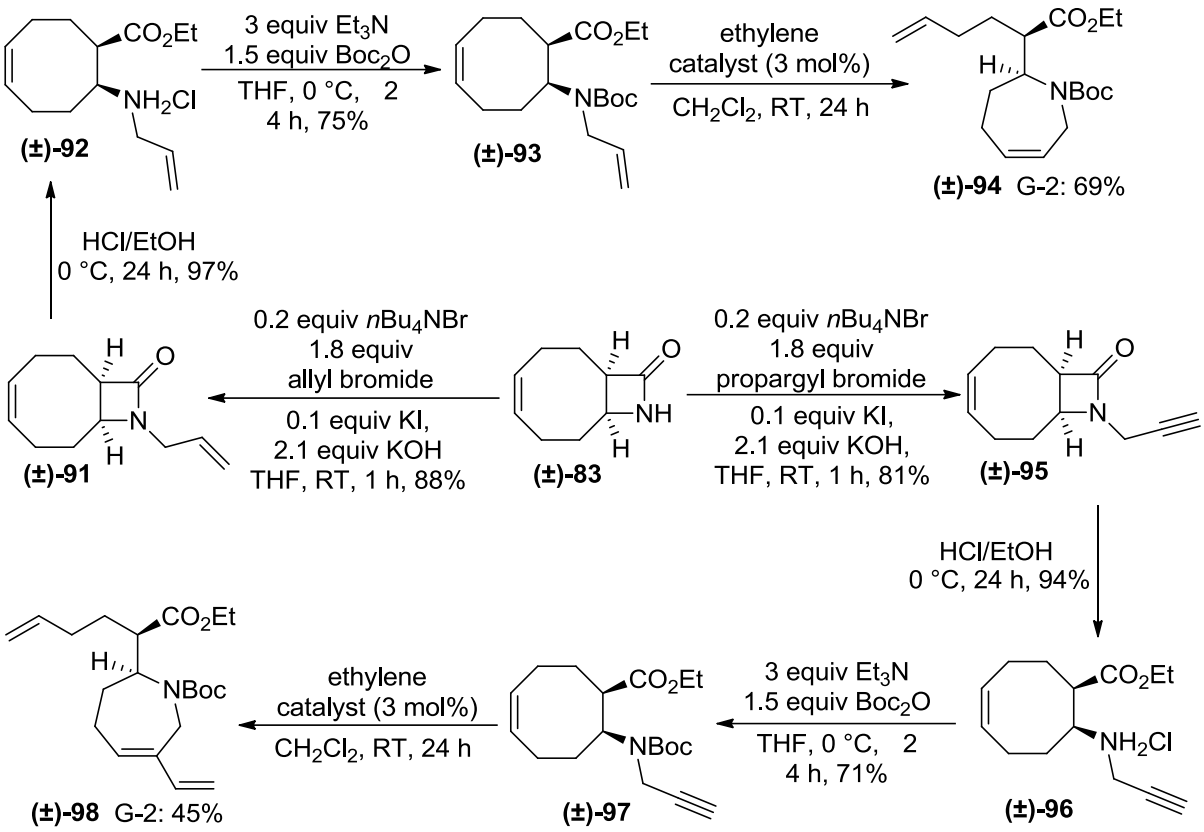
3.3 Stereocontrolled synthesis of some novel β-amino acid derivatives by ring-rearrangement metathesis of cyclooctene β-amino acid derivatives

The synthetic strategy was extended for the access of other *N*-heterocyclic compounds, β-amino lactones, and β-amino lactams. First, cyclooctene β-amino esters **(±)-86** and **(±)-88** were prepared and subjected to ring rearrangement metathesis (ROM/RCM or ROM/RCEYM). The reactions were successful with all four catalysts and led to the expected azaheterocycles **(±)-87** and **(±)-90**. G-1 catalyst was the most efficient (*Scheme 11*).



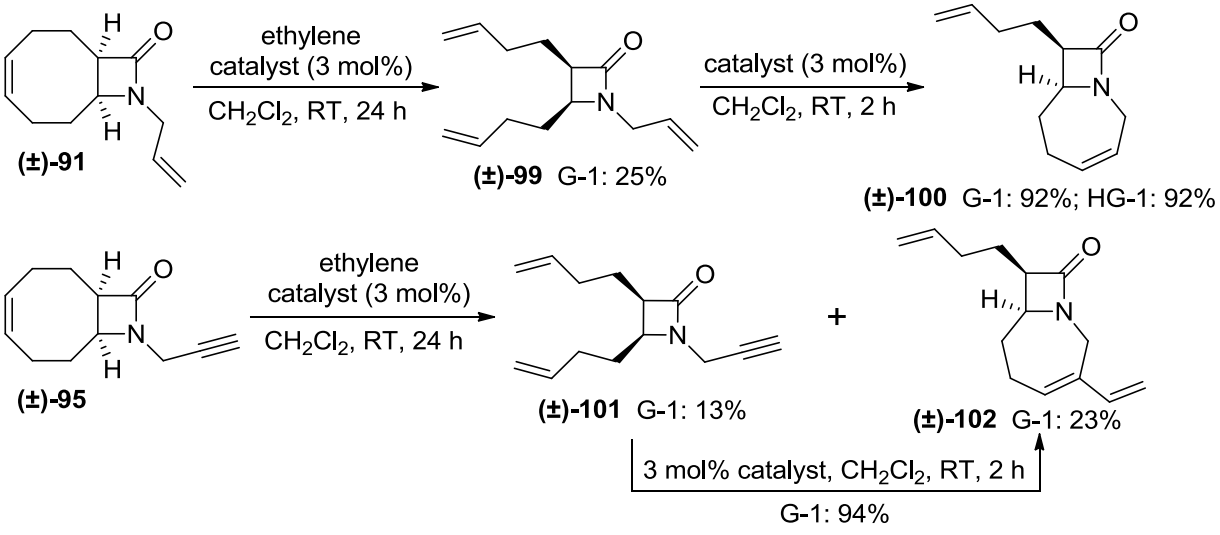
Scheme 11. Synthesis of seven-membered azaheterocyclic β-amino esters

Since removing the *N*-tosyl group is relatively difficult, we synthesized analogous *N*-Boc protected compounds, whose deprotection is easier. We applied the same alternative pathway that proved its usefulness for the synthesis of norbornene compounds (see *Scheme 4-5*). ROM/RCM of *N*-allyl β-amino ester **(±)-93** and ROM/RCEYM of *N*-propargyl β-amino ester **(±)-97** provided the desired azaheterocyclic products **(±)-94** and **(±)-98**, respectively (*Scheme 12*). The highest yields were achieved with G-2 catalyst.



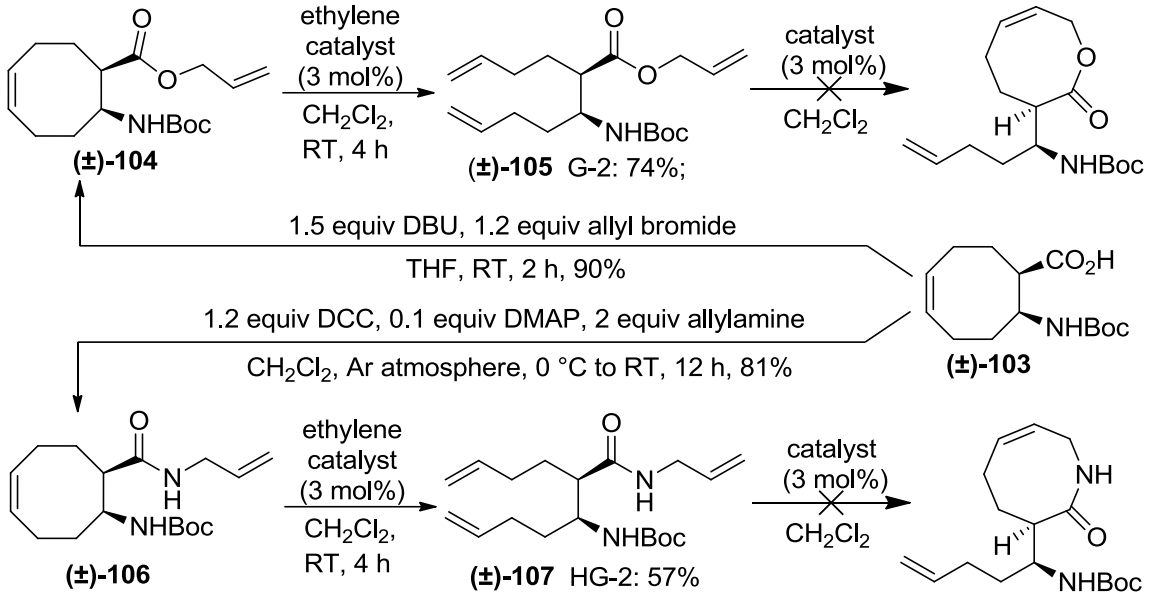
Scheme 12. Synthesis of *N*-Boc protected seven-membered azaheterocyclic β-amino esters

β-Lactam derivatives **(±)-91** and **(±)-95** were also subjected to olefin metathesis. In the case of compound **(±)-91**, the process stopped after the ring-opening step and afforded tris(alkenyl) β-lactam **(±)-99**. Fortunately, ring-closing metathesis of **(±)-99** provided the desired azaheterocycle **(±)-100** in excellent yield. In case of compound **(±)-95**, the transformation was partially successful and provided both ROM product **(±)-101** and RRM product **(±)-102**. The highest yields were achieved with G-1 catalyst in all cases (*Scheme 13*).



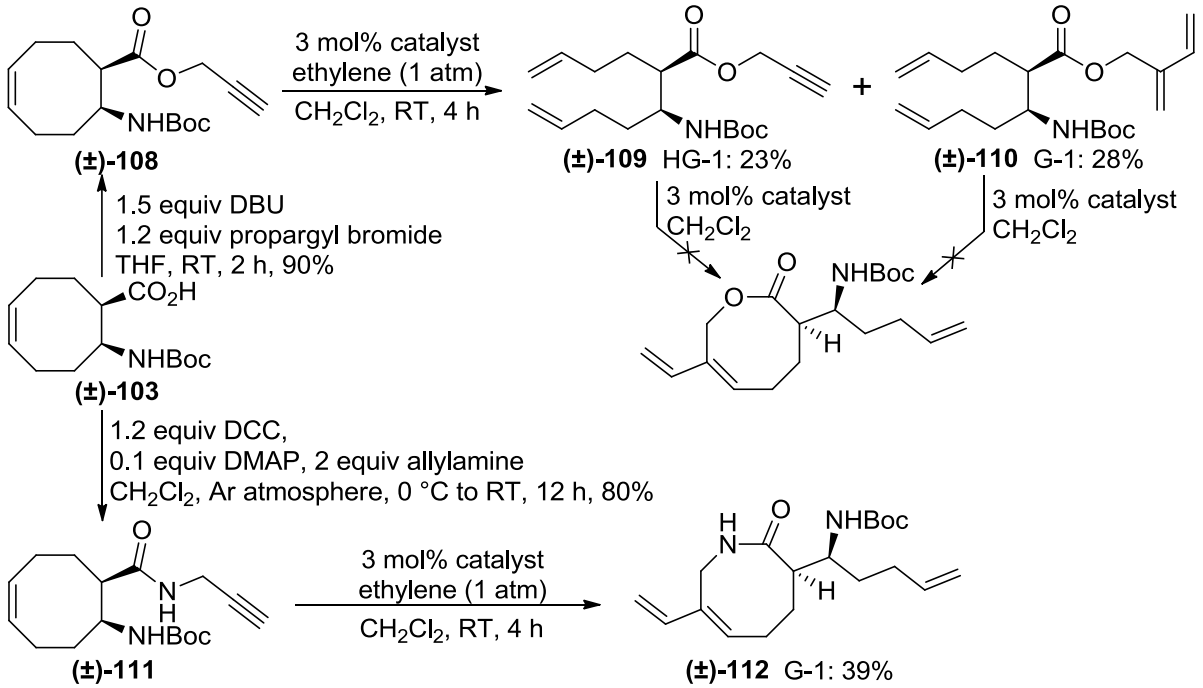
Scheme 13. Synthesis other *N*-heterocyclic derivatives

Next, RRM of allyl ester **(±)-104** and *N*-allylated amide **(±)-106** was investigated. In both cases, the ROM step took place readily and efficiently, but the intended RCM step failed (*Scheme 14*). The highest yields were achieved with G-2 catalyst [74% for product **(±)-105** and 57% for product **(±)-107**].



Scheme 14. Attempted ROM/RCM of cyclooctene compounds **(±)-104** and **(±)-106**

Afterward, metathesis of propargyl ester **(±)-108** under our usual RRM conditions provided mixtures of ROM and ROM/CEYM products. In contrast, transformation of propargyl amide **(±)-111** afforded directly the desired β-amino lactam **(±)-112** (*Scheme 15*).



Scheme 15. Synthesis of β-amino lactam (±)-**112** via ROM/ RCEYM

Generally, the success of a certain RRM reaction was determined by the release of ring strain (see *Figure 3*). Transformation of (oxa)norbornene systems to 5:6 fused azaheterocyclic systems (hexahydro-1*H*-cyclopenta[*b*]pyridines and hexahydrofuro[3,2-*b*]pyridines) almost always proceeded (both ROM/RCM and ROM/RCEYM was successful). Transformation of norbornene systems to 5:7 fused azaheterocyclic systems (8-amino-3,5a,6,7,8,8a-hexahydro-1*H*-cyclopenta[*c*]oxepin-1-ones and 8-amino-2,3,6,7,8,8a-hexahydrocyclopenta[*c*]azepin-1(5a*H*)-ones), however, only worked with ROM/RCEYM reactions. Transformation of oxanorbornene systems to 5:7 fused azaheterocyclic systems always failed (both ROM/RCM and ROM/RCEYM were unsuccessful). Transformation of cyclooctene systems to seven-membered 2,3,4,7-tetrahydro-1*H*-azepines always worked. In contrast, transformation of cyclooctene systems to unsaturated 8-membered lactams/lactons almost always failed [the sole exception is RRM of **(±)-111** to **(±)-112**].

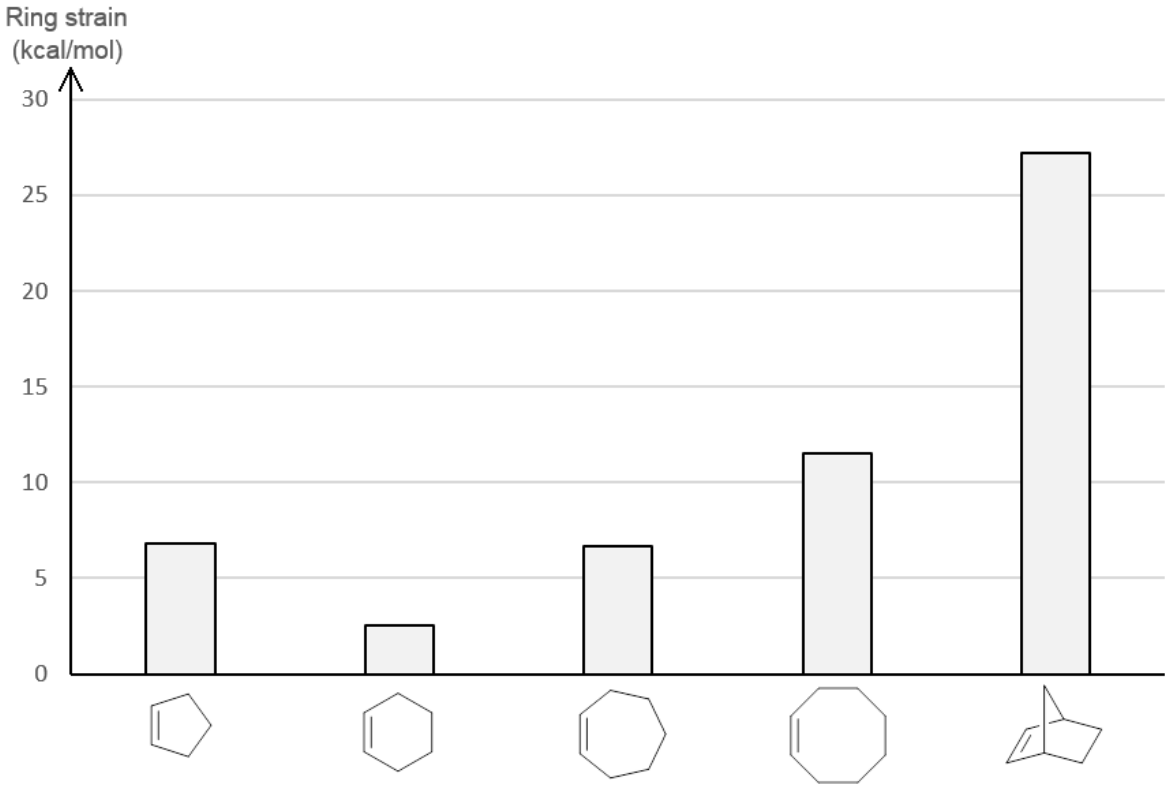


Figure 3. Ring strain of various cyclic olefins

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.

PUBLICATION LIST

Papers related to the thesis:

I. **Anas Semghouli**, Zsanett Benke, Attila M. Remete, Tamás T. Novák, Santos Fustero, Loránd Kiss:
Selective Transformation of Norbornadiene into Functionalized Azaheterocycles and β-Amino Esters with Stereo-and Regiocontrol
Chem. Asian J. **2021**, *16*(23), 3873-3881. IF: 4.839 Q1

II. **Anas Semghouli**, Attila M. Remete, Tamás T. Novák, Loránd Kiss:
Stereocontrolled Synthesis of Some Novel Azaheterocyclic β-Amino Ester Stereoisomers with Multiple Stereogenic Centers
Synlett **2022**, *33*(16), 1655-1659. IF: 2.170 Q2

III. **Anas Semghouli,** Attila M. Remete, Loránd Kiss:
Synthesis of New β-Amino Acid Scaffolds by Means of Ring-Rearrangement Metathesis
ChemistrySelect **2022**, *7*(46), IF 2.109. IF: 2.307 Q2

IV. **Anas Semghouli,** Attila M. Remete, Loránd Kiss:
Stereocontrolled synthesis of some novel functionalized heterocyclic β-amino ester and amide with multiple chiral centers
Submitted manuscript

Other publications:

V. Zsanett Benke, Attila M. Remete, **Anas Semghouli**, Loránd Kiss:
Selective functionalization of norbornadiene through nitrile oxide cycloaddition/ring-opening/cross-metathesis protocols
Asian J. Org. Chem. **2021**, *10*(5), 1184-1191. IF: 3.116 Q1

VI. Attila M. Remete, Melinda Nonn, **Anas Semghouli**, Sillanpää, Reijo, Loránd Kiss:
An improved synthesis of 3,3- and 5,5-difluoro-2-aminocyclohexanecarboxylates and extension of the method via organoselenium chemistry
Fluorine Notes **2021**, *1*, 1-31.

Conference lectures:

VII. **Anas Semghouli**:

Stereocontrolled transformation of N-protected norbornene β-amino esters into novel functionalized azaheterocycles through ring opening/ring closing metathesis

A Szegedi Ifjú Szerves Kémikusok Támogatásáért Alapítvány 21. tudományos előadóülése

Szeged, Hungary, 18 May, 2021, oral presentation

VIII. **Anas Semghouli**, Tamás T. Novák, Attila M. Remete, Loránd Kiss:

Selective transformation of norbornadiene into novel functionalized azaheterocycles and β-amino esters with stereo- and regiocontrol

Az MTA Alkaloid- és Flavonoidkémiai Munkabizottság Ülése

Mátrafüred, Hungary, 7-8 October, 2021, oral presentation

IX. **Anas Semghouli**, Attila M. Remete, Loránd Kiss:

Selective transformation of cyclooctadiene β-lactam into novel functionalized azaheterocycles and β-amino esters via ring-rearrangement metathesis

Az MTA Alkaloid- és Flavonoidkémiai Munkabizottság Ülése

Mátrafüred, Hungary, 6-7 October, 2022, oral presentation

X. **Anas Semghouli**, Attila M. Remete, Loránd Kiss:

Selective transformation of norbornene and oxanorbornene β-amino acid derivatives into novel functionalized azaheterocycles via ring-rearrangement metathesis

XLV. Chemistry Lectures

Szeged, Hungary, 25-27 October, 2023, oral presentation and communication